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References

Acevedo HF, Tong JY, Hartsock RJ. 1995 . Human chorionic gonadotropin-beta subunit gene expression in cultured human fetal and cancer cells of different types and origins. Cancer 76:1467-1475.
Abstract: BACKGROUND. The authors' previous investigations using living cultured human cancer cells and cells isolated from cancer tissues, analytical flow cytometry, and monoclonal antibodies directed to epitopes located in five different sites of the human chorionic gonadotropin (hCG) molecule, identified the presence of membrane-associated hCG, its subunits and fragments, by cells from all cancers, irrespective of type and origin, indicating that the expression of these sialoglycoproteins is a common phenotypic characteristic of cancer. Although benign neoplasms do not express these compounds, cultured human embryonic and fetal cells also express the same materials. To corroborate these findings, five fetal cell lines and 28 cancer cell lines were randomly selected from those previously studied, to determine the presence of translatable levels of hCG-beta (hCG beta) mRNA. METHODS. All cell lines were grown under identical conditions. Determination of hCG beta mRNA was made by extracting the total RNA from the cells, followed by synthesis of cDNA with RNase H- reverse transcriptase and polymerase chain reaction amplification using specific hCG beta-luteinizing hormone-beta (hLH beta) primers. The presence of amplified hCG beta cDNA was corroborated by hybridization of the product with an hCG beta-specific oligonucleotide and Southern blot analyses of the hybridization products. Gestational choriocarcinoma cells and HeLa adenocarcinoma of cervical cells, known producers of biologically active hCG, were positive control subjects, and human pituitary cells were used as negative control subjects. RESULTS. The results showed single and multiple hCG beta gene activation by the fetal cells and the different types of cancer, indicating that at any given time, there is the possibility of activation of as many as four genes of the six genes of the hCG beta-hLH beta gene cluster, even though alternative gene splicing cannot be ruled out. CONCLUSIONS. In addition to the authors' previous findings, the results of these studies support the concept that cancer is a problem of development and differentiation, and, to the authors' knowledge, prove definitively for the first time that synthesis and expression of hCG, its subunits, and its fragments, is a common biochemical denominator of cancer, providing the scientific basis for studies of its prevention and/or control by active and/or passive immunization against these sialoglycoproteins.

Acharya S, Jayabose S, Kogan SJ, Tugal O, Beneck D, Leslie D, Slim M. 1997. Prenatally diagnosed neuroblastoma. Cancer 80:304-310.
Abstract: BACKGROUND: Prenatally diagnosed neuroblastomas have been reported in increasing numbers over the past several years, and there are now a few reviews based on up to 21 cases. The purpose of this article is to review the clinical and biologic features of prenatally diagnosed neuroblastoma based on a review of 55 cases. METHODS: A review was conducted of 3 cases seen at the study institution and 52 other cases reported thus far in the literature. RESULTS: Prenatal diagnosis was made usually after 32 weeks of gestation. Approximately 93% of the tumors were adrenal in origin, and 44% of these were cystic. Thirty-seven patients (67%) had Stage I disease, 12 (22%) had Stage IV-S disease, and only 3 (5%) had Stage IV disease. The DNA index was favorable (> 1) in 14 of 16 patients studied. None of these 16 patients studied had amplification of the N-myc oncogene. Catecholamines were elevated in only 33% of the patients. The liver was the most common site of dissemination, which was observed in 25% of patients; bone involvement was not observed in any patient. Ultrasonography failed to detect existing hepatic metastasis in three patients. Primary surgical resection was performed in 47 patients (85%). Chemotherapy was given to five patients and radiotherapy to three. Of the 50 patients for whom follow-up information was available, 45 (90%) were alive at a range of 2-120 months from diagnosis. CONCLUSIONS: Prenatally diagnosed neuroblastomas are predominantly adrenal in origin and frequently cystic. The liver is the most common site of dissemination and bone involvement is notably absent. The vast majority of these infants have a favorable stage of disease (I, II, and IV-S) and favorable biologic features, and consequently have an excellent prognosis. Although surgery alone is curative for most patients, a period of observation may avoid surgery in some individuals who may achieve spontaneous regression.

Adami HO, Persson I, Ekbom A, Wolk A, Ponten J, Trichopoulos D. 1995. The aetiology and pathogenesis of human breast cancer. Mutation Research-Fundamental & Molecular Mechanisms of Mutagenesis 333:29-35.

Abstract: Whilst investigators have clearly shown that non-hereditary factors dominate the aetiology of human breast cancer, they have failed to identify quantitatively important causes, and prospects for prevention remain indeed limited. However, progress in epidemiological and basic research has taken place during the last few years. Current evidence suggests that breast cancer may be affected by the intra-uterine environment, that exposures during adolescence are particularly important, and that pregnancy has a dual effect on breast cancer risk: an early increase followed by long-term protection. Great variation exists in the structural development of the breast ductal system already in the newborn - and by inference in utero - and a pregnancy induces permanent structural changes in the mammary gland. We suggest that these observations fit into an aetiological model with the following key components: (1) breast cancer risk depends on the number of cells at risk, the susceptibility of individual cells to malignant transformation, and on the degree of cellular proliferation, notably cells which can act as founders of breast cancer; (2) the number of target cells is determined by the hormonal environment mainly early in life, perhaps already in utero; (3) in adult life, hormones which are non-genotoxic, increase breast cancer risk by increasing selective cell proliferation and thus number of target cells and the risk of retention of spontaneous somatic mutations; (4) while a pregnancy stimulates the growth of already malignant cells or cells close to malignant transformation (and thereby entails a short-term risk increase) the dominating long-term protection occurs due to permanent structural changes, terminal differentiation and perhaps decreased cell proliferation and carcinogen-binding in combination.

Adami J, Glimelius B, Cnattingius S, Ekbom A, Zahm SH, Linet M, Zack M. 1996. Maternal and perinatal factors associated with non-Hodgkin's lymphoma among children. Int J Cancer 65:774-777.

Abstract: This nested case-control study based on 1.7 million live births in Sweden explores the associations between maternal and perinatal factors and the occurrence of childhood non-Hodgkin's lymphoma (NHL). The National Swedish Cancer Registry ascertained 168 cases in successive birth cohorts from 1973 through 1989 recorded in the Swedish Medical Birth Registry. From the nationwide Birth Registry, 5 controls without NHL and alive at the date the case was diagnosed were randomly selected from the pool of children, with each case matched by gender, birth year and birth month. Standardized information on selected maternal and perinatal factors up to one month after delivery were recorded in the Medical Birth Registry. Mothers of children with NHL were more likely than mothers of controls to have undergone Cesarean section [Odds ratio (OR) 1.6] and to have been exposed to paracervical anesthesia during delivery (OR 1.8). Children with NHL were more likely than controls to have endocrine-metabolic disorders (OR 3.3). This study is one of the largest focusing on the etiology of childhood NHL. Most of the maternal and perinatal characteristics studied did not markedly affect risk for childhood NHL, which may be due to maternal and perinatal factors not included in these data or to exposures later in life. (C) 1996 Wiley-Liss, Inc.

Adey WR, Byus CV, Cain CD, Higgins RJ, Jones RA, Kean CJ, Kuster N, MacMurray A, Stagg RB, Zimmerman G, Phillips JL, Haggren W. 1999. Spontaneous and nitrosourea-induced primary tumors of the central nervous system in Fischer 344 rats chronically exposed to 836 MHz modulated microwaves. Radiat Res 152: 293-302.

Abstract: We have tested an 836.55 MHz field with North American Digital Cellular (NADC) modulation in a 2-year animal bioassay that included fetal exposure. In offspring of pregnant Fischer 344 rats, we tested both spontaneous tumorigenicity and the incidence of induced central nervous system (CNS) tumors after a single dose of the carcinogen ethylnitrosourea (ENU) in utero, followed by intermittent digital-phone field exposure for 24 months. Far-field exposures began on gestational day 19 and continued until weaning at age 21 days. Near-field exposures began at 35 days and continued for the next 22 months, 4 consecutive days weekly, 2 h/day. SAR levels simulated localized peak brain exposures of a cell phone user. Of the 236 original rats, 182 (77%) survived to the termination of the whole experiment and were sacrificed at age 709-712 days. The 54 rats (23%) that died during the study ("preterm rats") formed a separate group for some statistical analyses. There was no evidence of tumorigenic effects in the CNS from exposure to the TDMA field. However, some evidence of tumor-inhibiting effects of TDMA exposure was apparent. Overall, the TDMA field-exposed animals exhibited trends toward a reduced incidence of spontaneous CNS tumors ($P < 0.16$, two-tailed) and ENU-induced CNS tumors ($P < 0.16$, two-tailed). In

preterm rats, where primary neural tumors were determined to be the cause of death, fields decreased the incidence of ENU-induced tumors ($P < 0.03$, two-tailed). We discuss a possible approach to evaluating with greater certainty the possible inhibitory effects of TDMA-field exposure on tumorigenesis in the CNS.

Adey WR, Byus CV, Cain CD, Higgins RJ, Jones RA, Kean CJ, Kuster N, Macmurray A, Stagg RB, Zimmerman G. 2000. Spontaneous and nitrosourea-induced primary tumors of the central nervous system in Fischer 344 rats exposed to frequency-modulated microwave fields. Cancer Res 60:1857-1863.
Abstract: In a a-year bioassay, we exposed Fischer 341 rats to a frequency-modulated (FM) signal (836.55 MHz +/- 12.5 KHz deviation) simulating radiofrequency exposures in the head of users of hand-held mobile phones. We tested for effects on spontaneous tumorigenicity of central nervous system (CNS) tumors in the offspring of pregnant rats and also for modified incidence of primary CNS tumors in rats treated with a single dose of the neurocarcinogen ethylnitrosourea (ENU) in utero. ENU dosage (4 mg/kg) was selected to give an expected brain tumor incidence of 10-15% over the mean life span of 26 months. Pregnant dams (n = 102) were randomly assigned to six groups. Their offspring were treated as cohorts in each of the six groups (n = 90 per group; total, n = 540): Sham ENU/Sham Field, Sham ENU/Field Exposed, ENU/Sham Field, ENU/Field Exposed, ENU/Cage Control, and Sham ENU/Cage Control. Intermittent field exposures began on gestation day 19 and continued until weaning at 21 days, resuming thereafter at 31 days and continuing until experiment termination at 731-734 days. Energy absorption rates (SARs) in the rats' brains were similar to localized peak brain exposures of a phone user (female, 236 g, 1.0 W/kg; male, 450 g, 1.2 W/kg). Of the original 540 rats, 168 died before the termination of the experiment. In these rats, ENU significantly reduced survival from a mean of 708 days in three groups without ENU treatment to 645 days in three groups treated with ENU ($P < 0.0005$), There were no effects on survival attributable to FM field exposure in either ENU-treated or in sham-treated groups. Spontaneous CNS tumor incidence in control groups was 1.1-4.4% but sharply higher in rats receiving ENU (14.4-22.2%; $P < 0.0001$). No FM field-mediated changes were observed in number, incidence, or histological type of either spontaneous or ENU-induced brain tumors, nor were gender differences detected in tumor numbers, These negative findings with FM fields contrast with our study using standard digital phone fields pulsed on and off at 50/se, where a trend was noted toward reduced incidence of both spontaneous and ENU-induced CNS tumors (W. R. Adey et al,, Radiat, Res., 152: 293-302, 1999), Although consistent but not attaining significance in the experiment overall (spontaneous CNS tumors, $P < 0.08$ one-tailed; $P < 0.16$ two-tailed; ENU-induced CNS tumors, $P < 0.08$ one-tailed, $P < 0.16$ two-tailed), the trend was significant ($P < 0.015$ one-tailed, $P < 0.03$, two-tailed) in rats that received ENU and died prior to experiment termination, with a primary brain tumor as the cause of death. We discuss differences in the signaling structure of digital and FM fields. Certain bioeffects induced by either amplitude-modulated or pulsed radiofrequency fields at athermal levels have not been seen with fields of similar average power but unvarying in intensity (continuous wave or frequency-modulated fields).

Aflatoonian B, Moore H. 2006. Germ cells from mouse and human embryonic stem cells. Reproduction 132:699-707 .
Abstract: Mammalian gametes are derived from a founder population of primordial germ cells (PGCs) that are determined early in embryogenesis and set aside for unique development. Understanding the mechanisms of PGC determination and differentiation is important for elucidating causes of infertility and how endocrine disrupting chemicals may potentially increase susceptibility to congenital reproductive abnormalities and conditions such as testicular cancer in adulthood (testicular dysgenesis syndrome). Primordial germ cells are closely related to embryonic stem cells (ESCs) and embryonic germ (EG) cells and comparisons between these cell types are providing new information about pluripotency and epigenetic processes. Murine ESCs can differentiate to PGCs, gametes and even blastocysts - recently live mouse pups were born from sperm generated from mESCs. Although investigations are still preliminary, human embryonic stem cells (hESCs) apparently display a similar developmental capacity to generate PGCs and immature gametes. Exactly how such gamete-like cells are generated during stem cell culture remains unclear especially as in vitro conditions are ill-defined. The findings are discussed in relation to the mechanisms of human PGC and gamete development and the biotechnology of hESCs and hEG cells.

Ahlbom A, Day N, Feychting M, Roman E, Skinner J, Dockerty J, Linet M, McBride M, Michaelis J, Olsen JH, Tynes T, Verkasalo PK. 2000. A pooled analysis of magnetic fields and childhood leukaemia. Br J Cancer 83:692-698.

Abstract: Previous studies have suggested an association between exposure to 50-60 Hz magnetic fields (EMF) and childhood leukaemia. We conducted a pooled analysis based on individual records from nine studies, including the most recent ones. Studies with 24/48-hour magnetic field measurements or calculated magnetic fields were included. We specified which data analyses we planned to do and how to do them before we commenced the work. The use of individual records allowed us to use the same exposure definitions, and the large numbers of subjects enabled more precise estimation of risks at high exposure levels. For the 3203 children with leukaemia and 10 338 control children with estimated residential magnetic field exposures levels < 0.4 microT, we observed risk estimates near the no effect level, while for the 44 children with leukaemia and 62 control children with estimated residential magnetic field exposures >/= 0.4 microT the estimated summary relative risk was 2.00 (1.27-3.13), P value = 0.002). Adjustment for potential confounding variables did not appreciably change the results. For North American subjects whose residences were in the highest wire code category, the estimated summary relative risk was 1.24 (0.82-1.87). Thus, we found no evidence in the combined data for the existence of the so-called wire-code paradox. In summary, the 99.2% of children residing in homes with exposure levels < 0.4 microT had estimates compatible with no increased risk, while the 0.8% of children with exposures >/= 0.4 microT had a relative risk estimate of approximately 2, which is unlikely to be due to random variability. The explanation for the elevated risk is unknown, but selection bias may have accounted for some of the increase.

Ahlgren M, Sorensen T, Wohlfahrt J, Haflidadottir A, Holst C, Melbye M. 2003. Birth weight and risk of breast cancer in a cohort of 106,504 women. Int J Cancer 107:997-1000.
Abstract: The possible association between prenatal factors and breast cancer has been discussed for more than a decade. Birth weight has been used commonly as a proxy measure for intrauterine growth. Whereas some previous studies have found support for an association between birth weight and breast cancer, others have been inconclusive or found no association. We investigated the relationship between birth weight and risk of female breast cancer in a cohort of 106,504 Danish women. Birth weights were obtained from school health records on girls born between 1930-1975. Information on breast cancer came from linking the cohort with the Danish Cancer Registry and the Danish Breast Cancer Cooperative Groups Registry. A total of 2,334 cases of primary breast cancer were diagnosed in the cohort during 3,255,549 person-years of follow-up among women with birth weight between 500-6,000 g. Of these, 922 (40%) were diagnosed with primary breast cancer at the age of 50 years or older. A significant association between birth weight and breast cancer was found equivalent to an increase in risk of 9% per 1,000 g increase in birth weight (95% CI 2-17). The increase was observed for all age groups, representing both pre- and post-menopausal women, and irrespective of tumor characteristics. Adjustment for age at first birth and parity did not influence the results. Birth weight is positively associated with risk of breast cancer, indicating that prenatal factors are important in the etiology of breast cancer.

Ahlgren M, Wohlfahrt J, Olsen LW, Sorensen TI, Melbye M. 2007. Birth weight and risk of cancer. Cancer 110:112-119.
Abstract: BACKGROUND.: It is well established that prenatal biologic processes are important for the development of some childhood cancers, whereas less is known regarding their influence on adult cancer risk. High birth weight has been associated with risk of breast cancer, whereas studies of other specific cancers and all cancers together have been less conclusive. METHODS.: The authors established a cohort of more than 200,000 men and women who were born between 1936 and 1975. Birth weights were obtained from school health records and information concerning cancer from the Danish Cancer Registry. Follow-up was performed between April 1, 1968 and December 31, 2003. During 6,975,553 person-years of follow-up, a total of 12,540 primary invasive cancers were diagnosed. RESULTS.: Analyses of site-specific cancers revealed that the majority of cancers had a positive linear association with birth weight. Departures from a positive linear association were found to be statistically significant for cancers of the pancreas and bladder, which demonstrated a V-shaped association, and testicular cancer, which demonstrated an inverse association with birth weight. Excluding these 3 exceptions, the trends for the individual cancer sites were not heterogeneous, and the overall trend was a relative risk of 1.07 (95% confidence interval, 1.03-1.11) per 1000-g increase in birth weight. This trend was the same in men and women and in all age groups. CONCLUSIONS.: A 7% increase in cancer risk was observed per 1000-g increase in birth weight. Few cancers demonstrated a nonlinear association with birth weight, and testicular cancer was found to be negatively associated with birth weight. The authors hypothesized that the biologic

explanation behind the association between birth weight and cancer at different sites should be sought in a common pathway. Cancer 2007. (c) 2007 American Cancer Society.

Ahsan H, Whittemore AS, Chen Y, Senie RT, Hamilton SP, Wang Q, Gurvich I, Santella RM. 2005. Variants in Estrogen-Biosynthesis Genes Cyp17 and Cyp19 and Breast Cancer Risk: a Family-Based Genetic Association Study. Breast Cancer Research 7:R71-R81.
Abstract: Background Case-control studies have reported inconsistent results concerning breast cancer risk and polymorphisms in genes that control endogenous estrogen biosynthesis. We report findings from the first family-based association study examining associations between female breast cancer risk and polymorphisms in two key estrogen-biosynthesis genes CYP17 (T-->C promoter polymorphism) and CYP19 (TTTA repeat polymorphism). Methods We conducted the study among 278 nuclear families containing one or more daughters with breast cancer, with a total of 1123 family members (702 with available constitutional DNA and questionnaire data and 421 without them). These nuclear families were selected from breast cancer families participating in the Metropolitan New York Registry, one of the six centers of the National Cancer Institute's Breast Cancer Family Registry. We used likelihood-based statistical methods to examine allelic associations. Results We found the CYP19 allele with 11 TTTA repeats to be associated with breast cancer risk in these families. We also found that maternal (but not paternal) carrier status of CYP19 alleles with 11 repeats tended to be associated with breast cancer risk in daughters (independently of the daughters' own genotype), suggesting a possible in utero effect of CYP19. We found no association of a woman's breast cancer risk either with her own or with her mother's CYP17 genotype. Conclusion This family-based study indicates that a woman's personal and maternal carrier status of CYP19 11 TTTA repeat allele might be related to increased breast cancer risk. However, because this is the first study to report an association between CYP19 11 TTTA repeat allele and breast cancer, and because multiple comparisons have been made, the associations should be interpreted with caution and need confirmation in future family-based studies.

Akimoto J, Ikeda K, Tomonaga M, Saito F, Miwa T, Awaya A, Hashimoto Y, Fukui H. 1991 . [Mouse fetal brain specific protein "GP68" is expressed in human tumor cells]. No To Shinkei 43:25-29.
Abstract: It is well known that some fetal antigens are expressed in malignant tumor cells. Likewise, brain tumors, especially histologically malignant cases, may have any antigenic relationships with fetal brain. So, we investigated the relationship by immunohistochemical technique, utilizing a polyclonal antibody to mouse fetal stage-specific polypeptide "GP68". We prepared GP68 from homogenate of head part of embryos at the 14th day of gestation mice by RCA-1 agarose column chromatography. And immunized it to Japanese white rabbits and the titer was measured by enzyme-linked immunosorbent assay. We analyzed operatively resected brain tumors and autopsy brain tissues. Frozen tissues were fixed in cold acetone and immunostained with anti-GP68 serum according to biotin-streptavidin peroxidase method. Remained tissues were homogenized in Laemmli's sample buffer and electrophoresed. The proteins were transferred to nitrocellulose membrane and immunostained with anti-GP68. Normal brain tissues were not positively stained, except for capillary endothelium which showed a weak staining. On the other hand, brain tumors of neuroectodermal origin were positively stained in varying degrees, and other tumors were negative. It is especially noteworthy that, in astrocytoma cases, there exists a definite correlation between the intensity of stain and the degree of histological malignancy. Immunoblot studies demonstrated a very weak band at 68 KD in normal brain and meningioma. In contrast, very strong band at the same position was seen in malignant astrocytomas. These results suggested that in brain tumors, especially those of neuroectodermal origin, GP68 antigen is expressed and the degree of expression is related to their histological malignancy. So this fetal antigen may be useful for evaluation of biological malignancy of gliomas.(ABSTRACT TRUNCATED AT 250 WORDS)

Akre O, Ekbom A, Hsieh CC, Trichopoulos D, Adami HO. 1996. Testicular nonseminoma and seminoma in relation to perinatal characteristics. J Natl Cancer Inst 88:883-889.
Abstract: BACKGROUND: Testicular cancer incidence peaks during the third decade of life, and an increasing trend in the occurrence of this disease has been seen in many countries. Few risk factors have been established for testicular cancer, but evidence suggests that causal factors operate early in life, perhaps even in utero. PURPOSE: We performed a case-control study to evaluate specific perinatal characteristics as risk factors for the two main histopathologic types of testicular cancer: seminomas and nonseminomas. METHODS: Two hundred thirty-two case patients with invasive testicular cancer and 904 individually

matched control subjects (all singleton births), nested in a cohort of men born at 10 hospitals in Sweden from 1920 through 1978, were included in the study. Perinatal information about the study subjects and their parents was obtained from birth records. For the mothers, information was recorded concerning age at menarche, marital status, parity, age at delivery, maternal weight at delivery and at first visit to a maternal-care center, education and/or profession, and any medical problems encountered during pregnancy or after delivery. For the fathers, information was obtained concerning age at delivery and education and/or profession. For the study subjects, information was recorded about the following: gestational age, birth length and weight, placental weight, method of delivery (normal, cesarean section, or with forceps or vacuum extractor), medical problems during hospital stay, presence of jaundice, method of feeding at discharge, and duration of hospital stay after birth. Individuals diagnosed with testicular cancer were identified through the Swedish National Cancer Registry and the Uppsala Regional Cancer Registry. The data were analyzed by use of conditional logistic regression modeling. RESULTS: When testicular cancer was modeled as a single entity, significantly elevated risks were associated with neonatal jaundice (adjusted odds ratio [OR] = 2.30; 95% confidence interval [CI] = 1.07-4.94) and with either low (< 2500 g) or high (> or = 4000 g) birth weight (OR = 2.59; 95% CI = 1.05-6.38 and OR = 1.58; 95% CI = 1.10-2.29, respectively). When seminomas and nonseminomas were analyzed separately, high maternal socioeconomic status (OR = 2.54; 95% CI = 1.05-6.12), neonatal jaundice (OR = 3.96; 95% CI = 1.47-10.69), and low birth weight (OR = 7.62; 95% CI = 1.59-36.60) were associated with nonseminomas, whereas high placental weight (OR = 3.50; 95% CI = 0.97-12.62) suggested increased risk for seminomas. CONCLUSIONS AND IMPLICATIONS: Perinatal exposures appear to influence the risk of testicular cancer, and seminomas and nonseminomas may have somewhat different risk profiles. Future epidemiologic studies should consider the possibility of etiologic heterogeneity in the development of seminomas and nonseminomas.

Akre O, Forssell L, Kaijser M, Noren-Nilsson I, Lagergren J, Nyren O, Ekbom A. 2006. Perinatal risk factors for cancer of the esophagus and gastric cardia: A nested case-control study. Cancer Epidemiology Biomarkers & Prevention 15:867-871.
Abstract: Background: We have previously hypothesized that preterm birth or impaired fetal growth may cause esophageal adenocarcinomas through gastroesophageal reflux early in life. In this study, we aimed to test if there is an association between gestational duration and birth weight on the one hand, and risk of esophageal and cardia adenocarcinoma on the other. Methods: We conducted a nested case-control study of 67 cases of esophageal adenocarcinoma and 93 cases of cardia adenocarcinoma, whereas 50 cases of squamous cell carcinoma were studied for comparison. Birth records of cases were traced. Three matched controls per case were randomly selected. Perinatal data were extracted from birth records. Results: Long gestational duration was associated with a decreased risk of cardia adenocarcinoma (P-trend = 0.001) and a nonsignificant decreased risk of esophageal adenocarcinoma (P = 0.07), whereas no such association was found for esophageal squamous cell carcinoma (P = 0.96). Birth weight was not associated with risk of any of the studied cancers. Compared with lower maternal age (<= 24 years) at giving birth, maternal age of 25 to 29 years were associated with a decreased risk of esophageal adenocarcinoma and squamous cell carcinoma (odds ratio, 0.4; 95% confidence interval, 0.2-0.9 and odds ratio, 0.3; 95% confidence interval, 0.1-0.8, respectively). Conclusions: Numerical constraints hamper inference, but our results are somewhat consistent with the idea that future risk of esophageal and cardia cancer may in part be determined already perinatally or in infancy and give some limited support to the hypothesis that timing of birth influences risk.

Aksglaede L, Juul A, Leffers H, Skakkebaek NE, Andersson AM. 2006. The sensitivity of the child to sex steroids: possible impact of exogenous estrogens. Hum Reprod Update 12:341-349.
Abstract: The current trends of increasing incidences of testis, breast and prostate cancers are poorly understood, although it is assumed that sex hormones play a role. Disrupted sex hormone action is also believed to be involved in the increased occurrence of genital abnormalities among newborn boys and precocious puberty in girls. In this article, recent literature on sex steroid levels and their physiological roles during childhood is reviewed. It is concluded that (i) circulating levels of estradiol in prepubertal children are lower than originally claimed; (ii) children are extremely sensitive to estradiol and may respond with increased growth and/or breast development even at serum levels below the current detection limits; (iii) no threshold has been established, below which no hormonal effects can be seen in children exposed to exogenous steroids or endocrine disruptors; (iv) changes in hormone levels during fetal and

prepubertal development may have severe effects in adult life and (v) the daily production rates of sex steroids in children estimated by the Food and Drug Administration in 1999 and still used in risk assessments are highly overestimated and should be revised. Because no lower threshold for estrogenic action has been established, caution should be taken to avoid unnecessary exposure of fetuses and children to exogenous sex steroids and endocrine disruptors, even at very low levels.

al-Sheyyab M, Muir KR, Cameron AH, Raafat F, Pincott JR, Parkes SE, Mann JR. 1993. Malignant epithelial tumors in children - Incidence and etiology. Medical & Pediatric Oncology 21:421-428.
Abstract: The purpose of this study was to establish the incidence of carcinomas in children, changes in incidence over a 30-year period, and to identify features of possible aetiological significance. A total of 173 cases were identified, but after review of the histopathology, 30 patients were excluded because they were considered to have benign epithelial tumours or malignant tumours of nonepithelial origin. Seven other cases were excluded because pathology material was not available. Overall, in 28% of cases, the diagnoses were changed by pathology review. Thus, 136 children in the West Midlands Region diagnosed 1957-1986 were included, with carcinoid tumours (44) and tumours of skin (22), nasopharynx (14), salivary gland (13), adrenal cortex (13), thyroid (9), large bowel (5), other (16). Excluding carcinoids, the age-standardised incidence rate was 2.4 x 10(6) per year. Male:female ratio was 0.7:1 and 66% were aged >10 years. Incidence increased from 1.5 to 3.3 x 10(6) per year. Genetic factors predisposing to carcinoma included tyrosinosis, MEN II and III, congenital adrenal hyperplasia and basal cell naevus syndrome. There was a case of Li-Fraumeni syndrome and several other patients had relevant family histories. Probable "environmental" causes included antenatal exposure to stilboestrol or hydroxyprogesterone hexanoate, stilboestrol given for premature menarche, neonatal hepatitis and prior radiotherapy. The aetiology of carcinomas in children is multifactorial, both genetic and environmental factors being important. The incidence is increasing. (C) 1993 Wiley-Liss, Inc.

Aleksandrov VA, Schreiber D. 1978. [Combined transplacental carcinogenic action of N-nitrosomethylurea (NMU) and N-nitrosoethylurea (NEU) in rats]. Vopr Onkol 24:38-43.
Abstract: To reveal the relationship between teratogenesis and carcinogenesis, the author studied brain blastomogenesis features against the background of the development of deformities induced by the combined transplacental effect of NMU and NEU. To induce brain defects such as microcephaly NMU was injected on the 15th day, whereas to induce cerebellar defects- on the 21st day of embryogenesis. Moreover, at the 13th or 17th day NEU was additionally injected, which is found to be highly effective for inducing brain tumors. It was found that in NMU exposure (at the 15th day) until NEU exposure (at the 17th day of embryogenesis) no reliable decrease in brain tumor occurrence was noted, compared with that if only NEU was employed. In the reverse sequence, i. e. first the exposure to NEU (at the 13th day) and then to NMU (at the 15th day) the occurrence of tumors located in cerebral hemisphers was 3 times less. It is assumed that cytotoxic effect of NMU leading to microcephaly is likely to cause the death of a considerable amount of cell population previously transformed.

Alexander FE, Patheal SL, Biondi A, Brandalise S, Cabrera ME, Chan LC, Chen Z, Cimino G, Cordoba JC, Gu LJ, Hussein H, Ishii E, Kamel AM, Labra S, Magalhaes IQ, Mizutani S , Petridou E, De Oliveira MP, Yuen P, Wiemels JL, Greaves MF. 2001. Transplacental chemical exposure and risk of infant leukemia with MLL gene fusion. Cancer Res 61:2542-2546.
Abstract: Infant acute leukemia (IAL) frequently involves breakage and recombination of the MLL gene with one of several potential partner genes. These gene fusions arise in utero and are similar to those found in leukemias secondary to chemotherapy with inhibitors of topoisomerase II (topo II). This has led to the hypothesis that in utero exposures to chemicals may cause IAL via an effect on topo-II. We report a pilot case-control study of IAL across different countries and ethnic groups. Cases (n = 136) were population-based in most centers. Controls (II = 266) were selected from inpatients and outpatients at hospitals serving the same populations. MLL rearrangement status was derived by Southern blot analysis, and maternal exposure data were obtained by interviews using a structured questionnaire. Apart from the use of cigarettes and alcohol, very few mothers reported exposure to known topo-II inhibitors. Significant case-control differences were apparent for ingestion of several groups of drugs, including herbal medicines and drugs classified as "DNA-damaging," and for exposure to pesticides with the last two being largely attributable, respectively, to one nonsteroidal anti-inflammatory drug, dipyrone, and mosquitocidals (including Baygon). Elevated odds ratios were observed for MLL+ve (but not MLL-ve) leukemias (2.31 for

DNA-damaging drugs, P = 0.03; 5.84 for dipyrone, P = 0.001; and 9.68 for mosquitocidals, P = 0.003). Although it is unclear at present whether these particular exposures operate via an effect on topo-II, the data suggest that specific chemical exposures of the fetus during pregnancy may cause MLL gene fusions. Given the widespread use of dipyrone, Baygon, and other carbamate-based insecticides in certain settings, confirmation of these apparent associations is urgently required.

Alexandrov VA, Bespalov VG, Boone CW, Kelloff GJ, Malone WF. 1991. Study of postnatal effects of chemopreventive agents on offspring of ethylnitrosourea-induced transplacental carcinogenesis in rats .1. Influence of retinol acetate, alpha-tocopherol acetate, thiamine chloride, sodium selenite, and alpha-difluoromethylornithine. Cancer Lett 60:177-184.
Abstract: We studied the influence of the vitamins retinol acetate, alpha-tocopherol acetate and thiamine chloride; the antioxidant sodium selenite and an inhibitor of polyamine biosynthesis, alpha-difluoromethylornithine, on the offspring of transplacental carcinogenesis by ethylnitrosourea in rats. Ethylnitrosourea was given to pregnant rats as a single i.v. injection, at a dose of 75 mg/kg body wt. or 5.5 mg/kg body wt., on the 21st day after conception. Retinol, tocopherol or thiamine was added to the diet, and selenite and alpha-difluoromethylornithine to drinking water of the offspring throughout their postnatal life at moderate doses. In control groups, ethylnitrosourea induced tumors of brain, spinal cord, peripheral nervous system and kidneys in the offspring. alpha-Difluoromethylornithine exerted a slight inhibitory effect; this agent decreased the total tumor multiplicity and the multiplicity of peripheral nervous system tumors and also prolonged survival time. Retinol, tocopherol, thiamine and selenite did not influence the development of the transplacentally-induced tumors.

Allen RW Jr, Ogden B, Bentley FL, Jung AL. 1980 . Fetal hydantoin syndrome, neuroblastoma, and hemorrhagic disease in a neonate. JAMA 244:1464-1465.
Abstract: This is the first patient report of maternal ingestion of anticonvulsants associated with the triad of fetal hydantoin syndrome, neuroblastoma, and hemorrhagic disease. The neuroblastoma, a neural crest tumor, is the fourth of such origin reported after in utero exposure to phenytoin, suggesting that phenytoin is a transplacental carcinogen. Infants of epileptic mothers receiving anticonvulsants should be closely examined at birth for the fetal hydantoin syndrome and monitored for hemorrhagic problems. The neural crest tumor may be found at birth or later in childhood.

Almstrup K, Ottesen AM, Sonne SB, Hoei-Hansen CE, Leffers H, Rajpert-De Meyts E, Skakkebaek NE. 2005. Genomic and Gene Expression Signature of the Pre-Invasive Testicular Carcinoma in Situ. Cell Tissue Res 322:159-165.
Abstract: Testicular cancer is the most common malignancy among men in the reproductive age and the incidence is increasing, probably caused by environmental factors. Most testicular cancers are testicular germ cell tumours and all originate from a carcinoma in situ (CIS) pattern. In this review, we focus on the pre-invasive CIS and its possible fetal origin by reviewing recent data originating from DNA microarrays and comparative genomic hybridisations. A comparison of gene expression and genomic aberrations reveal chromosomal "hot spots" with mutual clustering of gene expression and genomic amplification. Some of the genes found in the hot spots may be involved in creating the CIS phenotype. On the other hand, many genes that are highly expressed in CIS are not present in the hotspot areas. The gene expression profile of CIS thus most likely reflects the combined result of genomic amplification and increased transcriptional activation and/or deficiency in the epigenetic silencing of specific loci. Amplification of chromosome 12p, appears to be a good genomic marker of the transition from the pre-malignant to malignant CIS cell; this is consistent with recent findings of propagation advantages in cultured undifferentiated embryonic stem cells after spontaneous amplification in similar regions. The gene expression profile of CIS cells has remarkable similarity to that of embryonic stem cells and supports our long-standing hypothesis of an early developmental origin of CIS and testicular germ cell cancer.

Almstrup K, Sonne SB, Hoei-Hansen CE, Ottesen AM, Nielsen JE, Skakkebaek NE, Leffers H, Rajpert-De Meyts E. 2006. From embryonic stem cells to testicular germ cell cancer-- should we be concerned? Int J Androl 29:211-218.
Abstract: Since the discovery of testicular carcinoma in situ (CIS) -- the precursor cell for the vast majority of germ cell tumours -- it has been proposed that CIS cells could be derived from transformed primordial germ cells or gonocytes. Here, we review recent discoveries not only substantiating that initial hypothesis

but also indicating that CIS cells have a striking phenotypic similarity to embryonic stem cells (ESC). Many cancers have been proposed to originate from tissue-specific stem cells [so-called 'cancer stem cells' (CSC)] and we argue that CIS may be a very good example of a CSC, but with exceptional features due to the retention of embryonic pluripotency. In addition, considering the fact that pre-invasive CIS cells are transformed from early fetal cells, possibly due to environmentally induced alterations of the niche, we discuss potential risks linked to the uncontrolled therapeutic use of ESC.

Althoff J, Grandjean C, Marsh S, Pour P, Takahashi M. 1977. Transplacental effects of nitrosamines in Syrian hamsters. II. Nitrosopiperidine. Z Krebsforsch Klin Onkol Cancer Res Clin Oncol 90:71-77.
Abstract: Nitrosopiperidine (NP) was found in Syrian hamsters quantitatively in the maternal blood for more than 8 h after subcutaneous injection, whereas it disappeared from placenta, fetus and amniotic fluid within the same time period. For N6MI, only traces were seen after 2 h in the same tissues. The long-term transplacental effect of a single dose of NP was weak, as demonstrated by a low respiratory tract tumor incidence (P-generation: 54%, F1- generation: 4%). Some tumors occurring in the digestive tract of exposed young were not found in their mothers and not commonly observed in controls. These tumors were considered a borderline transplacental effect. Tumors of other sites (i.e., the urogenital and genital tracts, reticuloendothelial system, endocrine organs and other tissues) corresponded in incidences to the overall fluctuations observed in this hamster colony.

Althoff J, Grandjean C, Pour P. 1977. Transplacental effect of nitrosamines in Syrian hamsters. IV. Metabolites of dipropyl- and dibutylnitrosamine. Z Krebsforsch Klin Onkol Cancer Res Clin Oncol 90:119-126.
Abstract: The present investigations showed that assumed and established metabolites of dipropylnitrosamine and dibutylnitrosamine reach the Syrian hamster fetus after subcutaneous (s.c.) treatment of their mothers (at day 14 of gestation). The compounds [2-hydroxypropylpropylnitrosamine, HPPN; 2-oxopropylpropylnitrosamine, OPPN; methylpropylnitrosamine, MPN; N-nitrosobis(2-hydroxypropyl)amine, BHP; and 4-hydroxybutylbutylnitrosamine, HBBN] were still present in the examined tissue (maternal blood, placenta, fetus, amniotic fluid) 4--6 h after s.c. injection. The overall incidence of transplacentally induced tumors was lower in the F1- than in the P-generation and comparatively longer latencies were also observed in the F1- generation. However, in some groups low incidences were found of tumors which did not occur in the mothers (i.e., nasal cavities: BHP, HBBN; trachea: HBBN; lungs: HPPN, BHP, HBBN; liver: OPN, MPN, BHP, HBBN). Compared to exposure at early gestation, the transplacental carcinogenic effect increased at day 14 of gestation. Neoplasms originating in other organs were not associated with a transplacental effect of the examined nitrosamines.

Althoff J, Pour P, Grandjean C, Eagen M. 1976. Transplacental effects of nitrosamines in Syrian hamsters: I. Dibutylnitrosamine and nitrosohexamethyleneimine. Z Krebsforsch Klin Onkol Cancer Res Clin Oncol 86:69-75.
Abstract: The transplacental carcinogenic effects of dibutylnitrosamine (DBN) and nitrosohexamethyleneimine (N-6-MI) were examined in Syrian hamsters. A proportion of both substances reached the fetal tissue unaltered. No macroscopic malformations were observed in the offspring; however, postnatal mortality was high. Respiratory tumours were found upon histologic examination of surviving animals. Single doses of 30 mg/kg body weight (b.w.) DBN and 2 doses of 10 mg/kg b.w. N-6-MI did not induce tumours in the P-generation, but led to a low tumour incidence in the F1-generation (DBN, 7.0%, N-6-MI, 2.0%). Treatment for up to eight days during the second half of pregnancy led to a higher tumour incidence in the P-generation (DBN, 22%; N-6-MI, 20%), than in the F1-generation (DBN, 6.0%; N-6-MI, 10%).

Anbazhagan R, Gusterson BA. 1994. Prenatal factors may influence predisposition to breast cancer. Eur J Cancer 30 A:1-3.

Anbazhagan R, Raman V. 1997. Homeobox genes: Molecular link between congenital anomalies and cancer. Eur J Cancer 33:635-637.
Abstract: Homeobox-containing genes play a major role in the control of segmental identity during embryonic development in Drosophila. Abnormalities of these genes have been shown to produce a wide variety of congenital anomalies in invertebrates and in vertebrates. Many transgenic mice, which are mutant for homeobox genes, show a specific skeletal abnormality, similar to the human cervical rib. In

humans, a relationship exists between malformations and tumours. Human cervical rib has been shown to be associated with an increased incidence of malignancy. Recent evidence indicates that homeobox genes might also play a role in carcinogenesis. In this article, we explore the possibility that alterations of homeobox genes might be the basic underlying aetiology for the association between congenital malformations and tumours, at least in a proportion of cases. We provide evidence in support of this argument and suggest areas of further research which would confirm this concept. (C) 1997 Elsevier Science Ltd.

Anderson D. 2001. Genetic and reproductive toxicity of butadiene and isoprene. Chem Biol Interact 135:65-80.
Abstract: Butadiene (BD) and its 2-methyl analogue, isoprene, have been extensively studied in animals and BD in population studies. Both chemicals are metabolised by liver cytochrome P450 dependent monogenases to monoepoxide and diepoxide intermediates. The diepoxide intermediates of both compounds were mutagenic in Salmonella typhimurium. However, unlike the monoepoxide of BD, the monoepoxides of isoprene were not mutagenic. It appears that they have no alkylating capacity. BD did not induce somatic cell mutation and recombination or sex-linked recessive lethal mutation in Drosophila melanogaster and isoprene produced no increase in chromosomal aberrations in CHO cells in vitro. Comparative concentrations of haemoglobin adducts in the blood of mice and rats after exposure to BD indicated that reaction with blood may decrease the levels of reactive intermediates available to tissues in rats, but not in mice contributing to greater potency of BD in the mouse. For isoprene, the adducts reach approximately the same concentrations in both species. DNA adducts have also been detected in testicular and lung cells of mice after BD exposure. The level of epoxybutene haemoglobin adducts was significantly elevated in BD-exposed workers, but lower than in rats and mice. In conjunction with the toxicology and carcinogenesis studies for BD and isoprene. additional mice were included for the evaluation of cytogenetic effects. Both chemicals produced increases in sister chromatid exchanges in bone marrow cells and in the frequency of micronuclei in normochromatic and polychromatic erythrocytes, but only BD produced an increase in the percent of bone marrow cells with chromosomal aberrations. At similar doses, the effects with BD were 2-3 times larger than with isoprene. There were also increased hprt mutation frequencies in rats and mice after BD exposure. Biomonitoring studies with hprt mutations in lymphocytes showed conflicting results, with both positive and negative findings. BD has been shown to be positive in one human cytogenetic biomonitoring study and not in three others, but chromosomal aberrations were increased in BD-exposed workers after challenge with gamma rays. Re-analysis of GSTT1 null individuals showed positive results. There was an increase in spermatid micronuclei in mice by BD and its metabolites and in rats only by its metabolites. The cytotoxic response of germ cells in mice is greater than in rats. Dominant lethal mutations have been induced by BD and diepoxybutane, but not by epoxybutene. There was some evidence of congenital malformations in mice after BD exposure and there was a linear concentration-related induction of heritable translocations in mice. There was no induction of dominant lethal mutations or congenital malformations in rats. Using the heritable translocation data in mice, it has been determined that if a worker is continually exposed over 5 or 6 weeks to 20-25 ppm of BD, the risk of producing a child with a balanced reciprocal translocation is twice as high as the background risk. Since genetic damage cannot be measured directly in human germ cells, risk to such cells can also be estimated from germ cells and somatic cells of the mouse and human somatic cells using the parallelogram approach. Using doubling doses. the fourth corner of the parallelogram was calculated as a doubling dose for human germ cells of 4390 ppm/h. However, it is still questioned if man is more like rat than mouse in terms of sensitivity to exposure. Similar germ cell data do not exist for isoprene. In conventional developmental studies. where rats and mice were exposed to BD, maternal toxicity was shown in rats but there was no evidence of developmental toxicity or teratogenic effects and there was a small effect on sperm morphology. After exposure to isoprene. there was no adverse effect on rat dams or other reproductive indices. In mice, there was reduced foetal body weight and decreased maternal weight gain and isoprene also affected ovarian follicles. There was a reduction in testicular function parameters such as testicular weight and sperm motility. (C) 2001 Elsevier Science Ireland Ltd. All rights reserved.

Anderson D, Edwards AJ, Brinkworth MH, Hughes JA. 1996. Male-mediated F-1 effects in mice exposed to 1,3-butadiene. Toxicology 113:120-127.
Abstract: We examined the effects on dominant lethality, the incidence of fetal abnormalities and tumour incidence in surviving offspring of acute and subchronic exposure of male mice by inhalation to the industrial monomer, 1,3-butadiene. In the acute study, CD-I mice were exposed to atmospheres containing

0 (it = 25), 1250 (n = 25) or 6250 ppm (it = 50) for 6 h, and each male was caged 5 days later for 1 week with two untreated virgin females. One of the females was killed humanely on day 17 of gestation. The other was allowed to deliver and rear her litter and the litters were monitored throughout adulthood. The killed female was examined for the number of live foetuses, the number of post implantation deaths (early and late) and the number and type of any gross malformations. In the subchronic study, males were exposed to 0 (n = 25), 12.5 (n = 25) or 1250 (n = 50) for 6 h per day on 5 days per week for 10 weeks and then mated the next morning. Mating and observation details were as for the acute study. Acute exposure to butadiene resulted in only a small decrease in implantations; after 10 weeks' subchronic exposure with either the high or low concentration, however, a wide variety of statistically significant effects was seen. At 1250 ppm, the number of implantations was reduced, dominant lethal mutations were induced, and the incidences of early and late deaths were increased; some of the live foetuses were malformed. The low dose also increased the frequency of malformations and late deaths but it did not affect the number of early deaths. Skeletal examination of malformed foetuses, randomly selected normal litter mates and controls confirmed the abnormalities seen at necropsy in malformed foetuses. However, karyotypic analysis of foetal liver from malformed foetuses, randomly selected normal litter mates and controls showed no karyotypic abnormalities. The number of gross suspected tumours in the F-1 adults did not appear to reveal an increase over control values. Thus, butadiene is mutagenic in the germ cells of male mice, as shown by the induction of dominant lethality at 1250 ppm, and the frequencies of late deaths and congenital malformations appear to be increased at the subchronic level of 12.5 ppm and skeletal examination of malformed foetuses confirmed the macroscopic abnormalities.

Anderson LE, Sheen DM, Wilson BW, Grumbein SL, Creim JA, Sasser LB. 2004. Two-year chronic bioassay study of rats exposed to a 1.6 GHz radiofrequency signal. Radiat Res 162:201-210.
Abstract: The purpose of this study was to determine whether longterm exposure to a 1.6 GHz radiofrequency (RF) field would affect the incidence of cancer in Fischer 344 rats. Thirty-six timed-pregnant rats were randomly assigned to each of three treatment groups: two groups exposed to a far-field RF Iridium signal and a third group that was sham exposed. Exposures were chosen such that the brain SAR in the fetuses was 0.16 W/kg. Whole-body far-field exposures were initiated at 19 days of gestation and continued at 2 h/day, 7 days/week for dams and pups after parturition until weaning (similar to23 days old). The offspring (700) of these dams were selected, 90 males and 90 females for each near-field treatment group, with SAR levels in the brain calculated to be as follows: (1) 1.6 W/kg, (2) 0.16 W/kg and (3) near-field sham controls, with an additional 80 males and 80 females as shelf controls. Confining, head-first, near-field exposures of 2 h/day, 5 days/week were initiated when the offspring were 36 at 1 days old and continued until the rats were 2 years old. No statistically significant differences were observed among treatment groups for number of live pups/litter, survival index, and weaning weights, nor were there differences in clinical signs or neoplastic lesions among the treatment groups. The percentages of animals surviving at the end of the near-field exposure were not different among the male groups. In females a significant decrease in survival time was observed for the cage control group. (C) 2004 by Radiation Research Society.

Anderson LM. 2004. Introduction and overview. Perinatal carcinogenesis: growing a node for epidemiology, risk management, and animal studies. Toxicology & Applied Pharmacology 199:85-90.
Abstract: Perinatal carcinogenesis as a cross-disciplinary concern is the subject of this special issue of Toxicology and Applied Pharmacology, which consists of a total of eight reviews or commentaries in the areas of epidemiology, risk assessment, and animal models. Some of the conclusions from these articles, and the Questions and Answers section that follows most of them, are summarized here. There is adequate reason to suspect that perinatal exposures contribute to human cancer risk, both childhood cancers, and those appearing later in life. The latter type of risk may actually be quantitatively the more important, and involve a wide range of types of effects, but has received only limited attention. With regard to childhood cancers, fetal irradiation and diethylstilbestrol exposure are known etiological agents, and it is likely, but not yet certain, there are additional external causes of a portion of these. Some current focal points of interest here include nitroso compounds, DNA topoisomerase inhibitors, viruses, anti-AIDS drugs, and endocrine disruptors. Regulatory agencies must rely heavily on animal data for estimation of human risk due to perinatal exposures to chemicals, and the quantity and quality of these data presently available for this purpose are greatly limiting. Correctly designed conventional animal studies with suspect chemicals are still needed. Furthermore, genetically engineered mouse models for childhood cancers, especially

medulloblastoma, have become available, and could be used for screening of candidate causative agents for this cancer type, and for better understanding of gene-environment interactions.

Anderson LM. 2004. Predictive values of traditional animal bioassay studies for human perinatal carcinogenesis risk determination. Toxicology & Applied Pharmacology 199:162-74.
Abstract: The many physiological, biochemical, and structure differences between rodents and humans, especially with regard to gestation and fetal development, invite questions as to the utility of rodent models for the prediction of risk of perinatal carcinogenesis in humans and for extrapolation of mechanistic studies. Here, the relevance of basic generalities, derived from rodent perinatal studies, to human contexts is considered. The cross-species usefulness of these generalities was upheld by the example of carcinogen activation and detoxification as determining factors. These have been established in rodent studies and recently indicted in humans by investigations of genetic polymorphisms in cytochromes P450, N-acetyltransferase, myeloperoxidase, quinone reductase, and glutathione S-transferase. Also, published data have been analyzed comparatively for diethylstilbestrol and irradiation, the two known human transplacental carcinogenic agents. At similar doses to those experienced by humans, both diethylstilbestrol and X- and gamma-irradiation in rodents and dogs yielded increased tumors at rates similar to those for humans. In rodents, there was a clearly negative relationship between total diethylstilbestrol dose and tumors per dose unit, and a similar pattern was suggested for radiation. Diethylstilbestrol had transgenerational effects that did not diminish over three generations. Overall, this analysis of the published literature indicates that there are basic qualitative and quantitative similarities in the responsiveness of human and rodent fetuses to carcinogens, and that dose effects may be complex and in need of further investigation.

Anderson LM. 2006. Environmental genotoxicants/carcinogens and childhood cancer: Bridgeable gaps in scientific knowledge. Mutation Research-Genetic Toxicology and Environmental Mutagenesis 608:136-156.
Abstract: Cancer in children is a major concern in many countries. An important question is whether these childhood cancers are caused by something, or are just tragic random events. Causation of at least some children's cancers is suggested by direct and indirect evidence, including epidemiological data, and animal studies that predict early life sensitivity of humans to carcinogenic effects. Candidate risk factors include genotoxic agents (chemicals and radiation), but also diet/nutrition, and infectious agents/immune responses. With regard to likelihood of risks posed by genotoxicants, there are pros and cons. The biological properties of fetuses and infants are consistent with sensitivity to preneoplastic genotoxic damage. Recent studies of genetic polymorphisms in carcinogen-metabolizing enzymes confirm a role for chemicals. On the other hand, in numerous epidemiological studies, associations between childhood cancers and exposure to genotoxicants, including tobacco smoke, have been weak and hard to reproduce. Possibly, sensitive genetic or ontogenetic subpopulations, and/or co-exposure situations need to be discovered to allow identification of susceptible individuals and their risk factors. Among the critical knowledge gaps needing to be bridged to aid in this effort include detailed tissue and cellular ontogeny of carcinogen metabolism and DNA repair enzymes, and associations of polymorphisms in DNA repair enzymes with childhood cancers. Perinatal bioassays in animals of specific environmental candidates, for example, benzene, could help guide epidemiology. Genetically engineered animal models could be useful for identification of chemical effects on specific genes. Investigations of interactions between factors may be key to understanding risk. Finally, fathers and newborn infants should receive more attention as especially sensitive targets. Published by Elsevier B.V.

Anderson LM, Diwan BA, Fear NT, Roman E. 2000. Critical windows of exposure for children's health: Cancer in human epidemiological studies and neoplasms in experimental animal models. Environ Health Perspect 108:573-594.
Abstract: In humans, cancer may be caused by genetics and environmental exposures; however, in the majority of instances the identification of the critical time window of exposure is problematic. The evidence for exposures occurring during the preconceptional period that have an association with childhood or adulthood cancers is equivocal. Agents definitely related to cancer in children, and adulthood if exposure occurs in utero, include: **maternal exposure to ionizing radiation during pregnancy and childhood leukemia and certain other cancers, and maternal use of diethylstilbestrol during pregnancy and clear-cell adenocarcinoma of the vagina of their daughters.** The list of environmental exposures that occur during the perinatal/postnatal period with potential to increase the risk of cancer is lengthening, but

evidence available to date is inconsistent and inconclusive. In animal models, preconceptional carcinogenesis has been demonstrated for a variety of types of radiation and chemicals, with demonstrated sensitivity for all stages from fetal gonocytes to postmeiotic germ cells. Transplacental and neonatal carcinogenesis show marked ontogenetic stage specificity in some cases. Mechanistic factors include the number of cells at risk, the rate of cell division, the development of differentiated characteristics including the ability to activate and detoxify carcinogens, the presence of stem cells, and possibly others. Usefulness for human risk estimation would be strengthened by the study of these factors in more than one species, and by a focus on specific human risk issues.

Anderson LM, Hagiwara A, Kovatch RM, Rehm S, Rice JM. 1989. Transplacental initiation of liver, lung, neurogenic, and connective tissue tumors by N-nitroso compounds in mice. Fundamental & Applied Toxicology 12:604-620.

Abstract: Epidemiological studies have implicated nitroso compounds as possible causative agents for human childhood cancers, including those of neurogenic origin. Published evidence from animal models, which is reviewed in this report, indicates that capacity for metabolic activation of nitrosamines is limited in rodent fetuses and that nitrosamines are correspondingly weak transplacental carcinogens. The C3H mouse fetus, however, has both moderate capability for activation of N-nitrosodimethylamine (NDMA) and proven susceptibility to transplacental causation of neurogenic tumors by a nitrosourea. We tested whether NDMA could act as a transplacental carcinogen in the C3H mouse, and whether it or N-nitrosodiethylamine (NDEA) would initiate neurogenic tumors. N-Nitrosoethylurea (NEU) served as positive control. C3H/HeNCr MTV- pregnant mice were treated ip on Gestation Day 16 or 19 with NDMA (0.1 mmol, 7.4 mg/kg, maximum nonfetotoxic dose), NDEA (0.5 mmol, 51 mg/kg), or NEU (0.4 mmol, 47 mg/kg). NDMA had significant transplacental carcinogenic effects, resulting in an increase in percentage female offspring with hepatocellular carcinomas and in average number of liver tumors after treatment on either gestational day, compared with controls. In the males there was a significant increase in numbers of liver tumors and carcinomas following Day 19 exposure. An increase in incidence of histiocytic and undifferentiated sarcomas was also of statistical significance. There was no change in number of pulmonary tumors. One intracranial schwannoma resulted. NDEA had no effect when given on Gestation Day 16, but caused a significant increase in liver and lung tumor numbers in both sexes when treatment was on Day 19. NEU induced the expected high incidence of lung tumors, significantly increased liver tumor incidence in females (Day 19 exposure), and produced schwannomas in 14 and 35% of the offspring after Days 16 or 19 treatment, respectively. The results show that NDMA at even a low dose had significant transplacental carcinogenic effects, including one schwannoma, which was most unlikely to have occurred spontaneously. However, this single neurogenic tumor contrasts with the absence of similar neoplasms in mice exposed transplacentally to NDEA, in view of the generally greater efficiency of ethylating agents as carcinogens for the nervous system in rodents. These data thus neither conclusively support nor refute the hypothesis that nitrosamines may initiate neurogenic tumors in fetuses.

Anderson LM, Hecht SS, Dixon DE, Dove LF, Kovatch RM , Amin S, Hoffmann D, Rice JM. 1989. Evaluation of the transplacental tumorigenicity of the tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone in mice. Cancer Res 49:3770-3775.

Abstract: The transplacental tumorigenicity of the tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) was assessed in three strains of mice: A/J; C3H/He x C57BL/6 F1 (hereafter called C3B6F1); and Swiss outbred [Cr:NIH(S)]. NNK (100 mg/kg) was administered i.p. on Days 14, 16, and 18 of gestation to A/J and C3H/He mice and on Days 15, 17 and 19 of gestation to the Swiss mice. The effects of postnatal treatment with tumor-promoting agents, including 0.05% sodium barbital in the drinking water until death or a single dose of Aroclor 1254 (a mixture of polychlorinated biphenyls, PCB) given on Postnatal Day 8 or 56, were also examined. Progeny were sacrificed at age 24 wk (A/J) or 72 wk (C3B6F1 and Swiss). Significant incidences of tumors occurred in the lungs of strain A/J progeny and in the livers of male C3B6F1 and Swiss progeny. Lung tumor incidence was 8 of 34 (24%) in the female offspring of the A/J mice treated with NNK, compared with 1 of 39 (3%) in controls (P less than 0.05). A 2-fold difference in lung tumor incidence in male offspring of NNK-treated (4 of 23, 13%) versus control (3 of 48, 6%) A/J mice was not of statistical significance. However, the incidence of lung tumors in NNK-exposed progeny A/J mice in both sexes combined (12 of 66, 18%) was also significantly greater than in controls (4 of 87, 5%). The incidence of liver tumors in the male C3B6F1 mice exposed transplacentally to NNK was 12 of 30 (40%) compared to 8 of 46 (17%) in controls (P less than 0.05). No effects of postnatal

sodium barbital or PCB were observed on transplacental NNK tumorigenicity in C3B6F1 mice. The combined incidence of liver carcinoma in male mice in all NNK-treated groups (13 of 141, 9%) was significantly greater (P less than 0.05) than in controls (5 of 144, 3%). In male Swiss mice exposed transplacentally to NNK, the incidence of liver tumors was 3 of 57 (5%) compared to 0 of 35 controls, and postnatal treatment with PCB on Day 56 caused a significant increase (5 of 26, 19%) (P less than 0.05) in the incidence of NNK-induced liver tumors. The combined incidence of liver tumors in the male offspring of the Swiss mice treated with NNK, with or without PCB, was 8 of 83 (10%) which was significantly greater (P less than 0.05) than in controls (0 of 66).(ABSTRACT TRUNCATED AT 400 WORDS)

Anderson LM, Jones AB, Riggs CW, Kovatch RM. 1989. Modification of transplacental tumorigenesis by 3-methylcholanthrene in mice by genotype at the Ah locus and pretreatment with beta-naphthoflavone. Cancer Res 49:1676-1681.
Abstract: Transplacental lung and liver tumorigenesis in the mouse by 3-methylcholanthrene (MC) was assessed as a function of inducibility of MC metabolism in fetus and in mother, and of pretreatment of the mothers with a noncarcinogenic inducer, beta-naphthoflavone (beta NF). Pregnant (C57BL/6 X DBA/2)F1 females (genotype Ahb Ahd, inducer responsive) mated to DBA/2 males received 45 or 100 mg/kg MC on gestation day 17, and DBA/2 females (genotype Ahd Ahd, nonresponsive) mated to F1 males were given 5 or 30 mg MC/kg. These crosses generated both responsive and nonresponsive offspring. Phenotype and tumor incidences were determined at 13 months of age. The transplacental action of MC was dose dependent and resulted in more lung and liver tumors in induction-responsive offspring than in nonresponsive littermates in most comparisons. beta NF alone did not result in increased numbers of tumors. Significant, complex effects were seen when the mothers were pretreated with beta NF (150 mg/kg) on gestation day 15, before MC on day 17. The beta NF pretreatment protected the fetuses of the F1 mothers: there was a significant overall 30 to 50% reduction in numbers of lung and liver tumors. The greatest effect was seen in the induction-responsive males, who experienced a 50% reduction in both incidence and multiplicity of lung tumors after 100 mg MC/kg, compared with males exposed to MC only. By contrast, beta NF pretreatment of DBA mothers had no general effect but rather potentiated the action of the 5 mg MC/kg dose on multiplicity of lung tumors in inducible males, causing a significant 4-fold increase. It also caused a 60% increase in inducible male liver tumor multiplicity when given before the 30 mg MC/kg dose. Thus, beta NF pretreatment was protective when the mother was inducible, especially in the inducible fetuses of such a mother, but when the mother was noninducible the beta NF pretreatment had no effect in some situations and potentiated the action of the carcinogen in others, mainly in inducible fetuses. These results underscore the fact that induced maternal and fetal metabolism contribute to risk of transplacental tumorigenesis by MC in qualitatively opposite ways.

Anderson LM, Ruskie S, Carter J, Pittinger S, Kovatch RM, Riggs CW. 1995. Fetal mouse susceptibility to transplacental carcinogenesis: Differential influence of Ah receptor phenotype on effects of 3-methylcholanthrene, 12-dimethylbenz[a]anthracene, and benzo[a]pyrene. Pharmacogenetics 5:364-372.
Abstract: Genetic backcrosses of C57BL/6 and DBA/2 mice were used to examine the influence of maternal and fetal polymorphisms at the Ahr locus on susceptibility to transplacental carcinogenesis by 3-methylcholanthrene, 7,12-dimethylbenz[a]anthracene, and benzo[a]pyrene, (C57BL/6 x DBA/2) F-1 mothers were backcrossed to DBA/2 males, and DBA/2 females to F-1 males to produce both Ahr-responsive (Ah(+)) and nonresponsive (Ah(-)) fetuses carried by mothers that were themselves either Ah(+) or Ah(-), 3-Methylcholanthrene was given intragastrically on gestation days 13-18 and 7,12-dimethylbenz[a]anthracene or benzo[a]pyrene on day 17 as a single intraperitoneal dose. Ahr phenotype was determined by the zoxazolamine sleeping time test after beta-naphthoflavone pretreatment at 6 weeks of age, The offspring were examined for rumours at 1 year, Both 3-methylcholanthrene and 7,12-dimethylbenz[a]anthracene treatments resulted in a two- to five-fold greater incidence and multiplicity of lung and liver rumours in the Ah(+) offspring compared with that in Ah(-) littermates. By contrast, there was no difference between Ah(+) and Ah(-) offspring with regard to numbers of tumours caused by benzo[a]pyrene, Maternal Ahr phenotype appeared to play a role also, in that the offspring of the Ahr-responsive F-1 mothers developed fewer tumours per unit dose than those of the nonresponsive DBA/2 mothers. The effect of maternal phenotype on risk was three- to five-fold. Fetal and maternal phenotype combined yielded a 10- to 20-fold risk differential for transplacental carcinogenesis by the methylated compounds, with greatest risk experienced by responsive fetuses in nonresponsive mothers, and least by nonresponsive progeny of responsive mothers.

Andersson SW, Bengtsson C, Hallberg L, Lapidus L, Niklasson A, Wallgren A, Hulthen L. 2001. Cancer risk in Swedish women: The relation to size at birth. Br J Cancer 84:1193-1198.
Abstract: The relationship between fetal growth as indicated by weight and length at birth, and cancer risk in 1080 adult Swedish women was examined. Birth factors were retrieved from original midwife records for the years 1914, 1918, 1922 and 1930, and primary cancer cases were identified by matching with national and regional cancer registries through the year 1998. A positive and statistically significant increased risk for cancer was found with increasing birth weight or birth length for all site cancer and non-hormone related cancer, defined as all cancer sites excluding breast, uterus and ovary. Addition of factors suspected to influence cancer risk, maternal proteinuria, birth order, own parity and age at menarche, did not attenuate this relation. Previously only breast cancer has been reported to be related to size at birth in adult women and this is the first study to report that cancer sites other than the major hormone-related sites may be influenced by size at birth, as measured by either weight or length at birth; these findings warrant further investigation.

Andreassen A, Mollersen L, Vikse R, Steffensen IL, Mikalsen A, Paulsen JE, Alexander J. 2002. One dose of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) or 2-amino-3-methylimidazo[4,5-f]quinoline (IQ) induces tumours in Min/+ mice by truncation mutations or LOH in the Apc gene. Mutation Research-Genetic Toxicology & Environmental Mutagenesis 517:157-166.
Abstract: The C57BL/6J-Min/+ (multiple intestinal neoplasia) mouse has a heterozygous nonsense Apc(Min) (adenomatous polyposis coli) mutation, and numerous adenomas spontaneously develop in the intestine. Neonatal exposure of Min/+ mice to the food carcinogens 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) or 2-amino-3-methylimidazo[4,5-f]quinoline (IQ) (one injection of 50 mg/kg) increased the number of small intestinal tumours about three- and two-fold, respectively. The number of colonic tumours was only increased in males. We examined whether the wild-type Ape allele was affected in intestinal tumours induced by either PhIP or IQ. In spontaneously formed and in IQ-induced small intestinal and colonic tumours from these mice, the main mechanism for tumour induction was loss of wild-type Ape allele, i.e. loss of heterozygosity (LOH). In contrast to the IQ-induced (84% LOH) and spontaneously (88% LOH) formed tumours, only 55% of the PhIP-induced small intestinal tumours from males showed LOH. Tumours that apparently had retained the wild-type Ape allele were further analysed for the presence of truncated Ape proteins by the in vitro synthesised protein (IVSP) assay. Truncated Ape proteins, indicating truncation mutations in exon 15 of the Apc gene, were detected in two of the 12 PhIP-induced tumours in segment 2 (codons 686-1217), and two of five IQ-induced tumours, one in segment 2 and the other in segment 3 (codons 1099-1693). Three of these four mutations, all in segment 2 of the Ape gene, were confirmed by sequencing. The PhIP-induced mutations were detected at codon 1125 (C deletion) and 1130 (G-T transversion), and the IQ-induced mutation was at codon 956 (C-T transition). Importantly, no truncated proteins were detected in tumours from unexposed mice with apparently retained wild-type Ape allele. These results show that one injection of either PhIP or IQ induces intestinal tumours in the Min/+ mice by inactivation of the wild-type Ape allele either by causing LOH or truncation mutations. (C) 2002 Elsevier Science B.V. All rights reserved.

Andreassen A, Vikse R, Steffensen IL, Paulsen JE, Alexander J. 2001. Intestinal tumours induced by the food carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine in multiple intestinal neoplasia mice have truncation mutations as well as loss of the wild-type Apc(+) allele. Mutagenesis 16:309-315.
Abstract: C57BL/6J-Min/+ (multiple intestinal neoplasia) is a murine model for familial adenomatous polyposis (FAP), where the mice are heterozygous for a nonsense Apc(Min) (adenomatous polyposis coli) mutation, and therefore develop numerous spontaneous adenomas in the small intestine and colon, Neonatal exposure of Min/+ mice to the food carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) (eight subcutaneous injections of 25 or 50 mg/kg PhIP to pups or 50 mg/kg PhIP to lactating dams) markedly increased (2-9-fold) the number of intestinal tumours, especially in the small intestine, We examined whether the Ape gene was affected in small intestinal and colonic tumours induced by PhIP. In spontaneous tumours formed in these mice, the main mechanism for tumour induction is loss of the wild-type Apc(+) allele, i.e. loss of heterozygosity (LOH), Also in the PhIP-induced tumours, this is a major mechanism, since large fractions of PhIP-induced tumours had LOH in Ape. However, mechanisms other than LOH must also prevail, since a lower frequency of LOH was found in the small intestinal tumours from male mice exposed to PhIP either via breast milk (65%) or by direct injection (68%), compared with the untreated controls (92%). Tumours that had retained the wild-type Ape allele were

further analysed for presence of truncated Ape proteins with in vitro synthesized protein (IVSP) assay, Truncated Ape proteins, indicating truncation mutations in exon 15 of the Ape gene, were detected in 20% (8 of 40) of the tumours not showing LOH from the small intestine after PhIP exposure, all in segment 2 (codons 686-1217). Seventeen percent (2 of 12) of the colonic tumours had a truncated Ape protein in segment 3 (codons 1099-1693). Importantly, no truncated proteins were detected in tumours from unexposed mice with apparently retained wild-type Ape i allele, These results show that PhIP induces intestinal tumours in the Min/+ mice both by causing LOH and truncation mutations in the wild-type Apc(+) allele.

Anisimov VN. 1995. Carcinogenesis induced by neonatal exposure to various doses of 5-bromo-2'-deoxyuridine in rats. Cancer Lett 91:63-71.
Abstract: Male and female outbred LIO rats were exposed to subcutaneous injections of 3.2 mg 5-bromo-2'-deoxyuridine (BrdUrd), on day 1; days 1 and 3; or days 1, 3, 7, and 21 following birth. The mean life-span decreased by 40.9, 31.2 and 38.9% in males exposed to 1, 2 or 4 injections of BrdUrd, respectively, and by 22.9, 10.5 and 23.4% in females, respectively, compared to the controls. The agent increased the population aging rate of the exposed male and female rats. Total tumor incidences in males exposed to 0, 3.2, 6.4 or 12.8 mg of BrdUrd were 21.1, 27.3, 40.0 and 33%, respectively, and in the females 44.3, 54.5, 48.1 and 56.3%, respectively. Only the largest dose of BrdUrd significantly increased the tumor incidence in the exposed rats as compared to the control ones ($P < 0.05$). However, tumor latency was shorter in any group of rats exposed to BrdUrd, as compared to the control one. The exposure to 0, 1, 2 or 4 injections of BrdUrd was followed by the development of testicular Leydigomas in 0, 0, 28 and 12% of males, respectively. There was no organ or tissue target for BrdUrd in the females. However, the development of tumours not typical for the rats and the widening of tumor spectrum was observed in the female rats exposed to the agent.

Anisimov VN. 1995. Effect of aging and interval between primary and secondary-treatment in cracinogenesis induced by neonatal exposure to 5-bromodeoxyuridine and subsequent administration of N-nitrosomethylurea in rats. Mutation Research-Dnaging Genetic Instability and Aging 316:173-187.
Abstract: LIO rats were exposed to s.c. injections (3.2 mg) of a synthetic analogue of thymidine, 5-bromo-2'-deoxyuridine (BrdUrd) on the 1st, 3rd, 7th and 21st days of life and at the age of 3 or 15 months they were i.v. injected with N-nitrosomethylurea (NMU) at a single dose of 10 or 50 mg/kg or with solvent. It was shown that early neonatal exposure to BrdUrd was followed by the increase in the incidence of tumor development and by the decrease of their latency. The carcinogenic effect of NMU alone correlated with the dose of the carcinogen in 3-month-old rats and did not correlate with dose in the 15-month-old ones. As compared to the 3-month-old rats, the incidence of total and malignant tumors and tumors of some localization was decreased in the elder ones, but survival of tumor-bearing rats was decreased in the elder group as compared to the younger one. These data suggests the age-related decrease in both the carcinogenic effect of NMU and in the number of events which are necessary for a tumor development. The exposure to BrdUrd was followed by the increase in the susceptibility of rats to subsequent carcinogenic effect of NMU injected at the doses of 10 or 50 mg/kg into 3- and 15-month-old rats, mostly to the tissues being target to NMU. Our data have demonstrated that the exposure to BrdUrd in the early life was followed by the irreversible initiating effect which persists over a long time in a several tissues.

Anisimov VN, Osipova GY. 1992. 2-Step carcinogenesis induced by neonatal exposure to 5-bromo-2'-deoxyuridine and subsequent administration of urethane in BALB/c mice. Cancer Lett 64:75-82.
Abstract: Male and female BALB/c mice were exposed to subcutaneous injections of 1 mg 5-bromo-2'-deoxyuridine (BrdUrd) at the 1st, 3rd and 7th days after their birth and/or starting from 3 months of age, and every third day were given 5 intraperitoneal injections of 0.1 ml of 5 % solution of urethane Treatment with BrdUrd alone followed by delay in mice development, reduction of the body and liver weight did not significantly increase the incidence of tumor development at 9 months of age. Exposure to both BrdUrd and urethanelead to summation or potentiation of their effects, manifested in increased lung adenoma incidence and their number per tumor-bearing mouse. In males, which received BrdUrd and urethan a significant increase in lung adenocarcinomas and haemoblastosis was observed in comparison to other groups. It was suggested that genome instability induced by exposure to BrdUrd facilitate the realization of the carcinogenic effect of urethane.

Anisimov VN, Osipova GY. 1993. Carcinogenesis induced by combined neonatal exposure to 5-bromo-2'-deoxyuridine and subsequent total-body X-ray irradiation in rats. Cancer Lett 70:81-90.
Abstract: Outbred LIO rats at 1, 3, 7 and 21 days of postnatal life were exposed to s.c. injections of 3.2 mg of 5-bromo-2'-deoxyuridine (BrdUrd) per animal and/or at the age of 3 months to a single total-body X-ray irradiation at a dose of 1.5 Gy. In males, treatment with BrdUrd alone decreases the latency of all tumors, increases the incidence of malignant tumors and their number per rat, in comparison with control. Combined exposure to BrdUrd and X-irradiation increases total and malignant tumor yield and multiplicity over that in all other groups. More testicular Leydigomas, tumors of prostata, kidney, adrenal cortex and leukemias were seen in rats exposed to BrdUrd plus X-rays, in comparison with males treated with BrdUrd or X-irradiation alone. In females, treatment with BrdUrd alone decreases the latency of total tumors and increases their incidence and number per rat, in comparison with controls. Combined exposure to BrdUrd and X-rays did not increase total tumor incidence in comparison with only irradiated females, however, it shortened tumor latency. The incidence and multiplicity of malignant tumors, incidences of pituitary adenomas, mammary adenocarcinomas and uterine polyps were significantly increased whereas the latency of kidney tumors was decreased in females exposed to BrdUrd plus X-rays, in comparison with all other groups. These data together with other studies provide the evidence that sole perturbations of DNA induced by a nucleoside analogue, BrdUrd, contributed substantially to the tumor development and enhanced the sensitivity of target cells to carcinogenesis induced by X-irradiation as well as by chemicals or hormones.

Anway MD, Leathers C, Skinner MK. 2006. Endocrine disruptor vinclozolin induced epigenetic transgenerational adult-onset disease. Endocrinology 147:5515-5523.
Abstract: The fetal basis of adult disease is poorly understood on a molecular level and cannot be solely attributed to genetic mutations or a single etiology. Embryonic exposure to environmental compounds has been shown to promote various disease states or lesions in the first generation (F1). The current study used the endocrine disruptor vinclozolin (antiandrogenic compound) in a transient embryonic exposure at the time of gonadal sex determination in rats. Adult animals from the F1 generation and all subsequent generations examined (F1-F4) developed a number of disease states or tissue abnormalities including prostate disease, kidney disease, immune system abnormalities, testis abnormalities, and tumor development (e. g. breast). In addition, a number of blood abnormalities developed including hypercholesterolemia. The incidence or prevalence of these transgenerational disease states was high and consistent across all generations (F1-F4) and, based on data from a previous study, appears to be due in part to epigenetic alterations in the male germ line. The observations demonstrate that an environmental compound, endocrine disruptor, can induce transgenerational disease states or abnormalities, and this suggests a potential epigenetic etiology and molecular basis of adult onset disease.

Arsic D, Beasley SW, Sullivan MJ. 2007 Jun. Switched-on Sonic hedgehog: a gene whose activity extends beyond fetal development - to oncogenesis. J Paediatr Child Health 43:421-3.
Abstract: Embryonic and fetal development is a highly complex process choreographed by several families of genes that regulate early development of the embryo. Disruption in the structure and/or function of developmental genes produces morphogenic errors of development. One such family is the Hedgehog (Hh) signalling pathway, which plays an important role in the embryonal development of both invertebrates and vertebrates, including normal development of the brain, eye, limbs, foregut and its derivatives. Disruption of the Sonic hedgehog expression during critical periods of development is associated with developmental disorders of the brain, namely, holoprosencephaly, and the VATER association. Inappropriate activation of the pathway in post-embryonic development has been demonstrated in several human malignancies, including those of the brain and skin, both in children and adults. Specific inhibition of Hh signalling in these tumours inhibits growth of a wide range of malignancies. This demonstrates a requirement for Hh signalling in these tumours. These observations suggest that a better understanding of the genetic control of morphogenesis can ultimately provide us with greater knowledge of how congenital structural abnormalities occur, as well as the processes that lead to several childhood and other tumours. There may be a closer relationship between embryogenesis and oncogenesis than previously realised.

Aschim EL, Haugen TB, Tretli S, Daltveit AK, Grotmol T. 2006. Risk factors for testicular cancer--differences between pure non-seminoma and mixed seminoma/non-seminoma? International Journal of Androl 29:458-67.
Abstract: The origin of testicular germ cell cancer (TGCC) is believed to be carcinoma in situ cells

developed in utero. Clinically, TGCCs are divided into two major histological groups, seminomas and non-seminomas, where the latter group includes non-seminomatous TGCCs with seminomatous components (mixed S/NS TGCC). Recent studies, however, have suggested that non-seminomas and mixed S/NS TGCCs could have certain differences in aetiology, and in this study the TGCCs were divided into three, rather than the conventional two histological groups. A large case-control study was undertaken on data on all live-born boys registered in the Medical Birth Registry of Norway during the period 1967-1998 (n=961 396). Among these were 1087 TGCC cases registered in the Cancer Registry of Norway until February 2004. We found several risk factors for TGCC, including low parity, low gestational age, epilepsy and retained placenta. Several of the variables studied seemed to be risk factors for specific histological groups, e.g. parity 0 vs. 2 and low gestational age being associated with increased risk of non-seminomas, but not of mixed S/NS TGCC, and low maternal age being associated with increased risk of mixed S/NS TGCC, but not of non-seminomatous TGCC. Therefore, our results might suggest that non-seminomas and mixed S/NS TGCCs have partially different risk factors, whose associations may be obscured by combining these two histological groups. The histological groups were not significantly different, however. Most of our findings on risk factors for TGCC are in agreement with at least some previous studies. An unexplainable exception is low birth weight being associated with reduced risk of TGCC in our study.

Athar M, Tang XW, Lee JL, Kopelovich L, Kim AL. 2006. Hedgehog signalling in skin development and cancer. Exp Dermatol 15:667-677.
Abstract: Basal cell carcinoma (BCC) is the most common human malignancy, affecting 750 000 Americans each year. The understanding of mutations that are known to activate hedgehog (Hh) signalling pathway genes, including PATCHED (PTCH), sonic hedgehog (Shh) and smoothened (Smo), has substantially expanded our current understanding of the genetic basis of BCC development. The Hh signalling pathway is one of the most fundamental signal transduction pathways in embryonic development. In skin, the Shh pathway is crucial for maintaining stem cell population, and for regulating hair follicle and sebaceous gland development. This pathway plays a minimal role in adult tissues, but is known to be activated in many neoplasms, including those arising in the skin. In this review, we attempt to summarize the results of published studies on some important aspects of the Shh pathway and its involvement in skin development and carcinogenesis. We also provide a description of various animal models that have been developed, based on our knowledge of the Shh pathway in human skin cancers. Additionally, we include a brief description of studies conducted in our laboratory and by others on the chemoprevention of BCCs. This review therefore provides a current understanding of the role of the Shh pathway in skin development and neoplasia. It also provides a basis for the molecular target-based chemoprevention and therapeutic management of skin cancer.

Aumuller G, Leonhardt M, Renneberg H, von Rahden B, Bjartell A, Abrahamsson PA. 2001 . Semiquantitative morphology of human prostatic development and regional distribution of prostatic neuroendocrine cells. Prostate 46:108-115.
Abstract: BACKGROUND: The neuroendocrine cells of the human prostate have been related to proliferative disorders such as prostatic cancer. Their origin, distribution, and development have therefore been studied and discussed in terms of current stem cell concepts in the prostate. METHODS: Prostatic tissue specimens (n = 20) from human fetuses (n = 8), prepubertal and pubertal children (n = 8) and mature men (n = 4) were studied immunohistochemically using antibodies directed against neuroendocrine, epithelial as well as secretory markers. Semiquantitative computer-assisted evaluation of different epithelial and stromal components based on stereological principles was performed on azan-stained sections representative of all developmental stages. RESULTS: By the end of gestational Week 9, neuroendocrine (NE) cells appear in the epithelium of the urogenital sinus and are subsequently closely associated with the formation of urethral prostatic buds. The fetal and postnatal distribution pattern of NE cells within the gland is characterized by a relatively constant number of cells per gland similar to prostatic smooth muscle cells. Likewise, a density gradient exists with the highest density in the large collicular ducts and almost no NE cells in subcapsular peripheral acini. In peripheral ducts, the distribution is random. Maturation of the NE cells precedes that of the secretory cells by about 10-16 years. CONCLUSIONS: A second prostatic stem cell lineage, different from the urogenital sinus (UGS)-lineage is hypothesized originating from immature neuroendocrine cells. Being morphologically indistinguishable from the UGS-derived prostatic secretory cell lineage, it gives rise to neuroendocrine cells. Their presence is apparently important for proliferation regulation of the UGS-derived lineage of the prostate.

Autrup H. 1993. Transplacental transfer of genotoxins and transplacental carcinogenesis. Environ Health Perspect 101 Suppl 2:33-38.
Abstract: A number of chemical compounds induce cancer in the offspring of animals treated with these compounds. The fetus is sensitive to the toxic and teratogenic effects of chemicals in the early embryonic stages, whereas it is sensitive to carcinogenic effects during late fetal stages. Carcinogens may be direct acting or may require metabolic oxidation such as those in tobacco smoke. Activation can occur in utero. Animal experiments indicate that tumors can be initiated in utero, commonly by activation of cellular proto-oncogenes, and that promotion can occur after birth by postnatal treatment with tumor promoters. This may have important implications for humans. The initial peak of cancer incidence during the first 5 years of life may be due to prenatal exposure of either parent to mutagens, but the role of paternal exposure in relation to childhood cancer is controversial. There is an increased risk of cancer in children whose fathers work in heavy industry or whose mothers work in medical or dental services. The exact etiological agents have not been unequivocally identified. Information on human transplacental exposure to carcinogens and genotoxins is limited and based on measurement of maternal plasma concentrations or analysis of cord blood. Transplacental transfer of carcinogens in smoke and smoke-related damage to fetal tissue have been demonstrated. The mycotoxin aflatoxin B1 or its metabolites have been detected in cord blood, as have metabolites of pesticides and polychlorinated biphenyls. New biomarkers may provide important information on the transplacental transfer of genotoxic compounds. Recent developments in the field of molecutlar biology such as polymerase chain reaction may disclose relevant biological changes occurring in utero as a consequence of exposure to environmental compounds.

Autrup H, Vestergaard AB. 1996. Transplacental transfer of environmental genotoxins--polycyclic aromatic hydrocarbon-albumin in nonsmoking women. Environ Health Perspect 104 Suppl 3:625-627.
Abstract: Transplacental transfer of genotoxic material has been determined by measuring the polycyclic aromatic hydrocarbon-albumin adduct level in serum isolated from the mother and the umbilical cord blood using a competitive enzyme-linked immunoadsorbent assay (ELISA) and the antibody (8E11(against benzo[a]pyrene (B[a]P) tetrols. Smoking women (median = 5.54 fmol B[a]P eq/micrograms albumin; n = 21 cases) and nonsmoking women living in rural areas (median = 4.99; n = 30) had higher adduct levels than nonsmoking women living in suburbia (median = 4.09; n = 37), whereas nonsmoking women living in the city of Aarhus had an intermediate level (median = 4.82; n = 40). The median adduct level in umbilical cord blood was significantly lower than in maternal blood, the maternal/fetal ratio being approximately 1.3. A positive association between the adduct levels in the mother and umbilical cord blood was observed. This study indicates that the competitive ELISA to detect B[a]P bound to serum albumin is sensitive enough to detect differences in the burden of genotoxic compounds in nonoccupationally exposed individuals. The lower adduct level in people living in suburbia suggests that local production of incomplete combustion products, like vehicle exhaust or heat generation, is a contributing factor to genotoxic compounds in the general environment.

Avigdor S, Zakheim D, Barnea ER. 1992. Quinone reductase-activity in the 1st trimester placenta - Effect of cigarette smoking and polycyclic aromatic-hydrocarbons. Reprod Toxicol 6:363-366.
Abstract: Quinone reductase (QR) is considered a major protective enzyme against cancer in the organism. In this study, the activity of QR was measured in first trimester placental tissue using colorimetric techniques. There were no significant differences between the mean enzyme activity of women who smoked more than 20 cigarettes per day during pregnancy and of nonsmokers (0.50 +/- 0.09 compared with 0.51 +/- 0.15-mu-mol/mg protein/10 min, respectively). Among the polycyclic aromatic hydrocarbons (PAH) studied, dimethyl benzanthracene (DMBA) increased QR activity in a dose-dependent manner in the first trimester placental explants at the 10- to 100-mu-M range after 6 h of incubation (440% increase) with the highest concentration. The effect of other PAH of different potency added at 50-mu-M concentrations showed that benz(a)anthracene (BA), dibenzo(a,h)anthracene (DBHA), dibenzo(a,c)anthracene (DBCA), or chrysene (CH) caused a significant 2- to 3-fold increase in the enzymatic activity after 6 h of incubation. At 24 h 50-mu-M DBCA effect was also stimulatory, while the 10-mu-M DMBA effect almost reached statistical significance. However, no differences were encountered in the response of placental tissues to PAH between cigarette smokers and nonsmokers at 6 and 24 h. The present data indicate that placental QR activity is increased by exposure to PAH in vitro, but it does not appear to be affected by in vivo exposure to cigarette smoking. Thus, the early placenta appears to have a significant potential to inactivate carcinogens/mutagens locally, thereby limiting their transfer to the embryo.

Ayers KM, Torrey CE, Reynolds DJ. 1997. A transplacental carcinogenicity bioassay in CD-1 mice with zidovudine. Fundamental & Applied Toxicology 38:195-198.
Abstract: In oral carcinogenicity bioassays, zidovudine (ZDV) induced vaginal epithelial cell tumors in mice given 30 or 40 mg/kg/day and rats given 300 mg/kg/day. To determine if lifetime exposure to ZDV, beginning perinatally, would alter this pattern of carcinogenicity, two groups of 60 pregnant CD-1 mice were given 20 or 40 mg/kg/day of ZDV in 0.5% methyl cellulose from Gestation Day 10 through Lactation Day 21, At weaning, 2 pups per sex from each of 35 litters in each group were assigned to the study and given 20 or 40 mg/kg/day of ZDV in the drinking water until 17-35 days of age, followed by daily gavage for 24 months. Two additional groups of 60 pregnant CD-1 mice each were given 40 mg/kg/day of ZDV daily from Gestation Day 10 through Lactation Day 21; in one, ZDV treatment was halted at weaning and in the other, treatment was stopped 90 days after weaning. Two other groups of 60 pregnant CD-1 mice were left untreated (environmental control) or were given 0.5% methyl cellulose beginning on Gestation Day 10 (vehicle control). Vehicle control progeny received plain drinking water for 17-35 days postweaning and then 0.5% methyl cellulose daily by gavage for 24 months. ZDV treatment did not affect survival or body weight in either sex. In females given 20 or 40 mg/kg/day of ZDV for 24 months there was mild macrocytic anemia, Similar, non-dose-related changes were seen in males in these groups, ZDV-related tumor findings were limited to the vagina, where there were 2 and 11 vaginal squamous cell carcinomas in mice given 20 or 40 mg/kg/day of ZDV daily, respectively. This incidence was not remarkably different from that seen in previously reported bioassays. It was perinatally, did not alter the previously reported pattern of carcinogenicity and that under the conditions tested ZDV was not a transplacental carcinogen. (C) 1997 Society of Toxicology.

Baggs RB, Miller RK, Odoroff CL. 1991. Carcinogenicity of diethylstilbestrol in the Wistar rat: effect of postnatal oral contraceptive steroids. Cancer Res 51:3311-3315.
Abstract: Diethylstilbestrol (DES) has been associated with vaginal neoplasia and malformations in humans. We have studied a test population of 504 female Wistar rats given diethylstilbestrol at from 0.0 to 0.5 mg/kg maternal body weight on days 18, 19, and 20 of gestation. Animals were euthanized in extremis, or at 2 years of age. The incidence of vaginal epithelial tumors was dose related. The types of epithelial tumors of the vagina were adenocarcinoma, squamous cell carcinoma, and mixed carcinoma, containing discrete adenomatous and squamous components. The incidence of vaginal epithelial tumors was determined to be dose related: rats exposed to 0 mg DES/kg maternal weight had an incidence of 0.6% (1 of 167 rats); 0.1 mg/kg, 4.1%; and 0.5 mg/kg, 4.3% (6 of 140); 25 mg/kg, 1.6% (1 of 63); and 50 mg/kg, 11.5% (3 of 26). Tumors of other reproductive tissues (mammary gland, ovary, oviduct, cervix, or uterus) demonstrated no discernible DES dose-response relationship. There was no oncogenic effect of postnatal administration of oral contraceptives (0 oral contraceptives, 31.25 μg/kg diet ethynylestradiol, and 31.25 μg/kg diet norethindrone or 104 μg/kg diet ethynylestradiol and 31.25 μg/kg diet norethindrone). Thus, vaginal tumors can be induced in a dose-related manner in the rat following in utero DES exposure. Oral contraceptive treatment did not increase the risk of neoplasia.

Baik I, Becker PS, DeVito WJ, Lagiou P, Ballen K, Quesenberry PJ, Hsieh CC. 2004. Stem cells and prenatal origin of breast cancer. Cancer Causes Control 15:517-530.
Abstract: The hypothesis that in utero exposure to pregnancy hormones, notably estrogens, is related to the occurrence of breast cancer in the offspring has been examined in a number of epidemiological and experimental studies. **Many studies have provided direct or indirect evidence that supports the hypothesis of an intrauterine component in the origin of breast cancer.** Human studies to examine the underlying biological mechanisms, however, have been limited. **We review the likely role of stem cells in hormone-mediated carcinogenic process, particularly as intermediate steps between in utero exposure to hormones and breast cancer. We summarize also studies related to the assumptions of the hypothesis concerning in utero exposure.** We propose the use of stem cell potential as a measurable variable of the 'fertile soil', a term that has been used to characterize the consequences of fetal exposure to intrauterine environment. **We conclude by outlining a feasible population-based study that measures stem cell potential to explore mechanisms mediating the relation between in utero exposure to pregnancy hormones and breast cancer risk in the offspring.**

Baik I, Devito WJ, Ballen K, Becker PS, Okulicz W, Liu Q, Delpapa E, Lagiou P, Sturgeon S, Trichopoulos D, Quesenberry PJ, Hsieh CC. 2005. Association of fetal hormone levels with stem cell potential: Evidence

for early life roots of human cancer. Cancer Res 65:358-363.
Abstract: Intrauterine and perinatal factors have been linked to risk of childhood leukemia, testicular cancer, and breast cancer in the offspring. The pool of stem cells in target tissue has been suggested as a critical factor linking early life exposures to cancer. We examined the relation between intrauterine hormone levels and measurements of stem cell potential in umbilical cord blood. Cord blood donors were 40 women, ages 2 18 years, who delivered, from August 2002 to June 2003, a singleton birth after a gestation of at least 37 weeks. We assayed plasma concentrations of estradiol, unconjugated estriol, testosterone, progesterone, prolactin, sex hormone binding globulin, insulin-like growth factor-I (IGF-I), and IGF binding protein-3. For stem cell potential, we measured concentrations of CD34(+) and CD34(+)CD38(-) cells and granulocyte-macrophage colony-forming unit (CFU-GM). We applied linear regression analysis and controlled for maternal and neonatal characteristics. We found strong positive associations between IGF-I and stem cell measures, 1 SD increase in IGF-I being associated with a 41% increase in CD34(+) (P = 0.008), a 109% increase in CD34(+)CD38(-) (P = 0.005), and a 94% increase in CFU-GM (P = 0.01). Similar associations were observed for IGF binding protein-3. Among steroid hormones, estriol and testosterone were significantly positively associated with CD34(+) and CFU-GM. These findings indicate that levels of growth factors and hormones are strongly associated with stem cell potential in human umbilical cord blood and point to a potential mechanism that may mediate the relationship between in utero exposure to hormones and cancer risk in the offspring.

Baldwin RT, Preston-Martin S. 2004. Epidemiology of brain tumors in childhood - A review. Toxicology & Applied Pharmacology 199:118-131.
Abstract: Malignant brain tumors are the leading cause of cancer death among children and the second most common type of pediatric cancer. Despite several decades of epidemiologic investigation, the etiology of childhood brain tumors (CBT) is still largely unknown. A few genetic syndromes and ionizing radiation are established risk factors. Many environmental exposures and infectious agents have been suspected of playing a role in the development of CBT. This review, based on a search of the medical literature through August 2003, summarizes the epidemiologic evidence to date. The types of exposures discussed include ionizing radiation, N-nitroso compounds (NOC), pesticides, tobacco smoke, electromagnetic frequencies (EMF), infectious agents, medications, and parental occupational exposures. We have chosen to focus on perinatal exposures and review some of the recent evidence indicating that such exposures may play a significant role in the causation of CBT. The scientific community is rapidly learning more about the molecular mechanisms by which carcinogenesis occurs and how the brain develops. We believe that advances in genetic and molecular biologic technology, including improved histologic subtyping of tumors, will be of huge importance in the future of epidemiologic research and will lead to a more comprehensive understanding of CBT etiology. We discuss some of the early findings using these technologies. (C) 2004 Elsevier Inc. All rights reserved.

Ballin A, Cohen I, Iscovich J. 1997. Cancer of infancy in Israel - A seven-year epidemiologic survey. International Journal of Pediatric Hematology/Oncology 4:347-352.
Abstract: Malignant tumors were diagnosed in 129 Jewish Israeli infants in the years 1983 through 1989. This gives an incidence of 217.94 per million. The incidence of primary liver tumors, neuroblastomas and soft tissue malignancies was higher in Israel than reported elsewhere. Birth weight was significantly higher than the average in infants with leukemia ($p > 0.025$) and lower in those with sarcoma ($p > 0.05$). A higher than expected percentage of twins was found among the patients. A high rate of malignancy was found in children who had one of their parents born in Asia compared with those born in Israel, Africa, Europe or America, and in relation to the population demography ($p > 0.025$ for the father and the mother). The results of our work emphasize the importance of genetic background in the pathogenesis of infantile malignancy.

Baptista T, Araujo H, Rada P, Hernandez L. 1998. Congenital neuroblastoma in a boy born to a woman with bipolar disorder treated with carbamazepine during pregnancy. Progress in Neuro-Psychopharmacology & Biological Psychiatry 22:445-454.
Abstract: 1. A metastatic neuroblastoma was detected immediately after birth in a boy born to a 26 year old woman with bipolar disorder, who received carbamazepine (400 mg/day) all through her pregnancy. The primary tumor was probably located in the adrenal gland of the right side, and multiple metastatic lesions were detected in the skin. 2. In this report the authors review the literature about the side effects teratogenic

and carcinogenic effects of carbamazepine, the epidemiology and evolution of the neuroblastoma, and the current scientific opinion about the pharmacological treatment of the pregnant with mood disorders. 3. A causal relationship between the use of carbamazepine and the neuroblastoma development in the present case can not be established; however, as the carcinogenic and teratogenic effects of the drug have been basically assessed in epileptic women, our aim is to alert the medical community in order to conduct further research in psychiatric patients.

Bastide M, Youbicier-Simo BJ, Lebecq JC, Giaimis J. 2001. Toxicologic study of electromagnetic radiation emitted by television and video display screens and cellular telephones on chickens and mice. Indoor & Built Environment 10:291-298.
Abstract: The effects of continuous exposure of chick embryos and young chickens to the electromagnetic fields (EMFs) emitted by video display units (VDUs) and GSM cell phone radiation, either the whole spectrum emitted or attenuated by a copper gauze, were investigated. Permanent exposure to the EMFs radiated by a VDU was associated with significantly increased fetal loss (47-68%) and markedly depressed levels of circulating specific antibodies (IgG), corticosterone and melatonin. We have also shown that under chronic exposure conditions, GSM cell phone radiation was harmful to chick embryos, stressful for healthy mice and, in this species, synergistic with cancer insofar as it depleted stress hormones, The same pathological results were observed after substantial reduction of the microwaves radiated from the cell phone by attenuating them with a copper gauze. Copyright (C) 2002 S. KargerAG, Basel.

Batukan C, Ozgun MT, Basbug M, Caglayan O, Dundar M, Murat N. 2007. Sacrococcygeal teratoma in a fetus with prenatally diagnosed partial trisomy 10q (10q24.3-->qter) and partial monosomy 17p (p13.3-->pter). Prenat Diagn 27:365-8 .
Abstract: OBJECTIVE: Clinical features of the distal 10q trisomy syndrome consist of mental retardation, facial dysmorphism and renal and cardiac anomalies. The presence of a sacrococcygeal teratoma (SCT) in a fetus with distal 10q trisomy has not been reported yet. METHODS: A 33-year-old, G5, P2 woman with a singleton pregnancy was referred to our clinic at 24 weeks of gestation for further evaluation of a fetal sacral exophytic mass. Detailed fetal sonographic examination together with chromosomal analysis by amniocentesis was performed. RESULTS: The scan revealed a large SCT together with a persistent right umbilical vein, cardiomegaly, bilateral mild hydronephrosis and intrauterine growth retardation. The fetal karyotype showed distal 10q trisomy (10q24.3-->qter) distal monosomy 17 (p13-->pter). The fetus died after a preterm delivery at 28 weeks of gestation. Postnatal examination confirmed the prenatal findings and added the typical facial features of this syndrome, which consisted of prominent forehead, small nose with depressed nasal bridge, micrognathia and bow-shaped mouth. CONCLUSION: This case provides further evidence of a possible association between chromosomal aberrations in SCTs.

Bay K, Asklund C, Skakkebaek NE, Andersson AM. 2006. Testicular dysgenesis syndrome: possible role of endocrine disrupters. Best Practice & Research Clinical Endocrinology & Metabolism 20:77-90.
Abstract: The testicular dysgenesis syndrome (TDS) hypothesis proposes that the four conditions cryptorchidism, hypospadias, impaired spermatogenesis and testis cancer may all be manifestations of disturbed prenatal testicular development. The TDS hypothesis is based on epidemiological, clinical and molecular studies, all suggestive of an interrelation between the different symptoms. The aetiology of TDS is suspected to be related to genetic and/or environmental factors, including endocrine disrupters. Few human studies have found associations/correlations between endocrine disrupters, including phthalates, and the different TDS components. However, for ethical reasons, evidence of a causal relationship between prenatal exposure and TDS is inherently difficult to establish in human studies, rendering the recently developed animal TDS model an important tool for investigating the pathogenesis of TDS. Clinically, the most common manifestation of TDS is probably a reduced sperm concentration, whereas the more severe form may include a high risk of testis cancer. Clinicians should be aware of the interconnection between the different features of TDS, and inclusion of a programme for early detection of testis cancer in the management of infertile men with poor semen quality is recommended.

Bay K, Asklund C, Skakkebaek NE, Andersson AM. Mar 2006. Testicular Dysgenesis Syndrome: Possible Role of Endocrine Disrupters. Best Practice & Research Clinical Endocrinology & Metabolism 20:77-90.
Abstract: The testicular dysgenesis syndrome (TDS) hypothesis proposes that the four conditions cryptorchidism, hypospadias, impaired spermatogenesis and testis cancer may all be manifestations of

disturbed prenatal testicular development. The TDS hypothesis is based on epidemiological, clinical and molecular studies, all suggestive of an interrelation between the different symptoms. The aetiology of TDS is suspected to be related to genetic and/or environmental factors, including endocrine disrupters. Few human studies have found associations/correlations between endocrine disrupters, including phthalates, and the different TDS components. However, for ethical reasons, evidence of a causal relationship between prenatal exposure and TDS is inherently difficult to establish in human studies, rendering the recently developed animal TDS model an important tool for investigating the pathogenesis of TDS. Clinically, the most common manifestation of TDS is probably a reduced sperm concentration, whereas the more severe form may include a high risk of testis cancer. Clinicians should be aware of the interconnection between the different features of TDS, and inclusion of a programme for early detection of testis cancer in the management of infertile men with poor semen quality is recommended.

Beebe LE, Kim YE, Amin S, Riggs CW, Kovatch RM, Anderson LM. 1993. Comparison of transplacental and neonatal initiation of mouse lung and liver-tumors by n-nitrosodimethylamine (NDMA) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and promotability by a polychlorinated-biphenyls mixture (Aroclor 1254). Carcinogenesis 14:1545-1548.
Abstract: We have previously shown a positive tumor-promoting effect of a single dose of Aroclor 1254 on lung and liver tumors initiated neonatally in the mouse by N-nitrosodimethylamine (NDMA). In this study, we have confirmed and extended this observation with NDMA and the tobacco-specific nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) given either transplacentally or postnatally, followed by a single dose of Aroclor 1254 on day 56. This polychlorinated biphenyl (PCB) mixture was an effective promoter of both lung and liver tumors; however, there were specific initiator and sex-related differences in this response. Aroclor administration significantly increased the incidence of lung tumors initiated transplacentally by NDMA or NNK in male mice. Neither nitrosamine initiated tumors transplacentally in females, but lung tumors initiated with NNK and liver tumors caused by NDMA in neonatal females were promoted by PCBs. Both liver and lung tumors initiated neonatally by NDMA in male animals, but not NNK-initiated tumors, were promoted by PCBs. These data confirm that PCBs are able to promote both NDMA- and NNK-initiated tumors, but with chemical-, sex- and age-dependent difference; this suggests influences of both quantitative and qualitative factors in susceptibility to tumor promotion.

Begum M, Tashiro H, Katabuchi H, Suzuki A, Kurman RJ, Okamura H. 2006. Neonatal Estrogenic Exposure Suppresses Pten-Related Endometrial Carcinogenesis in Recombinant Mice. Lab Invest 86:286-296.
Abstract: Human endometrial carcinomas, as well as complex atypical hyperplasias (CAH), are estrogen related and frequently have mutations in the PTEN gene. However, the mutual contribution of estrogen and PTEN mutations to endometrial carcinogenesis in vivo is unknown. To address this issue, we investigated whether neonatal estrogenic treatments augment the incidence of CAH and carcinomas in murine PTEN (mPTEN) heterozygous (+/-) mutant mice, an animal model for endometrial carcinoma. Low doses of diethylstilbestrol (1 ng/g/day), genistein (50 mu g/g/day) in phytoestrogens, estriol (E-3) (4 mu g/g/day), and vehicle (ethanol and corn oil) were administered subcutaneously daily to neonatal pups from the 1st to 5th day after birth. At 52 weeks of age, the morphological changes in the endometrium, and uterine expression of Hoxa 10 and Hoxa 11, were evaluated. These Hoxa genes are abdominal B-type homeobox genes, which normally regulate differentiation of the Mullerian duct. The incidence of CAH and adenocarcinomas of the endometrium was significantly decreased by the neonatal estrogenic treatments in the mPTEN+/- mice. Coincidentally, all treatments significantly decreased the stromal cell density, and CAH and adenocarcinomas rarely developed in the epithelium adjacent to the affected endometrial stroma. Moreover, the uterine expression of Hoxa 10 in mice with neonatal genistein and E3 treatments, and that of Hoxa 11 in mice with all treatments, was significantly lower when compared with vehicle alone. Taken together, neonatal estrogenic exposure induced stromal atrophy and/or hyalinization accompanied by repressed expression of Hoxa 10 and Hoxa 11, and exerted an inhibitory effect on PTEN-related tumorigenesis. These findings provide new insight into the interaction between endometrial epithelium and stroma in endometrial carcinogenesis in vivo.

Benjamin SA, Lee AC, Angleton GM, Saunders WJ, Keefe TJ, Mallinckrodt CH. 1998. Mortality in beagles irradiated during prenatal and postnatal development. II. Contribution of benign and malignant neoplasia. Radiat Res 150:330-348.
Abstract: To evaluate the lifetime carcinogenic hazards of exposure to ionizing radiation during

development, 1,680 beagles received whole-body exposures to Co-60 gamma rays or sham exposures. Eight groups of 120 dogs each received mean doses of 15.6-17.5 or 80.8-88.3 cGy in early, mid; or late gestation, at 8, 28 or 55 days postcoitus or at 2 days after birth. Another group of 120 dogs received a mean dose of 82.6 cGy as 70-day-old juveniles and one group of 240 dogs received a mean dose of 81.2 cGy as 365-day-old young adults. Sham irradiations mere given to 360 controls. Sexes were equally represented. In 1,343 dogs allowed to live out their life span, neoplasia was a major disease, contributing to mortality in 40% of the dogs. There was a significant increase in benign and malignant neoplasms occurring in young dogs (<4 years old), including fatal malignancies, after irradiation in the perinatal (late fetal and neonatal) periods. The lifetime incidence of fatal neoplasms was also increased in dogs irradiated perinatally. Three malignancies-lymphomas, hemangiosarcomas and mammary carcinomas-accounted for 51% of all fatal tumors. There was an apparent lifetime increase and earlier onset of lymphomas in dogs exposed as fetuses. Fatal hemangiosarcomas were increased in dogs irradiated early and late in gestation. Fatal mammary carcinomas were not increased by irradiation, although non-fatal carcinomas were increased after perinatal exposure. Myeloproliferative disorders and central nervous system astrocytomas appeared to be increased in perinatally irradiated dogs. These data suggest that irradiation in both the fetal and neonatal periods is associated with increased early onset and lifetime cancer risk. (C) 1998 by Radiation Research Society.

Benjamin SA, Saunders WJ, Angleton GM, Lee AC. 1991. Radiation carcinogenesis in dogs irradiated during prenatal and postnatal development. Journal of Radiation Research (Tokyo) 32 Suppl 2:86-103.
Abstract: To evaluate the lifetime hazards of ionizing radiation exposure, 1680 beagles received whole-body, 60-Cobalt gamma exposures or sham-exposures during development. Eight groups of 120 dogs each received mean doses of 16 or 83 cGy at 8 (preimplantation), 28 (embryonic), or 55 (late fetal) days postcoitus (dpc), or 2 (neonatal) days postpartum (dpp). One group of 120 dogs received 83 cGy at 70 dpp (juvenile), and one group of 240 dogs received 83 cGy at 365 dpp (young adult). Sham-irradiations were delivered to 360 controls. Sexes were equally represented. Young dogs, up to 4 years of age, had an increase in benign and malignant neoplasms after irradiation in the perinatal period at 55 dpc or 2 dpp. Among these, 4 fatal cancers were observed. No malignancies occurred in comparably-aged controls. The increase in both fatal neoplasms and all neoplasms in the perinatally-exposed groups were statistically significant. Over the full lifetime, dogs irradiated in the perinatal period also had the strongest evidence for an increased risk for fatal malignancies of all types. Though not as strong, there was a trend for increased risk for fatal cancer in dogs irradiated at all other ages. The risk of fatal malignancy after irradiation was greater in females than in males. Dogs exposed at 55 dpc had a significant increase in lymphoid neoplasia and dogs exposed at 8 and 55 dpc had increased risk for hemangiosarcoma. There was no evidence for an increased risk for mammary carcinoma in irradiated females. Dogs exposed as juveniles at 70 dpp had a significant increase in all benign and malignant thyroid neoplasms, including fatal thyroid carcinoma.

Benvenuti LA, Aiello VD, Fukasawa S, Higuchi ML. 2001 . Cardiac rhabdomyomas exhibit a fetal pattern of atrial natriuretic peptide immunoreactivity. Experimental & Molecular Pathology 70:65-69.
Abstract: Rhabdomyomas are the most common heart tumors seen in infancy. However, whether they represent hamartomas or true neoplasms derived from cardiomyocytes is still controversial. The fetal pattern of atrial natriuretic peptide (ANP) expression (predominant in the atrial and ventricular subendocardium) becomes altered during the early postnatal period to that typical of the adult (all atrial cardiomyocytes and some cells in the ventricular impulse-conducting system). To better comprehend the nature and origin of cardiac rhabdomyomas, we investigated the immunohistochemical expression of ANP in seven surgically excised ventricular specimens and two necropsy cases of multiple, atrial, and ventricular rhabdomyomas in children aged 1 to 34 days. Immunogold labeling for ANP at the ultrastructural level was also performed on three ventricular tumors. Although all atrial tumors were immunoreactive for ANP, these usually showed a variable number of faintly positive cardiomyocytes, contrasting with the diffuse and intense immunoreactivity of the surrounding atrial myocardium. ANP was detected in the ventricular tumors of five (56%) of the nine cases. The positive ventricular tumor cells predominated in the subendocardium and areas with prominent fibrous tissue, usually around blood vessels. Immunoelectron microscopy of the ventricular tumors demonstrated rare, positive cytoplasmic granules surrounded by membranes, usually located near the nuclei. We conclude that cardiac rhabdomyomas exhibit a fetal pattern of ANP immunoreactivity, which suggests delayed maturation of the tumoral cardiomyocytes, reinforcing the notion that cardiac rhabdomyomas are fetal hamartomas.

Bernstein L, Pike MC, Depue RH, Ross RK, Moore JW, Henderson BE. 1988. Maternal hormone levels in early gestation of cryptorchid males: A case-control study. Br J Cancer 58:379-381.
Abstract: A case-control study was conducted to assess maternal hormonal factors associated with increased risk of bearing a cryptorchid son. Serum samples were collected during the first trimester of pregnancy from participants in the US Collaborative Perinatal Study. Twenty-five mothers of normal offspring (controls) were individually matched on medical center, age, parity, weight and length of gestation at the time of sampling to women bearing sons who had a diagnosis of cryptorchidism at one year of age or older. Compared with controls, mothers of cryptorchid sons (cases) had significantly greater percentages of non-protein bound (P = 0.010) and albumin-bound (P = 0.014) estradiol during the first trimester of the index pregnancy. On average, cases had 16% more bioavailable oestradiol than controls. Levels of human chorionic gonadotropin, testosterone, non-protein bound testosterone and sex-hormone binding globulin did not differ between the two groups. The data presented support the hypothesis that cryptorchidism results from elevated maternal oestrogen levels early in pregnancy.

Bhatia S, Neglia JP. 1995. Epidemiology of childhood acute myelogenous leukemia. J Pediatr Hematol Oncol 17:94-100.
Abstract: Acute myelogenous leukemia (AML) is the second most common leukemia in children, with similar to 400 new cases occurring annually in the United States. Worldwide, the highest rates of childhood AML occur in Asia and the lowest rates are reported from India and South America. Numerous genetic risk factors for childhood AML have been defined, including Down syndrome, neurofibromatosis, and Fanconi anemia. Research into environmental risk factors has been limited by the rarity of this disease; however, studies of AML in adults have implicated ionizing radiation, solvents, and petroleum products as potential etiologic agents. The largest analytic study of childhood AML found that occupational exposures of either parent to pesticides, paternal exposure to petroleum products, and postnatal exposures to pesticides are increased in children with AML. In addition, maternal use of maijuana during pregnancy was associated with an increased risk of AML, especially the monocytic subtypes. Further study of childhood AML, including occurrence of the disease as a second malignancy, is needed in order to confirm these findings and to increase our understanding of this leukemia.

Bibbo M, Al-Naqeeb M, Baccarini I, Gill W, Newton M, Sleeper KM, Sonek RN, Wied GL. 1975. Follow-up study of male and female offspring of DES-treated mothers a preliminary report. J Reprod Med 15:29-32.
Abstract: This is a follow-up study of male and female offspring of mothers who were part of a double-blind placebo controlled investigation during the years 1951-1952, originally aimed at determining the usefulness of DES administration in maintaining pregnancy. So far, 84 DES-exposed females, 43 female controls, 42 DES-exposed males and 37 male controls have been examined. Circumferential ridges of the vagina and cervix were seen in 39% of the DES-exposed females but in none of the controls. Colposcopy revealed vaginal epitheleal changes in 78% of the DES-exposed females 2% of the female controls. Cytology proved to be reliable as a screening test for vaginal epithelial changes in the DES-exposed female. Urine cytology was negative for tumor cells in all patients. The main abnormal finding in the DES-exposed males was that cysts in the epididymis were detected in 10%. No cases of cancer were observed in either the male or female offspring.

Bigbee WL, Day RD, Grant SG, Keohavong P, Xi LQ, Zhang LF, Ness RB. 1999. Impact of maternal lifestyle factors on newborn HPRT mutant frequencies and molecular spectrum - Initial results from the Prenatal Exposures and Preeclampsia Prevention (PEPP) Study. Mutation Research-Fundamental & Molecular Mechanisms of Mutagenesis 431:279-289.
Abstract: Epidemiological studies have demonstrated associations between maternal tobacco smoke exposure and consumption of alcohol during pregnancy and increased risk of pediatric malignancies, particularly infant leukemias. Molecular evidence also suggests that somatic mutational events occurring during fetal hematopoiesis in utero can contribute to this process. As part of an ongoing multi-endpoint biomarker study of 2000 mothers and newborns, the HPRT T-lymphocyte cloning assay was used to determine mutant frequencies (M-f) in umbilical cord blood samples from an initial group of 60 neonates born to a sociodemographically diverse cohort of mothers characterized with respect to age, ethnicity, socioeconomic status, and cigarette smoke and alcohol exposure. Non-zero M-f (N = 47) ranged from 0.19 to 5.62 X 10(-6), median 0.70 x 10(-6), mean +/- SD 0.98 +/- 0.95 X 10(-6). No significant difference in M-f was observed between female and male newborns. Multivariable Poisson regression analysis revealed

that increased HPRT M-f were significantly associated with maternal consumption of alcohol at the beginning [Relative Rate (RR)= 1.84, 95% CI = 0.99-3.40, P = 0.052) and during pregnancy (RR = 2.99, 95% CI = 1.14-7.84, P = 0.026. No independent effect of self-reported active maternal cigarette smoking, either at the beginning or throughout pregnancy, nor maternal passive exposure to cigarette smoke was observed. Although based on limited initial data, this is the first report of a positive association between maternal alcohol consumption during pregnancy and HPRT M-f in human newborns. In addition, the spectrum of mutations at the HPRT locus was determined in 33 mutant clones derived from 19 newborns of mothers with no self-reported exposure to tobacco smoke and 14 newborns of mothers exposed passively or actively to cigarette smoke. In the unexposed group, alterations leading to specific exon 2-3 deletions, presumably as a result of illegitimate V(D)J recombinase activity, were found in five of the 19 mutants (26.3%); in the passively exposed group, two exon 2-3 deletions were present among the seven mutants (28.6%); and in the actively exposed group, six of the seven mutants (85.7%) were exon 2-3 deletions. Although no overall increase in HPRT Mi was observed and the number of mutant clones examined was small, these initial results point to an increase in V(D)J recombinase-associated HPRT gene exon 2-3 deletions in cord blood T-lymphocytes in newborns of actively smoking mothers relative to unexposed mothers (P = 0.011). Together, these results add to growing molecular evidence that in utero exposures to genotoxicants result in detectable transplacental mutagenic effects in human newborns. (C) 1999 Elsevier Science B.V. All rights reserved.

Bilrha H, Roy R, Moreau B, Belles-Isles M, Dewailly E, Ayotte P. 2003. In vitro activation of cord blood mononuclear cells and cytokine production in a remote coastal population exposed to organochlorines and methyl mercury. Environ Health Perspect 111:1952-1957.
Abstract: Remote coastal populations that rely on seafood for subsistence often receive unusually high doses of organochlorines and methyl mercury. Immunosuppression resulting from prenatal exposure to organochlorines has been reported in wildlife species and humans. In this study, we assessed lymphocyte activation and associated cytokine secretion in 47 newborns from a remote maritime population living on the Mid and Lower North Shore regions of the St. Lawrence River (Quebec, Canada; subsistence fishing group) and 65 newborns from nearby urban settings (reference group). Cord blood samples were collected for organochlorine and mercury analyses and also to isolate cord blood mononuclear cells (CBMCs) for the in vitro assessment of cytokine production and expression of surface markers after mitogenic stimulation (CD(4+)CD45RO(+), CD(8+)CD45RO(+), CD3(+)CD25(+), and CD8(+)HLA-DR+). Blood mercury and plasma concentrations of polychlorinated biphenyls (PCBs), 1, 1-dichloro-2,2-bis (4-chlorophenyl) ethylene (p,p'-DDE), and hexachlorobenzene (HCB) were significantly higher in the subsistence fishing group than in the reference group ($P < 0.001$). No difference was observed between the two groups regarding subsets of lymphocytes showing markers of activation. In vitro secretion of cytokines by CBMCs after mitogenic stimulation was lower in the subsistence fishing group than in the reference group ($p < 0.05$). Moreover, we found an inverse correlation between tumor necrosis factor-alpha (TNF-alpha) secretion and plasma PCB, pp'-DDE, and HCB concentrations ($p < 0.05$). Our data support a negative association between TNF-alpha secretion by CBMCs and prenatal organochlorine exposure. If the relationship between organochlorine and TNF-alpha secretion is causal, it would suggest a role for this important proinflammatory cytokine in mediating organochlorine-induced immunotoxicity in infants developmentally exposed to these compounds.

Birnbaum LS, Fenton SE. 2003. Cancer and developmental exposure to endocrine disruptors. Environ Health Perspect 111:389-394.
Abstract: Developing organisms have increased susceptibility to cancer if they are exposed to environmental toxicants during rapid growth and differentiation. Human studies have demonstrated clear increases in cancer after prenatal exposure to ionizing radiation, and there is suggestive evidence that brain tumors and leukemia are associated with parental exposures to chemicals. Animal experiments have demonstrated increased tumor formation induced by prenatal or neonatal exposure to a variety of chemicals, including direct-acting carcinogens and drugs. Recently, natural estrogens have been classified as known human carcinogens. Prenatal exposure to natural and synthetic estrogens is associated with increases in breast and vaginal tumors in humans as well as uterine tumors in animals. Synthetic halogenated chemicals increase liver tumors after early life-stage exposure. Recently, a prototypical endocrine-disrupting compound, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, has been shown to be a developmental toxicant of the mammary gland in rodents. Dioxin alters multiple endocrine systems, and its

effects on the developing breast involve delayed proliferation and differentiation of the mammary gland, as well as an elongation of the window of sensitivity to potential carcinogens. Implications of these new findings suggest that causes of endocrine-related cancers or susceptibility to cancer may be a result of developmental exposures rather than exposures existing at or near the time of tumor detection.

Blass-Kampmann S, Bilzer T, Rajewsky MF. 1998. gp130(RB13-6)-positive neural progenitor cells are susceptible to the oncogenic effect of ethylnitrosourea in pre-natal rat brain. Neuropathology & Applied Neurobiology 24:9-20.
Abstract: Proliferation-competent rat brain precursor cells of glial lineages are thought to preferentially undergo malignant transformation after transplacental exposure to ethylnitrosourea (EtNU), We recently have reported that monoclonal antibody (mAb) RB13-6 recognizes a developmentally regulated 130 kDa cell surface glycoprotein (gp130(RB13-6)) transiently expressed by a small subpopulation of glial progenitor cells in pre-natal rat brain. The expression of gp130(RB13-6) has now been analysed immunocytochemically in malignant gliomas induced on day 15, 18 or 21 of gestation and in long-term cultures of fetal brain cells (FBC) isolated after in vivo-exposure to EtNU on day 18 of gestation, Malignant gliomas induced at different gestational stages contained varying proportions of gp130(RB13-6)-positive cells, whereas a subpopulation of proliferative neural progenitor cells exhibiting sustained gp130(RB13-6) expression persisted in long-term FEC cultures after 3 months. This subpopulation, which was not selected for in control cultures of FBC derived from buffer-treated rats, gave rise to malignant cell lines after a period of time similar to the latency period required for glioma development in vivo, These data suggest that gp130(RB13-6)-positive cells of the immature rat nervous system may represent a subset of neural progenitor cells particularly susceptible to the oncogenic effect of EtNU.

Block K, Kardana A, Igarashi P, Taylor HS. 2000. *In utero* diethylstilbestrol (DES) exposure alters Hox gene expression in the developing müllerian system. FASEB J 14:1101-1108.
Abstract: Diethylstilbestrol (DES) was widely used to treat pregnant women through 1971. The reproductive tracts of their female offspring exposed to DES in utero are characterized by anatomic abnormalities. Here we show that DES administered to mice in utero produces changes in the expression pattern of several Hox genes that are involved in patterning of the reproductive tract. DES produces posterior shifts in Hox gene expression and homeotic anterior transformations of the reproductive tract. In human uterine or cervical cell cultures, DES induces HOXA9 or HOXA10 gene expression, respectively, to levels approximately twofold that induced by estradiol. The DES-induced expression is not inhibited by cyclohexamide. Estrogens are novel morphogens that directly regulate the expression pattern of posterior Hox genes in a manner analogous to retinoic acid regulation of anterior Hox genes. Alterations in HOX gene expression are a molecular mechanism by which DES affects reproductive tract development. Changes in Hox gene expression are a potential marker for the effects of in utero drug use that may become apparent only at late stages of development.

Blot WJ, Henderson BE, Boice JD. 1999. Childhood cancer in relation to cured meat intake: Review of the epidemiological evidence. Nutrition & Cancer-An International Journal 34:111-118.
Abstract: Over the past two decades a series of epidemiological studies have examined the relationship between consumption of cured meats during pregnancy and the subsequent risk of brain tumors, as well as other cancers, in the offspring. The research was prompted in large part by experimental investigations showing that transplacental exposure to certain N-nitroso compounds, i.e., nitrosoureas, could produce brain tumors in laboratory animals. Fourteen such epidemiological studies, 13 of which used the case-control approach, are reviewed here. Most of the studies showed no significant association between total cured meat intake and childhood cancer risk but more found positive than negative relationships. Furthermore, several studies reported significant positive associations for maternal and sometimes childhood or paternal consumption of one or more cured meats, with odds ratios of twofold or greater reported among the highest consumers. On the other hand a correlation analysis found no positive concordance between temporal trends from the 1970s to 1990s in childhood brain cancer rates and cured meat consumption inasmuch as cancer rates rose over time while residual nitrite levels in cured meats fell sharply. Because of the potential for bias, especially recall bias, and/or confounding, the relatively weak magnitude of the associations reported, and the inconsistency between study findings, at this time it cannot be concluded that eating cured meat has increased the risk of childhood brain cancer or any other cancers. Moreover, although N-nitroso compounds are sometimes found in cured meats or may be formed

endogenously there is no empirical evidence that eating cured meats results in human neural nitrosourea exposure. Nevertheless, the hypothesis that eating nitrite-cured meats may influence childhood and perhaps adult brain cancer cannot be dismissed. Unbiased evaluation of the hypothesis may derive from the conduct of cohort studies, where the interview-derived information on cured meat intake precedes, or is nor otherwise associated with, the diagnosis of cancer.

Bluhm EC, Daniels J, Pollock BH, Olshan AF. 2006. Maternal use of recreational drugs and neuroblastoma in offspring: a report from the Children's Oncology Group (United States). Cancer Causes & Control 17:663-669.
Abstract: Objective To evaluate whether maternal use of recreational drugs around conception and pregnancy influences the risk of childhood neuroblastoma. Methods Self-reported use of recreational drugs from one month prior to pregnancy until diagnosis was assessed among mothers of 538 children with neuroblastoma (diagnosed 1992-1994 and identified through the Children's Cancer Group and Pediatric Oncology Group) and 504 age-matched controls (identified by random-digit dialing). Odds ratios (OR) and 95% confidence intervals (CI) were estimated using unconditional logistic regression, adjusting for age at diagnosis and household income. Results Maternal use of any illicit or recreational drug around pregnancy was associated with an increased risk of neuroblastoma in offspring (OR = 1.82, 95% CI: 1.13, 3.00), particularly use of marijuana in the first trimester of pregnancy (OR = 4.75, 95% CI: 1.55, 16.48). Marijuana use in the month before pregnancy did not increase risk. The effect of gestational marijuana exposure was strongest in subjects diagnosed before age one. Evaluation of recreational drugs other than marijuana was limited by infrequent use, and analyses of drug use by fathers were not carried out due to missing data. Conclusions Maternal recreational drug use and marijuana use during pregnancy were associated with increased risk of neuroblastoma in offspring. Further examination of these drugs and the risk of childhood cancer is warranted.

Bocskay KA, Orjuela MA, Tang D, Liu X, Warburton D, Perera FP. 2007. Fluorescence in situ hybridization is necessary to detect an association between chromosome aberrations and polycyclic aromatic hydrocarbon exposure in utero and reveals nonrandom chromosome involvement. Environ Mol Mutagen 48:114-23.
Abstract: Chromosome aberrations are associated with environmental exposures in infants and children. Recently we reported that prenatal exposure to airborne polycyclic aromatic hydrocarbons (PAHs) was significantly ($P < 0.01$) associated with stable aberration frequencies in cord blood from a subset of 60 newborns from the Columbia Center for Children's Environmental Health Prospective Cohort Study (Bocskay K et al. [2005]: Cancer Epidemiol Biomarkers Prev 14:506-511). To determine whether the environmental exposures may be targeting specific chromosomes and to compare various methods for measuring chromosome aberrations, we further evaluated this same subset of subjects composed of African-American and Dominican nonsmoking mother-newborn pairs residing in low-income neighborhoods of New York City, and exposed to varying levels of airborne PAHs. Chromosome aberrations were measured in cord blood lymphocytes, both by whole chromosome probe (WCP) fluorescence in situ hybridization (FISH) and traditional Giemsa-staining. Prenatal exposures were assessed by personal air monitoring. Breaks in chromosomes 1-6, as detected by WCP FISH, were nonrandomly distributed, underscoring the importance of appropriate chromosome probe selection to capture cytogenetic damage in response to exposure. FISH for stable aberrations was found to be a more sensitive method for detecting aberration frequencies associated with environmental exposures, when compared with FISH for unstable aberrations or Giemsa-staining for aberrations. Together, these results suggest that PAHs may be targeting specific chromosomes and highlight the importance of using the more sensitive detection methods to assess risk in populations with low levels of exposure.

Bocskay KA, Tang DL, Orjuela MA, Liu XH, Warburton DP, Perera FP. 2005. Chromosomal aberrations in cord blood are associated with prenatal exposure to carcinogenic polycyclic aromatic hydrocarbons. Cancer Epidemiology Biomarkers & Prevention 14:506-511.
Abstract: Molecular and traditional epidemiology studies have indicated a possible relationship between in utero environmental exposures and increased risk for childhood cancers, especially acute leukemias. Chromosomal aberrations have been associated with environmental exposures and cancer risk in adults. In order to more clearly define the association between prenatal exposures to carcinogenic polycyclic aromatic hydrocarbons (PAH) and chromosomal aberrations, chromosomal aberration frequencies were measured in a subset of 60 newborns from the Columbia Center for Children's Environmental Health (CCCEH)

Prospective Cohort Study. The subset was composed of African American and Dominican, nonsmoking mother-newborn pairs residing in low-income neighborhoods of New York City, who were exposed to varying levels of airborne PAHs. Prenatal exposure was assessed by questionnaire, personal air monitoring during the third trimester, and PAH-DNA adducts in umbilical cord blood. Chromosomal aberrations were measured in cord blood lymphocytes by fluorescence in situ hybridization. PAH-DNA adducts were not associated with chromosomal aberrations. However, airborne PAHs were significantly associated with stable aberration frequencies in cord blood ($P < 0.01$). Moreover, stable aberration frequencies were significantly higher among African American newborns compared with Dominican, despite no significant differences in PAH exposure. These results show for the first time an association between prenatal exposure to airborne carcinogenic PAHs and chromosomal aberrations in cord blood, suggesting that such prenatal exposures have the potential to cause cytogenetic damage that has been related to increased cancer risk in other populations. If confirmed, this finding may open new avenues for prevention.

Boffetta P, Tredaniel J, Greco A. 2000. Risk of childhood cancer and adult lung cancer after childhood exposure to passive smoke: A meta-analysis. Environ Health Perspect 108:73-82.
Abstract: We identified more than 30 studies on the association between exposure to maternal tobacco smoke during pregnancy and cancer in childhood. We combined their results in meta-analyses based on a random effects model. The results of the meta-analyses suggest a small increase in risk of all neoplasms [relative risk (RR) 1.10; 95% confidence interval (CI), 1.03-1.19; based on 12 studies], but not of specific neoplasms such as leukemia (RR 1.05; CI, 0.82-1.34; 8 studies) and central nervous system tumors (RR 1.04; CI, 0.92-1. 18; 12 studies). Results for other specific neoplasms were sparse, but the available data did not suggest a strong association for any type of tumor. No clear evidence of dose response was present in the studies that addressed this issue. The results on exposure to maternal tobacco smoke before or after pregnancy are too sparse to allow a conclusion. The results on exposure to paternal tobacco smoke suggest an association with brain tumors (RR 1.22; CI, 1.05-1. 40; based on 10 studies) and lymphomas (RR 2.08; CI, 1.08-3.98; 4 studies). The data are too sparse for the other neoplasms, although the results of a few recent large studies are compatible with a weak carcinogenic effect of paternal smoke. For exposure from either maternal or paternal smoke, bias and confounding cannot yet be ruled out. Further studies are needed to confirm the hypothesis that parental tobacco smoke, from the father in particular, is a risk factor of childhood cancer. Results on the risk of lung cancer in adulthood and childhood passive smoking exposure are available from 11 studies: they do not provide evidence of an increased risk (summary RR 0.91; CI, 0.80-1.05).

Boice JD, Miller RW. 1999. Childhood and adult cancer after intrauterine exposure to ionizing radiation. Teratology 59:227-233.
Abstract: Since the reports in 1956 and 1958 that in utero radiation was associated with an increased risk of leukemia and solid cancers during childhood, this issue has been debated. Many epidemiological studies have been performed. Evidence for a causal association derives almost entirely from case-control studies, whereas practically all cohort studies find no association, most notably the series of atomic bomb survivors exposed in utero. Although it is likely that in utero radiation presents a leukemogenic risk to the fetus, the magnitude of the risk remains uncertain. The causal nature of the risk of cancers other than leukemia is less convincing, and the similar relative risks (RR = 1.5) for virtually all forms of childhood cancer suggests an underlying bias. Few studies have addressed the potential risk of adult cancer after intrauterine exposure. Radiotherapy given to newborns, however, has been linked to cancers of the thyroid and breast later in life. (C) 1999 Wiley-Liss, Inc.

Bolognesi C, Parrini M, Aiello C, Rossi L. 1991. DNA damage induced by 7,12-dimethylbenz[a]anthracene in the liver and the mammary-gland of rats exposed to polycyclic aromatic hydrocarbon enzyme inducers during perinatal life. Mutagenesis 6:113-116.
Abstract: The long-lasting modulating effect induced by the prenatal or neonatal exposure to phenobarbital (PB) and aroclor on the genotoxic activity of 7,12-dimethylbenz[a]anthracene (DMBA) in female Sprague-Dawley rats was studied. The effect was measured as DNA damage evaluated in the liver and in the mammary gland of 55-day-old animals, 4 and 24 h after an i.g. injection of 80 mg/kg of DMBA. PB was given per os, i.g. or in drinking water to pregnant females and by i.g. only to neonates or in adult progeny. Aroclor was injected i.g. in prenatal and in neonatal life, and a second dose was given in adult life. Under these experimental conditions it was shown that DNA damage kinetics caused by DMBA are modulated by

exposure to PB and, to a minor extent, by aroclor. The amount and persistence of DNA damage were highest when PB was administered to neonates. An average 2-fold increase in the elution constants (K) of DNA in the liver and the mammary gland was observed 4 h after DMBA treatment, as compared to uninduced animals. Repeated enzyme induction by PB seems to reduce DMBA genotoxicity, as shown by a decrease in DNA damage and persistence in the liver and mammary gland. The inducibility of the monooxygenase enzyme system in perinatal life favouring metabolic activation or inactivation of polycyclic aromatic hydrocarbons might be critical in determining individual susceptibility of adult progeny to chemical carcinogenesis by DMBA.

Bombail V, Moggs JG, Orphanides G. 2004. Perturbation of epigenetic status by toxicants. Toxicol Lett 149:51-58.
Abstract: It is becoming increasingly apparent that toxicant-induced changes in epigenetic status, particularly DNA methylation patterns, may play a role in some mechanisms of toxicity. Here, we discuss briefly the evidence that alterations in DNA methylation accompany, and may even promote, carcinogenesis induced by non-genotoxic chemicals. We also address recent findings indicating that the availability of dietary methyl donors can modulate DNA methylation levels and precipitate adverse effects. (C) 2004 Elsevier Ireland Ltd. All rights reserved.

Bonde JPE. 1993. The risk of male subfecundity attributable to welding of metals. Studies of semen quality, infertility, fertility, adverse pregnancy outcome and childhood malignancy. Int J Androl 16:1-29.
Abstract: These studies were initiated by the results of two Danish investigations of infertility clients, which indicated the reduced fecundity of male metal welders. The objective was to refute or corroborate the effects of welding on male reproductive capability and - if there was any effect - to identify the causal exposures. The initial hypothesis postulated reduced spermatogenesis, spontaneous abortion, congenital malformation and childhood malignancy following exposure to hexavalent chromium among stainless steel welders. Subsequently, a hypothesis concern with the significance of exposure to radiant heat on reduced semen quality was put forward. These studies comprised a case-referent study of infertility, cross-sectional and longitudinal studies of semen quality and historical cohort studies of fertility, pregnancy outcome and cancer in offspring. Exposure to welding was reported with a higher frequency during periods of infertility than prior to conception in the case-referent study (OR 2.0, 95% CI 1.0-4.0). This finding is consistent with the main cross-sectional study showing reduced semen quality in welders [average reduction ranging from 8% (sperm penetration rate in eggwhite) to 28% (total sperm count)] and with the cohort study revealing reduced fertility in relation to welding (OR 0.89, 95% CI 0.83-0.97). However, reduced semen quality and fertility were not attributable to the welding of stainless steel but to the welding of mild steel; and no relationship was found between biological measures of exposure to chromium and parameters of semen quality. If the unexpected association between mild steel welding and reduced fecundity is causal, the biological mechanisms involved are obscure. A separate longitudinal study leaves little doubt that moderate radiant heat exposure may cause reversible deterioration of semen quality, but it is not justified to generalize this observation to the entire population of welders. Male-mediated effects on occurrence of congenital malformation and cancer in offspring from stainless steel welding are not indicated by the studies. Weak indications of an increased risk of spontaneous abortion among partners to stainless steel welders (OR 1.9, 95% CI 1.1-3.2) need to be refuted or corroborated in future studies. Suggested effects of mild steel welding on male fecundity should be corroborated by longitudinal controlled studies of semen quality examined before and during exposure and by prospective studies of fecundability in couples trying to conceive a child. On account of the present knowledge it is not possible to recommend rational preventative measures with the exception of elimination of radiant heat exposure in cases of infertility. Temporary transfer to jobs not involving welding work should be considered when cases of unexplained infertility are encountered in clinical practice.

Bonde JPE, Olsen JH, Hansen KS. 1992. Adverse pregnancy outcome and childhood malignancy with reference to paternal welding exposure. Scandinavian Journal of Work, Environment & Health 18:169-177.
Abstract: Welding may deteriorate spermatogenesis and increase reproductive failures. This study examines reproductive end points in a Danish cohort of 10 059 metalworkers who fathered 3569 children in 1973 through 1986. Occupational histories were gathered by postal questionnaires. Information on pregnancy outcomes and offspring was obtained by record linkage to medical registers. The occurrence of reduced birthweight, preterm delivery, infant mortality, and congenital malformation was not increased among children at risk from paternal welding exposure in comparison with children not at risk. The overall

incidence of childhood malignancies among 23 264 children born in 1968 through 1986 with a total of 259 113 person-years of follow-up was equal to national rates (relative risk 0.97, 95% confidence interval 0.63-1.42). However, pregnancies preceding a birth at risk from paternal exposure to stainless steel welding were more often terminated by spontaneous abortion (odds ratio 1.9, 95% confidence interval 1.1-3.2). This finding needs cautious interpretation and should be further investigated in future studies.

Bosland MC. 1996. Hormonal factors in carcinogenesis of the prostate and testis in humans and in animal models. In: Huff J, Boyd J, Barrett JC, eds. Cellular and Molecular Mechanisms of Hormonal Carcinogenesis: Environmental InfluencesVolume 394. Wiley-Liss, Inc. p 309-352 (Ch. 16).
Abstract: The etiology of human testicular tumors is poorly defined. With the possible exception of prenatal estrogen exposure, no specific chemical exposures have been associated with testicular cancer risk in men. Prenatal as well as postnatal estrogen treatments induce testicular tumors in some mouse strains, but not in other mouse strains or in rats. Prenatal estrogen exposure also causes cryptorchid testes in mice and possibly rats. Cryptorchidism is a consistent risk factor for testicular cancer in men, and estrogen- or surgically-induced cryptorchidism is associated with Leydig cell tumorigenesis in mice. In rats, however, surgically induced cryptorchidism inhibits Leydig cell tumor formation. Overall, it appears that the mouse is the most appropriate species as animal model for testicular tumorigenesis in humans. Any of the following hormonal exposures can cause testicular tumor formation in rodents: 1) chronic exposure to estrogenic compounds of adult mice and hamsters; 2) prenatal exposure to estrogenic compounds of mice and possibly humans; and 3) any treatment or condition that induces cryptorchidism in mice and humans. The mechanisms whereby these treatments or conditions may cause testicular tumorigenesis are poorly understood. Undefined local testicular factors appear to be dominant in tumorigenesis in cryptorchid human and rodent testes. Pituitary factors, most likely LH and perhaps prolactin, play a critical but poorly defined role in estrogen-induced and spontaneous testicular tumorigenesis in rodents. In the mouse, estrogen receptor-mediated mechanisms seem to be involved in induction of testicular tumors by prenatal estrogen exposure, and a direct, perhaps estrogen receptor-mediated, inhibiting effect of estrogens on the action of mullerian inhibiting substance is probably central in the induction of cryptorchidism in this species.

Bove KE, Bhathena D, Wyatt RJ, Lucas BA, Holland NH. 1979 . Diffuse metanephric adenoma after in utero aspirin intoxication. A unique case of progressive renal failure. Archives of Pathology & Laboratory Medicine 103:187-190.
Abstract: Diffuse persistent glomerular immaturity and focal proximal tubular ectasia were seen in bilateral open renal biopsy specimens for an infant with fluid and salt depletion and slowly progressive renal failure. Subsequently, diffuse tubulopapillary renal adenoma subtotally replaced each kidney, thereby, necessitating renal transplantation. Origin of diffuse metanephric adenoma from persistent primitive epithelium of the proximal nephron is postulated and partly substantiated. We propose that this case of persistent proximal nephronic epithelial immaturity and diffuse metanephric adenoma is a variant of nephroblastomatosis and that in this case, a first trimester suicide attempt with aspirin may have initiated the maturation defect that preceded neoplastic transformation.

Boylan ES, Calhoon RE. 1979 . Mammary tumorigenesis in the rat following prenatal exposure to diethylstilbestrol and postnatal treatment with 7,12-dimethylbenz[a]anthracene. Journal of Toxicology & Environmental Health 5:1059-1071.
Abstract: Pregnant rats were injected with vehicle or 1,2 microgram diethylstilbestrol (DES) during wk 2 or 3 of gestation; their female offspring (approximately 50 d old) were fed 7,12-dimethylbenz[a]anthrocene (DMBA). The survivors (27 per group) were sacrificed 30 wk later. The three groups did not differ in the number of tumor-bearing animals; however, significantly more palpable mammary tumors arose in both DES-exposed groups than in controls. When DES was given during the second trimester, palpable tumors appeared earlier than in the other two groups. Thus, transplacental exposure to DES potentiated the action of a known carcinogen (DMBA) on rat mammary tissue. These results raise the possibility that, for young women, DES exposure in utero may have affected tissues other than the vagina. Further investigation is warranted, with special emphasis on the effects of DES on mammary and other estrogen-sensitive tissues.

Branstetter DG, Moseley PP. 1991. Effect of lung development on the histological pattern of lung tumors induced by ethylnitrosourea in the C3HeB/FeJ mouse. Exp Lung Res 17:169-179.
Abstract: The number, size, and histological pattern of lung tumors collected 6 months after being induced

in C3HeB/FeJ mice by ethylnitrosourea (ENU) treatment on one of days 13-19 of gestation, or days 5, 15, or 35 after birth, or as 9-month-old adults was investigated. The number of lung tumors induced increased when treatment occurred between days 13-16 and then decreased when treatment occurred on days 17-19 of gestation. There was a marked increase in lung tumor numbers induced on day 5 after birth, which decreased to much lower levels on days 15 and 35 after birth and in the treated adult mice. The size of lung tumors was greater in males than females in all groups and decreased as the age at the time of ENU treatment increased. A greater proportion (60-65%) of papillary tumors were induced following treatment on days 13-16 whereas, with one exception, alveolar lining tumors were the predominant histological type when treatment occurred after day 16. When treatment occurred on day 5 after birth, papillary tumors were once again the predominant type (66%) induced. The changes in tumor numbers induced and in the histological type of tumor induced occur at periods when major shifts in the histological development of the lung occur. The results indicate that the histological type of tumor induced by ENU treatment is developmentally regulated and suggests that alveolar lining and papillary tumors behave as two separate populations of tumors.

Branstetter DG, Stoner GD, Budd C, Conran PB, Goldblatt PJ. 1988 . Effect of gestational development of lung tumor size and morphology in the mouse. Cancer Res 48:379-386.
Abstract: Pregnant C3HeB/FeJ mice were treated with ethylnitrosourea (ENU) on one of gestation Days 10, 13, or 15 to determine if ENU treatment at different stages of gestation would result in qualitative or quantitative differences in lung tumors induced in the offspring. Lung tumors were counted and measured 6 mo after treatment with ENU. Offspring of mice treated with ENU on Day 10 of gestation had a small increase in lung tumors while those treated on gestation Day 13 or 15 had significantly more tumors than controls and 6- to 8-fold more tumors than the treated mothers. An inverse relationship between age at the time of treatment and lung tumor size was found. The mean lung tumor volume of mice exposed on Day 10 of gestation was 167-fold larger than that of mice exposed to ENU as adults. The difference between mean lung tumor volume in mice which had been exposed to ENU on Day 10, 13, or 15 of gestation appeared to be associated with the exponential growth of the fetus during this period of gestation. Lung tumors induced on Days 10 and 13 of gestation were irregular in contour and were multinodular. Sixty-five to 85% of the lung tumors in offspring treated during gestation versus 20% in mice treated as adults had a papillary morphology. These differences in tumor size and morphology indicate that cells transformed during early development may pose a greater biological hazard than cells transformed in older animals.

Branstetter DG, Stoner GD, Budd C, Conran PB, Goldblatt PJ. 1989 . Relationship between in utero development of the mouse liver and tumor development following transplacental exposure to ethylnitrosourea. Cancer Res 49:3620-3626 .
Abstract: Pregnant C3HeB/FeJ mice were treated with ethylnitrosourea (ENU) on one of gestation Days 10, 13, or 15 to determine if ENU treatment at different stages of gestation would result in morphological or quantitative differences in liver tumors induced in the offspring. Liver tumors were counted and measured 6 mo after treatment with ENU. Foci of cellular alteration were identified histologically and counted. Liver tumor number and foci of cellular alteration increased as a function of increasing dose and age at the time of ENU treatment. An inverse relationship between age at the time of treatment and the size of liver tumors was found. The mean tumor volume of male mice exposed on Day 10 of gestation was 123-fold larger than for spontaneous tumors observed in controls. The differences between mean liver tumor volume in mice which had been exposed to ENU on Days 10, 13, or 15 of gestation appeared to be associated with the exponential growth of the fetus during this period of gestation. Unique, large, multinodular foci of cellular alteration were found in mice treated on Day 10 of gestation. The relationship between the stage of gestation and the size of chemically induced liver tumors in these mice is similar to previous observations with transplacentally induced lung tumors in C3HeB/FeJ mice. This indicates that developmentally regulated cell proliferation occurring at the time of carcinogen exposure may affect the subsequent extent of tumor development in both the liver and lung. Therefore, cells transformed during early development may result in tumors that pose a greater biological hazard than those transformed in later development.

Braun MM, Ahlbom A, Floderus B, Brinton LA, Hoover RN. 1995. Effect of twinship on incidence of cancer of the testis, breast, and other sites (Sweden). Cancer Causes & Controls 6:519-524.
Abstract: It has been suggested that cancers of the testis and breast are associated with exposure to estrogens and other hormones in utero. Twin pregnancies have higher levels of pregnancy-associated

hormones than singleton pregnancies, and these levels may be higher in dizygotic than in monozygotic twin pregnancies. Through a large population-based study of twins, we assessed the hypothesis that levels of pregnancy-associated hormones have etiologic importance for cancers of the testis, breast, and other sites. The incidence of all cancers among 46,767 members of the Swedish Twin Registry was compared with the incidence among the Swedish general population. We found testicular cancer excess among dizygotic twins (observed/expected[O/E ratio = 2.3, CI = 1.1-4.2) compared with older men (O/E ratio = 1.2, CI = 0.5-2.4). In addition, a substantially elevated incidence of breast cancer was observed in dizygotic twin women aged 20 to 29 years (O/E = 6.7, CI = 2.9-13.1). None of the other age or zygosity groups showed notable elevations in incidence of testicular, breast, or other cancers. We conclude that dizygotic twinship may be associated with cancer of the breast and testis among young adults. These findings support the concept that pregnancy hormones are associated with risk of testicular and breast cancer, although non-hormonal aspects of twin pregnancy that vary with respect to zygosity cannot be excluded as explanatory factors.

Briegel KJ. 2006. Embryonic transcription factors in human breast cancer. Iubmb Life 58:123-132.
Abstract: Growing evidence suggests that breast cancer cells often reactivate latent developmental programs in order to efficiently execute the multi-step process of tumorigenesis. This review focuses on key transcriptional regulators of embryonic development that are deregulated in breast cancer and discusses the molecular mechanisms by which these proteins control carcinogenesis. Reminiscent of their function during development, embryonic transcription factors regulate changes in gene expression that promote tumor cell growth, cell survival and motility, as well as a morphogenetic process called epithelial-mesenchymal transition (EMT), which is implicated in both breast metastasis and tumor recurrence. Because of their pivotal roles in breast tumor progression, these factors represent valuable new biomarkers for breast cancer detection as well as promising new targets for anti-invasive drugs.

Brinkworth MH. 2000. Paternal transmission of genetic damage: findings in animals and humans. Int J Androl 23:123-135.
Abstract: The concept that mutations can be induced in the male germ-line and result in adverse effects in the offspring has achieved only limited acceptance despite considerable theoretical appeal. This is partly because fetal malformations are generally perceived to be induced solely as a result of maternally mediated events during gestation and partly because the low incidence of the end-points concerned make experimental approaches costly and time-consuming. Nonetheless, a substantial body of work relating to the hypothesis has accumulated in the last 20 years, which has never been reviewed in its entirety. A consideration of the available evidence indicates that preconceptional paternal exposure to mutagens (particularly radiation, cyclophosphamide and ethylnitrosourea) can indeed, under certain conditions, have adverse effects on offspring. The results suggest two principal mechanisms by which such effects may be induced: the induction of germ-line genomic instability or the suppression of germ cell apoptosis.

Brogly S, Williams P, Seage GR, Van Dyke R. 2006. In Utero Nucleoside Reverse Transcriptase Inhibitor Exposure and Cancer in Hiv-Uninfected Children: an Update From the Pediatric Aids Clinical Trials Group 219 and 219c Cohorts. Jaids-Journal of Acquired Immune Deficiency Syndromes 41:535-536.

Brondum J, Shu XO, Steinbuch M, Severson RK, Potter JD, Robison LL. 1999. Parental cigarette smoking and the risk of acute leukemia in children. Cancer 85:1380-1388.
Abstract: BACKGROUND. Studies of the relation between parental smoking and childhood leukemia have produced inconsistent results. In the largest case-control studies of childhood acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) conducted to date, the authors evaluated leukemia risk relative to parental self-report of cigarette smoking. METHODS. In telephone interviews in which a structured questionnaire was used, parents of 1842 ALL patients, 517 AML patients, and their matched controls were asked about their cigarette smoking habits before, during, and after the pregnancy with the index child. Risk of leukemia was examined by histologic type, age of the child at diagnosis, immunophenotype (for ALL), and French-American-British morphology group (for AML). RESULTS. The risk of ALL was not associated with the father's ever having smoked (odds ratio [OR] = 1.04, 95% confidence interval [CI] 0.90-1.20) or the mother's ever having smoked (OR = 1.04, 95% CI 0.91-1.19). Similarly no significant risk of AML was observed for paternal (OR = 0.88, 95% CI 0.67-1.16) or maternal smoking (OR = 0.95, 95% CI 0.74-1.22). The relative risk of leukemia was not significantly different from the null for parental smoking in any time period during or around the index pregnancy, nor was it related to the number of

cigarettes, the number of years of smoking, or the number of pack-years. A small number of sporadic, statistically significant associations were found, but overall there appeared to be no association between parental cigarette smoking and ALL or AML, or any subgroup of leukemia. CONCLUSIONS. Parenteral smoking while pregnant or exposure to cigarette smoke shortly after birth is unlikely to contribute substantially to the risk of childhood leukemia in North America. Cancer 1999;85:1380-8. (C) 1999 American Cancer Society.

Brooks DR, Mucci LA, Hatch EE, Cnattingius S. 2004. Maternal smoking during pregnancy and risk of brain tumors in the offspring. A prospective study of 1.4 million Swedish births. Cancer Causes & Control 15:997-1005.
Abstract: Objective: Studies of the effect of maternal smoking during pregnancy on development of brain tumors in the offspring generally have found no increase in risk but most have mainly relied on retrospective exposure assessment. We conducted a prospective study on a large birth cohort in Sweden. Methods: Women giving birth during 1983-1997 were classified as smokers or non-smokers based on information ascertained at the first prenatal visit and recorded in the Swedish Birth Register. Follow-up of brain tumor incidence among offspring through 1997 was achieved by linkage with the Swedish Cancer Register. Hazard ratios were estimated using Cox proportional hazard regression, adjusting for demographic characteristics available in the Birth Register. Results: Brain tumors (n = 480) occurred at a rate of 4.5 cases per 100,000 person-years. Children of women who smoked during pregnancy had an increased incidence of brain tumors (hazard ratio = 1.24; 95% confidence interval: 1.01-1.51). The increase in risk was similar for benign and malignant tumors, and was most apparent for astrocytoma. The effect of smoking on the occurrence of brain tumors was seen most strongly among 2-4 year-old children. Conclusions: These results support a role for maternal smoking during pregnancy in the etiology of childhood brain tumors. Our findings should be confirmed in other prospective studies.

Brown NM, Manzolillo PA, Zhang JX, Wang J, Lamartiniere CA. 1998. Prenatal TCDD and predisposition to mammary cancer in the rat. Carcinogenesis 19:1623-1629.
Abstract: Prenatal exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) was investigated for its potential to predispose to breast cancer. Analysis of mammary gland differentiation and cell proliferation were used as biomarkers. Timed pregnant Sprague-Dawley CD rats were gavaged with 1 microg TCDD/kg on day 15 post-conception. Control animals were treated with the same volume of vehicle (sesame oil) on the same schedule. Mammary gland differentiation studies revealed that prenatal TCDD treatment, as compared with sesame oil treatment, resulted in significantly more terminal end buds and fewer lobules II in 50-day-old offspring, but no significant alterations to mammary gland differentiation in 21-day-old offspring. Terminal end buds are the most susceptible terminal ductal structures and lobules the least susceptible to carcinogenesis. Prenatal TCDD treatment did not alter labeling index in the mammary terminal ductal structures of 21- and 50- day-old rats, but the total proliferative compartment in terminal end buds of 50-day-old rats was larger. Prenatal TCDD treatment resulted in an increased number of chemically induced mammary adenocarcinomas in rats. TCDD delayed time of vaginal opening and caused disruption to the estrous cycle. Alteration to mammary gland differentiation (increased number of terminal end buds) is correlated with increased susceptibility to mammary cancer from prenatal exposure to TCDD.

Buckler AJ, Pelletier J, Haber DA, Glaser T, Housman DE. 1991 . Isolation, characterization, and expression of the murine Wilms' tumor gene (WT1) during kidney development. Molecular & Cellular Biology 11:1707-1712.
Abstract: The human Wilms' tumor predisposition gene, WT1, is a Cys-His zinc finger polypeptide which appears to be a transcription factor controlling gene expression during embryonic kidney development. In order to analyze the role of the WT1 gene in nephroblast differentiation, we have isolated the murine homolog of human WT1. An extremely high level of amino acid sequence conservation (greater than 95%) extends throughout all regions of the predicted mouse and human WT1 polypeptides. Two alternative splices within the WT1 transcript have been conserved between mice and humans, suggesting that these have functional significance. Expression of the mouse WT1 mRNA in fetal kidney increases during late gestation, peaks just prior to or shortly after birth, and declines dramatically by 15 days postpartum. Developmental regulation of WT1 expression appears to be selective for the kidney. The restriction of WT1 expression to a limited number of tissues is in contrast to previously described tumor suppressor genes. In addition, the narrow window of time during which WT1 is expressed at high levels in the kidney

is consistent with the origin of Wilms' tumor from primitive nephroblasts and the postulated role of this gene as a negative regulator of growth.

Buckley JD, Meadows AT, Kadin ME, Le Beau MM, Siegel S, Robison LL. 2000. Pesticide exposures in children with non-Hodgkin lymphoma. Cancer 89:2315-2321.
Abstract: BACKGROUND. The association between pesticide exposure and non-Hodgkin lymphoma (NHL) in adults has been the subject of numerous case-control and cohort studies. However, to the authors' knowledge, data regarding pesticide exposures in children diagnosed with NHL have been lacking. METHODS. The Children's Cancer Group conducted a study comparing 268 children who developed NHL or leukemia with bulk disease with a group of matched, randomly selected regional population controls. The telephone interviews of both the case and control mothers included selected questions regarding occupational and home exposures to pesticides around the time of the index pregnancy and exposure of the child. RESULTS. A significant association was Pound between risk of NHL and increased frequency of reported pesticide use in the home (odds ratio [OR] = 7.3 for use most days; trend P = 0.05), professional exterminations within theome (OR = 3.0; P = 0.002), and postnatal exposure (OR = 2.4; P = 0.001). Elevated risks were found for T-cell and B-cell lymphomas; for lymphoblastic, large cell, and Burkitt morphologies: and in both young (age < 6 years) and older children. There was an increased risk of NHL with occupational exposure to pesticides (OR = 1.7) that was not significant overall, but that was significant for Burkitt lymphoma (OR = 9.6; P < 0.05). CONCLUSIONS. The results of the current study provide further evidence linking pesticide exposure to the risk of NHL, but the authors were unable to implicate any specific agent. Cancer 2000;89:2315-21. (C) 2000 American Cancer Society.

Buckley JD, Robison LL, Swotinsky R, Garabrant DH, LeBeau M, Manchester P, Nesbit ME, Odom L, Peters JM, Woods WG, et al. 1989. Occupational exposures of parents of children with acute nonlymphocytic leukemia: A report from the Childrens Cancer Study Group. Cancer Res 49:4030-4037.
Abstract: The Childrens Cancer Study Group conducted a case-control study of occupational exposures of parents of 204 children (under 18 yr of age) with acute nonlymphoblastic leukemia. The most consistent finding was an association of acute nonlymphoblastic leukemia risk with pesticide exposure. Controls matched by date of birth and race were obtained through random digit dialing. Odds ratio (OR) for paternal pesticide exposure in jobs held for longer than 1000 days was 2.7 (95% confidence interval, 1.0 to 7.0; trend, P = 0.06), and seven case mothers and no control mothers had prolonged exposure (trend, P = 0.008). Risk estimates for parental pesticide exposure were substantially increased for children under age 6 at diagnosis (OR for prolonged exposure to either parent = 11.4; trend, P = 0.003) and for those with myelomonocytic and monocytic subtypes (OR, 13.6; trend, P = 0.007). Moreover, there were significantly elevated risks for direct exposure of the child to pesticides in the household (OR for exposure most days = 3.5; trend, P = 0.04) and for maternal exposure to household pesticides at the time of pregnancy (eight case mothers versus no controls for exposure most days; trend, P = 0.05). Paternal exposures to solvents (OR, 2.1; P = 0.003) and petroleum products (OR, 2.4; P = 0.002) were reported more commonly for cases than controls. Other occupational exposures reported significantly more often by case parents were paternal exposure to plastics or lead and maternal exposure to paints and pigments, metal dusts, and sawdust. These data provide further evidence for a role of occupational risk factors in the etiology of childhood cancer.

Bunin G. 2000 . What causes childhood brain tumors? Limited knowledge, many clues. Pediatr Neurosurg 32:321-326.
Abstract: Little is known about the causes of brain tumors in children. Children with one of several genetic disorders including tuberous sclerosis and Li-Fraumeni syndrome are at increased risk, as are children who have received therapeutic irradiation to their head. The multifactorial causation of brain tumors, the inaccuracies of recall of past exposures, and the study of all pediatric brain tumors as a single etiologic entity may be contributing to the difficulty in identifying additional risk factors. The evidence that frequent cured meat consumption by the mother during pregnancy increases the risk is suggestive but not conclusive. For other potential risk factors, the evidence is limited and/or conflicting. These exposures and characteristics include pesticides, carcinogen metabolizing genes, and polyomaviruses.

Bunin GR. 2004. Nongenetic causes of childhood cancers: evidence from international variation, time trends, and risk factor studies. Toxicology & Applied Pharmacology 199:91-103.
Abstract: Ionizing radiation and a variety of genetic conditions are thought to explain 5-10% of childhood

cancers. Infection with Epstein-Barr virus (EBV) in parts of Africa and human immunodeficiency virus (HIV) increase the risk of Burkitt's lymphoma and Kaposi's sarcoma, respectively. Other risk factors have not been conclusively identified. A review of the data on international variation in incidence, recent changes in incidence, and risk factors suggests that many childhood cancers are likely to have nongenetic causes. The pattern of international variation and associations with surrogates of infection suggest an infectious etiology for acute lymphoblastic leukemia, although no agent has been identified. The biologic plausibility is strong that maternal consumption of food containing DNA topoisomerase II inhibitors may increase the risk of acute myeloid leukemia, although the data are limited now. For brain tumors, cured meats, polyomaviruses, and farm exposures may have etiologic roles. Changes in the incidence and characteristics of children with hepatoblastoma as well as risk factor studies suggest a role for an exposure of very low birth weight babies. High birth weight, tea or coffee consumption, and certain paternal occupations have shown some consistency in their association with Wilms' tumor. For most of the other cancers, very few epidemiologic studies have been conducted, so it is not surprising that nongenetic risk factors have not been detected. The most important difference between the cancers for which there are good etiologic clues and those for which there are not may be the number of relevant studies.

Bunin GR, Buckley JD, Boesel CP, Rorke LB, Meadows AT. 1994. Risk factors for astrocytic glioma and primitive neuroectodermal tumor of the brain in young children: A report from the Children's Cancer Group. Cancer Epidemiol Biomarkers Prev 3:197-204.

Abstract: We conducted a matched case-control study to investigate risk factors for the two most common types of brain tumors in children, astrocytic glioma and primitive neuroectodermal tumor (PNET). Since the study focused on gestational exposures, we restricted it to young children because these exposures would be expected to act early in life. Parents of 155 astrocytic glioma cases, 166 PNET cases, and controls identified by random digit dialing completed telephone interviews. Few associations occurred with the hypothesized risk factors, which were gestational exposure to alcohol, hair coloring products, farms, and substances containing N-nitroso compounds (passive smoking, makeup, incense, new cars, pacifiers, baby bottles, beer). Of the products studied that contain N-nitroso compounds, only beer was associated with a significantly increased risk of either tumor type [odds ratio (OR) for PNET = 4.0; 95% confidence interval (CI), 1.1-22.1; P = 0.04]. Elevated ORs for PNET were observed for farm residence of the mother during the pregnancy (OR = 3.7; 95% CI, 0.8-23.9; P = 0.06) and of the child for at least a year (OR = 5.0; 95% CI, 1.1-46.8; P = 0.04). Significant associations with astrocytoma were observed for mother's use of kerosene (OR = 8.9; 95% CI, 1.1-71.1; P = 0.04) and birth by Caesarean section (OR = 1.8; 95% CI, 1.1-3.2; P = 0.03). History of miscarriage was associated with a lower risk of PNET (OR = 0.5; 95% CI, 0.3-0.9; P = 0.02).(ABSTRACT TRUNCATED AT 250 WORDS)

Bunin GR, Kuijten RR, Boesel CP, Buckley JD, Meadows AT. 1994 . Maternal diet and risk of astrocytic glioma in children: A report from the Childrens Cancer Group (United States and Canada). Cancer Causes & Control 5:177-187.

Abstract: N-nitroso compounds and their precursors, nitrites and nitrates, have been hypothesized as risk factors, and vitamins C and E, which inhibit N-nitroso formation, as protective factors for brain tumors. A case-control study of maternal diet during pregnancy and risk of astrocytoma, the most common childhood brain tumor, was conducted by the Childrens Cancer Group. The study included 155 cases under age six at diagnosis and the same number of matched controls selected by random-digit dialing. A trend was observed for consumption of cured meats, which contain preformed nitrosamines (a class of N-nitroso compounds) and their precursors (adjusted odds ratio [OR] for highest quartile of intake relative to lowest = 1.7, P trend = 0.10). However, no strong trends were observed for nitrosamine (OR = 0.8, P = 0.60); nitrite (OR = 1.3, P = 0.54); nitrate (OR = 0.7, P = 0.43); vitamin C (OR = 0.7, P = 0.37); or vitamin E (OR = 0.7, P = 0.48). Iron supplements were associated with a significant decrease in risk (OR = 0.5, 95 percent confidence interval = 0.3-0.8). The effect of several dietary factors differed by income level, making interpretation of the results difficult. Future research should investigate the effect of dietary components not assessed in this study, as these may explain the disparate effects by income level. The results of this study provide limited support for the nitrosamine hypothesis.

Bunin GR, Kuijten RR, Buckley JD, Rorke LB, Meadows AT. 1993. Relation between maternal diet and subsequent primitive neuroectodermal brain tumors in young children. N Engl J Med 329:536-541.

Abstract: BACKGROUND. It has been hypothesized that a high dietary intake of nitrosamines and their

precursors, nitrites and nitrates, is a risk factor for brain tumors. Vitamins C and E inhibit the formation of nitrosamines and thus may be protective. METHODS. We conducted a case-control study of maternal diet and the risk of primitive neuroectodermal tumors of the brain in children. The case patients were under the age of six years at diagnosis in 1986 to 1989. The controls were selected by random-digit telephone dialing and were matched for age and race to 166 case patients. Telephone interviews with the mothers included questions on the frequency of consumption of alcohol, vitamin and mineral supplements, and 53 foods during pregnancy. RESULTS: Significant protective trends were observed for vegetables (odds ratio for the highest quartile group for intake relative to the lowest, 0.37; P for trend = 0.005), fruits and fruit juices (odds ratio, 0.28; P = 0.003), vitamin A (odds ratio, 0.59; P = 0.03), vitamin C (odds ratio, 0.42; P = 0.009), nitrate (odds ratio, 0.44; P = 0.002), and folate (odds ratio, 0.38; P = 0.005). A nonsignificant trend of increasing risk was observed for nitrosamine (odds ratio, 1.65; P = 0.15). The use of iron (odds ratio, 0.43; P = 0.004), calcium (odds ratio, 0.42; P = 0.05), and vitamin C (odds ratio, 0.35; P = 0.04) supplements at any time during the pregnancy and the use of multivitamins during the first six weeks (odds ratio, 0.56; P = 0.02) were associated with decreased risk. In multivariate analyses, folate, early multivitamin use, and iron supplements generally remained protective. CONCLUSIONS. These results do not support the hypothesis that nitrosamines have a role in the development of primitive neuroectodermal tumors in young children, but they do suggest that certain other aspects of maternal diet can influence the risk.

Burjanivova T, Madzo J, Muzikova K, Meyer C, Schneider B, Votava F, Marschalek R, Stary J, Trka J, Zuna J. 2006. Prenatal origin of childhood AML occurs less frequently than in childhood ALL. BMC Cancer 6:100.

Abstract: BACKGROUND: While there is enough convincing evidence in childhood acute lymphoblastic leukemia (ALL), the data on the pre-natal origin in childhood acute myeloid leukemia (AML) are less comprehensive. Our study aimed to screen Guthrie cards (neonatal blood spots) of non-infant childhood AML and ALL patients for the presence of their respective leukemic markers. METHODS: We analysed Guthrie cards of 12 ALL patients aged 2-6 years using immunoglobulin (Ig) and T-cell receptor (TCR) gene rearrangements (n = 15) and/or intronic breakpoints of TEL/AML1 fusion gene (n = 3). In AML patients (n = 13, age 1-14 years) PML/RARalpha (n = 4), CBFbeta/MYH11 (n = 3), AML1/ETO (n = 2), MLL/AF6 (n = 1), MLL/AF9 (n = 1) and MLL/AF10 (n = 1) fusion genes and/or internal tandem duplication of FLT3 gene (FLT3/ITD) (n = 2) were used as clonotypic markers. Assay sensitivity determined using serial dilutions of patient DNA into the DNA of a healthy donor allowed us to detect the pre-leukemic clone in Guthrie card providing 1-3 positive cells were present in the neonatal blood spot. RESULTS: In 3 patients with ALL (25%) we reproducibly detected their leukemic markers (Ig/TCR n = 2; TEL/AML1 n = 1) in the Guthrie card. We did not find patient-specific molecular markers in any patient with AML. CONCLUSION: In the largest cohort examined so far we used identical approach for the backtracking of non-infant childhood ALL and AML. Our data suggest that either the prenatal origin of AML is less frequent or the load of pre-leukemic cells is significantly lower at birth in AML compared to ALL cases.

Buzard GS, Enomoto T, Anderson LM, Perantoni AO, Devor DE, Rice JM. 1999. Activation of neu by missense point mutation in the transmembrane domain in schwannomas induced in C3H/HeNCr mice by transplacental exposure to N-nitrosoethylurea. Journal of Cancer Research & Clinical Oncology 125:653-659.

Abstract: Transplacentally initiated schwannomas in mice and rats arise preferentially in the Gasserian ganglion of the trigeminal nerve and spinal root ganglia, while those of the Syrian golden hamster most commonly occur subcutaneously. Rat and hamster schwannomas almost invariably contain a mutationally activated neu oncogene. In rat schwannomas, the mutant allele predominates, while the relative abundance of mutant alleles is very low in hamster nerve tumors. We investigated whether neu is mutated in mouse schwannomas and whether the pattern and allelic ratio of the mutation resemble those for the hamster or the rat, Pregnant C3H/HeNCr mice received 0.4 mu mol N-nitrosoethylurea/g body weight on day 19 of gestation. Ten trigeminal and one peripheral nerve schwannomas developed in II of the 201 offspring. Missense T --> A transversion mutations were detected in the neu transmembrane domain in eight of ten schwannomas analyzed, as determined by MnlI digestion of polymerase chain reaction products. The mutant allele was pre dominantly detected in two tumors and was abundant in six others. Transfection of eight out of ten mouse tumor DNAs into hamster cells yielded transformed foci; seven out of eight contained mutant mouse neu. Mouse schwannomas closely resembled those of rats both in the preferred

anatomical site and in the mutant/wild-type neu allele ratios.

Buzard GS, Enomoto T, Hongyo T, Perantoni AO, Diwan BA, Devor DE, Reed CD, Dove LF, Rice JM. 1999. neu mutation in schwannomas induced transplacentally in Syrian golden hamsters by N-nitrosoethylurea: High incidence but low allelic representation. Journal of Cancer Research & Clinical Oncology 125:529-540.
Abstract: Peripheral nerve tumors (PNT) and melanomas induced transplacentally on day 14 of gestation in Syrian golden hamsters by N-nitrosoethylurea were analyzed for activated oncogenes by the NIH 3T3 transfection assay, and for mutations in the neu oncogene by direct sequencing, allele-specific oligonucleotide hybridization, MnlI restriction-fragment-length polymorphism, single-strand conformation polymorphism, and mismatch amplification mutation assays. All (67/67) of the PNT, but none of the melanomas, contained a somatic missense T --> A transversion within the neu oncogene transmembrane domain at a site corresponding to that which also occurs in rat schwannomas transplacentally induced by N-nitrosoethylurea. In only 2 of the 67 individual hamster PNT did the majority of tumor cells appear to carry the mutant neu allele, in contrast to comparable rat schwannomas in which it overwhelmingly predominates. The low fraction of hamster tumor cells carrying the mutation was stable through multiple transplantation passages. In the hamster, as in the rat, specific point-mutational activation of the neu oncogene thus constitutes the major pathway for induction of PNT by transplacental exposure to am alkylating agent, but the low allelic representation of mutant neu in hamster PNT suggests a significant difference in mechanism by which the mutant oncogene acts in this species.

Cahill DF, Wright JF, Godbold JH, Ward JM, Laskey JW, Tompkins EA. 1975 . Neoplastic and life-span effects of chronic exposure to tritium. II. Rats exposed in utero. J Natl Cancer Inst 55:1165-1169.
Abstract: A study was conducted to determine the effects on neoplasia incidence and life-span of exposure in utero to a major environmental radionuclide. Sprague-Dawley rats were continuously exposed to tritiated water (HTO) from conception through birth in doses of 0, 1, 10, 50, and 100 muCi HTO/ml body water. HTO administration was terminated at birth. Calculated cumulative doses during gestation were approximately 0, 6.6, 66, 330, and 660 rads of total body irradiation. Under these exposure conditions, the two highest doses resulted in sterile offspring. Animals surviving through 30 days postnatally were defined as the study population and observed until their deaths. Intrauterine exposures to doses up to 66 rads had no significant effects on either sex with respect to life-span, overall neoplasia incidence, incidence rate, or onset of mammary fibroadenomas. Females exposed to 330 or 660 rads were sterile and had lower incidence rates of mammary fibroadenomass than did controls; at 660 rads females had a lower incidence of overall neoplasia and reduced mean life-spans. Sterile male offspring had reduced mean longevity after irradiation at 660 rads. Regardless of dose group, females had significantly higher incidences of neoplasia and longer life-spans than males.

Cahill DF, Wright JF, Godbold JH, Ward JM, Laskey JW, Tompkins EA. 1975. Neoplastic and life-span effects of chronic exposure to tritium. I. Effects on adult rats exposed during pregnancy. J Natl Cancer Inst 55:371-374.
Abstract: Female Sprague-Dawley rats were continuously exposed to equilibrium levels of tritiated water (HTO) during pregnancy. The tritium activities were 1, 10, 50, and 100 muCi HTO/ml body water which provided cumulative, whole-body radiation doses of approximately 6.6, 66, 330, and 660 rads. Administration of the radioisotope was terminated at parturition. Throughout their life-spans and at autopsy, the dams showed an increased incidence of mammary fibroadenomas at exposure to 330 and 660 rads. Although the data for the incidence of malignant mammary neoplasms were consistent with a linear dose response, the small numbers of tumors preclude specific definition of the dose-response curve. Postexposure life-spans for dams chronically exposed to 66, 330, and 660 rads during pregnancy were reduced by 14, 24, and 22%, respectively. Accelerated aging was also demonstrated in these rats: The mean age for mammary fibroadenoma onset decreased with an increasing dose of radiation.

Canfield KN, Spector LG, Robison LL, Lazovich D, Roesler M, Olshan AF, Smith FO, Heerema NA, Barnard DR, Blair CK, Ross JA. 2004. Childhood and maternal infections and risk of acute leukaemia in children with Down syndrome: a report from the Children's Oncology Group. Br J Cancer 91:1866-1872.
Abstract: Children with Down syndrome (DS) are highly susceptible to acute leukaemia. Given the potential role of infections in the aetiology of leukaemia in children without DS, we investigated whether there was an association between early-life infections and acute leukaemia in children with DS. Maternal

infections during pregnancy were also examined. We enrolled 158 incident cases of acute leukaemia in children with DS (97 acute lymphoblastic leukaemia (ALL) and 61 acute myeloid leukaemia (AML)) diagnosed at Children's Oncology Group institutions between 1997 and 2002. DS controls (N = 173) were selected from the cases' primary care clinics and frequency matched on age at leukaemia diagnosis. Data were collected on demographics, child's medical history, mother's medical history, and other factors by maternal interview. Analyses were conducted using unconditional logistic regression adjusted for potential confounders. A significant negative association was observed between acute leukaemia and any infection in the first 2 years of life (adjusted odds ratio (OR) = 0.55, 95% confidence interval (CI) (0.33 - 0.92); OR = 0.53, 95% CI (0.29 - 0.97); and OR = 0.59, 95% CI (0.28 - 1.25) for acute leukaemia combined, ALL, and AML respectively). The association between acute leukaemia and maternal infections during pregnancy was in the same direction but not significant. This study offers support for the hypothesis that early-life infections may play a protective role in the aetiology of acute leukaemia in children with DS.

Cardy AH, Little J, Mckean-Cowdin R, Lijinsky W, Choi NW, Cordier S, Filippini G, Holly EA, Lubin F, Mccredie M, Mueller BA, Peris-Bonet R, Arslan A, Preston-Martin S. 2006. Maternal medication use and the risk of brain tumors in the offspring: The SEARCH international case-control study. Int J Cancer 118:1302-1308.
Abstract: N-nitroso compounds (NOC) have been associated with carcinogenesis in a wide range of species, including humans. There is strong experimental data showing that nitrosamides ((R1NNOCOR2)-C-.), a type of NOC, are potent neuro-carcinogens when administered transplacentally. Some medications are a concentrated source of amides or amines, which in the presence of nitrites under normal acidic conditions of the stomach can form NOC. Therefore, these compounds, when ingested by women during pregnancy, may be important risk factors for tumors of the central nervous system in the offspring. The aim of the present study was to test the association between maternal use of medications that contain nitrosatable amines or amides and risk of primary childhood brain tumors (CBT). A case-control study was conducted, which included 1,218 cases and 2,223 population controls, recruited from 9 centers across North America, Europe and Australia. Analysis was conducted for all participants combined, by tumor type (astroglial, primitive neuroectodermal tumors and other glioma), and by age at diagnosis (< 5 years; > 5 years). There were no significant associations between maternal intake of medication containing nitrosatable amines or amides and CBT, for all participants combined and after stratification by age at diagnosis and histological subtype. This is the largest case-control study of CBT and maternal medications to date. Our data provide little support for an association between maternal use of medications that may form NOC and subsequent development of CBT in the offspring. (c) 2005 Wiley-Liss, Inc.

Carlsen NLT. 1996. Neuroblastomas presenting in the first year of life: Epidemiological differences from those presenting at older ages. Cancer Detection & Prevention 20:251-261.
Abstract: In a population-based study comparing neuroblastomas presenting in the first year of life with those presenting at older ages, the following aggregate associations were found: Presentation of the disease before 1 year of age was associated with (i) multiorigin of primary tumors, (ii) young parental age, (iii) lower socioeconomic circumstances, and (iv) complications during pregnancy. Presentation after the first year of life was associated with (i) unifocal disease, (ii) a higher frequency of hereditary diseases in the family, and (iii) parental age above 34 years. Maternal occupation in medical services appeared to be associated with multiorigin of tumors; otherwise, the occupations held by the parents at the time of the child's birth did not differ between the two groups of patients. We hypothesized that differences between the two groups of patients might point to (i) risk factors for germ line mutations and (ii) genomic imprinting. An alternative explanation of the differences could, however, be that neuroblastoma represents at least two distinct disease entities.

Carozza SE, Olshan AF, Faustman EM, Gula MJ, Kolonel LN, Austin DF, West ED, Weiss NS, Swanson GM, Lyon JL, Hedleywhyte T, Gilles FH, Aschenbrener C, Leviton A. 1995. Maternal exposure to N-nitrosatable drugs as a risk factor for childhood brain-tumors. Int J Epidemiol 24:308-312.
Abstract: Background. Animal models suggest that compounds containing a nitrosyl group (N-nitroso compounds (NNO)) can act as potent transplacental carcinogens. Many common drug formulations have the potential to undergo nitrosation in vivo. The association between maternal use of nitrosatable drugs during pregnancy and development of brain tumours in the offspring was examined in a SEER-based case-control study. Methods. Maternal exposure to nitrosatable drugs during pregnancy was compared among 361 childhood brain tumour cases and 1083 matched controls recruited through random-digit dialling.

Results. There was no increase in risk observed for childhood brain tumours overall (OR = 1.15; 95% CI : 0.69-1.94) or for astrocytomas individually (OR = 1.16; 95% CI : 0.50-2.69). A slight elevation in risk was noted for medulloblastomas (OR = 1.47; 95% CI : 0.28-7.62) and 'other' tumours (OR = 1.27; 95% CI : 0.56-2.86), however, both estimates were based on small numbers. Conclusions. Our findings suggest that no increased risk of childhood brain tumours was associated with maternal exposure to nitrosatable drugs. The study results should be Viewed with caution given the imprecision of the point estimates as well as the lack of data on specific timing and dosage of exposure and degree of nitrosatability of drugs taken.

Castro P, Eknaes M, Teixeira MR, Danielsen HE, Soares P, Lothe RA, Sobrinho-Simoes M. 2005. Adenomas and Follicular Carcinomas of the Thyroid Display Two Major Patterns of Chromosomal Changes. J Pathol 206:305-311.
Abstract: It was recently shown by flow and static cytometry that a large sub-group of follicular adenomas of the thyroid - fetal/embryonal adenomas - display an aneuploid phenotype. It was also shown that thyroid lesions with a DNA content within the triploid range were either fetal adenomas or follicular carcinomas with a fetal adenoma growth pattern. Follicular tumours with growth patterns other than the so-called fetal adenoma-like pattern were usually diploid or near-diploid. In an attempt to clarify the pattern of chromosomal imbalances in follicular tumours, comparative genomic hybridization (CGH) analysis was performed in a series of 18 follicular neoplasms (ten fetal/embryonal and four common follicular adenomas and four minimally invasive follicular carcinomas). For each tumour, the DNA content was determined by flow cytometry and, in some cases, also by static cytometry. Finally, the copy number of selected chromosomes was determined by interphase fluorescence in situ hybridization (FISH) using centromere probes. With the exception of the single diploid fetal adenoma, all fetal adenomas displayed several DNA copy number changes, with frequent gains of several chromosomes, which were found to be either tetrasomic or trisomic by FISH. This genetic pattern was also present in the single case of follicular carcinoma with aneuploidy and fetal adenoma-like growth pattern. Follicular adenomas other than fetal adenomas, and the remaining follicular carcinomas, showed more losses than gains of chromosomes. These results suggest that follicular tumourigenesis may follow at least two pathways: one characterized by prominent aneuploidy and numerous gains, in which the tumours display a fetal adenoma-like growth pattern; and another accompanied by less obvious aneuploidy or even quasi-diploidy and dominant chromosome losses, in which the tumours display a common follicular architecture. Copyright (c) 2005 Pathological Society of Great Britain and Ireland. Published by John Wiley & Sons, Ltd.

Castronovo FP. 1999. Teratogen update: Radiation and Chernobyl. Teratology 60:100-106.
Abstract: The 1986 nuclear reactor accident at Chernobyl caused nonuniform radiocontamination of air and land, primarily within regions of the former Soviet Union and Western Europe. Major exposure groups included the reactor workers, villagers evacuated from within 30 km of the accident, the "liquidators" who decontaminated the evacuation zone afterward, those in radiocontaminated villages not evacuated, and "others" not in the latter categories. The possibility of being exposed to radiation caused considerable anxiety, especially among pregnant women. Were teratogenic levels of radiation (greater than or equal to 0.1 Gy) exposure attained? To date there is no consistent proof that this level of radiation exposure was received. Nevertheless, thousands of induced abortions were performed. Radioiodine (I-131) caused thyroid cancer in young children in portions of Belarus, the Ukraine, and Russia. It is not known but very possible that I-131 fetal thyroid exposure contributed to this observation. The relationship between mental retardation and radiation exposure has not been confirmed. Leukemia and other cancers, while predicted for the liquidators (mainly males), has not been found in the other exposure groups at this time. Investigations of aborted fetuses and newborns in Belarus showed an increase in the frequency of both congenital and fetal abnormalities in high and low Cs-137 contaminated regions. This study is unreliable due to detection and selection biases. Accident and environmental factors unrelated to radiation doses may have contributed to these observations. Occasional positive teratogenic studies in less contaminated regions of Western Europe are suspect because of the low radiation doses received. There is no substantive proof regarding radiation-induced teratogenic effects from the Chernobyl accident. (C) 1999 Wiley-Liss, Inc.

Cerhan JR, Kushi LH, Olson JE, Rich SS, Zheng W, Folsom AR, Sellers TA. 2000. Twinship and risk of postmenopausal breast cancer. J Natl Cancer Inst 92:261-265.
Abstract: Background: Intrauterine exposure to high levels of endogenous estrogens has been hypothesized to:increase the risk of breast cancer. Because estrogens and other pregnancy hormones are substantially

elevated in twin pregnancies, and possibly more so in dizygotic twin pregnancies, we evaluated the association between aspects of twin membership (i.e., belonging to a twin pair) and the risk of breast cancer. Methods: In a cohort of 29 197 postmenopausal Iowa women with no prior diagnosis of cancer (except for nonmelanoma skin cancer), breast cancer risk factors were determined by use of a mailed questionnaire in 1986 (baseline); twin membership, sex of the twin, and zygosity were determined by use of a follow-up questionnaire in 1992, Results: Within the cohort, 1.8% (n = 538) of the women reported being a twin; of these, 24% (n = 130) were monozygotic twins, 63% (n = 337) were dizygotic twins, and 13% (n = 71) did not-know their zygosity, From 1986 through 1996, 1230 breast cancers in the cohort were ascertained by linkage to the Iowa Cancer Registry. Compared with singletons, women who belonged to a twin pair were at elevated risk of breast cancer (multivariate-adjusted risk ratio [RR] = 1.72; 95% confidence interval [CI] = 1.22-2.42), with adjustment for educational level, family history of breast cancer, height, body mass index, body fat distribution, age at menarche, age at first live birth, use of hormone replacement therapy, and alcohol use. Multivariate-adjusted risk was elevated (in comparison with singletons) if the sex of the other twin was female (RR = 1.82; 95% CI = 1.20-2.75); however, this risk was limited to female dizygotic twins (RR = 2.14; 95% CI = 1.21-3.79), since no excess risk was evident for monozygotic twins (RR = 1.04; 95% CI = 0.43-2.50), The risk to women with a male twin was also elevated (RR = 1.49; 95% CI = 0.80-2.78) in comparison with singletons, but this estimate was not statistically significant, Conclusions: This cohort study lends further support to the theory that there are important intrauterine influences on carcinogenesis of the breast.

Chadduck WM, Gollin SM, Gray BA, Norris JS, Araoz CA , Tryka AF. 1987 . Gliosarcoma with chromosome abnormalities in a neonate exposed to heptachlor. Neurosurgery 21:557-559.
Abstract: A neonate with a cerebral gliosarcoma was found to have chromosome abnormalities in tissue culture of the tumor, but normal karyotyping of peripheral blood. Similarities to and differences from chromosome abnormalities found in other human gliomas are noted. Unusual exposure of the child to heptachlor during prenatal development and the neonatal period suggests the need for further studies on the role of toxins in oncogenesis.

Chang JS, Selvin S, Metayer C, Crouse V, Golembesky A, Buffler PA. 2006. Parental smoking and the risk of childhood leukemia. Am J Epidemiol 163:1091-100.
Abstract: Cigarette smoke has been linked to adult myeloid leukemia; however, the association between parental smoking and childhood leukemia remains unclear. Parental smoking and the risk of childhood leukemia were examined in the Northern California Childhood Leukemia Study, a case-control study, between 1995 and 2002. The present analysis included 327 acute childhood leukemia cases (281 acute lymphoblastic leukemia (ALL) and 46 acute myeloid leukemia (AML)) and 416 controls matched on age, sex, maternal race, and Hispanic ethnicity. Maternal smoking was not associated with an increased risk of either ALL or AML. Paternal preconception smoking was significantly associated with an increased risk of AML (odds ratio = 3.84, 95% confidence interval: 1.04, 14.17); an increased risk for ALL was suggestive for paternal preconception smoking (odds ratio = 1.32, 95% confidence interval: 0.86, 2.04). Greater risks of ALL were observed compared with the risk associated with paternal preconception smoking alone, when paternal preconception smoking was combined with maternal postnatal smoking (p(interaction) = 0.004) or postnatal passive smoking exposure (p(interaction) = 0.004). These results strongly suggest that exposure to paternal preconception smoking alone or in combination with postnatal passive smoking may be important in the risk of childhood leukemia.

Chen CS, Wells PG. 2006. Enhanced tumorigenesis in p53 knockout mice exposed in utero to high-dose vitamin E. Carcinogenesis 27: 1358-68.
Abstract: The limited antioxidative capacity of the embryo and fetus may increase their risk for cancer initiation and/or promotion by reactive oxygen species (ROS)-mediated oxidative DNA damage and/or signaling. To determine if cancer can originate in utero, a high dietary dose of the antioxidant vitamin E (VE) (10% dl-alpha-tocopherol-acetate) was given to cancer-prone p53 knockout mice throughout pregnancy. Although reducing fetal death ($P < 0.05$), in utero exposure to VE enhanced postnatal tumorigenesis in both +/- ($P < 0.04$) and -/- ($P < 0.0008$) p53-deficient offspring. VE did not alter maternal weights, offspring p53 genotypic distribution or tumor spectrum. Constitutive embryonic DNA oxidation in untreated -/- p53 embryos [gestational day (GD) 13] was higher than in +/- and +/+ p53 littermates ($P < 0.05$). VE reduced DNA oxidation in -/- p53 embryos ($P < 0.05$) without affecting +/- and +/+ p53

littermates. VE had contrasting, tissue-dependent effects on fetal (GD 19) DNA oxidation, with reductions in -/- and +/- p53-deficient fetal brains ($P < 0.01$), increases in skin ($P < 0.05$) and no effect in liver and thymus. The 250-fold increase in dietary VE levels produced only 1.6-6.3-fold, tissue-dependent increases in tissue concentrations. The greatest increase, in fetal skin, correlated with increased DNA oxidation in that tissue in -/- and +/- p53-deficient fetuses and enhanced tumorigenesis in these genotypes. These results show that some cancers may originate in utero and the risk can be enhanced by embryonic and fetal exposure to high dietary levels of VE. The elevated DNA oxidation in some tissues of untreated -/- p53 offspring suggests that ROS may contribute to their higher baseline tumor incidence. The limited and tissue-dependent disposition of VE indicates substantial conceptal regulation. The similarly selective and contrasting effects of VE on DNA oxidation may contribute to its controversial protective efficacy and suggest that its effects on tumorigenesis are cell-specific, possibly in high doses involving a pro-oxidative mechanism.

Chen Z, Robison L, Giller R, Krailo M, Davis M, Davies S, Shu XO. 2006. Environmental exposure to residential pesticides, chemicals, dusts, fumes, and metals, and risk of childhood germ cell tumors. International Journal of Hygiene and Environmental Health 209:31-40.
Abstract: We examined relationships between exposure to residential pesticides, chemicals, dusts, fumes, and metals, and childhood germ cell tumors (GCTs) in the largest case-control study to date on the topic. We recruited 272 children under 15 years old who had GCT diagnosed between January 1, 1993 and December 31, 2001. Controls were selected by random-digit dialing and were frequency matched to cases by sex, age, and geographic area. Telephone interviews and self-administered questionnaires of parents were used to collect exposure information. We used unconditional logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI). Maternal and paternal exposure from 6 months before pregnancy to during breastfeeding and children's postnatal exposure to residential pesticides were generally unrelated to risk of childhood GCT. Elevated OR were, observed for mothers' exposure to hair dyes I month before pregnancy for boys (OR = 1.7, 95% CI = 1.0-2.8) and during breastfeeding for boys and girls combined, and for girls (OR = 1.5, 95% CI = 1.0-2.2 and OR = 1.7, 95% CI = 1.1-2.6, respectively). Among boys, OR for paternal exposure to insecticides more often than four times or exposure to indoor insecticides more often than three times were 0.5 (95% CI = 0.2-0.9, trend test p = 0.05) and 0.3 (95% CI = 0.2-0.8, trend test p, = 0.02) during the index pregnancy. Overall this study produced no strong evidence linking parental and child residential exposure to pesticides, certain chemicals, dusts, fumes, and metals to increased risk of childhood GCT. Statistically significant associations need to be confirmed in future studies. (c) 2005 Elsevier GmbH. All rights reserved.

Chen Z, Robison L, Giller R, Krailo M, Davis M, Gardner K, Davies S, Shu XO. 2005. Risk of childhood germ cell tumors in association with parental smoking and drinking. Cancer 103:1064-1071.
Abstract: BACKGROUND. The etiology of childhood germ cell tumors (GCT) is not well understood. The Children's Oncology Group conducted the largest case-control study of childhood GCT to investigate whether parental exposures to smoking and alcohol contributed to the disease. METHODS. Cases included 274 children with GCT diagnosed between January 1, 1993 and December 31, 2001 who were age < 15 years. Controls (n = 421) were selected by random digit dialing and were frequency matched based on gender, age (+/-1 year), and geographic area. Exposure information was collected from subjects' parents using independent telephone interviews and self-administrated questionnaires. RESULTS. No association was found between parental smoking or drinking alcohol and risk of childhood GCT (for smoking: odds ratio [OR] = 1.0, 95% confidence interval [95% CI], 0.8-1.3 and OR = 1.2, 95% CI, 0.9-1.5, for mothers and fathers, respectively; for drinking: OR = 0.9, 95% CI, 0.7-1.2 and OR = 1.0, 95% CI, 0.8-1.3, for mothers and fathers, respectively). No significant trend was observed for length of maternal exposure to passive smoking during the index pregnancy and GCT risk (for total subject: P = 0.77; boys: P = 0.52; girls: P = 0.93). CONCLUSIONS. The authors found no evidence that childhood GCT was related to prenatal exposure to parental cigarette smoking, alcohol drinking, and maternal passive smoking. (C) 2005 American Cancer Society.

Cheng RYS, Hockman T, Crawford E, Anderson LM, Shiao YH. 2004. Epigenetic and gene expression changes related to transgenerational carcinogenesis. Mol Carcinog 40:1-11.
Abstract: Transgenerational carcinogenesis refers to transmission of cancer risk to the untreated progeny of parents exposed to carcinogens before mating. Accumulated evidence suggests that the mechanism of this

process is epigenetic, and might involve hormonal and gene expression changes in offspring. To begin to test this hypothesis, we utilized a mouse model (NIH Swiss) in which exposure of fathers to Cr(III) chloride 2 wk before mating can alter incidence of neoplastic and nonneoplastic changes in offspring tissues. Utilizing a MS-RDA approach, we found that the sperm of these fathers had a significantly higher percentage of undermethylated copies of the 45S ribosomal RNA gene (rRNA); this finding was confirmed by bisulfite sequencing. Because gene methylation is a known mechanism of expression control in germ cells, and ribosomal RNA levels have been linked to cancer, these findings are consistent with the hypothesis. Secondly, we observed that offspring of Cr(III)-treated fathers were significantly heavier than controls, and had higher levels of serum T3. Possible effects of T3 levels on gene expression in the offspring were examined by microarray analysis of cDNAs from liver. A total of 58 genes, including 25 named genes, had expression ratios that correlated significantly with serum T3 ratios at P less than or equal to 0.001. Some of these genes have potential roles in growth and/or tumor suppression. These results also support the hypothesis of an epigenetic and/or gene expression-based mechanism for transgenerational carcinogenesis. Published 2004 Wiley-Liss, Inc.

Choi H, Shim Y, Kaye W, Ryan PB. 2003. Childhood brain cancer and potential residential exposure to toxic release inventory chemicals during pregnancy: A population-based case-control study. Am J Epidemiol 157:S23.

Choi HS, Shim YK, Kaye WE, Ryan PB. 2006 Jul. Potential residential exposure to toxics release inventory chemicals during pregnancy and childhood brain cancer. Environ Health Perspect 114:1113-8.
Abstract: BACKGROUND: Although the susceptibility of the developing fetus to various chemical exposures is well documented, the role of environmental chemicals in childhood brain cancer etiology is not well understood. OBJECTIVES: We aimed to evaluate whether mothers of childhood brain cancer cases had greater potential residential exposure to Toxics Release Inventory (TRI) chemicals than control mothers during pregnancy. METHODS: We included 382 brain cancer cases diagnosed at < 10 years of age from 1993 through 1997 who were identified from four statewide cancer registries. One-to-one matched controls were selected by random-digit dialing. Computer-assisted telephone interviews were conducted. Using residential history of mothers during pregnancy, we measured proximity to TRI facilities and exposure index, including mass and chemicals released. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) using conditional logistic regression to estimate brain cancer risk associated with TRI chemicals. RESULTS: Increased risk was observed for mothers living within 1 mi of a TRI facility (OR = 1.66 ; 95% CI, 1.11-2.48) and living within 1 mi of a facility releasing carcinogens (OR = 1.72 ; 95% CI, 1.05-2.82) for having children diagnosed with brain cancer before 5 years of age, compared to living > 1 mi from a facility. Taking into account the mass and toxicity of chemical releases, we found a nonsignificant increase in risk (OR = 1.25 ; 95% CI, 0.67-2.34) comparing those with the lowest versus highest exposure index. CONCLUSIONS: Risk of childhood brain cancers may be associated with living near a TRI facility ; however, this is an exploratory study and further studies are needed.

Chow EJ, Friedman DL, Mueller BA. 2007. Maternal and perinatal characteristics in relation to neuroblastoma. Cancer 109:983-92.
Abstract: BACKGROUND: Neuroblastoma is the most common malignancy among infants, but risk factors remain poorly understood. Because most patients present in the first few years of life, it has been hypothesized that prenatal and perinatal exposures may contribute to the pathogenesis of neuroblastoma. METHODS: A population-based case-control study was conducted by using linked birth and cancer registry records from 1980 to 2004 in Washington State. Maternal and infant characteristics from birth and hospital discharge records for 240 cases of neuroblastoma and 2400 controls were compared. RESULTS: Neuroblastoma was associated with the presence of major congenital abnormalities (odds ratio [OR], 6.86; [95% CI], 2.92-16.08), particularly with cardiac abnormalities (OR, 5.84; 95% CI, 1.93-17.66), even after excluding abnormalities near the primary tumor. A borderline association was observed with maternal gestational diabetes (OR, 1.84; 95% CI, 0.98-3.47). The magnitude of both associations was greater when the analysis was limited to children who were diagnosed at age <1 year. CONCLUSIONS: The findings from this population-based study supported prior case-control studies that identified an etiologic link between neuroblastoma and congenital abnormalities. However, to the authors' knowledge, the association between neuroblastoma and maternal diabetes has not been reported previously and requires further study.

Clemmesen J. 1997. Is pregnancy smoking causal to testis cancer in sons? A hypothesis. Acta Oncol 36:59-63.

Abstract: Inquiry studies into smoking during pregnancy as a possible cause of testis cancer in sons are found misinterpreted as purely negative. Danish quinquennial incidence rates for patients aged 25-39 years are compared with rates for tobacco-induced neoplasms among the corresponding maternal generation, primarily of bladder tumours including papillomas, and of lung-both for ages 50-64 years, allowing for period of latency. Corresponding to a delay of increase, earlier demonstrated for incidence rates of testis cancer among men born 1939-1945, delays of increase are found for female bladder and lung with allowance for lag-times of 30 and 20 years respectively. Comparison of data from Scandinavian nationwide cancer registries show a noteworthy parallelism of trends from first to last plotting of testis/female bladder ratios. The rise for lung is found steeper in consequence of age distribution.

Cnattingius S, Zack MM, Ekbom A, Gunnarskog J, Kreuger A, Linet M, Adami HO. 1995. Prenatal and neonatal risk factors for childhood lymphatic leukemia. J Natl Cancer Inst 87:908-914.
Abstract: BACKGROUND: Because the incidence of childhood acute lymphatic leukemia peaks between 2 and 4 years of age, the risk factors may exert their influence during the prenatal and/or the neonatal periods. Results of previous studies of perinatal risk factors have been contradictory, perhaps because most studies either have been hospital based or have been restricted to limited geographical areas. PURPOSE: A nationwide case-control study was carried out to identify maternal and perinatal risk factors for this disease. METHODS: The case-control study was nested in cohorts defined by all live births in Sweden recorded in the nationwide Medical Birth Register. Since 1973, this register has routinely collected information on all hospital births in regard to maternal demographic data, reproductive history, pregnancy, delivery, and the neonatal period. From the Swedish National Cancer Register, 613 case subjects were identified in successive birth cohorts from 1973 through 1989. Five control subjects per case subject were randomly selected from the pool of children matched by sex and month and year of birth. Conditional logistic regression was used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) for potential risk factors and to estimate their effects after adjustment for possible confounders. RESULTS: Risk of childhood lymphatic leukemia at all ages increased with Down's syndrome (OR = 20.0; 95% CI = 4.2-94.2), maternal renal disease (OR = 4.4; 95% CI = 1.6-12.1), use of supplementary oxygen (OR = 2.3; 95% CI = 1.5-3.6), postpartum asphyxia (OR = 1.8; 95% CI = 1.2-2.6), birth weight of more than 4500 g (OR = 1.7; 95% CI = 1.1-2.7), and hypertensive disease during pregnancy (OR = 1.4; 95% CI = 1.0-1.9). Down's syndrome affected risk mostly in children younger than 5 years, whereas other factors affected those children 5 years old or older. Being one of a multiple birth also increased risk among older children (OR = 2.5; 95% CI = 1.0-6.0). Use of supplementary oxygen may act as a causal intermediate (surrogate) for postpartum asphyxia and its causes, as would high birth weight for its causes. CONCLUSIONS: Several maternal and perinatal risk factors were found to be associated with childhood lymphatic leukemia, but they showed age-specific differences. Overall, only a few risk factors were identified, and these accounted for a small proportion of cases. We concluded that most risk factors for childhood lymphatic leukemia remain unidentified in very young children.

Cocco P, Rapallo M, Targhetta R, Biddau PF, Fadda D. 1996. Analysis of risk factors in a cluster of childhood acute lymphoblastic leukemia. Arch Environ Health 51:242-244.
Abstract: A case-control investigation of childhood acute lymphoblastic leukemia was conducted in the town of Carbonia (Sardinia, Italy). Parents of 9 eases diagnosed between 1980 and 1989 and 36 controls were interviewed at their respective residences. None of the risk factors analyzed was associated significantly with childhood acute lymphoblastic leukemia. The following were associated with an increased risk for childhood acute lymphoblastic leukemia: parents born outside of Carbonia, family history of cancer, alcohol consumption by fathers that exceeded 60 g/d, exposure of fathers to solvents at their workplaces, maternal smoking, use of antinausea meditations during pregnancy, and presence of a well in the backyard. Chance and recall bias likely played a role in generating positive associations. The increases in childhood leukemia risk associated with the presence of a well and with use of antinausea medications during pregnancy are consistent with previous reports and require further investigation.

Coghlin J, Gann PH, Hammond SK, Skipper PL, Taghizadeh K, Paul M, Tannenbaum SR. 1991. 4-Aminobiphenyl hemoglobin adducts in fetuses exposed to the tobacco-smoke carcinogen *in utero*. J Natl Cancer Inst 83:274-280.
Abstract: Maternal-fetal exchange of a potent tobacco-related human carcinogen, 4-aminobiphenyl, was studied in smoking (n = 14) and nonsmoking (n = 38) pregnant women. N-Hydroxy-4-aminobiphenyl, the

active metabolite of 4-aminobiphenyl, forms chemical addition products (adducts) with hemoglobin. Levels of 4-aminobiphenyl hemoglobin adducts were measured in maternal-fetal paired blood samples obtained from smoking and nonsmoking women during labor and delivery. Carcinogen-hemoglobin adducts were detected in all maternal and fetal blood samples. Levels of such adducts were significantly higher ($P < .001$) in maternal and fetal blood samples from smokers: the mean 4-aminobiphenyl hemoglobin adduct level was 92 +/- 54 pg/g of hemoglobin in blood samples from fetuses of smokers, and 17 +/- 13 pg/g of hemoglobin in blood samples from fetuses of nonsmokers; the mean maternal 4-aminobiphenyl hemoglobin adduct level was 183 +/- 108 pg/g of hemoglobin in smokers, and 22 +/- 8 pg/g of hemoglobin in nonsmokers. Fetal carcinogen-adduct levels were consistently lower than maternal levels: the mean maternal to fetal ratio was 2.4 +/- 1.1 in smokers and 1.9 +/- .98 in nonsmokers. Fetal 4-aminobiphenyl hemoglobin adduct levels were strongly associated (correlation coefficient [r2] = .51, $P = .002$) with maternal 4-aminobiphenyl hemoglobin adduct levels when paired samples from smoking mothers were analyzed. A measure of third-trimester tobacco smoke exposure based on number of cigarettes smoked per day, amount of each cigarette smoked, and depth of inhalation was associated (r2 = .59, $P = .029$) with maternal 4-aminobiphenyl levels but not with fetal 4-aminobiphenyl levels. This study demonstrates that a potent tobacco-related carcinogen, 4-aminobiphenyl, or its active metabolite, N-hydroxy-4-aminobiphenyl, crosses the human placenta and binds to fetal hemoglobin in concentrations that are significantly higher in smokers than in nonsmokers.

Cohen JA, Yachnis AT, Arai M, Davis JG, Scherer SS. 1992. Expression of the neu protooncogene by Schwann-cells during peripheral-nerve development and wallerian degeneration. J Neurosci Res 31:622-634.
Abstract: The neu gene, which encodes a putative tyrosine kinase growth factor receptor termed p185neu, was originally identified as a dominant transforming gene in neurogliomas and schwannomas induced by transplacental treatment of rat embryos with ethylnitrosourea. The present studies were undertaken to determine the expression pattern of the neu gene in peripheral nerve. Northern blot analysis of total RNA isolated from rat sciatic nerves demonstrated prominent neu mRNA expression on postnatal days 1 and 7, with substantially lower expression up to adulthood. Immunohistochemical studies confirmed expression of p185neu by Schwann cells (SC) in developing sciatic nerve and minimal p185neu immunoreactivity in adult nerves. However, neu mRNA and p185neu protein progressively increased following sciatic nerve transection in adult animals. In addition, neu mRNA and p185neu were found in neonatal rat sciatic nerve SC and several SC-derived cell lines. In resting SC, neu mRNA was expressed at a low level, but was greatly increased by treatment with forskolin and glial growth factor. These studies demonstrate that the neu gene and its protein product, p185neu, are expressed by SC both in vivo and in vitro and suggest that p185neu plays a role in the regulation of SC proliferation or differentiation.

Cohen SM, Anderson TA, De Oliveira LM, Arnold LL. 1998. Tumorigenicity of sodium ascorbate in male rats. Cancer Res 58:2557-2561.
Abstract: Sodium ascorbate, like other sodium salts such as saccharin, glutamate, and bicarbonate, produces urinary alterations when fed at high doses to rats, which results in mild superficial urothelial cytotoxicity and regeneration but not tumors in a standard 2-year bioassay, Sodium saccharin was shown to produce a low incidence of bladder tumors in rats if administered in a two-generation bioassay, In the present study, we evaluated sodium ascorbate in a two-generation bioassay that involved feeding to the male and female parental F344 rats for 4 weeks before mating, feeding the dams during gestation and lactation, and then feeding the weaned (at 28 days of age) male F-1 generation rats for the remainder of their lifetime (up to 128 weeks of the experiment). Dietary levels of 1.0, 5.0, and 7.0% sodium ascorbate were tested. At 5.0 and 7.0% sodium ascorbate, there was an increase in urinary bladder urothelial papillary and nodular hyperplasia and the induction of a few papillomas and carcinomas. There was a dose-responsive increase in renal pelvic calcification and hyperplasia and inhibition of the aging nephropathy of rats even at the level of 1% sodium ascorbate, Because the short-term urothelial effects of sodium ascorbate in rats are inhibited by treatments producing urinary acidifi cation to $pH < 6.0$, we coadministered high doses of long-term NH4Cl to groups of rats with 5.0 or 7.0% sodium ascorbate to evaluate the longterm effects. The combination of 7.0% sodium ascorbate plus 2.78% NH4Cl in the diet was toxic, and the group was terminated early during the course of the experiment. The group fed 5.0% sodium ascorbate plus 2.04 NH4Cl showed complete inhibition of the urothelial effects of sodium ascorbate and significant inhibition of its renal effects. We also demonstrated the presence of a calcium phosphate-containing urinary precipitate in rats fed sodium ascorbate at all doses, in a dose-responsive manner. The formation of the precipitate was inhibited by

coadministration with NH4Cl. The proliferative effects of sodium ascorbate on the male rat urinary tract in this study are similar to those seen with sodium saccharin when administered in a two-generation bioassay, Mechanistic information suggests that this is a high-dose, rat-specific phenomenon.

Colt JS, Blair A. 1998. Parental occupational exposures and risk of childhood cancer. Environ Health Perspect 106 Suppl 3:909-925.
Abstract: Occupational exposures of parents might be related to cancer in their offspring. Forty-eight published studies on this topic have reported relative risks for over 1000 specific occupation/cancer combinations. Virtually all of the studies employed the case-control design. Occupations and exposures of fathers were investigated much more frequently than those of the mother. Information about parental occupations was derived through interviews or from birth certificates and other administrative records. Specific exposures were typically estimated by industrial hygienists or were self-reported. The studies have several limitations related to the quality of the exposure assessment, small numbers of exposed cases, multiple comparisons, and possible bias toward the reporting of positive results. Despite these limitations, they provide evidence that certain parental exposures may be harmful to children and deserve further study. The strongest evidence is for childhood leukemia and paternal exposure to solvents, paints, and employment in motor vehicle-related occupations; and childhood nervous system cancers and paternal exposure to paints. To more clearly evaluate the importance of these and other exposures in future investigations, we need improvements in four areas: a) more careful attention must be paid to maternal exposures; b) studies should employ more sophisticated exposure assessment techniques; c) careful attention must be paid to the postulated mechanism, timing, and route of exposure; and d) if postnatal exposures are evaluated, studies should provide evidence that the exposure is actually transferred from the workplace to the child's environment.

Connelly JM, Malkin MG. 2007. Environmental risk factors for brain tumors. Curr Neurol Neurosci Rep 7:208-14.
Abstract: Primary brain tumors, whether malignant or nonmalignant, have devastating consequences. Unfortunately, few known causes exist. Despite decades of epidemiologic research to identify environmental causes of brain tumors, very little progress has been made. The purpose of this paper is to review the most recent studies in the epidemiology of brain tumors. Popular topics of interest in adult brain tumor epidemiology include electromagnetic fields (particularly cellular phones), occupational exposures, nitroso-containing compounds (especially smoking), hair products, and allergic and immunologic factors. Some of these topics are also applicable to the etiology of childhood brain tumors, but additional areas of interest in the pediatric population focus on parental exposure prior to conception, maternal exposure during pregnancy, and childhood exposure to infectious agents. After an extensive review of the literature since 2001, we present the most relevant studies. Although there are many proposed associations with brain tumors, none possess the statistical significance to confidently ascribe causation. However, new findings and associations, particularly those in allergy and immunology, will present interesting opportunities for further development.

Cook JD, Davis BJ, Cai SL, Barrett JC, Conti CJ, Walker CL. 2005. Interaction between genetic susceptibility and early-life environmental exposure determines tumor-suppressor-gene penetrance. Proc Natl Acad Sci U S A 102:8644-8649.
Abstract: Gene-environment interactions are important determinants of cancer risk. Traditionally, gene-environment interactions are thought to contribute to tumor-suppressor-gene penetrance by facilitating or inhibiting the acquisition of additional somatic mutations required for tumorigenesis. Here, we demonstrate that a distinctive type of gene-environment interaction can occur during development to enhance the penetrance of a tumor-suppressor-gene defect in the adult. Using rats carrying a germ-line defect in the tuberous sclerosis complex 2 (Tsc-2) tumor-suppressor gene predisposed to uterine leiomyomas, we show that an early-life exposure to diethylstilbestrol during development of the uterus increased tumor-suppressor-gene penetrance from 65% to >90% and tumor multiplicity and size in genetically predisposed animals, but it failed to induce tumors in wild-type rats. This exposure was shown to impart a hormonal imprint on the developing uterine myometrium, causing an increase in expression of estrogen-responsive genes before the onset of tumors. Loss of function of the normal Tsc-2 allele remained the rate-limiting event for tumorigenesis; however, tumors that developed in exposed animals displayed an enhanced proliferative response to steroid hormones relative to tumors that developed in unexposed animals. These data suggest that exposure to environmental factors during development can permanently reprogram

normal physiological tissue responses and thus lead to increased tumor-suppressor-gene penetrance in genetically susceptible individuals.

Cook MN, Olshan AF, Guess HA, Savitz DA, Poole C, Blatt J, Bondy ML, Pollock BH. 2004. Maternal medication use and neuroblastoma in offspring. Am J Epidemiol 159:721-731.
Abstract: The association between a mother's use of specific medications during pregnancy and lactation and neuroblastoma in her offspring was evaluated in a case-control study. Newly diagnosed cases of neuroblastoma (n = 504) in the United States and Canada were identified between 1992 and 1994 at 139 hospitals affiliated with the Pediatric Oncology Group or the Children's Cancer Group clinical trial programs. One age-matched control was sampled from the community of each case by means of random digit dialing. Exposure information was ascertained retrospectively from mothers in a structured telephone interview. Odds ratios were estimated using conditional logistic regression, with adjustment for maternal sociodemographic factors. The results did not support an association between neuroblastoma and maternal exposure to diuretic agents, antiinfective agents, estrogens, progestins, sedatives, anticonvulsant drugs, or drugs that may form N-nitroso derivatives. Mothers of cases were more likely to report using medications containing opioid agonists while they were pregnant or nursing than were mothers of controls (odds ratio = 2.4, 95% confidence interval: 1.3, 4.3). Specifically, more mothers of cases reported using medications containing codeine while pregnant or nursing than did mothers of controls (odds ratio = 3.4, 95% confidence interval: 1.4, 8.4). This preliminary finding may be due to bias, confounding, or chance, and additional studies are needed for confirmation.

Cooney MA, Daniels JL, Ross JA, Breslow NE, Pollock BH, Olshan AF. 2007 . Household pesticides and the risk of Wilms tumor. Environ Health Perspect 115:134-137.
Abstract: BACKGROUND: Previous epidemiologic studies have suggested that exposure to pesticides in utero and during early childhood may increase the risk for development of childhood cancer, including Wilms tumor, a childhood kidney tumor. OBJECTIVES: In this analysis we evaluated the role of residential pesticide exposure in relation to the risk of Wilms tumor in children using data from a North American case-control study. METHODS: The National Wilms Tumor Study Group (NWTSG) collected information on exposure to residential pesticides from the month before pregnancy through the diagnosis reference date using detailed phone interviews from 523 case mothers and 517 controls frequency matched on child's age and geographic region and identified by list-assisted random digit dialing. Pesticides were grouped according to type of pesticide and where they were used. RESULTS: A slightly increased risk of Wilms tumor was found among children of mothers who reported insecticide use [odds ratio (OR) = 1.4, 95% confidence interval (CI), 1.0-1.8; adjusted for education, income, and the matching variables]. Results from all other categories of pesticides were generally close to the null. CONCLUSIONS: This study is the largest case-control study of Wilms tumor to date. We were unable to confirm earlier reports of an increased risk for Wilms tumor among those exposed to residential pesticides during pregnancy through early childhood.

Cordier S, Iglesias MJ, Legoaster C, Guyot MM, Mandereau L, Hemon D. 1994. Incidence and risk-factors for childhood brain-tumors in the Ile-de-France. Int J Cancer 59:776-782.
Abstract: A case-control study investigating risk factors for childhood brain tumors was conducted in the ile de France (Pan's region). During a 2-year period (1985-1987) 109 newly diagnosed cases were identified and, of these, 75 could be interviewed. In the same region, 113 population controls, frequency-matched for year of birth, were interviewed. Odds ratios adjusted for child's age and sex and for maternal age were estimated for each risk factor present in utero or during childhood by conditional logistic regression. Statistically significant associations were found for the following risk factors: farm residence, cat scratches, home treated with pesticides, passive smoking, family history of cancer, antihistamine intake. Intake of vitamin supplements during childhood was associated with a decrease in risk. This study is part of a multicentric case-control study coordinated by the International Agency for Research on Cancer and its results wilt be compared for consistency, and pooled with those of other centers using the same protocol. (C) 1994 Wiley-Liss, Inc.

Cordier S, Lefeuvre B, Filippini G, Peris-Bonet R, Farinotti M, Lovicu G, Mandereau L. 1997 . Parental occupation, occupational exposure to solvents and polycyclic aromatic hydrocarbons and risk of childhood brain tumors (Italy, France, Spain). Cancer Causes & Controls 8:688-697.

Abstract: The role of parental occupational exposure in childhood brain tumors was investigated in a population-based case-control study grouping 251 cases and 601 controls from three European centers: Milan (Italy), Paris (France), and Valencia (Spain). Parental occupational exposure to solvents and polycyclic aromatic hydrocarbons (PAH) during the five-year period before birth was estimated using a job-exposure matrix developed earlier in the same countries. Odds ratios (OR) of brain tumors for each occupation and occupational exposure were estimated by logistic regression, adjusting for child's age, gender, exposure to tobacco smoke and ionizing radiation, mother's age and years of schooling, and center. The risk of childhood brain tumors rose when fathers worked in agriculture (OR = 2.2, 95 percent confidence interval [CI] = 1.0-4.7) and motor-vehicle-related occupations. In the latter group, the risk increased for primitive neuroectodermal tumors in particular (OR = 2.7, CI = 1.1-6.6). Astroglial tumors were more frequent among children of mothers in health services (OR = 2.2, CI = 1.0-4.9). Paternal exposure to PAHs was associated with an increased, but not dose-related, risk of primitive neuroectodermal tumors (OR = 2.0, CI = 1.0-4.0), and maternal exposure to solvents at a high level was associated with an increased risk of both astroglial (OR = 2.3, CI = 0.9-5.8) and primitive neuroectodermal tumors (OR = 3.2, CI = 1.0-10.3).

Cordier S, Monfort C, Filippini G, Preston-Martin S, Lubin F, Mueller BA, Holly EA, Peris-Bonet R, Mccredie M, Choi W, Little J, Arslan A. 2004. Parental exposure to polycyclic aromatic hydrocarbons and the risk of childhood brain tumors - The SEARCH International Childhood Brain Tumor Study. Am J Epidemiol 159:1109-1116.
Abstract: Experimental evidence suggests that parental exposure to polycyclic aromatic hydrocarbons (PAH), which occurs primarily through tobacco smoke, occupational exposure, and air pollution, could increase the risk of cancer during childhood. Population-based case-control studies carried out in seven countries as part of the SEARCH Program compared data for 1,218 cases of childhood brain tumors and 2,223 controls (1976-1994). Parental occupational exposure to PAH during the 5-year period before birth was estimated with a job exposure matrix. Risk estimates were adjusted for child's age, sex, and study center. Paternal preconceptional occupational exposure to PAH was associated with increased risks of all childhood brain tumors (odds ratio (OR) = 1.3, 95% confidence interval: 1.1, 1.6) and astroglial tumors (OR = 1.4, 95% confidence interval: 1.1, 1.7). However, there was no trend of increasing risk with predicted level of exposure. Paternal smoking alone (OR = 1.4) was also associated with the risk of astroglial tumors in comparison with nonsmoking, non-occupationally-exposed fathers. Risks for paternal occupational exposure were higher, with (OR = 1.6) or without (OR = 1.7) smoking. Maternal occupational exposure to PAH before conception or during pregnancy was rare, and this exposure was not associated with any type of childhood brain tumor. This large study supports the hypothesis that paternal preconceptional exposure to PAH increases the risk of brain tumors in humans.

Corton JC, Lapinskas PJ. 2005. Peroxisome Proliferator-Activated Receptors: Mediators of Phthalate Ester-Induced Effects in the Male Reproductive Tract? Toxicol Sci 83:4-17.
Abstract: Many phthalate ester plasticizers are classified as peroxisome proliferators (PP), a large group of industrial and pharmaceutical chemicals. Like PP, exposure to some phthalates increases hepatocyte peroxisome and cellular proliferation, as well as the incidence of hepatocellular adenomas in mice and rats. Most effects of PP are mediated by three nuclear receptors called peroxisome proliferator-activated receptors (PPARalpha,beta,gamma). An obligate role for PPARalpha in PP-induced events leading to liver cancer is well-established. Exposure of rats in utero or in the neonate to a subset of phthalate esters causes profound, sometimes irreversible malformations in the male reproductive tract. We review here the data that supports or discounts roles for PPARs in phthalate-induced testis toxicity including (1) toxic effects of phthalates on the male reproductive tract, (2) expression of PPARs in the testis, (3) activation of PPARs by phthalates, (4) role of PPARalpha in testis toxicity, (5) gene targets of phthalates involved in steroid biosynthesis and catabolism, and (6) interactions between PPARs and other nuclear receptors that play roles in testis development and homeostasis. Critical research needs are identified that will help determine the significance of PPARs in phthalate-induced effects in the rat male reproductive tract and the relevance of toxicity to humans.

Cosgrove MD, Benton B, Henderson BE. 1977. Male genitourinary abnormalities and maternal diethylstilbestrol. J Urol 117:220-222.
Abstract: In view of the risk of vaginal cancer developing in young female subjects exposed in utero to

maternally ingested diethylstilbestrol a pilot study was undertaken of male subjects similarly exposed. A healthy questionnaire was mailed to 306 male subjects whose mothers were known to have taken diethylstilbestrol in the early part of their pregnancies and to 231 age and sex-matched controls identified from the same record source. Although there was no increased history of cancer, heart disease or asthma when the groups were compared there was a higher incidence of reported urinary tract symptoms and genital abnormalities in the group exposed to diethylstilbestrol. The presence of these abnormalities was confirmed by physical examination of 15 respondents. Studies in experimental animals also have shown that in certain species maternally ingested stilbestrol may result in abnormalities of the genitaltensive clinical studies be undertaken to determine the level of risk, if any, to which many thousands of young men are subject.

Costas K, Knorr RS, Condon SK. 2002. A case-control study of childhood leukemia in Woburn, Massachusetts: the relationship between leukemia incidence and exposure to public drinking water. Sci Total Environ 300:23-35.
Abstract: A 1981 Massachusetts Department of Public Health study confirmed a childhood leukemia cluster in Woburn, Massachusetts. Our follow-up investigation attempts to identify factors potentially responsible for the cluster. Woburn has a 130-year industrial history that resulted in significant local deposition of tannery and chemical manufacturing waste. In 1979, two of the city's eight municipal drinking water wells were closed when tests identified contamination with solvents including trichloroethylene. By 1986, 21 childhood leukemia cases had been observed (5.52 expected during the seventeen year period) and the case-control investigation discussed herein was begun. Nineteen cases and 37 matched controls comprised the study population. A water distribution model provided contaminated public water exposure estimates for subject residences. Results identified a non-significant association between potential for exposure to contaminated water during maternal pregnancy and leukemia diagnosis, (odds ratio = 8.33, 95% CI 0.73-94.67). However, a significant dose-response relationship ($P < 0.05$) was identified for this exposure period. In contrast, the child's potential for exposure from birth to diagnosis showed no association with leukemia risk. Wide confidence intervals suggest cautious interpretation of association magnitudes. Since 1986, expected incidence has been observed in Woburn including 8 consecutive years with no new childhood leukemia diagnoses. (C) 2002 Elsevier Science B.V. All rights reserved.

Coupland CAC, Forman D, Chilvers CED, Davey G, Pike MC, Oliver RTD. 2004. Maternal risk factors for testicular cancer: a population-based case-control study (UK). Cancer Causes & Control 15:277-283.
Abstract: Objective: To investigate the role of a range of maternal and pre-natal characteristics as potential risk factors for testicular cancer. Methods: A population-based case - control study of testicular cancer. Mothers of participants completed a questionnaire about their reproductive and obstetric history. Results: The risk of testicular cancer was approximately doubled for sons of mothers aged 15 - 19 years at conception compared with mothers with older ages at conception. Nausea or vomiting during the first trimester of pregnancy was associated with a reduced risk of testicular cancer (odds ratio of 0.73, 95% confidence interval 0.53-1.00). There was also a borderline reduction in risk in men who had been breastfed for 6 months or more (odds ratio 0.65, 95% confidence interval 0.41 - 1.04). Men who had low birthweights (< 2500 g) or had been born two or more weeks early had slightly increased risks, as did men whose mothers had used oral contraception in the 12 months before their conception. Conclusions: These findings support previous reports of increased risks in men born early or with low birthweight, but the direction of the association with maternal age is contrary to some other studies. The suggestion of a protective effect of breastfeeding requires further confirmation.

Couto E, Chen B, Hemminki K. Nov 28 2005. Association of Childhood Acute Lymphoblastic Leukaemia With Cancers in Family Members. Br J Cancer 93:1307-1309.
Abstract: Children whose twins have had leukaemia have a higher risk of contracting acute lymphoblastic leukaemia (ALL), confirming a prenatal origin of the disease. This association was not true when considering other types of affected first-degree relatives. Children whose fathers were diagnosed with testicular cancer have a higher risk of ALL.

Daniels JL, Olshan AF, Savitz DA. 1997. Pesticides and childhood cancers. Environ Health Perspect 105:1068-1077.

Abstract: To evaluate the possible association between pesticides and the risk of childhood cancers, epidemiologic studies published between 1970 and 1996 were critically reviewed. Thirty-one studies investigated whether occupational or residential exposure to pesticides by either parents or children was related to increased risk of childhood cancer. In general, the reported relative risk estimates were modest. Risk estimates appeared to be stronger when pesticide exposure was measured in more detail. Frequent occupational exposure to pesticides or home pesticide use was more strongly associated with both childhood leukemia and brain cancer than either professional exterminations or the use of garden pesticides. Occupational pesticide exposure was also associated with increased risk of Wilms' tumor, Ewing's sarcoma, and germ cell tumors. Residence on a farm, a proxy for pesticide exposure, was associated with increased risk of a number of childhood cancers. Although increased risk of some childhood cancers in association with pesticide exposure is suggested by multiple studies, methodological limitations common to many studies restrict conclusions; these include indirect exposure classification, small sample size, and potential biases in control selection. Opportunities for methodologic improvement in future studies of pesticides and childhood cancers are described.

Darby SC, Olsen JH, Doll R, Thakrar B, Brown PD , Storm HH, Barlow L, Langmark F, Teppo L, Tulinius H. 1992. Trends in childhood leukemia in the Nordic countries in relation to fallout from atmospheric nuclear-weapons testing. Br Med J 304:1005-1009.
Abstract: Objective - To obtain further information about the risks of childhood leukaemia after exposure to ionising radiation at low doses and low dose rates before or after birth or to the father's testes shortly before conception. Design - Observational study of trends in incidence of childhood leukaemia in relation to estimated radiation exposures due to fallout from atmospheric nuclear weapons testing during the 1950s and 1960s. Setting - Nordic countries. Subjects - Children aged under 15 years. Main outcome measures - Incidence rates of leukaemia by age at diagnosis, sex, country, and calendar year of diagnosis or year of birth; exposure category; relation between leukaemia and exposure for children aged 0-14 and 0-4 separately. Results - During the high fallout period the average estimated dose equivalent to the fetal red bone marrow was around 140-mu-Sv and the average annual testicular dose 140-mu-Sv. There was little evidence of increased incidence of leukaemia among children born in these years. Doses to the red bone marrow of a child after birth were higher, and during the high exposure period children would have been subjected to an additional dose equivalent of around 1500-mu-Sv, similar to doses received by children in several parts of central and eastern Europe owing to the Chernobyl accident and about 50% greater than the annual dose equivalent to the red bone marrow of a child from natural radiation. Leukaemia incidence and red marrow dose was not related overall, but rates of leukaemia in the high exposure period were slightly higher than in the surrounding medium exposure period (relative risk for ages 0-14: 1.07, 95% confidence interval 1.00 to 1.14; for ages 0-4: 1.11, 1.00 to 1.24). Conclusions - Current predicted risks of childhood leukaemia after exposure to radiation are not greatly underestimated for low dose rate exposures.

Dass SB, Heflich RH, Casciano DA. 1998. Mutational response at the splenic T-lymphocyte hprt locus in mice treated as neonates: Contrasting effects of the carcinogens N-ethyl-N-nitrosourea, dimethylnitrosamine, and 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine. Environmental & Molecular Mutagenesis 31:243-247.
Abstract: The newborn mouse tumorigenicity assay, which involves the treatment of animals during the first two weeks after birth and monitoring tumor induction after a year, has been suggested as a cost- and time-effective alternative to the conventional two year rodent bioassay. In order to evaluate whether or not lymphocyte hprt mutant induction is an accurate predictor of carcinogenicity in the assay, we determined the frequencies of 6-thioguanine-resistant (TG(r)) lymphocytes in the spleens of mice neonatally treated with the carcinogenic mutagens N-ethyl-N-nitrosourea (ENU), dimethylnitrosamine (DMN), and 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhlP). Male C57BL/6 pups were injected on postnatal days 8 and 15, and the frequency of TG(r) T-lymphocytes was measured in groups of three animals, sacrificed periodically up to 31 weeks post-treatment. Compared to background frequencies of 1.1-2.9 x 10(-6), mutant frequencies (MFS) reached 155.1 x 10(-6) following a cumulative dose of 49 mg ENU/kg body weight and 172.3 x 10(-6) following a cumulative dose of 142 mg ENU/kg. These results show that TG(r) lymphocyte mutations can be induced and measured in mice treated as neonates and that the induced MFs found for mice treated neonatally with ENU are comparable with frequencies reported For the treatment of adult animals with the some chemical. In contrast, treatment with the promutagenic and procarcinogenic compounds DMN (at a maximum concentration of 10.5 mg/kg) and PhlP (26.2 mg/kg) did not result in on increase in lymphocyte MF, suggesting that reactive metabolites of these compounds may not be reaching

cells that are sensitive for mutation fixation. The results indicate that the lymphocyte hprt assay may fail to predict the carcinogenicity of some test chemicals in the neonatal mouse bioassay. (C) 1998 Wiley-Liss, Inc.

Davis DL, Friedler G, Mattison D, Morris R. 1992. Male-mediated teratogenesis and other reproductive effects: biologic and epidemiologic findings and a plea for clinical research. Reprod Toxicol 6:289-292.
Abstract: This paper reviews biologic and epidemiologic evidence that prefertilization and perifertilization exposures to fathers influence a variety of reproductive outcomes, including fertilization, miscarriage, low birth weight, congenital anomalies, cancer, and neurodevelopmental and other childhood health problems. Males and females bring an equal number of chromosomes to their progeny, but their genomes may affect different aspects of reproduction. While the key male role principally ends at fertilization, there is growing experimental and human evidence that factors relating both to prefertilization and perifertilization exposure also play a role post fertilization. Some negative human epidemiologic findings reflect the fact that routinely gathered inflormation usually generates detailed descriptions of maternal exposures and does not collect records regarding prefertilization paternal exposures. The absence of extensive human evidence should be interpreted as a deficiency in research rather than an absence of male-mediated adverse reproductive outcomes. More than 60 different compounds or industrial processes have been identified as increasing defects in human sperm and possibly increasing the risk to offspring from male-mediated exposures. Further research needs to include better characterizations of both maternal and paternal prefertilization and perifertilization exposures, in order to assess more accurately their relative effects. Pediatricians confronted with adverse pregnancy and antenatal health outcomes should obtain detailed information on relevant prefertilization exposures of both parents.

Davis S, Day RW, Kopecky KJ, Mahoney MC, Mccarthy PL, Michalek AM, Moysich KB, Onstad LE, Stepanenko VF, Voilleque PG, Chegerova T, Falkner K, Kulikov S, Maslova E, Ostapenko V, Rivkind N, Shevchuk V, Tsyb AF. 2006. Childhood Leukaemia in Belarus, Russia, and Ukraine Following the Chernobyl Power Station Accident: Results From an International Collaborative Population-Based Case-Control Study. Int J Epidemiol 35:386-396.
Abstract: Background There is little evidence regarding the risk of leukaemia in children following exposure to radionuclides from the Chernobyl Nuclear Power Plant explosion on April 26, 1986. Methods This population-based case-control study investigated whether acute leukaemia is increased among children who were in utero or < 6 years of age at the time of the Chernobyl accident. Confirmed cases of leukaemia diagnosed from April 26, 1986 through December 31, 2000 in contaminated regions of Belarus, Russia, and Ukraine were included. Two controls were matched to each case on sex, birth year, and residence. Accumulated absorbed radiation dose to the bone marrow was estimated for each subject. Results Median estimated radiation doses of participants were < 10 mGy. A significant increase in leukaemia risk with increasing radiation dose to the bone marrow was found. This association was most evident in Ukraine, apparent (but not statistically significant) in Belarus, and not found in Russia. Conclusion Taken at face value, these findings suggest that prolonged exposure to very low radiation doses may increase leukaemia risk as much as or even more than acute exposure. However the large and statistically significant dose-response might be accounted for, at least in part, by an overestimate of risk in Ukraine. Therefore, we conclude this study provides no convincing evidence of an increased risk of childhood leukaemia as a result of exposure to Chernobyl radiation, since it is unclear whether the results are due to a true radiation-related excess, asampling-derived bias in Ukraine, or some combination thereof. However, the lack of significant dose-responses in Belarus and Russia also cannot convincingly rule out the possibility of an increase in leukaemia risk at low dose levels.

De Assis S, Hilakivi-Clarke L. 2006. Timing of dietary estrogenic exposures and breast cancer risk. Ann N Y Acad Sci 1089:14-35.
Abstract: The same dietary component, such as fat or phytochemicals in plant foods, can have an opposite effect on breast cancer risk if exposed in utero through a pregnant mother or at puberty. Dietary exposures during pregnancy often have similar effects on breast cancer risk among mothers and their female offspring. High fat intake and obesity are illustrative examples: excessive pregnancy weight gain that increases high birth weight is associated with increased breast cancer risk among mothers and daughters. High body weight during childhood is inversely linked to later breast cancer risk. The main reason why the age when dietary exposures occur determines their effect on breast cancer risk likely reflects the extensive

programming of the mammary gland during fetal life and subsequent reprogramming at puberty and pregnancy. Programming is a series of epigenetic/transcriptional modifications in gene expression that can be influenced by changes in the hormonal environment induced, for example, by diet. Because epigenetic modifications are inherited by daughter cells, they can persist throughout life if they occur in mammary stem cells or uncommitted mammary myoepithelial or luminal progenitor cells. Our results indicate that the estrogen receptor (ER), mitogen-activated protein kinase (MAPK), and the tumor suppressors BRCA1, p53, and caveolin-1 are among the genes affected by diet-induced alterations in programming/reprogramming. Consequently, mammary gland morphology may be altered in a manner that increases or reduces susceptibility to malignant transformation, including an increase/reduction in cell proliferation, differentiation, and survival, or in the number of terminal end buds (TEBs) or pregnancy-induced mammary epithelial cells (PI-MECs) that are the sites where breast cancer is initiated. Thus, dietary exposures during pregnancy and puberty may play an important role in determining later risk by inducing epigenetic changes that modify vulnerability to breast cancer.

de Assis S, Khan G, Hilakivi-Clarke L. 2006. High birth weight increases mammary tumorigenesis in rats. Int J Cancer 119:1537-1546.
Abstract: Epidemiological studies have investigated whether a high birth weight is associated with increased breast cancer risk, but the results remain inconclusive. This study was designed to determine whether high birth weight increases later susceptibility to carcinogen-induced mammary tumorigenesis in an animal model and to determine mechanisms mediating this association. Pregnant female Sprague Dawley rats were fed either a control or a high-fat diet during the extent of gestation. Maternal exposure to the high-fat diet increased pregnancy leptin levels and offspring's birth weight, but had no effect on pregnancy estradiol or insulin-like growth factor 1 levels. Changes in the offspring's mammary gland morphology and protein expression were assessed. The mammary epithelial tree of the high-birth-weight offspring was denser, contained more terminal end buds and exhibited higher number of proliferating cells. Further, their mammary glands expressed lower levels of ER-alpha, but higher levels of activated MAPK. No alterations in apoptosis were noted. High-birth-weight rats developed 7,12-dimethylbenz[a]anthracene-induced mammary tumors significantly earlier, and tumors grew larger than in the controls. The tumors in this group expressed higher levels of leptin receptor and activated Akt, and contained fewer apoptotic cells than those in the controls. Our results indicate that high birth weight is related to shortened latency to develop mammary tumors-perhaps reflecting an increase in activated MAPK levels and increased tumor growth-perhaps caused by a lower apoptotic response due to higher leptin receptor and activated Akt levels in the tumors. (c) 2006 Wiley-Liss, Inc.

De Flora S, Iltcheva M, Balansky RM. 2006. Oral chromium(VI) does not affect the frequency of micronuclei in hematopoietic cells of adult mice and of transplacentally exposed fetuses. Mutation Research-Genetic Toxicology and Environmental Mutagenesis 610:38-47.
Abstract: Chromium(VI) compounds are genotoxic in a variety of cellular systems. Their potential carcinogenicity is affected by toxicokinetic patterns restricting bioavailability to certain targets, and by metabolic pathways affecting interaction of chromate-derived reactive species with DNA. Epidemiological data indicate that chromium(VI) can be carcinogenic to the human respiratory tract following inhalation at doses that are only achieved in certain occupational settings. However, concern has been raised that adverse effects may also result from oral intake. In order to further explore this issue, we performed studies in BDF1 and Swiss mice of both genders and various age. Sodium dichromate dihydrate and potassium dichromate were administered either with the drinking water, up to a concentration of 500 mg chromium(VI)/l for up to 210 consecutive days, or in a single intragastric dose of 17.7 mg/kg body weight. Under these conditions, no increase of the micronucleus frequency was observed in either bone marrow or peripheral blood erythrocytes. Conversely, the same compounds induced a clastogenic damage following intraperitoneal injection, which by-passes detoxitication mechanisms. In addition, due to the hypothesis that susceptibility may be increased during the period of embryogenesis, we treated pregnant mice, up to a concentration of 10 mg chromium(VI)II drinking water. There was no effect on the numbers of fetuses/dam and on body weight of fetuses. Again, no toxic or genotoxic effect was observed either in bone marrow of pregnant mice or in liver and peripheral blood of their fetuses. Thus, even at doses that largely exceed drinking water standards (up to 10,000 times) or by massive intragastric administration, chromium(VI) is not genotoxic to hematopoietic cells of either adult mice or transplacentally exposed fetuses. These conclusions are consistent with the poor toxicity and lack of carcinogenicity of oral chromium(VI), and are

mechanistically explained by the high efficiency of chromium(VI) detoxification processes in the gastrointestinal tract. (c) 2006 Elsevier B.V. All rights reserved.

de la Chica RA, Ribas I, Giraldo J, Egozcue J, Fuster C. 2005. Chromosomal instability in amniocytes from fetuses of mothers who smoke. JAMA 293:1212-1222.
Abstract: CONTEXT: Tobacco increases the risk of systemic diseases, and it has adverse effects on pregnancy. However, only indirect data have been published on a possible genotoxic effect on pregnancy in humans. OBJECTIVES: To determine whether maternal smoking has a genotoxic effect on amniotic cells, expressed as an increased chromosomal instability, and to analyze whether any chromosomal regions are especially affected by exposure to tobacco. DESIGN, SETTING, AND PATIENTS: In this prospective study, amniocytes were obtained by routine amniocentesis for prenatal diagnosis from 25 controls and 25 women who smoke (> or =10 cigarettes/d for > or =10 years), who were asked to fill out a smoking questionnaire concerning their smoking habits. Chromosomal instability was analyzed in blinded fashion by 2 independent observers in routine chromosome spreads. Breakpoints implicated in chromosomal abnormalities were identified by G-banding. MAIN OUTCOME MEASURES: Association between maternal smoking and increased chromosomal instability in amniotic fluid cells, expressed as chromosomal lesions (gaps and breaks) and structural chromosomal abnormalities. RESULTS: Comparison of cytogenetic data between smokers and nonsmokers (controls) showed important differences for the proportion of structural chromosomal abnormalities (smokers: 12.1% [96/793]; controls: 3.5% [26/752]; P = .002) and to a lesser degree for the proportion of metaphases with chromosomal instability (smokers: 10.5% [262/2492]; controls: 8.0% [210/2637]; P = .04), and for the proportion of chromosomal lesions (smokers: 15.7% [391/2492]; controls: 10.1% [267/2637]; P = .045). Statistical analysis of the 689 breakpoints detected showed that band 11q23, which is a band commonly implicated in hematopoietic malignancies, was the chromosomal region most affected by tobacco. CONCLUSIONS: Our findings show that smoking 10 or more cigarettes per day for at least 10 years and during pregnancy is associated with increased chromosomal instability in amniocytes. Band 11q23, known to be involved in leukemogenesis, seems especially sensitive to genotoxic compounds contained in tobacco.

De Preter K, Vandesompele J, Heimann P, Yigit N, Beckman S, Schramm A, Eggert A, Stallings RL, Benoit Y, Renard M, De Paepe A, Laureys G, Pahlman S, Speleman F. 2006. Human fetal neuroblast and neuroblastoma transcriptome analysis confirms neuroblast origin and highlights neuroblastoma candidate genes. Genome Biology 7.
Abstract: Background: Neuroblastoma tumor cells are assumed to originate from primitive neuroblasts giving rise to the sympathetic nervous system. Because these precursor cells are not detectable in postnatal life, their transcription profile has remained inaccessible for comparative data mining strategies in neuroblastoma. This study provides the first genome-wide mRNA expression profile of these human fetal sympathetic neuroblasts. To this purpose, small islets of normal neuroblasts were isolated by laser microdissection from human fetal adrenal glands. Results: Expression of catecholamine metabolism genes, and neuronal and neuroendocrine markers in the neuroblasts indicated that the proper cells were microdissected. The similarities in expression profile between normal neuroblasts and malignant neuroblastomas provided strong evidence for the neuroblast origin hypothesis of neuroblastoma. Next, supervised feature selection was used to identify the genes that are differentially expressed in normal neuroblasts versus neuroblastoma tumors. This approach efficiently sifted out genes previously reported in neuroblastoma expression profiling studies; most importantly, it also highlighted a series of genes and pathways previously not mentioned in neuroblastoma biology but that were assumed to be involved in neuroblastoma pathogenesis. Conclusion: This unique dataset adds power to ongoing and future gene expression studies in neuroblastoma and will facilitate the identification of molecular targets for novel therapies. In addition, this neuroblast transcriptome resource could prove useful for the further study of human sympathoadrenal biogenesis.

De Sanjose S, Viladiu P, Cordon F, Vilardell L, Marcos R, Izquierdo A. 1998. Breast cancer and inheritance: results from a population based case-control study in Girona, Spain. Med Clin (Barc) 110:370-372.
Abstract: BACKGROUND: TO characterise the relationship between breast cancer and different aspects of the reproductive life, use of drugs and alcohol by family history of breast cancer, PATIENTS AND METHODS: From the cancer registry of Girona, Spain, 330 women were identified with histologically confirmed breast cancer during 1986-1989, For each case, a control women was selected from a random

sample of the population living in the matched area to the case by age (+/- 5 yr.). The information was collected by a personal interview and included: family history of breast cancer, reproductive history, presence of acne during the teenage years, use of oral contraceptives and drugs for sleep and anxiety disorders, and alcohol consumption. RESULTS: 18.5% of breast cancer cases and 8.9% of all controls had a family history of breast cancer, Family history on a first degree relative (mother or sister) was present in 10.6% of the cases and 2.8% of controls, which represented an odds ratio for breast cancer of 3.7 (95% CI, 1.8-7.8) higher than the general population. Women with a first degree family history of breast cancer were at higher risk for breast cancer ii the had a history of acne during the teenage period (OR = 2.4; 95% CI, 1.1-5.2) and if they referred long menstrual periods in the early years of menarche (OR = 3.1; 95% CI, 1.3-7.0), Women with no family history had a higher breast cancer risk if they had a late menarche, long menstrual periods, late first full term pregnancy, and history of acne during puberty, Alcohol consumption and use of drugs for anxiety and sleep disorders were associated with a decreased risk of breast cancer. CONCLUSIONS: First degree family history of breast cancer seems to be the best risk indicator for developing breast cancer. Long menstrual periods and presence of acne during puberty may indicate hormonal imbalance that act independently of the family history in breast cancer development.

Delongchamp RR, Mabuchi K, Yoshimoto Y, Preston DL. 1997. Cancer mortality among atomic bomb survivors exposed in utero or as young children, October 1950 May 1992. Radiat Res 147:385-395.
Abstract: Cancer mortality for the period from October 1950 through May 1992 was analyzed in atomic bomb survivors exposed in utero. Risk estimates for this group were also compared to those for survivors who were less than 6 years old at the time of exposure. The cohorts studied include 807 in utero survivors and 5,545 persons exposed during childhood with all members of both groups having estimated doses of at least 0.01 Sv. The comparison group includes 10,453 persons with little (< 0.01 Sv) or no exposure. Analyses were limited mainly to cancer deaths occurring between the ages of 17 and 46. Only 10 cancer deaths were observed among persons exposed in utero. However, there is a significant dose response with an estimate of excess relative risk per sievert (ERR/Sv) of 2.1 (90% confidence interval of 0.2 to 6.0). This estimate does not differ significantly from that for survivors exposed during the first 5 years of life. The cancer deaths among those exposed in utero involved leukemia (2), female-specific organs (3) and digestive organs (5). Nine deaths occurred in females, where the excess risk for all solid cancers has a 90% confidence interval on the ERR/Sv of 1.6 to 17. Significant risks were found for cancers of the digestive system [90% confidence interval (CI) on the ERR/Sv of 0.7 to 20] and for female-specific cancers (90% CI on the ERR/SV of 0.7 to 42). These risks do not differ significantly from those seen in females exposed as children. There were no deaths from solid cancer in men exposed in utero. The ERR/Sv has an upper 95% confidence bound of 2.5 which does not differ from that for exposed children, where the upper 95% confidence bound is 1.5. The sexes differ even when female-specific cancers are excluded from the comparison. Although there were only two leukemia deaths among those exposed in utero, the leukemia death rate for this group is higher than that in the comparison group (P = 0.054) with an exposure effect that is about half the magnitude and not significantly different from that seen after childhood exposure (P = 0.103). However, there is no evidence of a dose response among those exposed in utero because no high-dose leukemia deaths were observed, a result that differs considerably from that for those exposed as children. There is a need for caution in the interpretation of these data. First, the number of cancer deaths is small; second, there is unexplained significant difference in the mortality from solid cancer between the sexes; and third, the excess of leukemia in those exposed in utero is not reflected in an increasing dose response. (C) 1997 by Radiation Research Society.

DeMars LR, Van Le L, Huang I, Fowler WC. 1995. Primary non-clear-cell adenocarcinomas of the vagina in older DES-exposed women. Gynecol Oncol 58:389-392.
Abstract: The association between in utero diethylstilbestrol (DES) exposure and the development of clear-cell adenocarcinoma of the vagina and cervix has been well described. However, non-clear-cell mucin-secreting adenocarcinoma in women with DES exposure has not been previously reported. We present two cases of non-clear-cell mucinous adenocarcinoma in women having a history of in utero DES exposure. These cancers were found in older women and were more advanced than the clear-cell adenocarcinoma associated with DES. Histologic features of these tumors were notable for atypical, irregular glands lined by endocervical, intestinal, and endometrioid epithelium. The development of non-clear-cell adenocarcinoma of the vagina in these patients may be associated with DES exposure in utero. Long-term surveillance of DES-exposed women may be warranted.

Denning DW, Allen R, Wilkinson AP, Morgan MR. 1990. Transplacental transfer of aflatoxin in humans. Carcinogenesis 11:1033-1035.
Abstract: This study quantified aflatoxin (AFB1, AFG1 and AFQ1) by enzyme-linked immunosorbent assay in human cord sera obtained at birth and in serum obtained immediately after birth from the mother. The subjects of the study were residents of Songkhla, Thailand. Of the 35 samples of cord sera, 17 (48%) contained aflatoxin in concentrations from 0.064 to 13.6, mean 3.1 nmol/ml. By comparison only two (6%) of 35 maternal sera contained aflatoxin (mean 0.62 nmol/ml). These results demonstrate transplacental transfer and concentration of aflatoxin by the feto-placental unit which may be of biological importance. Aflatoxins are mutagenic, carcinogenic and teratogenic and cause immunosuppression in animals. The implications of these findings are potentially profound and deserve further study.

Depue RH, Pike MC, Henderson BE. 1983. Estrogen exposure during gestation and risk of testicular cancer. J Natl Cancer Inst 71:1151-1155.
Abstract: In this case--control study of 108 cases of testicular cancer in men under 30 years of age, cryptorchidism was a major risk factor [relative risk (RR) = 9.0]. Low birth weight was also associated with increased risk (RR = 3.2). Having severe acne at puberty was protective (RR = 0.37). Interviews with mothers of cases revealed that exposure of the mother to exogenous estrogen during pregnancy created a significant risk in the son (RR = 8.0). In first pregnancies, excessive nausea indicated an increased risk of testicular cancer (RR = 4.2). Increased body weight in the mother also increased the risk. The relation between these factors and testicular hypoplasia is discussed. Severe perimenopausal menorrhagia was a factor in the mother associated with reduced risk of testicular cancer in the son (RR = 0.10). A modified hormonal milieu in the mother appears to be important in the later development of testicular cancer in her sons.

Desaulniers D, Leingartner K, Russo J, Perkins G, Chittim BG, Archer MC, Wade M, Yang J. 2001. Modulatory effects of neonatal exposure to TCDD, or a mixture of PCBs, p,p '-DDT, and p-p '-DDE, on methylnitrosourea-induced mammary tumor development in the rat. Environ Health Perspect 109:739-747.
Abstract: The role of organochlorine (OC) exposure in the etiology of breast cancer remains controversial. Thus, our objective was to determine whether the most abundant and toxic OCs found in human milk could, when ingested during the neonatal period, modulate the development of mammary tumors in the rat. We prepared a mixture composed of p,p ' -dichlorodiphenyltrichloroethane (DDT), its major metabolite, p,p ' -dichlorodiphenyldichloroethene (DDE), and 19 polychlorinated biphenyls (PCB) based on their concentrations found in the milk of Canadian women. Neonate rats at 1, 5, 10, 15, and 20 days of age were gavaged with this mixture, at 10, 100, and 1,000 times the amount that a human baby would consume. An additional group received 2.5 mug 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)/kg body weight (bw) by gavage at 18 days of age, instead of the mixture. On day 21, all treatment groups, except for a control group and a 1,000-mix group, received a single intraperitoneal injection of methylnitrosourea (MNU, 30 mg/kg bw), the initiator of the carcinogenic process. The average number of rats per treatment group was 33. Rats were sacrificed when their tumors reached I cm in size, or at 308 days of age. We prepared mammary tumors and mammary gland whole mounts for histologic analysis. There were no significant effects when only the malignant or only the benign tumors were considered. After all benign and malignant lesions were pooled, the number of mammary tumors differed among all MNU-treated groups ($p = 0.02$) with more lesions developing in the MNU-1,000x (median = 4.5; $p = 0.05$) and MNU-TCDD (median = 5.5; $p = 0.07$) compared to the MNU-0 rats (median = 2). Compared to the MNU-0 group, the percentage of rats that developed palpable tumors (benign plus malignant) was slightly higher ($p = 0.06$) in the MNU-TCDD group, but riot in the MNU-1,000x group. The percentage of palpable tumors that were malignant was higher ($p = 0.02$) in the MNU-100x group (15/16, 94%) than in the MNU-0 group (10/18, 56%). The highest dose of the mixture delayed ($p = 0.03$) the development of tumors, but this was not observed with the MNU-TCDD treatment. These results suggest that neonatal exposure to high doses of organochlorines could favor the development of MNU-induced mammary lesions, but also delays the development of palpable tumors in the rat.

Devi PU, Hossain M. 2000. Induction of solid tumours in the Swiss albino mouse by low-dose foetal irradiation. Int J Radiat Biol 76:95-99.
Abstract: Purpose: To study the tumourigenic effect of prenatal low-dose gamma-irradiation in the mouse. Methods and materials: Pregnant Swiss albino mice were exposed to 0.1-1.5 Gy gamma-radiation on days

14 or 17 of gestation. The F-1 offspring were observed up to 18 months of age. All the mice were killed at 18 months and the incidence of tumours in different organs was recorded. Results: Exposure to doses from 0.1 to 1.5 Gy on days 14 or 17 of gestation produced a linear-quadratic dose-dependent increase in tumour incidence in adult F-1 mice. The main organs affected were the ovary, uterus, liver and spleen. The highest incidence was observed in the ovaries, which was significantly higher than spontaneous incidence, even at 0.25 Gy. In other organs the tumour incidence was not significant compared with controls at doses <0.5-1.0 Gy. Tumours in the ovary and uterus developed at an earlier age than in the liver and spleen. Conclusions: Exposure to gamma-radiation <1.0 Gy at the foetal period (days 14 or 17 of gestation) can cause induction of rumours in the Swiss albino mouse. The carcinogenic effect, particularly on the ovary among the female mouse, is detectable after low-dose foetal irradiation.

Dickinson HO, Nyari TA, Parker L. 2002. Childhood solid tumours in relation to infections in the community in Cumbria during pregnancy and around the time of birth. Br J Cancer 87:746-750.
Abstract: In a retrospective cohort study of all 99 976 live births in Cumbria, 1975-1992, we investigated whether higher levels of community infections during the mother's pregnancy and in early life were risk factors for solid tumours (brain/spinal and other tumours), diagnosed 1975-1993 under age 15 years. Logistic regression was used to relate risk to incidence of community infections in three prenatal and two postnatal quarters. There was an increased risk of brain/spinal tumours among children exposed around or soon after birth to higher levels of community infections, in particular measles (OR for trend = 2.1, 95% Cl: 1.3-3.6, P = 0.008) and influenza (OR for exposure = 3.3, 95% Cl: 1.5-7.4, P = 0.005). There was some evidence of an association between exposure to infections around and soon after birth and risk of other tumours, but this may have been a chance finding. The findings are consistent with other recent epidemiological studies suggesting brain tumours may be associated with perinatal exposure to infections. (C) 2002 Cancer Research UK.

Dieckmann KP, Endsin G, Pichlmeier U. 2001. How valid is the prenatal estrogen excess hypothesis of testicular germ cell cancer? A case control study on hormone-related factors. Eur Urol 40:677-83; discussion 684.
Abstract: PURPOSE/AIMS: The prenatal estrogen excess hypothesis postulates abnormally high estrogen levels during pregnancy which predispose the developing gonad to testicular germ cell cancer (GCT) in adulthood. As no direct measurements are possible to support this hypothesis, evidence must come from clinical and epidemiological observations. The present study looked to surrogate parameters that purportedly point to high estrogenic influence in utero. METHODS/PATIENTS: In a case-control study design, 418 cases with GCT were compared to 636 controls having fractures, injuries or nephrolithiasis. A second comparison was done with 120 men suffering from malignant melanoma. The following factors were investigated: maternal and paternal age at birth of proband, birth-order, distribution of brothers and sisters in sibs of patients, sibship size, status of being a twin, status of being a singleton child, handedness, and frequency of breast cancer in mothers and sisters. RESULTS: Status of being a twin was significantly associated with GCT risk (OR 2.41; 95% CI 1.04- 5.63) if compared to men with fractures or stones. Comparison with melanoma controls showed only a nonsignificant trend. Frequency of breast cancer was insignificantly higher in mothers of GCT patients. Maternal age above 30 years was associated with decreased risk of GCT, which is contradictory to the hypothesis. No other parameter was significantly different in cases and controls. CONCLUSION: The present investigation failed to produce evidence for the estrogen excess hypothesis. Obviously, the parameters tested are only weak indicators of estrogenic influence during embryogenesis. Thus, the sample size and statistical power of the trial might have been too low to show any significant association. But, assessing the negative results of this study in light of equally negative results in previous investigations, the estrogen excess hypothesis still remains to be hypothetic.

Diwan BA, Anderson LM, Ward JM. 1997. Proliferative lesions of oviduct and uterus in CD-1 mice exposed prenatally to tamoxifen. Carcinogenesis 18:2009-2014.
Abstract: Tamoxifen (TAM) is widely used as adjuvant breast cancer therapy after surgery and as a chemopreventive agent in women of child-bearing age, However, TAM therapy has been shown to result in an increased incidence of endometrial carcinoma in women. The present study was designed to investigate the effects of TAM (5 mg/kg and 7.5 mg/kg body wt) given i.g. to pregnant CD-1 mice (1x/day, days 12 through 18 of gestation) on their female offspring, Progressive proliferative hyperplasia of the oviduct was frequently seen in TAM-exposed offspring, reaching 100% incidence by 52 weeks in both treatment

groups. These females also developed progressive proliferative uterine lesions, including moderate/severe cystic endometrial hyperplasia (34-50%) and polypoid adenomas (27-30%) between 53 and 78 weeks, Deciduomas (15%) occurred at young ages (12 and 24 weeks) while leiomyomas (14%), a malignant leiomyosarcoma, and ovarian granulosa cell tumors (14%), were found between 72 and 78 weeks, Our findings thus suggest a strong association between transplacental TAM and reproductive tract abnormalities in female CD-1 mice.

Diwan BA, Anderson LM, Ward JM, Henneman JR, Rice JM. 1995. Transplacental carcinogenesis by cisplatin in F344/NCr rats - Promotion of kidney tumors by pastnatal administration of sodium barbital. Toxicology & Applied Pharmacology 132:115-121.
Abstract: Transplacental carcinogenic effects of cis-dichlorodiammineplatinum (cis-DDP) in F344 rats were investigated. Pregnant F344 rats were given a single ip administration of either cis-DDP (5 mg/kg body wt; group 1) or saline only (group 2) on Day 18 of gestation, Offspring of groups 1 and 2 were randomly and equally divided into two subgroups: 1a, 1b and 2a, 2b, respectively, Beginning at 4 weeks of age, offspring in groups 1b and 2b received 500 ppm of sodium barbital (NaBB) in diet, while those in groups 1a and 2a received normal diet. The experiment was terminated at 79 weeks of age. A low incidence (2/19; 10.5%) of male offspring exposed to transplacental cis-DDP (group 1a) developed renal cell adenomas, Postnatal administration of NaBB significantly enhanced this incidence (10/22; $p < 0.01$) in cis-DDP-initiated offspring. Also, multiple kidney tumors were more common in group 1b than any other group and three animals in this group developed frank renal cell carcinomas, cis-DDP, administered transplacentally, was a complete carcinogen for rat liver as the incidence of hepatocellular adenomas was significantly higher in offspring exposed transplacentally to cis-DDP than in those exposed to saline (20/82 vs 3/75; $p < 0.05$). NaBB, a known promoter of hepatocellular carcinogenesis in adult rats initiated with N-nitrosodiethylamine, failed to promote liver carcinogenesis initiated by transplacental cis-DDP. Tumors of the central nervous system (3/82; gliomas) and peripheral nervous system (2/82; schwannomas) were found only in offspring exposed transplacentally to cis-DDP. Thus, cis-DDP, administered transplacentally, was a strong initiator of renal cell tumors and a complete carcinogen for multiple organs in rat offspring. (C) 1995 Academic Press, Inc.

Diwan BA, Kasprzak KS, Rice JM. 1992 . Transplacental carcinogenic effects of nickel(II) acetate in the renal cortex, renal pelvis and adenohypophysis in F344/NCr rats. Carcinogenesis 13:1351-1357.
Abstract: Nickel(II) acetate (NiAcet), a soluble nickel salt known to be an effective initiator of renal epithelial tumors in adult rats, was studied for possible transplacental carcinogenicity. Pregnant F344/NCr rats were given NiAcet i.p. either once a day on day 17 (90 mumol/kg body wt; group 1) or twice on days 16 and 18 of gestation (45 mumol/kg body wt/day; group 2). Offspring of these rats were further subdivided into groups 1A and B and 2A and B, respectively. Groups 1A and 2A received ordinary tap water while groups 1B and 2B received drinking water containing 500 p.p.m. sodium barbital (NaBB) during weeks 4-85 of age. Renal cortical epithelial and renal pelvic transitional epithelial tumors occurred in male offspring given NiAcet prenatally followed by NaBB postnatally (group 1B, 15 tumors in 8/15 rats; group 2B, 10 tumors in 7/15), but not in male offspring given NiAcet only (0/32) or in controls given prenatal sodium acetate (NaAcet) only (0/15) and rarely in males given NaAcet followed by the promoter NaBB (1/15). No renal tumors occurred in females. Pituitary tumor incidence was significantly higher in offspring of both sexes given NiAcet prenatally (NaAcet controls, 4/31, both sexes combined; group 1A, 14/33, $P = 0.012$; group 2A, 14/31, $P = 0.008$). Pituitary tumors appeared much earlier in rats given NiAcet prenatally, with or without postnatal NaBB, and often were malignant by cytologic and histologic criteria including pleomorphism and invasion of adjacent structures, unlike the well-differentiated adenomas that occurred less frequently in untreated rats. These results are the first evidence that Ni(II) is a potent transplacental initiator of epithelial tumors in fetal rat kidney and a complete transplacental carcinogen for rat pituitary.

Diwan BA, Ohshima M, Rice JM. 1989. Effects of postnatal administration of tumour-promoting barbiturates on the development of tumours initiated by prenatal exposure of fetal rats and mice to N-alkylnitrosoureas. IARC Sci Publ :75-80.
Abstract: Prenatal administration of chemical carcinogens followed by postnatal application of tumour promoters can result in tumour formation at sites where no tumours would occur in the absence of promotion. Three different epithelia in mice and rats have been shown to be susceptible to transplacental

initiation by N-nitroso compounds or polynuclear aromatic hydrocarbons, yielding potentially neoplastic cells in fetal tissues which can remain latent indefinitely until stimulated to proliferate by postnatal exposure to a promoting agent. These include epidermal squamous epithelium in mice, renal cortical epithelium in mice, and thyroid follicular epithelium in both mice and rats. The fact that effective promoters of carcinogenesis in nonsquamous epithelia include drugs such as phenobarbital that are administered to humans in high doses for prolonged periods suggests that prenatal initiation followed by postnatal promotion may pose significant risks for humans, and should be considered in designing epidemiological searches for etiological factors that contribute to the incidence of epithelial tumours in man.

Diwan BA, Rehm S, Rice JM. 1996. Age- and dose-dependent transplacental carcinogenesis by N-nitrosoethylurea in Syrian golden hamsters. Journal of Cancer Research & Clinical Oncology 122:643-652.
Abstract: Syrian golden hamsters have a very short period (15 days) of gestation. The implantation of the blastocyst occurs on day 5, embryogenesis proceeds very rapidly thereafter and neural tube closure is completed by day 9. In the present study the effects of two different doses of N-nitrosoethylurea (NEU) administered at various stages of gestation were quantitatively evaluated in Syrian golden hamsters. NEU at either 0.2 or 0.5 mmol/kg was administered transplacentally as a single i.p. injection to pregnant hamsters on gestation days 7, 8, 9, 10, 11, 12, 13, or 14. The incidence, latency period and multiplicity of tumors varied with the dose of NEU and the stage of development at the time of NEU administration. Although tumors of the peripheral nervous system predominated, a variety of other tumors, including melanomas and visceral tumors of epithelial and mesenchymal origin, were also observed in hamster offspring exposed transplacentally to NEU. Sensitivity to transplacental carcinogenesis was maximal during late gestation and very low before day 9.

Diwan BA, Rice JM. 1995. Effect of stage of development on frequency and pathogenesis of kidney tumors induced in Noble (Nb) rats exposed prenatally or neonatally to N-nitrosoethylurea. Carcinogenesis 16:2023-2028.
Abstract: Wilms' tumor of kidney, a common human childhood neoplasm, is modeled by nephroblastomas induced by prenatal exposure of some rodents to alkylating agents. Noble (Nb) rats are especially susceptible. We studied the ontogeny of susceptibility by treatment with N-nitrosoethylurea (NEU) on gestation day 10, 12, 14, 16 or 18 or neonatal day 1, 3, 5, 7, or 10. No nephroblastomas were observed in offspring exposed to NEU on day 10 or 12 of gestation. In contrast, nephroblastomas commonly occurred in rats exposed on gestation day 14, 16 or 18 of gestation, with the highest incidence (48%) after treatment on day 18. Nephroblastomas were rare (< 10%), but renal mesenchymal tumors were common (25-30%) in rats exposed to NEU on day 1 or 3 after birth. In rats exposed to NEU on day 7 or 10 only renal mesenchymal tumors were seen. Thus our results suggest that the stage of differentiation of fetal and neonatal kidneys at the time of NEU administration determines the frequency and type of kidney tumors induced in Nb rats. Since NEU induces both nephroblastomas and mesenchymal tumors in this strain, this experimental model may prove useful for the study of molecular mechanisms involved in the development of these two histogenetically different types of kidney tumors.

Diwan BA, Riggs CW, Logsdon D, Haines DC, Olivero OA, Rice JM, Yuspa SH, Poirier MC, Anderson LM. 1999. Multiorgan transplacental and neonatal carcinogenicity of 3'-azido-3'-deoxythymidine in mice. Toxicology & Applied Pharmacology 161:82-99.
Abstract: The anti-HIV drug 3'-azido-3'-deoxythymidine (AZT) is used successfully for reduction of perinatal viral transmission. However toxic side effects including carcinogenesis are possible. To test this, pregnant CD-1 Swiss mice were given 25.0 or 12.5 mg AZT on gestation days 12-18. Previously we reported an increase in lung, liver, and female reproductive system tumors in offspring euthanized at 1 year (Olivero et al., J. Natl. Cancer Inst. 89, 1602-1608, 1997). Findings for all remaining offspring up to 2 years old are reported here. AZT effects were most prominent in female offspring, with a significant threefold increase in lung tumors, a reduction in lymphoblastic and follicle center cell lymphomas, and a significant increase in histiocytic sarcomas (0 in controls, 3% after low-dose AZT, and 8% after high-dose AZT, p = 0.022). Dose-dependent incidences of mammary gland, ovarian, and seminal vesicle tumors were low but significant: 0/106 controls, 3/105 low-dose, and 8/105 high-dose mice presented one of these neoplasms (p = 0.0025). Incidences of females showing any clearly AZT-related neoplasm, in lung, liver, ovary, or mammary gland or histiocytic sarcoma, in the second year, were 12/32 after the low dose and 14/27 after the high dose vs 3/23 controls (p = 0.0045). Also, the sensitivity of neonatal mice was assessed

by administration of 25, 50, 100, or 200 mg/kg AZT on postnatal days 1 through 8. The effects at 2 years were similar to those seen after transplacental exposure, with significant increases in lung, liver, and mammary tumors in females. The results confirm that AZT is a moderately effective perinatal carcinogen in mice, targeting several tissue types.

Dmitrenka V, Shostak K, Boyka O, Khomenko O, Rozumenko V, Malisheva T, Shamayev M, Zozulya Y, Kavsan V. 2005. Reduction of the Transcription Level of the Mitochondrial. Genome in Human Glioblastoma. Cancer Lett 218:99-107.
Abstract: Screening of human fetal brain cDNA library by glioblastoma (GB) and normal human brain total cDNA probes revealed 80 differentially hybridized clones. Hybridization of the DNA from selected clones and the same cDNA probes confirmed this difference for 38 clones, of which eight clones contained Alu-repeat inserts with increased levels in GB. Thirty clones contained cDNAs corresponding to mitochondrial genes for ATP synthase subunit 6 (ATP6), cytochrome c oxidase subunit II (COXII), cytochrome c oxidase subunit III (COXIII), NADH dehydrogenase subunit 1 (ND 1), NADH dehydrogenase subunit 4 (ND4), and mitochondrial 12S rRNA. The levels of all these mitochondrial transcripts were decreased in glioblastomas as compared to tumor-adjacent histologically normal brain. Earlier we found the same for cytochrome c oxidase subunit I (COXI) Serial Analysis of Gene Expression (SAGE) showed lower content of the tags for all mitochondrial genes in GB SAGE libraries and together with our experimental data could serve as evidence of general inactivation of the mitochondrial genome in glioblastoma-the most malignant and abundant form of human brain tumor. (C) 2004 Published by Elsevier Ireland Ltd.

Dolinoy DC, Weidman JR, Jirtle RL. 2007 Apr-May. Epigenetic gene regulation: linking early developmental environment to adult disease. Reprod Toxicol 23:297-307.
Abstract: Traditional studies on the combined effects of genetics and the environment on individual variation in disease susceptibility primarily focus on single nucleotide polymorphisms that influence toxicant uptake and metabolism. A growing body of evidence, however, suggests that epigenetic mechanisms of gene regulation, such as DNA methylation and chromatin modification, are also influenced by the environment, and play an important role in the fetal basis of adult disease susceptibility. Studying the influence of early environmental exposures on metastable epialleles and imprinted genes offers insight into the mechanisms affecting the fetal epigenome and subsequent adult disease susceptibility. In this review, we introduce the reader to the field of environmental epigenomics, provide information on the important epigenetic control mechanisms and epigenetic phenomena in mammals, and summarize the current body of literature on nutritional and environmental influences affecting the epigenome.

Doll R, Wakeford R. 1997 . Risk of childhood cancer from fetal irradiation. Br J Radiol 70:130-139.
Abstract: The association between the low dose of ionizing radiation received by the fetus in utero from diagnostic radiography, particularly in the last trimester of pregnancy, and the subsequent risk of cancer in childhood provides direct evidence against the existence of a threshold dose below which no excess risk arises, and has led to changes in medical practice. Initially reported in 1956, a consistent association has been found in many case-control studies in different countries. The excess relative risk obtained from combining the results of these studies has high statistical significance and suggests that, in the past, a radiographic examination of the abdomen of a pregnant woman produced a proportional increase in risk of about 40%. A corresponding causal relationship is not universally accepted and this interpretation has been challenged on four grounds. On review, the evidence against bias and confounding as alternative explanations for the association is strong. Scrutiny of the objections to causality suggests that they are not, or may not be, valid. A causal explanation is supported by evidence indicating an appropriate dose-response relationship and by animal experiments. It is concluded that radiation doses of the order of 10 mGy received by the fetus in utero produce a consequent increase in the risk of childhood cancer. The excess absolute risk coefficient at this level of exposure is approximately 6% per gray, although the exact value of this risk coefficient remains uncertain.

Donovan PJ. 1999. Cell sensitivity to transplacental carcinogenesis by N-ethyl-N-nitrosourea is greatest in early post-implantation development. Mutation Research-Fundamental and Molecular Mechanisms of Mutagenesis 427:53-64.
Abstract: In a clear demonstration of the changing sensitivity of the developing mammal to transplacental carcinogenesis, Ivankovic and Druckrey [S. Ivankovic, ii. Druckrey, Transplacentare Erzeugung maligner

Tumoren des Nervensystem: I.;Athyl-nitroso-harnstoff (ANH) an ED IX-Ratten, Z. Krebsforsch. 71 (1968) 320-360] exposed pregnant ED IX rats to a pulse of N-ethyl-N-nitrosourea (ENU), a reactive carcinogen with a half-life of 20 min. No tumors were seen with ENU exposure before gestation day 12, but the multiplicity of neurogenic tumors increased steadily thereafter and was greatest with treatment on day 30, followed by a decline in sensitivity for the last three days of gestation. Similarly, a transplacental study of ENU in the Syrian hamster [B.A. Diwan, S. Rehm, J.M. Rice, Age- and dose-dependent transplacental carcinogenesis by N-nitrosoethylurea in Syrian golden hamsters, J. Cancer Res. Clin. Oncol. 122 (1996) 643-652] found that the numbers of tumors induced were greatest after exposure of late fetal stages. While these observations suggested that embryonic cells are refractory to carcinogenesis, an alternative explanation could be that a significant tumor yield was not observed because too few target cells were present in the embryo. I have resolved this issue by combining these published data with others on the numbers of neuroectodermal cells in the developing ED IX rat brain [R. Miiller, M.F. Rajewsky, Elimination of O-6-ethylguanine from the DNA of brain, liver, and other rat tissues exposed to ethylnitrosourea at different stages of prenatal development? Cancer Res. 43 (1983) 2897-2904] and total cell counts of successive developmental stages of the Syrian hamster fetus [P.J. Donovan, G.T. Smith, Cell sensitivity to transplacental mutagenesis by N-ethyl-N-nitrosourea is greatest during early gestation in the Syrian hamster, Mutation Res., 1999, this issue], allowing the risk per cell at different stages of gestation to be calculated. Sensitivity to carcinogenesis was found to be greatest early in gestation and to decrease as gestation proceeds. For the rat model, tumor frequency per cell changed from 1.3 X 10(-6) at day 12 exposure to 2.6 x 10(-6) at day 23 exposure, a 50-fold decrease. For the hamster model, the tumor-initiation rate decreased 1250-fold from 1.2 X 10(-5) at day 7 exposure to 9.6 X 10(-9) at day 13 exposure. Thus, two independent experiments with different rodent species demonstrate that sensitivity of individual cells to damage leading to transplacental carcinogenesis is greatest in the early fetus and lessens markedly as gestation proceeds, in parallel with changing sensitivity to mutation (Donovan et al,, Mutat. Res., this issue).

Donovan PJ, Smith GT. 1999. Cell sensitivity to transplacental mutagenesis by N-ethyl-N-nitrosourea is greatest during early gestation in the Syrian hamster. Mutation Research-Fundamental & Molecular Mechanisms of Mutagenesis 427:47-58.

Abstract: The extremely high rate of cell division that occurs during early embryogenesis is hypothesized to predispose to high rates of mutation after chemical exposure, We tested this supposition experimentally. To probe the variation in susceptibility to mutation induction as a function of gestation stage, somatic cells of the developing Syrian hamster were isolated after transplacental treatment with N-ethyl-N-nitrosourea (ENU), Mutants were quantified using either 6-thioguanine (6-TG) or diphtheria toxin (DT) as selective agents. Several different approaches were used. In one, three litters were exposed on each gestation day and fetuses were removed on day 13. Maximum fetal sensitivity to ENU's genotoxic action was noted when treatment was at days 8 and 9, fewer mutants being obtained with earlier and later exposures. To compensate for the low numbers of target cells early in gestation, this experiment was repeated using larger numbers of litters exposed at the earlier time points, and the highest mutation frequency was now found to occur after treatment on gestation days 6 and 7, In the second approach, mutations were quantified in cells harvested 24 h after transplacental ENU exposure. Hen again, embryos exposed at earlier times of gestation were more susceptible than those treated at later periods. Based on the total cell numbers in embryos and fetuses at each gestation day, we conclude that mutation frequency is maximal on day 6, corresponding to the primitive streak stage with extremely high rates of cell division. (C) 1999 Elsevier Science B.V. All rights reserved.

Donovan PJ, Smith GT. 2002. X-ray induced mutation in Syrian hamster fetal cells. Mutation Research-Fundamental & Molecular Mechanisms of Mutagenesis 500:9-15.

Abstract: Transabdominal X-rays are a risk factor for childhood leukemia, and X-ray exposure of mouse fetuses has led to increases in both mutations and initiated tumors in offspring. However, fetal sensitivity and dose-response characteristics with regard to transplacental mutagenesis by X-rays have never been quantified. In the current experiment, pregnant Syrian hamsters at day 12 of gestation were irradiated with 300-kV X-rays. Twenty-four hours later, the fetuses were removed and their cells were allowed a 5 day expression time in culture. They were then seeded for colony formation and also for mutation selection by 6-thioguanine (6-TG). Mutation frequency was linear over the entire dose range, 10-600 R. The average induced 6-TG mutant frequency was 4.7 x 10(-7) per R. These results suggest that fetal cells are highly

sensitive to induction of mutations by X-rays, and that a no-effect threshold is not likely. The 10 R dose caused a 25-fold increase in mutation frequency over the historical control, 45 x 10(-7) versus 1.8 x 10(-7), an increase per R of 2.5-fold. Increased risk of childhood cancer related to obstetrical transabdominal X-ray has also been estimated at 2.5-fold per R. Thus, our results are consistent with mutation contributing to this effect. Published by Elsevier Science B.V.

Donovan PJ, Smith GT, Nardone R. 2004. The mutagenic effects of 7,12-dimethylbenz[a]anthacene, 3-methylcholanthrene and benzo[a]pyrene to the developing Syrian hamster fetus measured by an in vivo/in vitro mutation assay. Mutation Research-Fundamental & Molecular Mechanisms of Mutagenesis 554:111-120.

Abstract: The transplacental mutagenicity of three polycylic aromatic hydrocarbons, 7,12-dimethylbenz[a]anthacene (DMBA), 3-methylcholanthrene (MC) and benzo[a]pyrene (BP), was measured by an in vivo/in vitro mutation assay. Fetal sensitivity and dose-response characteristics with regard to transplacental mutagenesis by these compounds have never been quantified. In the current experiment, pregnant Syrian hamsters were exposed to these compounds at day 12 of gestation. Twenty-four hours later the fetuses were removed and their cells were allowed a 5-day expression time in culture. They were then seeded for colony formation and also for mutation selection by diphtheria toxin. DMBA at 0.2 mmol/kg (51.3 mg/kg) had an induced mutant frequency of 1.56 x 10(-4) Mutants per surviving cell. This was 598 times the historical control. DMBA at 0.2 mmol/kg was 3.6 times more potent than the highly mutagenic positive control, ethylnitrosourea, at 1 mmol/kg. DMBA also caused a dose-dependent increase in cloning efficiency, which was highly correlated with mutation rate. BP and MC were less effective than DMBA, causing increased mutations that were 31.6 and 17.7 times the historical control, respectively, and for neither was there any correlation of mutation rate with cloning efficiency. The special effectiveness of DMBA as a transplacental mutagen may relate to its ability to cause increased cell division and fixation of DNA lesions as mutations. (C) 2004 Elsevier B.V. All rights reserved.

Draper G, Vincent T, Kroll ME, Swanson J. 2005 . Childhood cancer in relation to distance from high voltage power lines in England and Wales: A case-control study. Br Med J 330:1290.

Abstract: OBJECTIVE: To determine whether there is an association between distance of home address at birth from high voltage power lines and the incidence of leukaemia and other cancers in children in England and Wales. DESIGN: Case-control study. SETTING: Cancer registry and National Grid records. SUBJECTS: Records of 29 081 children with cancer, including 9700 with leukaemia. Children were aged 0-14 years and born in England and Wales, 1962-95. Controls were individually matched for sex, approximate date of birth, and birth registration district. No active participation was required. MAIN OUTCOME MEASURES: Distance from home address at birth to the nearest high voltage overhead power line in existence at the time. RESULTS: Compared with those who lived > 600 m from a line at birth, children who lived within 200 m had a relative risk of leukaemia of 1.69 (95% confidence interval 1.13 to 2.53); those born between 200 and 600 m had a relative risk of 1.23 (1.02 to 1.49). There was a significant ($P < 0.01$) trend in risk in relation to the reciprocal of distance from the line. No excess risk in relation to proximity to lines was found for other childhood cancers. CONCLUSIONS: There is an association between childhood leukaemia and proximity of home address at birth to high voltage power lines, and the apparent risk extends to a greater distance than would have been expected from previous studies. About 4% of children in England and Wales live within 600 m of high voltage lines at birth. If the association is causal, about 1% of childhood leukaemia in England and Wales would be attributable to these lines, though this estimate has considerable statistical uncertainty. There is no accepted biological mechanism to explain the epidemiological results; indeed, the relation may be due to chance or confounding.

Dubois M, Pfohlleszkowicz A, Grosse Y, Kremers P. 1995. DNA adducts and P450 induction in human, rat and avian liver cells after exposure to polychlorobiphenyls. Mutation Research-Genetic Toxicology 345:181-190.

Abstract: Polychlorinated biphenyls (PCBs) are industrial chemicals which have been detected in fish, birds and humans. They are known to exert marked effects on the liver. They induce hepatocellular carcinoma in rats and birds, and are suspected of being carcinogenic to humans. To better understand the genotoxic effects of PCBs, we used P-32-postlabelling to investigate DNA adduct formation, after exposure to PCBs (Aroclor 1254 and 3,3',4,4'-tetrachlorobiphenyl), in primary cultures of fetal hepatocytes from two animal species and in a human cell line (Hep G2). We also studied the induction of 7-ethoxyresorufin-O-

deethylase (EROD) in these PCB-treated cells. The three cell types used are known to express different cytochrome P450 families. The aim was to see whether a correlation could be established between EROD activity (a CYP1A1-related activity) and DNA adduct formation, DNA adducts were found in all three models after exposure to 50 mu M 3,3',4,4'-tetTachloiphenyl, The number of adducts was higher in quail hepatocytes (37 adducts per 10(9) nucleotides) than in rat hepatocytes or Hep G2 cells (20 adducts per 10(9) nucleotides in both cases). The major adduct was the same in all three cell types, but some adducts were found in only one or two species. These inter-species differences probably reflect metabolic differences leading to different ultimate carcinogens. Exposure to Aroclor 1254 failed to produce significant levels of DNA adducts, suggesting that pre-treated cells are required to magnify Aroclor 1254 metabolism. No correlation was found between adduct formation and the level of EROD induction.

Duch DS, Bigner DD, Bowers SW, Nichol CA. 1979. Dihydrofolate reductase in primary brain tumors, cell cultures of central nervous system origin, and normal brain during fetal and neonatal growth. Cancer Res 39:487-491.

Abstract: Dihydrofolate reductase (DHFR) was measured during the development in rats of brain tumors induced following inoculation with avian sarcoma virus. Increasing activity of this enzyme in brain was correlated with the course of primary brain tumor growth. The specific activities of DHFR in primary human brain tumor tissues were comparable to those found in avian sarcoma virus-induced brain tumors in rats. Specific activities of DHFR in cell cultures derived from human and rat primary intracranial gliomas and sarcomas were up to 6 times those found in adult rat liver. The presence of DHFR in neoplasms of central nervous system origin is relevant to the development of folate antagonists which, unlike methotrexate, can readily cross the blood-brain barrier. In normal developing rat brain, DHFR specific activity was high in embryos at 19 days of gestation and declined thereafter, until at 20 days after birth the activity was very low. The methotrexate titration assay was used to measure enzyme levels in the brains of fetal and newborn rats, and good correlation with the spectrophotometric assay was observed. The pattern was different in liver, showing maximum activity 11 days after birth and retaining high activity in adult liver. Both the cofactor requirement and the sensitivity to methotrexate indicate that the enzyme in the brain is DHFR.

Durando M, Kass L, Piva J, Sonnenschein C, Soto AM, Luque E, Munoz-de-Toro M. 2007. Prenatal bisphenol A exposure induces preneoplastic lesions in the mammary gland in Wistar rats. Environ Health Perspect 115:80-86.

Abstract: Background: Humans are routinely exposed to bisphenol-A (BPA), an estrogenic compound that leaches from dental materials, food and beverage containers and other consumer products. Prenatal exposure to BPA produced long-lasting and profound effects on rodent hormone dependent tissues that are manifested one to six months after the end of exposure. Objective: The aim of the present work was to examine whether *in utero* exposure to BPA alters mammary gland development and increases it susceptibility to carcinogen N-nitroso-N-methylurea (NMU). Methods: Pregnant Wistar rats were exposed to BPA (25 µg/kg body weight-bw-/day) or to vehicle. Female offspring were sacrificed at postnatal day (PND) 30, 50, 110 or 180. On PND 50 a group of rats received a single subcarcinogenic dose of NMU (25 mg/kg) and they were sacrificed at either PND 110 or 180. Results: At puberty, animals exposed prenatally to BPA howed an increased proliferation/apoptosis ratio both in the epithelial and stromal compartments. During adulthood (PND 110 and 180), BPA exposed animals showed an increased number of hyperplastic ducts and augmented stromal nuclear density. Moreover, the stroma associated with hyperplastic ducts showed signs of desmoplasia and contained an increased number of mast cells, suggesting a heightened risk of neoplastic transformation. Administration of a subcarcinogenic dose of NMU to animals exposed prenatally to BPA increased the percentage of hyperplastic ducts and induced the development of neoplastic lesions. 6 Conclusions: Our results demonstrate that the prenatal exposure to low doses of BPA perturbs mammary gland histoarchitecture and increases the carcinogenic susceptibility to a chemical challenge administered 50 days after the end of BPA exposure.

Edwards AJ, Anderson D, Brinkworth MH, Myers B, Parry JM. 1999. An investigation of male-mediated F1 effects in mice treated acutely and sub-chronically with urethane. Teratogenesis, Carcinogenesis, & Mutagenesis 19:87-103.

Abstract: In order to investigate the alleged potential of paternally administered urethane to cause foetal abnormalities and heritable tumours, male CD-1 mice were treated with urethane, either acutely by

intraperitoneal injection at doses of 1.25 and 1.75 g/kg bodyweight (bwt) or sub-chronically in the drinking water at 1.25 for 10 weeks, and 3.75 mg/ml for 9 weeks or vehicle for the control groups. They were mated to untreated females 1 week later. Uterine contents of half the pregnant females were examined just before full term, while the remaining females were allowed to deliver their litters. The resulting F1 offspring were observed for approximately 18 months and 12 months for acute and sub-chronic exposures respectively and subjected to necropsy examination. Some of the mice treated acutely with 1.75 g/kg bwt exhibited partial infertility but none of those treated with 1.25 g/kg bwt had an adverse effect on their reproductive ability. There was no genetic effect of acute urethane treatment on male germ cells as indicated by dominant lethality. After birth, there was an increase ($P < 0.05$) in post-implantation deaths possibly due to perinatal mortality. There was an increased incidence and earlier onset of liver tumours induced in F1 male offspring from F0 males treated with 1.75 g/kg bwt, (20.7% vs. 10.1%, $P = 0.026$) but not in the female offspring. F1 males from both treatment groups had mean bodyweights significantly higher than controls ($P < 0.01$). Some males from each dose group of the acute study were examined using the restriction site mutation assay involving analysis of exon sequences. No mutations were identified in testes, liver or spleen of DNA isolated from the urethane-treated animals. No reproductive or genetic effects were seen with sub-chronic treatment at either 1.25 or 3.75 mg/ml urethane nor was there any predisposition of F1 animals to tumours although observation times were shorter.

Efird JT, Holly EA, Preston-Martin S, Mueller BA, Lubin F, Filippini G, Peris-Bonet R, Mccredie M, Cordier S, Arslan A, Bracci PM. 2003. Farm-related exposures and childhood brain tumours in seven countries: Results from the SEARCH International Brain Tumour Study. Paediatric & Perinatal Epidemiology 17:201-211.
Abstract: A total of 1218 cases of childhood brain tumours (CBT) and 2223 control subjects from the general population were included in a population-based case-control study conducted in nine centres in seven countries. Mothers were asked about farm- or agriculture-related exposures. Significantly elevated odds ratios (OR) for CBT were associated with children's personal and maternal prenatal exposure while living on a farm with pigs (child OR = 1.7, mother OR = 2.3), horses (child OR = 1.6, mother OR = 1.8), dogs (child OR = 1.5, mother OR = 1.5) and cats (child OR = 1.5, mother OR = 1.7). Children who were exposed to pigs, horses and cats combined, while living on a farm, had a threefold elevated OR for CBT. Increased ORs for primitive neuroectodermal tumours (PNET) were associated with children's farm exposure to dogs (OR = 1.9) and cats (OR = 2.2), and maternal farm exposure to pigs (OR = 4.2). The OR for CBT was elevated (OR = 2.3) for children of mothers who had preconception/prenatal farm- or agriculture-related employment involving potential contact with animals, relative to no farm- or agriculture-related employment. In particular, increased ORs for CBT were observed for children of mothers who were employed as general farmers (OR = 4.1) or general farm workers (OR = 3.8). During the 5 years preceding the index child's birth, maternal exposures were related to CBT, relative to no maternal exposure to agricultural chemicals or animal products: fertilisers (OR = 1.8), pesticides (OR = 2.0), animal manure (OR = 2.0) and unprocessed wool (OR = 3.0). Our findings suggest that various farm-related exposures are positively associated with CBT and warrant further investigation into the public health importance of these associations.

Ekbom A, Erlandsson G, Hsieh C, Trichopoulos D, Adami HO, Cnattingius S. 2000 . Risk of breast cancer in prematurely born women. J Natl Cancer Inst 92:840-841.

Ekbom A, Hsieh CC, Lipworth L, Wolk A, Ponten J, Adami HO, Trichopoulos D. 1996. Perinatal characteristics in relation to incidence of and mortality from prostate cancer. Br Med J 313:337-341.
Abstract: Objective-To test the hypothesis that factors causing morbidity and mortality from prostate cancer may operate in utero. Design-Matched case-control study of singleton men born between 1874 and 1946 at one hospital. Setting-Uppsala University Hospital. Subjects-250 patients with prostate cancer and 691 controls, including 80 patients who died from prostate cancer and their 196 matched controls. Main outcome measures-Mother's age at menarche, parity, pre-eclampsia or eclampsia before delivery, age at delivery and socioeconomic status; case or control's birth length and weight, placental weight, prematurity derived from gestational age, and presence of jaundice. Results-Both pre-eclampsia (odds ratio 0, 95% confidence interval 0 to 0.71) and prematurity (0.31, 0.09 to 1.04) were inversely associated with incidence of prostate cancer. Among subjects born full term, placental weight, birth weight, and ponderal index (weight/height(3)) showed non-significant positive associations with prostate cancer incidence, and

stronger associations with mortality. Conclusion-Prenatal exposures that are likely correlates of pregnancy hormones and other growth factors are important in prostate carcinogenesis and influence the natural course as well as the occurrence of this cancer.

Ekbom A, Trichopoulos D, Adami H-O, Hsieh C-C, Lan S-J. 1992. Evidence of prenatal influences on breast cancer risk. Lancet 340:1015-1018.
Abstract: Intrauterine exposure to high concentrations of endogenous pregnancy estrogens may be important in the etiology of breast cancer. In a nested-case control study study we have assessed the relation between breast cancer risk and indicators of pregnancy estrogen concentrations; pre-eclampsia/eclampsia is negatively related and measures of fetal size are positively related to estrogen concentrations. Standard records for women born at Uppsala University hospital between 1874 and 1954 were linked with records of invasive breast cancer cases, identified through their unique national registration numbers in the Swedish Cancer Registry during 1958-90. For each breast cancer case, we selected as potential controls female offspring of the first three mothers admitted to the hospital after the case's mother; only controls still living in Sweeden and free from breast cancer when it was diagnosed in the case were finally included. Conditional logistic regression analysis was done for 458 breast cancer cases and 1197 matched controls. Pre-eclampsia/eclampsia was associated with a breast cancer rate ratio of 0.24 (95 % confidence interval 0.09-0.70, p=0.01). Linear trends for breast cancer incidence with increasing birth weight, birth length, and placental weight were positive but not significant. Thus prenatal factors are important in breast carcinogenesis. Concentrations of pregnancy estrogens may be one such factor, but other prenatal or perinatal factors cannot be excluded.

Ekbom A, Wuu J, Adami HO, Lu CM, Lagiou P, Trichopoulos D, Hsieh C. 2000 . Duration of gestation and prostate cancer risk in offspring. Cancer Epidemiology, Biomarkers & Prevention 9:221-223.
Abstract: This large population-based nested case-control study investigated the importance of perinatal characteristics as risk factors for prostate cancer in later life in a cohort of men who were born between 1889 and 1941 in Stockholm, Sweden. Eight hundred and thirty-four prostate cancer cases over 18 years of age and of singleton birth were identified from the cohort between 1958 and 1994. For each case, singleton males born live to the first four mothers admitted after the case's mother were selected as potential controls; 1880 eligible controls were included in the study. For each study subject, we obtained data on mother's parity, pre-eclampsia or eclampsia before delivery, age at delivery, and socioeconomic status, as well as child's birth length and weight, placental weight, and gestational age. Odds ratio (OR) estimates and 95% confidence intervals (CIs) were derived from logistic regression analyses. We found no statistically significant differences between cases and controls with respect to maternal age, socioeconomic status, or parity. Birth weight, birth length, and placental weight were also not significantly related to prostate cancer risk. Pregnancy toxemia (OR = 0.33; 95% CI, 0.07-1.45) and longer gestation age were associated with a reduced risk of prostate cancer; the OR estimate was 0.94 (95% CI, 0.89-0.99) for each 1-week prolongation of the duration of gestation. Our results suggest that birth size indicators are not important risk factors for prostate cancer in later life. In addition, our data on gestation age indicate that the late in utero environment may be as important as the early in utero environment in the modulation of prostate cancer risk in offspring.

Ellender M, Harrison JD, Kozlowski R, Szluinska M, Bouffler SD, Cox R. 2006. In utero and neonatal sensitivity of Apc(Min/+) mice to radiation-induced intestinal neoplasia. Int J Radiat Biol 82:141-151.
Abstract: Purpose: To assess the sensitivity of Apc(Min/+) mice (adenomatous polyposis coli Apc, multiple intestinal neoplasia, Min) to the development of intestinal adenomas after x-irradiation in utero, as neonates, or as young adults. Materials and methods: CHB6 Apc(Min/+) mice were exposed to an acute dose of 2 Gy x-rays either in utero on day 7 or 14 post-conception, as 2-day or 10-day neonates or as 35-day young adults. Tumour identification and counting was performed 200-214 days later. Results: Irradiation as 10-day-old neonates resulted in a significantly greater overall tumour incidence (average of about 130 tumours per animal) than irradiation as 35-day-old young adults (about 70 tumours). Irradiation as 2-day-old neonates resulted in an intermediate incidence (about 85 tumours). In contrast, the greatest tumour incidence observed after in utero irradiation of Apc(Min/+) mice, of about 44 tumours per animal after 2 Gy irradiation at 14 days post-conception, was significantly lower than the incidence in irradiated adults. Tumour incidences after irradiation as 7-day embryos was not significantly raised above numbers in unirradiated controls (about 30 tumours). These tumour numbers include cystic crypts, largely radiation-

induced, which were classed as early stage microadenomas on the basis of loss of wild-type Apc(+) and expression of beta-catenin. Conclusions: The sensitivity of Apc(Min/+) mice to the induction of intestinal tumours by radiation was shown to be in the order: 10 d neonates 42 d neonates 435 d young adults 414 d fetus 47 d embryo.

Emura M, Richter-Reichhelm HB, Boning W, Eichinger R, Schoch C, Althoff J, Mohr U. 1982. A fetal respiratory epithelial cell line for studying some problems of transplacental carcinogenesis in Syrian golden hamsters. Journal of Cancer Research & Clinical Oncology 104:133-144.
Abstract: Using repeated cloning and treatment with cis-HPL (200 micrograms/ml), an analogue of a procollagen precursor inhibitory to the growth of collagen-synthesizing cells of mesenchymal origin, clonally premature epithelial cell lines were isolated from fetal SGH lungs cultured on the 15th day of gestation. One of the cell lines, M3E3/C3, which has been extensively studied for biological characterization, developed poorly differentiated carcinomas in injected hamsters after transformation by MNNG. Moreover, when grown on collagen gel, this cell line indicated an obvious potency for in vitro differentiation in response to vitamin A by developing activated Golgi regions, well developed rER and a number of mucus-like granules. Since such a differentiative responses is expected to be definable in the light of respiratory epithelium developing in utero, this cell line may be useful for studying mechanisms of differentiation-dependent sensitivity of fetal organs to transplacental carcinogen exposure.

Emura M, Richter-Reichhelm HB, Schneider P, Mohr U. 1980. Sensitivity of Syrian golden hamster fetal lung cells to benzo[a]pyrene and other polycyclic hydrocarbons in vitro. Toxicology 17:149-155.
Abstract: Dose responses were compared of cultured fetal Syrian golden hamster lung cells (FSHL) to the toxic and transforming effects of benzo[a]pyrene (B[a]P), benzo[b]fluoranthene (B[B]F), benz[a]anthracene (B[a]A, indeno[1,2,3-c,d]pyrene (I[c,d]P), benzo[k]fluoranthene (B[k]F) and benzo[e]pyrene (B[e]P). Effort was first given to standardising the techniques for evaluating B[a]P dose-responses. These polycyclic aromatic hydrocarbons (PAH) were then tested at concentrations of up to 1 microgram/ml, and only B[a]P showed clear cytotoxicity. The transforming effects of B[b]F, B[a]A and I[c,d]P at 1 microgram/ml appeared comparable to those of B[a]P at 0.05 microgram/ml.

Enomoto K, Dempo K, Mori M, Onoe T. 1978 . Histopathological and ultrastructural study on extramedullary hematopoietic foci in early stage of 3'-methyl-4-(dimethylamino)azobenzene hepatocarcinogenesis. Gann 69:249-254.
Abstract: A quantitative analysis was performed on the extramedullary hematopoietic foci which appeared in the liver during the early stages of hepatocarcinogenesis with 3'-methyl-4-(dimethylamino)azobenzene in rats. The frequency in the appearance of the foci reached a maximum at around 3 weeks of azo-dye feeding. Since the liver in this period has been known to show deviation of various characteristics toward fetal liver, an intimate correlation of the appearance of the foci and fetal character of the liver was suggested. Histologically the hematopoietic foci were always observed in the sinusoidal space of original hepatocytes adjacent to the oval cell proliferating area. Ultrastructurally the cells of the foci were identified as erythroblasts and were found in the space of Disse as seen in the hematopoiesis in fetal liver.

Ericson A, Kallen B. 1994. Pregnancy outcome in Sweden after the Chernobyl accident. Environ Res 67:149-159.
Abstract: Objective. To study pregnancy outcome including development of childhood cancer in areas within Sweden with the highest radioactive fallout after the Chernobyl accident in 1986. Methods, Various Swedish health registries were used in order to identify all pregnancies and their outcome in Sweden according to the measured radioactive fallout. Results. A reduction in conception rate occurred after the accident, as well as possible increase in induced abortion rate during the fall after the accident. No changes in the rate of spontaneous abortions or congenital malformations occurred in pregnancies exposed at the time of the accident. There was a temporary increase in low birth weight which could well be random. Among infants conceived after the accident, a slight excess of Down syndrome infants was found in the most exposed areas but this observation is based on small numbers. No certain excess of childhood cancer was seen in the most exposed areas, but three infants, in utero at the time of the accident, developed leukemia. Conclusions. No major effects on pregnancy outcome were seen but the indicated increase in Down syndrome and childhood leukemia-if not random-could be a result of radioactive exposure. (C) 1994 Academic Press, Inc.

Ernst H, Emura M, Bellmann B, Seinsch D, Mohr U. 1987. Failure to transmit diethylnitrosamine tumorigenicity from transplacentally exposed F1 generation Syrian hamsters to the respiratory tract of F2 and F3 generations. Cancer Res 47:5112-5115.
Abstract: A multigeneration study with four successive generations of Syrian hamsters was conducted to determine whether a single s.c. injection of different doses of diethylnitrosamine (DEN) (1.25, 2.5, 5, 10, and 20 mg/kg body weight) on day 15 of pregnancy induces respiratory tract tumors not only in the treated P generation mothers and their F1 progeny but also in F2 and F3 generations. In this study, the P generation mothers only were given a single injection of DEN during the period of gestation. Fifty-six % of the 36 DEN-treated mothers and 52% of their F1 generation offspring (total, 233 animals) developed neoplasms in the respiratory tract. A single respiratory tract tumor was found in one DEN-unexposed F1 generation control hamster as well as in one F2 generation animal (total, 209 animals) descended from DEN-exposed P generation. Both tumors were considered to have arisen spontaneously. No respiratory tract tumors were observed in the F3 generation (total, 160 animals) descended from a DEN-exposed P generation. Thus our results indicate that the vertical transmission of the tumorigenic effect of DEN in Syrian hamsters is limited to one generation and does not persist in the F2 and F3 generations.

Fasching K, Panzer S, Haas OA, Marschalek R, Gadner H, Panzer-Grumayer ER. 2000 . Presence of clone-specific antigen receptor gene rearrangements at birth indicates an in utero origin of diverse types of early childhood acute lymphoblastic leukemia. Blood 95:2722-2724.
Abstract: There is strong evidence that infant leukemias with a t(4;11) translocation originate in utero. To test whether other subtypes of childhood leukemias are also initiated during fetal life, we used clone-specific genetic markers for the analysis of neonatal blood spots from 5 children aged 6 months to 4 years 8 months at diagnosis of pro-B, common acute lymphoblastic leukemia (ALL), and T-ALL. In all children, the clonotypic antigen receptor gene rearrangements were already present at birth. The estimated amount of clonotypic cells was in the range of 10 to 100 cells per blood spot. In 2 infants with a t(4;11) positive ALL, we detected similar amounts of the fusion gene sequences compared with the clonal antigen receptor gene rearrangements, suggesting the presence of both markers in the same cells. Our data indicate that the first leukemogenic event of diverse types of childhood ALL may already occur in utero. (Blood. 2000;95:2722-2724)

Fasching K, Panzer S, Haas OA, Marschalek R, Gadner H, Panzer-Grumayer ER. 2000. Presence of clone-specific antigen receptor gene rearrangements at birth indicates an in utero origin of diverse types of early childhood acute lymphoblastic leukemia. Blood 95:2722-2724.
Abstract: There is strong evidence that infant leukemias with a t(4;11) translocation originate in utero, To test whether other subtypes of childhood leukemias are also initiated during fetal life, we used clone-specific genetic markers for the analysis of neonatal blood spots from 5 children aged 6 months to 4 years 8 months at diagnosis of pro-B, common acute lymphoblastic leukemia (ALL), and T-ALL, In all children, the clonotypic antigen receptor gene rearrangements were already present at birth. The estimated amount of clonotypic cells was in the range of 10 to 100 cells per blood spot, in 2 infants with a t(4;11) positive ALL, we detected similar amounts of the fusion gene sequences compared with the clonal antigen receptor gene rearrangements, suggesting the presence of both markers in the same cells. Our data Indicate that the first leukemogenic event of diverse types of childhood ALL may already occur in utero.(Blood. 2000;95:2722-2724) (C) 2000 by The American Society of Hematology.

Fear NT, Roman E, Ansell P, Bull D. 2001. Malignant neoplasms of the brain during childhood: the role of prenatal and neonatal factors (United Kingdom). Cancer Causes & Control 12:443-449.
Abstract: OBJECTIVES: To evaluate whether factors in pregnancy and around birth influence the risk of childhood malignant neoplasms of the brain or other parts of the nervous system. METHODS: The distribution of certain characteristics of pregnancy and birth among 83 cases of malignant neoplasms of the brain and other parts of the nervous system (diagnosed between 0 and 14 years of age) and 166 controls (individually matched on date of birth, sex, and hospital of birth) were compared. Odds ratios (OR), 95% confidence intervals (95% CI) and two-sided p-values were calculated using conditional logistic regression for matched sets. RESULTS: Children whose mothers had documented evidence of a clinically diagnosed viral infection during pregnancy had an approximately 11-fold increase in risk of developing a malignant neoplasm of the brain or other part of the nervous system (OR = 10.6, 95% CI = 1.1-503.2). In addition, non-statistically significant increased risks were observed among children who had a non-cephalic

presentation (OR = 3.3, 95% CI = 0.8-13.9) or a low 1-minute apgar score (OR = 2.7, 95% CI = 1.0-7.4). No other aspects of the index pregnancy, delivery, or maternal characteristics were associated with an increased risk of childhood brain tumors. CONCLUSIONS: The results reported here provide limited evidence for the role of prenatal and neonatal factors in the etiology of childhood malignant neoplasms of the brain. The finding for maternal viral infection during pregnancy warrants further investigation.

Feingold L, Savitz DA, John EM. 1992. Use of a job-exposure matrix to evaluate parental occupation and childhood cancer. Cancer Causes & Control 3:161-169.
Abstract: We examined the association between parental occupation and childhood cancer among 252 incident cases of childhood cancer (ages 0-14, diagnosed 1976-83) and 222 controls selected by random digit dialing in Denver, Colorado (USA). A job-exposure matrix was used to assign parental exposures based on job titles, emphasizing chemicals that were implicated in previous studies. All cancers, acute lymphocytic leukemia (ALL), and brain cancer were examined in relation to parental occupation during the year prior to the birth of the child. Elevated odds ratios (OR), all with confidence intervals extending below the null, were found for maternal exposure to benzene (OR = 1.9), petroleum/coke pitch/tar (OR = 2.2), and soot (OR = 3.3) in relation to total cancers. The ORs for total cancer and paternal exposure to all hydrocarbons combined was 1.0. Results for individual hydrocarbons and ALL showed larger odds ratios, including aniline (OR = 2.1), benzene (OR = 1.6), and petroleum/coke pitch/tar (OR = 1.6). Potential exposure to creosote was strongly associated with brain cancer (OR = 3.7) based on five exposed cases (95 percent confidence interval = 0.8-16.6). Control for other potential childhood cancer risk factors did not alter the results substantially. In spite of uncertainties due to small numbers and errors in exposure classification, results tend to corroborate past research that suggests an association between specific parental occupational exposures and childhood cancer.

Fenton SE. 2006. Endocrine-disrupting compounds and mammary gland development: Early exposure and later life consequences. Endocrinology 147:S18-S24.
Abstract: Breast cancer is the most common non-skin cancer among women in this country. Breast cancer risk is significantly influenced by genetics, but over 70% of the women that are diagnosed have noninherited or sporadic cancer. The risk of breast cancer is thought to be modified by lifestyle and environment. Exposures to certain chemicals and hormone-mimicking or endocrine-disrupting compounds (EDCs) are suspected of contributing to increased breast cancer incidence as well as precocious puberty in the United States. Studies of EDC effects in rodents indicate that multiple toxicants can alter mammary gland development, with or without changing other markers of puberty. EDCs can cause transient and persistent effects on mammary gland development depending on dose, exposure parameters, and whether exposure was during critical periods of gland growth or differentiation. Adverse effects from these abnormal developmental patterns include the presence of carcinogen-sensitive structures in greater numbers or for longer periods in the gland and inhibited functional differentiation leading to malnutrition or increased mortality of their offspring. Developmental toxicants of the mammary gland could lead to an increase in the incidence of mammary tumors if they alter circulating or tissue-localized hormone levels, gland receptor expression patterns, hormone transport, or metabolism that results in altered response to endogenous hormones or growth factors. Environmental disruptors of rodent mammary gland development must be identified for informed decisions in epidemiological studies aimed at identification of environmental factors contributing to breast cancer risk, altered breast development during puberty, or inability to produce sufficient breast milk.

Fenton SE, Hamm JT, Birnbaum LS, Youngblood GL. 2002. Persistent abnormalities in the rat mammary gland following gestational and lactational exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Toxicol Sci 67:63-74.
Abstract: 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) exposure during gestation has revealed reproductive anomalies in rat offspring, including inconclusive reports of stunted mammary development in females (Brown et al., 1998, Carcinogenesis 19, 1623-1629; Lewis et al., 2001, TOXICOL: Sci. 62, 46-53). The current studies were designed to examine mammary-gland development in female offspring exposed in utero and lactationally to TCDD, and to determine a critical exposure period and cellular source of these effects. Long-Evans rats were exposed to 1 microg TCDD/kg body weight (bw) or vehicle on gestation day (GD) 15. TCDD-exposed females sacrificed on postnatal days (PND) 4, 25, 33, 37, 45, and 68 weighed significantly less than control litter mates, and peripubertal animals exhibited delayed vaginal opening and

persistent vaginal threads, yet did not display altered estrous cyclicity. Mammary glands taken from TCDD-exposed animals on PND 4 demonstrated reduced primary branches, decreased epithelial elongation, and significantly fewer alveolar buds and lateral branches. This phenomenon persisted through PND 68 when, unlike fully developed glands of controls, TCDD- exposed rats retained undifferentiated terminal structures. Glands of offspring exposed to TCDD or oil on gestation days 15 and 20 or lactation days 1, 3, 5, and 10 were examined on PND 4 or 25 to discern that GD 15 was a critical period for consistent inhibition of epithelial development. Experiments using mammary epithelial transplantation between control and TCDD-exposed females suggested that the stroma plays a major role in the retarded development of the mammary gland following TCDD exposure. Our data suggest that exposure to TCDD prior to migration of the mammary bud into the fat pad permanently alters mammary epithelial development in female rat offspring.

Fernandez-Twinn DS, Ekizoglou S, Gusterson BA, Luan J, Ozanne SE. 2007. Compensatory mammary growth following protein restriction during pregnancy and lactation increases early-onset mammary tumor incidence in rats. Carcinogenesis 28:545-552.
Abstract: Breast cancer incidence is increased in women with both high and low birth weight. The latter is also associated with hyperglycaemia, insulin resistance and type-2 diabetes, each of which independently increases breast cancer risk. We showed previously in our model of poor early-growth that pregnancy estradiol levels were raised while offspring developed type-2 diabetes. We hypothesized that nutritionally-induced poor early-growth influences breast cancer risk and investigated this in our model. Wistar rat dams were given either a control diet (20% casein) or an isocaloric low-protein (LP) diet (8% casein) throughout pregnancy and lactation. Offspring postnatal mammary gland development was assessed by morphometry. To identify potential growth mechanisms, we measured protein expression of receptors involved in insulin and hormone signaling, both in cleared mammary gland lysates and isolated epithelial cells. Mammary tumor incidence and latency (n = 96) was monitored after three weekly intraperitoneal nitrosomethylurea injections (50 mg/kg body wt). LP offspring displayed reduced postnatal ductal branching and epithelial invasion at 3 weeks, followed by compensatory mammary growth 1 week later coinciding with increased protein expression of receptors to insulin, IGF-1 and estrogen. Significantly, early-mammary tumor incidence (0-16 weeks post-treatment) was doubled in LP offspring [RR, 2.13 (1.02, 4.45); P = 0.046]. The data suggest that poor early nutrition has an important influence on the mammary primordium, and increases future susceptibility to breast cancer. Up-regulated growth factor and hormone signaling during compensatory mammary growth may mediate this increased susceptibility and present potential targets for intervention.

Feychting M, Ahlbom A. 1993. Magnetic fields and cancer in children residing near Swedish high-voltage power lines. Am J Epidemiol 138:467-481.
Abstract: A case-control study was conducted to test the hypothesis that exposure to magnetic fields of the type generated by high-voltage power lines increases cancer incidence in children. The study base consisted of everyone under age 16 years who had lived on a property located within 300 meters of any of the 220 and 400 kV power lines in Sweden during the period 1960-1985. Subjects were followed from their entry into the study base through 1985. A total of 142 cancer cases were identified through a record linkage to the Swedish Cancer Registry. There were 39 leukemia and 33 central nervous system tumor cases. A total of 558 controls were selected at random from the study base. Exposure was assessed by spot measurements and by calculations of the magnetic fields generated by the power lines, taking distance, line configuration, and load into account. Information about historical loads on the power lines was used to calculate the magnetic fields for the year closest in time to diagnosis. When historical calculations were used as exposure assessment for childhood leukemia with cutoff points at 0.1 and 0.2 microtesla (microT), the estimated relative risk increased over the two exposure levels and was estimated at 2.7 (95% confidence interval (CI) 1.0-6.3) for 0.2 microT and over; p for trend = 0.02. When the upper cutoff point was shifted to 0.3 microT, the relative risk was 3.8 (95% CI 1.4-9.3); p for trend = 0.005. These results persisted when adjustment for potential confounding factors was made. For central nervous system tumor, lymphoma, and all childhood cancers combined, there was no support for an association.

Feychting M, Floderus B, Ahlbom A. 2000. Parental occupational exposure to magnetic fields and childhood cancer (Sweden). Cancer Causes & Control 11:151-156.
Abstract: OBJECTIVES: To test the hypothesis that parental occupational exposure to magnetic fields

before conception and during pregnancy increases the risk of cancer in the offspring. METHODS: The study is designed as a cohort study based on a population of 235,635 children born shortly after two different censuses in Sweden. The children were followed from birth to 14 years and cases of cancer were identified in the Swedish cancer registry. The parents' occupational titles in the censuses were linked to a job-exposure matrix with information about magnetic field levels in different occupations. The cancer incidence among the exposed was compared to that among the unexposed using Cox proportional hazards modeling. RESULTS: There was no association between childhood cancer and maternal occupational magnetic field exposure. Paternal exposure was associated with an increased risk of childhood leukemia, with a relative risk of 2.0 (95% CI 1.1-3.5) for exposures > or = 0.30 microT. A decreased risk was found for brain tumors (RR = 0.5; 95% CI 0.3-1.0). CONCLUSIONS: The results do not support previous findings of an increased risk of childhood brain tumors associated with paternal occupational exposure to magnetic fields. The finding for childhood leukemia has to be interpreted with caution.

Filippini G, Farinotti M, Lovicu G, Maisonneuve P, Boyle P. 1994. Mothers active and passive smoking during pregnancy and risk of brain-tumors in children. Int J Cancer 57:769-774.
Abstract: As part of a collaborative study of risk factors for childhood brain tumours, the effects of the mother's smoking and her potential for passive smoking exposure during the pregnancy were assessed in a case-control study. Parents of 91 cases and 321 population controls from Northern Italy, matched for age, sex and residence, were interviewed about their lifetime smoking habits. Mother's smoking during pregnancy was associated with an odds ratio (OR) of 1.7 (95% CI 0.8, 3.8) of brain tumour in her child although this was not statistically significant. Among non-smoking mothers, the risk for light and heavy exposure to passive smoking was 1.7 (0.8, 3.6) and 2.2 (1.1, 4.5) respectively, and a statistically significant dose-response relationship was found (p trend = 0.02). These results must be interpreted within the constraints of the relatively small sample size and the likely misclassification produced by the difference between the potential for exposure to passive smoke and the true exposure. However, they add another piece of information to the growing body of evidence available about the health consequences both of active and of passive smoking and highlight the need for more information about this putative association. (C) 1994 Wiley-Liss, Inc.

Filippini G, Maisonneuve P, McCredie M, Peris-Bonet R, Modan B, Preston-Martin S, Mueller BA, Holly EA, Cordier S, Choi NW, Little J, Arslan A, Boyle P. 2002. Relation of childhood brain tumors to exposure of parents and children to tobacco smoke:The SEARCH international case-control study. Surveillance of Environmental Aspects Related to Cancer in Humans. Int J Cancer 100:206-213.
Abstract: The etiology of childhood brain tumors (CBTs) remains unknown. Tobacco smoke contains several known carcinogens and can induce DNA adducts in human placenta and hemoglobin adducts in fetuses. We present the results of an international case-control study to evaluate the association between CBTs and exposure of parents and children to cigarette smoke. The study was undertaken as part of the SEARCH program of the IARC. Nine centers in 7 countries were involved. The studies mainly covered the 1980s and early 1990s. Cases (1,218, ages 0-19 years) were children newly diagnosed with a primary brain tumor; there were 2,223 population-based controls. Most mothers who agreed to participate were interviewed in person at home. Odds ratios (ORs) were calculated by unconditional logistic regression, adjusted for age, sex and center, for all types of CBT combined, 4 CBT histotypes, 5 age groups and each center. There was no association between the risk of brain tumors in the child and parental smoking prior to pregnancy, maternal smoking or regular exposure to others' cigarette smoke during pregnancy at home or at work, or passive smoking by the child during the first year of life. These results did not change considering the child's age at diagnosis, the histologic type of tumor or center.

Fischer M, Schwieger M, Horn S, Niebuhr B, Ford A, Roscher S, Bergholz U, Greaves M, Lohler J, Stocking C. 2005. Defining the Oncogenic Function of the Tel/Aml1 (Etv6/Runx1) Fusion Protein in a Mouse Model. Oncogene 24:7579-7591.
Abstract: The t(12;21) translocation, generating the TEL/AML1 fusion protein, is the most common genetic lesion in childhood cancer. Using a bone marrow transplantation model, we demonstrate that TEL/AML1 expression impinges on normal hematopoietic differentiation, leading to the in vivo accumulation and persistence of an early progenitor compartment with a Sca1(+)/Kit(hi)/CD11b(+) phenotype and an increased self- renewal capacity, as documented by replating assays in vitro. Differ entiation of these cells is not blocked, but the frequency of mature blood cells arising from TEL/AML1- transduced progenitors is

low. Impa ired differentiation is prominently observed in the pro- B- cell compartment, resulting in an proportional increase in early progenitors in vivo, consistent with the t(12;21) ALL phenotype. Desp ite the accumulation of both multipotent and B- cell progenitors in vivo, no leukemia induction was observed during an observation period of over 1 year. These results are consistent with. ndings in twins with concordant ALL, showing that TEL/AML1 generates a preleukemic clone in utero that persists for several years in a clinically covert fashion. Fur thermore, our studies showed that the pointed domain of TEL/AML1, which recruits transcriptional repressors and directs oligomerization with either TEL/AML1 or wild-type TEL, was essential for the observed differentiation impairment and could not be replaced with another oligomerization domain.

Flaws JA, Sommer RJ, Silbergeld EK, Peterson RE, Hirshfield AN. 1997. *In utero* and lactational exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) induces genital dysmorphogenesis in the female rat. Toxicology & Applied Pharmacology 147:351-362.
Abstract: Recently, Gray and Ostby (Toxicol. Appl. Pharmacol. 133, 285-294, 1995) reported that in utero and lactational TCDD exposure causes striking abnormalities in the rat female reproductive system, including reduced fecundity and vaginal threads. The mechanism by which TCDD induces such abnormalities is unknown. Thus, we sought to determine: (1) whether TCDD reduced fecundity by destroying ovarian follicles and (2) whether the vaginal threads resulted from a TCDD-induced developmental defect during embryogenesis or abnormal vaginal opening at puberty. Pregnant Holtzman rats were treated with 1.0 mu g TCDD/kg or vehicle by a single oral dose on gestation day (GD) 11, 15, or 18. Female offspring were monitored for vaginal opening and terminated on postnatal days 2, 21, and 42. The reproductive tract was removed and evaluated for structural abnormalities. The number of primordial follicles also was determined for each ovary. TCDD exposure on GD 11, 151 or 18 did not change the day of vaginal opening, affect ovarian morphology, or reduce the number of primordial follicles. However, this exposure induced the cleft clitoris and vaginal thread originally described by Gray and Ostby (1995) in approximately 55-96% and 36-44% of the litters in our study, respectively. Histologically the thread presented as a thick cord of mesenchyme surrounded by epithelial cells. This defect was clearly visible in histological sections at birth and was noted in the closed vaginas of prepubertal animals. These data suggest that in utero and lactational exposure to TCDD does not reduce the size of the primordial follicle pool; however, it induces developmental abnormalities in the vaginal canal. (mention of Diethylstilbestrol (DES)?)

Forman MR, Cantwell MM, Ronckers C, Zhang YW. 2005. Through the looking glass at early-life exposures and breast cancer risk. Cancer Invest 23:609-624.
Abstract: The global increase in the proportion of women diagnosed with breast cancer, inadequate access to screening and high cost of treatment for breast cancer argue strongly for a greater focus on preventive strategies. But at what age is it appropriate to begin targeting preventive approaches? The recognized role of perinatal nutrition in neurologic development and the relation of maternal nutritional status to birthweight and subsequent risk of hypertension, diabetes, and cardiovascular disease identify pregnancy and early childhood as potential phases for prevention. This review examines indicators of hormonal and nutritional exposures in early life and breast cancer risk through the lens of the life course paradigm integrated with maternal and child health research and methodology. Compared to women who were normal birthweight (2500-3999 g), women who weighed >= 4,000 g at birth have a 20 percent to 5-fold increased risk of premenopausal breast cancer. Women born preterm and likely to be small- or large-for-date also have an increased risk. Birth length is directly associated with risk and has a larger magnitude of effect than birthweight. Prior preeclamptics and their daughters have a lower risk of breast cancer than comparable normotensives. An association between infant feeding practices and breast cancer is unclear without improved exposure assessment and analysis. Rapid childhood and pubertal linear growth increases breast cancer risk, while greater body fat over the same periods reduces risk. Growth data thus far have not been calculated in Z-scores from reference growth curves for comparison across studies. Events and secular trends influencing birth cohorts may not be adequately addressed, thereby limiting

Foster PMD. 2005. Mode of action: Impaired fetal Leydig cell function - Effects on male reproductive development produced by certain phthalate esters. Crit Rev Toxicol 35:713-719.
Abstract: Certain phthalate esters (di-2-ethylhexyl; di-n-butyl and butyl benzyl) have profound effects on the developing male reproductive system when administered orally to pregnant experimental animals

during a critical window of development. These esters produce a syndrome of adverse effects that are characteristic of a disturbance in androgen-mediated development and include a variety of reproductive tract malformations and effects on developmental phenotypic markers. A testicular dysgenesis syndrome has been proposed to explain the secular increases in a number of human male reproductive deficits, including decreased semen parameters, increased incidence of cryptorchidism and hypospadias (two of the most common human birth defects), and increased incidence of testicular (germ cell derived) cancer. The rodent phthalate data lend support to the hypothesis. This example illustrates a number of points in the use of the Human Relevance Framework. First, chemical agents may have more than one mode of action (MOA): for example, phthalate-induced peroxisome proliferation leading to hepatocarcinogensis, compared with the induction of developmental effects via effects on androgen signaling. Second, the case demonstrates the life-stage sensitivity of the response to these compounds. Third, because humans may be exposed to multiple phthalate esters producing adverse effects on reproductive development, these compounds may be useful in testing the utility of the Human Relevance Framework (HRF) approach for evaluating cumulative and aggregate risk.

Foster WG, Younglai EV, Boutross-Tadross O, Hughes CL, Wade MG. 2004. Mammary gland morphology in Sprague-Dawley rats following treatment with an organochlorine mixture in utero and neonatal genistein. Toxicol Sci 77:91-100.
Abstract: In a related reproductive toxicology study designed to investigate the effects of in utero exposure to environmental toxicants and potential interaction with postnatal genistein, gross enlargement of thoracic mammary glands was observed in female offspring at 200 days of age. Therefore, the objective of this study was to analyze the effect of in utero exposure to a mixture of toxicants on mammary gland morphology. Time-mated Sprague-Dawley rats were treated on days 9-16 of gestation with vehicle or a mixture of environmental toxicants at 1x the acceptable daily intake. Furthermore, it is unclear whether postnatal exposure to phytoestrogens in soy formulas poses breast cancer benefit or risk, and potential interactions with environmental toxicants are unknown. Therefore, half the female pups from each treatment group received either subcutaneous vehicle or genistein (10 microg/g body weight [bw]/day) on postnatal days 2-8. Following necropsy at 200 days of age, a pathologist, blinded to treatment groups, examined mammary gland histopathology. Only mild histological changes were found in mammary glands of rats exposed to the mixture in utero while pronounced ductal hyperplasia, lactational changes, and fibrosis were observed in mammary glands from the genistein group and were more prominent in the mixture + genistein group. Mammary glands of the control group were histologically normal. Collectively, our results reveal that postnatal exposure to pharmacological levels of genistein induces profound morphological changes in the mammary glands of adult female rats, and that high levels of phytoestrogens possess the potential to modulate the toxicological effects of toxicant mixtures.

Fox RR, Diwan BA, Meier H. 1975. Transplacental induction of primary renal tumors in rabbits treated with 1-ethyl-1-nitrosourea. J Natl Cancer Inst 54:1439-1448.
Abstract: Pregnant rabbits of the two partially inbred strains III and WH were given ip injections of a single dose of 1-ethyl-1-nitrosourea (ENU) (60 mg/kg) in trioctanoin on day 18 of gestation. Controls were treated on the same day with solvent alone. Fourteen of 15 strain III progeny that survived more than 8 weeks developed primary renal tumors at a mean age of 3.3 months. Five other treated strain III progeny died at an early age due to other causes. In contrast, only 3 of 7 strain WH offspring surviving more than 8 weeks developed renal tumors; they had about the same latency period (3.9 months). In each strain, either renal tubular cystadenomas or mixed nephroblastomas appeared to develop within small renal cortical cysts. In strain III, the presence of these cysts may have been due to a high frequency of a recessive gene (rc) for renal cysts, but in strain WH they were induced by ENU. The differential strain incidence suggests that susceptibility to renal tumor inducibility by ENU is increased by the presence of the rc/rc genotype for cyst formation.

Francis AJ, Anderson D, Evans JG, Jenkinson PC, Godbert P. 1990. Tumours and malformations in the adult offspring of cyclophosphamide-treated and control male rats--preliminary communication. Mutat Res 229:239-246.
Abstract: Adult offspring aged 52-104 weeks, from male Sprague-Dawley rats treated chronically with cyclophosphamide (CP) were examined for tumours and gross abnormalities. Litter size at birth and at weaning was found to be greatly reduced as a result of paternal CP treatment. No unusual abnormalities

were found at post-mortem examination but there was an increase in the incidence of hydronephrosis in offspring from CP-treated males compared with offspring from control males. This increase could have been indirectly caused by CP-treatment through reduced litter size. Histological examination of 26 tumours showed a variety of tumour types in the offspring of CP-treated and control males. Two of the four uterine tumours in offspring from CP-treated males were examined histologically; one was a sarcoma and the other an adenocarcinoma. Although no uterine tumours were found in offspring from control males, it is not clear whether this difference in frequency was treatment-related. The most common tumour site in female offspring from both CP-treated and control males was the mammary gland, and all six of these tumours which were examined histologically were adenofibromas. Abnormal karyotypes were observed in 2 out of 21 offspring showing abnormalities from CP-treated males and none out of 2 offspring with abnormalities from control males. These were not associated with tumours. It was concluded from this limited study that there was no clear evidence of increased tumour incidence in the offspring from CP-treated males. There was an indication that abnormal karyotypes may have been caused by the paternal CP treatment and these abnormalities persisted into adulthood.

Fritz WA, Lin TM, Moore RW, Cooke PS, Peterson RE. 2005. In Utero and Lactational 2,3,7,8-Tetrachlorodibenzo-P-Dioxin Exposure: Effects on the Prostate and Its Response to Castration in Senescent C57bl/6j Mice. Toxicol Sci 86:387-395.

Abstract: In utero and lactational 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure inhibits ventral, dorsolateral, and anterior prostate development in C57BL/6 mice. To determine if prostatic abnormalities persist into senescence, mice born to dams given TCDD (5 mu g/kg, po) or vehicle on gestation day 13 were examined at 100 and 510 days of age. Half the mice were castrated ten days prior to necropsy in order to assess androgen dependence, while the remaining mice were sham castrated. Effects of TCDD on the dorsolateral and anterior prostate of senescent sham-castrated mice were relatively subtle, whereas the ventral prostate was rudimentary or absent. Castration of vehicle-exposed mice caused far greater reductions in prostate lobe weights, epithelial cell height, and androgen-dependent gene expression (MP25 and probasin) in young mice than in senescent ones, while cell proliferation was decreased by castration in young mice and increased in senescence. Responses to castration were similar at 100 days of age in vehicle- and TCDD-exposed mice. At 510 days, however, TCDD-exposed mice were substantially more responsive to castration by most indices than vehicle-exposed mice. These results demonstrate that prostatic androgen dependence in mice declines substantially with age in several key ways, and that in utero and lactational TCDD exposure protects against this decline. Surprisingly, TCDD increased the incidence of cribriform structures in dorsolateral prostate ducts, from 2-3% in vehicle-exposed senescent mice to 16% in sham-castrated and to 7% in castrated senescent mice. Collectively, these results demonstrate that effects of in utero and lactational TCDD exposure on the prostate persist into senescence, and suggest that in utero and lactational TCDD exposure retards the aging process in the prostate. However, because cribriform structures are often considered to be associated with prostate carcinogenesis, these results also suggest that TCDD exposure early in development may increase susceptibility to prostate cancer.

Fu PP, Von Tungeln LS, Chiu LH, Zhan DJ, Deck J, Bucci T, Wang JC. 1998. Structure, tumorigenicity, microsomal metabolism, and DNA binding of 7-nitrodibenz[a,h]anthracene. Chem Res Toxicol 11:937-945.

Abstract: It has been previously proposed that a nitropolycyclic aromatic hydrocarbon (nitro-PAH) with its nitro functional group perpendicular or nearly perpendicular to the aromatic moiety exhibits lower tumorigenicity than the corresponding parent aromatic hydrocarbon. We also hypothesized that reduction of the nitro group is not involved, or contributed less significantly in the metabolic activation of this class of nitro-PAHs. To verify this hypothesis, we selected 7-nitrodibenz[a,h]anthracene (7-NDB[a,h]A) for study. The X-ray crystallographic structure of 7-NDB[a,h]A was determined and indicated that the dihedral angle between the nitro functional group and the aromatic dibenz[a,h]anthracenyl moiety was 80.6 degrees, indicating the nitro group preferentially adopts a nearly perpendicular orientation. The tumorigenicity of 7-NDB[a,h]A and dibenz[a,h]anthracene (DB[a,h]A) was determined in the male B6C3F(1) neonatal mouse. Mice were administered ip injections of 1/7, 2/7, and 4/7 of the total dose of 7-NDB[a,h]A (400 nmol in 35 mu L of DMSO per mouse) within 24 h of birth and at 8 and 15 days of age, respectively, and sacrificed at 12 months of age. DB[a,h]A induced 78 and 96% hepatocellular adenomas and carcinomas, respectively. However, 7-NDB[a,h]A induced only 50 and 8% hepatocellular adenomas and carcinomas compared with

the 8 and 4% hepatocellular adenomas and carcinomas induced by the solvent vehicle, DMSO. Aerobic metabolism of 7-NDB[a,h]A by liver microsomes of 15-day old male B6C3F(1) neonatal mice resulted in trans-3,4-dihydroxy-3,4-dihydro-7-nitrodibenz[a,h]anthracene (7-NDB[a,h]A trans-3,4-dihydrodiol) and trans-10,11-dihydroxy-10,11-dihydro-7-nitrodibenz[a,h]anthracene (7-NDB[a,h]A trans-10,11-dihydrodiol) as predominant metabolites. Under anaerobic conditions, 7-NDB[a,h]A was not metabolized (nitroreduced). The DNA adduct levels in liver and lung tissues of male B6C3F1 mice treated with 7-NDB[a,h]A and sacrificed 24 h and 6 days after final dosing were determined by P-32-postlabeling/TLC. In all cases, the DNA adducts derived from 7-NDB[a,h]A trans-3,4-dihydrodiol and 7-NDB[a,h]A trans-10,11-dihydrodiol were formed. These results suggest that both of the metabolites, 7-NDB[a, h]A trans-3,4-dihydrodiol and 7-NDB[a,h]A trans-10,11-dihydrodiol, are involved in the metabolic activation of 7-NDB[a,h]A, leading to tumor induction in the neonatal mouse. Thus, our results described in this paper support our hypotheses that a nitro-PAH with a perpendicular nitro orientation exhibits lower tumorigenicity than the corresponding parent PAH and that nitroreduction contributes less significantly in the metabolic activation.

Fu PP, Vontungeln LS, Zhan DJ, Bucci T. 1996. Potent tumorigenicity of 7-chlorobenz[a]anthracene and 7-bromobenz[a]anthracene in the neonatal B6C3F(1) male mouse. Cancer Lett 101:37-42.
Abstract: The tumorigenicity of 7-chlorobenz[alpha]anthracene (7-Cl-BA), an environmental contaminant, and 7-bromobenz[alpha]anthracene (7-Br-BA) was determined in the male B6C3F(1) newborn mouse. Mice receiving 7-Cl-BA and 7-Br-BA by i.p. injec tions at a dose of 1600 nmol per mouse on 1, 8, and 15 days after birth developed 92 and 96% hepatocellular adenomas, and 100 and 83% hepatocellular carcinoma, respectively. Metabolism by liver microsomes of 15-day-old mice each produced the corresponding trans-3,4-dihydrodiol. Analysis by P-32-postlabeling/HPLC indicated the presence of DNA adducts derived from 7-Cl-BA trans-3,4-dihydrodiol and 7-Br-BA trans-3,4-dihydrodiol. Our results indicate that both 7-Cl-BA and 7-Br-BA are potent carcinogens and that bay-region diol epoxides are the ultimate metabolites that lead to DNA adduct formation and tumor initiation.

Fujimoto S, Ohyama Y, Shrestha RD, Ohta M, Kokubun M, Koike S, Okui K. 1987 . The presence of an aberrant type of human chorionic gonadotropin in patients with gastric or colorectal cancer. Jpn J Surg 17:382-387.
Abstract: Beta subunits of human chorionic gonadotropin (beta-hCG) and human chorionic gonadotropin-like substance (hCGLS) were measured radioimmunologically in the serum and malignant tissue from patients with gastrointestinal cancer. Since serum beta-hCG and hCGLS correlate closely to those in cancer tissues, it is assumed that these two gonadotropins originate from cancer tissues. The serum hCGLS levels in 54 patients with gastrointestinal cancer were significantly higher, when compared with the findings in 19 healthy volunteers and 10 peptic ulcer patients. The frequency of high levels of serum hCGLS accounted for 71 per cent of those with operable gastric cancer, 44 per cent of those with inoperable gastric cancer, 100 per cent of those with operable colorectal cancer, and 67 per cent of those with inoperable colorectal cancer. On the contrary, serum beta-hCG levels did not differ between the volunteers and the cancer patients. In the 17 sera and 15 cancer tissues assayed, beta-hCG did not correlate to hCGLS. Moreover, the high levels of beta-hCG in cancer patients occurred in only 1/14 (7.1 per cent) of the assayed serum, and in 5/14 (35.7 per cent) of the cancer tissue. The increased production of these two hCGs may result from neoplastic transformation of an unrestrained fetal genome responsible for hCG production during gestation. It is assumed that the increased producibility of a defective hCG, i.e., an aberrant hCG such as hCGLS, is characteristic of malignant tumors.

Gagnon ZE, Newkirk C, Conetta JA, Sama MA, Sisselman S. 2003. Teratogenic effect of broad-band electromagnetic field on neonatal mice (*Mus musculus*). Journal of Environmental Science and Health Part a-Toxic/Hazardous Substances & Environmental Engineering 38:2465-2481.
Abstract: Pregnant mice (*Mus musculus*), strain Swiss Webster, were exposed to a continuous electromagnetic field (12.8V/m) beginning in the third week of pregnancy. Histological and hematological analysis showed gender specific responses in 21 day-old mice after in-utero and post-natal continuous exposure. Automated lymphocyte percentage and total white blood cell counts were significantly elevated in exposed 21 day-old female mice compared to control mice. Lymphoma-like cells were seen in higher numbers in exposed 21 day-old male mice. Megaloblastic changes, such as hypersegmented neutrophils, were observed in exposed mice. The blood from control neonatal mice was more viscous than that of exposed mice, enough to interfere with making a blood smear. The adult female mice showed no

significant differences in the above hematologic parameters between exposed and control groups. Histological study showed the following pathological changes in the adrenal cortex: degeneration/necrosis in the zoni glomerulosa; hypertrophy in zona reticularis; degeneration/necrosis, intracytoplasmic inclusions and inflammation in the zona fasciculata/reticularis, more prominent in exposed female neonates; and lipidosis in the zona fasciculata. In the adrenal medulla: atrophy was more common in exposed female neonates; and intracytoplasmic inclusions and vacuolation were more common in exposed male neonates. Cystic proliferations were found in the cortical area of the thymus. In the medulla of the thymus, there was vacuolation, inflammation, or eosinophilic intracytoplasmic inclusions in exposed adults: Behavioral differences occurred in both neonates and adult females. Control neonates were able to manipulate through a maze more quickly than exposed neonates; and control adult females displayed more thorough grooming behavior than exposed mothers, and maintained more distance between the nest and dropping location than did the exposed group.

Garcia Calatayud S, Arteaga R, Herranz JL. 2001 . [Microcephaly, bilateral corneal opacity and congenital lobar holoprosencephaly with subsequent development of a rhabdomyosarcoma in a patient exposed to prenatal radiation]. Rev Neurol 33:948-951.
Abstract: INTRODUCTION: Most congenital malformations of which the cause is known are due to genetic or multifactorial causes or are secondary to a teratogen. Many congenital malformations are of unknown origin. However, the association of different malformations allows us to define the moment in which the noxous agent affected embryonic or foetal development. CLINICAL CASE: We present the case of a baby born after 40 weeks gestation, who had been exposed to ionising radiation before birth. Prenatal echography showed microcephaly and the karyotype was normal. The newborn baby had corneal opacities, microcephaly and complex encephalic malformations. The corneal opacity together with congenital glaucoma constitute Peters syndrome which leads to blindness, and is treated by trabeculectomy and bilateral corneal transplants. The microcephaly and lobar holoprosencephaly with agenesis of the corpus callosum led to reduced psychomotor development, hypertonia and epilepsy with an electroencephalogram recording of hemihypsarrythmia which was unsuccessfully treated with valproate and vigabatrine. At the age of 21 months the patient developed an embryonic rhabdomyosarcoma of the base of the tongue. He died with systemic infection whilst being treated with chemotherapy. CONCLUSIONS: The association of the malformations described has not previously been reported in the international data bases. Although it was not possible to prove that prenatal exposure to radiation caused the clinical condition described, the possibility of teratogenesis and carcinogenesis following such exposure means that pregnant women or those who may be pregnant should not be in places where radiodiagnosis is carried out.

Gardner MJ, Snee MP, Hall AJ, Powell CA, Downes S , Terrell JD. 1990 . Results of case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. BMJ 300:423-429.
Abstract: OBJECTIVE--To examine whether the observed excess of childhood leukaemia and lymphoma near the Sellafield nuclear plant is associated with established risk factors or with factors related to the plant. DESIGN--A case-control study. SETTING--West Cumbria health district. SUBJECTS--52 Cases of leukaemia, 22 of non-Hodgkin's lymphoma, and 23 of Hodgkin's disease occurring in people born in the area and diagnosed there in 1950-85 under the age of 25 and 1001 controls matched for sex and date of birth taken from the same birth registers as the cases. MAIN OUTCOME MEASURES--Antenatal abdominal x ray examinations, viral infections, habit factors, proximity to and employment characteristics of parents at Sellafield. RESULTS--Expected associations with prenatal exposure to x rays were found, but little information was available on viral illnesses. Relative risks for leukaemia and non-Hodgkin's lymphoma were higher in children born near Sellafield and in children of fathers employed at the plant, particularly those with high radiation dose recordings before their child's conception. For example, the relative risks compared with area controls were 0.17 (95% confidence interval 0.05 to 0.53) for being born further than 5 km from Sellafield 2.44 (1.04 to 5.71) for children of fathers employed at Sellafield at their conception, and 6.42 (1.57 to 26.3) for children of fathers receiving a total preconceptual ionising radiation dose of 100 mSv or more. Other factors, including exposure to x rays, maternal age, employment elsewhere, eating seafood, and playing on the beach did not explain these relationships. Focusing on Seascale, where the excess incidence has predominantly been reported, showed for the four out of five cases of leukaemia and one case of non-Hodgkin's lymphoma whose fathers were employed at Sellafield and for whom dose information was obtained that the fathers of each case had higher radiation doses before

their child's conception than all their matched control fathers; the father of the other Seascale case (non-Hodgkin's lymphoma) was not employed at the plant. These results seem to explain statistically the geographical association. For Hodgkin's disease neither geographical nor employment associations with Sellafield were found. CONCLUSIONS--The raised incidence of leukaemia, particularly, and non-Hodgkin's lymphoma among children near Sellafield was associated with paternal employment and recorded external dose of whole body penetrating radiation during work at the plant before conception. The association can explain statistically the observed geographical excess. This result suggests an effect of ionising radiation on fathers that may be leukaemogenic in their offspring, though other, less likely, explanations are possible. There are important potential implications for radiobiology and for protection of radiation workers and their children.

Gardner WA. 1995 . Hypothesis: The prenatal origins of prostate cancer. Hum Pathol 26: 1291-1292.

Garnis C, Campbell J, Davies JJ, Macaulay C, Lam S, Lam WL. 2005. Involvement of Multiple Developmental Genes on Chromosome 1p in Lung Tumorigenesis. Hum Mol Genet 14:475-482.
Abstract: Lung cancer is the leading cause of cancer death in North America. Despite advances in lung cancer treatment, the overall 5 year survival rate for those diagnosed with the disease is bleak presumably due to the late stage of diagnosis. Owing to the difficulty of early detection, preneoplastic specimens are rare. However, studying both preinvasive and invasive stages of disease is necessary to fully understand lung cancer progression. Aberration of chromosome arm 1p is common in lung and other cancers. In this study, we used a genomic array with complete tiling coverage of 1p to profile preinvasive and invasive squamous non-small cell lung carcinoma samples. With this technology, multiple novel submegabase alterations were identified. Three of the 1p alterations harbored genes belonging to gene families known to be involved in cancer development through either the Writ or the Notch developmental pathways. Our finding of a 0.4 Mb amplified region at 1p36.12 containing WNT4 in preinvasive lung cancer, coupled with the identification of three additional alterations in invasive tumors that also contain genes related to the Notch and Writ pathways, strongly suggests an intricate role of these pathways in early and late stages of lung cancer development. Furthermore, ectopic expression of DVL1, LRP8 and Notch2 in malignant lung tissue validates the biological impact of these genetic alterations. Importantly, this implication of pathways known only to be activated in fetal lung development lends support to the proposed model of lung cancer ontology whereby tumors arise from dysregulated pleuripotent stem cells.

Garnis C, Davies JJ, Buys TPH, Tsao MS, Macaulay C , Lam S, Lam WL. 2005. Chromosome 5p Aberrations Are Early Events in Lung Cancer: Implication of Glial Cell Line-Derived Neurotrophic Factor in Disease Progression. Oncogene 24:4806-4812.
Abstract: Lung cancer is the most widely diagnosed malignancy in the world. Understanding early-stage disease will give insight into its pathogenesis. Despite the fact that pre-invasive lesions are challenging to isolate, and often yield insufficient DNA for the analysis of multiple loci, genomic pro. ling of such lesions will lead to the discovery of causal genetic alterations, which may be otherwise masked by the gross instability associated with tumors. In this study, we report the identification of multiple early genetic events on chromosome 5p in lung cancer progression. Using a high-resolution 5p-specific genomic array, which contains a tiling path of DNA segments for comparative genomic hybridization, nine novel minimal regions of loss and gain were discovered in bronchial carcinoma in situ (CIS) specimens. Within these regions we identified two candidate genes novel to lung cancer. The 0.27 Mbp region at 5p15.2 contains a single gene, Triple Functional Domain, which we determined to be differentially expressed in tumors. The 0.34 Mbp region at 5p13.2 contains Glial Cell Line-Derived Neurotrophic Factor (GDNF), which is a ligand for the RET oncogene product and is normally expressed during lung development (but absent in adult lung tissue). Our data showed not only that GDNF is overexpressed at the transcript level in squamous non-small-cell lung carcinoma, but also that the GDNF protein is present in early-stage lesions. Reactivation of the fetal lung expressed GDNF in early lesions and its amplification in CIS suggests an early role in tumorigenesis. These results highlight the value of examining the genomes of pre-invasive stages of cancer at tiling resolution.

Ghali MH, Yoo KY, Flannery JT, Dubrow R. 1992 . Association between childhood rhabdomyosarcoma and maternal history of stillbirths. Int J Cancer 50:365-368.
Abstract: A case/control study of childhood rhabdomyosarcoma (RMS) was conducted utilizing

information from birth records. Cases among Connecticut residents age 19 and younger diagnosed between 1960 and 1988 were identified from the Connecticut Tumor Registry files. Connecticut birth certificates were located for 103 of the 130 cases identified. A random sample of control birth certificates was frequency-matched to the cases by year of birth, sex, and ethnic origin, with a control:case ratio of 2:1. Information abstracted from birth certificates included birth weight, length of pregnancy, plurality, birth order, mother's prior stillbirths, mother's age, father's age, and father's occupation. Data were analyzed by conditional logistic regression. The major finding was an association between RMS and the mother having had one prior stillbirth or more (odds ratio = 3.7; 95% confidence interval = 1.5 to 8.9). Particularly noteworthy was the observation that 6 mothers of cases, but no mothers of controls, had had 2 or more prior stillbirths. The trend for increasing risk of RMS with increasing number of mother's prior stillbirths was highly significant (p = 0.0004). This association suggests that RMS and a class of stillbirths share a common etiologic factor. This factor may be genetic or may involve in utero exposure to an exogenous or endogenous agent.

Gill WB, Schumacher GF, Bibbo M, Straus FH, Schoenberg HW. 1979. Association of diethylstilbestrol exposure in utero with cryptorchidism, testicular hypoplasia and semen abnormalities. J Urol 122:36-39.
Abstract: Epididymal cysts and/or hypoplastic testes have been found in 31.5 percent of 308 men exposed to diethylstilbestrol in utero, compared to 7.8 per cent of 307 placebo-exposed controls. Analyses of the spermatozoa have revealed severe pathological changes (Eliasson score greater than 10) in 134 diethylstilbestrol-exposed men (18 percent) and 87 placebo-exposed men (8 percent). Further investigation of the 26 diethylstilbestrol-exposed men with testicular hypoplasia has revealed that 65 percent had a history of cryptorchidism. Only 1 of the 6 placebo-exposed controls with testicular hypoplasia had a history of testicular maldescent. Although none of our Diekmann's lying-in study group has had carcinoma to date one must keep in mind the reported increased risk of testicular carcinoma in testes that are or were cryptorchid. A 25-year-old man who was not part of the study group was treated recently by us for a testicular carcinoma (mixed anaplastic seminoma plus embryonal cell carcinoma) and he had a history of diethylstilbestrol exposure in utero and cryptorchidism.

Gillman MW, Barker D, Bier D, Cagampang F, Challis J, Fall C, Godfrey K, Gluckman P, Hanson M, Kuh D, Nathanielsz P, Nestel P, Thornburg KL. 2007. Meeting Report on the 3rd International Congress on Developmental Origins of Health and Disease (DOHaD). Pediatr Res 61:625-629.
Abstract: Developmental origins of health and disease (DOHaD) focuses on the earliest stages of human development, and provides a novel paradigm to complement other strategies for lifelong prevention of common chronic health conditions. The 3(rd) International Congress on DOHaD, held in 2005, retained the most popular features from the first two biannual Congresses, while adding a number of innovations, including increased emphasis on implications of DOHaD for the developing world; programs for trainees and young investigators; and new perspectives, including developmental plasticity, influences of social hierarchies, effects of prematurity, and populations in transition. Emerging areas of science included, first, the controversial role. of infant weight gain in predicting adult obesity, diabetes, and cardiovascular disease. Second, in the era of epidemic obesity, pacing attention to the over-nourished fetus is as important as investigating the growth retarded one. Third, environmental toxins appear to have abroad range of long-lasting effects on the developing human. Fourth, epigenetic mechanisms could unite several strands of human and animal observations, and explain how genetically identical individuals raised in similar postnatal environments can nonetheless develop widely differing phenotypes. Improving the environment to which an individual is exposed during development may be as important as any other public health effort to enhance population health world wide.

Gimmler-Luz MC, Cardoso VV, Sardiglia CU, Widholzer DD. 1999. Transplacental inhibitory effect of carrot juice on the clastogenicity of cyclophosphamide in mice. Genetics and Molecular Biology 22:65-68.
Abstract: Genetic damage during the prenatal period can provoke important neoplastic alterations and other diseases in postnatal life. Beta-carotene (RC) is considered to be one of the most important anticarcinogens in the diet and can protect mammalian cells against genotoxic events. As carrots are important dietary source of OC, we decided to test the effect of fresh carrot juice (CaJ) on cyclophosphamide (CP)-induced genotoxicity in maternal and fetal erythropoietic tissues. The treatment with CaJ started on the 7th day of the pregnancy of BALB/c female mice. We observed, on the 16th gestational day, that this treatment did not modify the spontaneous frequency of micronucleated polychromatic erythrocytes (mPCE) in the bone

marrow of the females nor in the livers of their fetuses. The mPCE frequency observed 24 h after an intraperitoneal injection of CP (40 mg/kg) on the 15th day was significantly lower in CaJ-pretreated pregnant female bone marrow and in the liver of their fetuses than those observed in the group treated with CP only. These results demonstrate the presence of natural anticlastogens in carrots.

Giordana MT, Migheli A, Mocellini C, Villare F, Schiffer D. 1992. Immunohistochemical observations on rat radial glia: Relationship with the origin of ethylnitrosourea-induced tumors. Acta Neuropathologica (Berlin) 84:387-393.
Abstract: Gliomas induced in the rat by transplacental administration of ethylnitrosourea (ENU) are intensely immunoreactive for vimentin and scarcely for glial fibrillary acidic protein (GFAP). Since tumoral transformation takes place during the late fetal and early postnatal period, the sequential expression of the two glial antigens has been investigated in this age period in ENU-treated and control rats. Immunohistochemical and immunoelectron microscopical methods have been employed. Vimentin was widely expressed starting from embryonal day 14 (E 14) in the processes of radial glia; as long as radial glia was present, vimentin decorated it. GFAP was, at earliest, observed at E 20 and expressed by glial cells with a stellate, i.e., mature shape. No GFAP-positive radial process was observed. No difference was found between ENU-treated and control rats. Since ENU is most effective in producing tumors when administered at the 16-17th day of fetal life, vimentin-positive radial glia is a candidate target of ENU. The similarity of intermediate filament pattern between radial glia in the late fetal life and tumors induced by transplacental ENU suggests that radial glia might be the cell of origin.

Giurgiovich AJ, Anderson LM, Jones AB, Dove LF, Moskal TJ, Rice JM, Olivero OA, Poirier MC. 1997. Transplacental cisplatin exposure induces persistent fetal mitochondrial and genomic DNA damage in patas monkeys. Reprod Toxicol 11:95-100.
Abstract: A previous attempt to model transplacental cisplatin exposure and genotoxicity employed several pregnant Erythrocebus patas monkeys; most of the animals were exposed near the end of gestation and cisplatin-DNA adduct analyses included only genomic DNA. Here, both genomic and mitochondrial DNA adduct formation have been determined in fetuses from two pregnant monkeys exposed at the end of the second trimester of gestation, Multiple fetal tissues were obtained after doses of 0.315 mg cisplatin/kg body weight (5.3 mg/m(2) total) on days 101 and 106 of gestation, Cesarean sections were performed 24 h after exposure and 27 d after exposure, Cisplatin genomic (g)-DNA adducts were observed in fetal adrenal, brain, heart, kidney, liver, skin, spleen, and thymus, When placentas from the two animals were divided into four concentric regions at increasing distances from the umbilical cord, and g-DNA was assayed, cisplatin DNA adduct levels were similar in all four regions, Mitochondrial (mt)-DNA adducts were higher than g-DNA adducts in maternal liver and fetal liver, brain and kidney, suggesting that the mitochondria may constitute a particular target for cisplatin genotoxicity. The study demonstrates significant fetal genotoxicity in g-DNA and mt-DNA of patas monkeys exposed to cisplatin in utero, suggesting that similarly exposed human fetuses may also sustain drug-induced DNA damage. (C) 1997 Elsevier Science Inc.

Giurgiovich AJ, Diwan BA, Lee KB, Anderson LM, Rice JM, Poirier MC. 1996. Cisplatin-DNA adduct formation in maternal and fetal rat tissues after transplacental cisplatin exposure. Carcinogenesis 17:1665-1669.
Abstract: Cis-diamminedichloroplatinum (II) (cisplatin), given to pregnant rats at 5 mg/kg body weight (bw) is a trans placental carcinogen for fetal liver, kidney, nervous system and lung, resulting in tumor incidences of 22.5, 10.5, 6.1 and 7.5% respectively, in offspring grown to adulthood (B.A, Diwan ef al., 1995, Toxicol, Appl. Pharm., 132, 115), In this study, the capacity of cisplatin to pass through the placental barrier and bind covalently to DNA in maternal and fetal tissues was evaluated, Pregnant F344/NCr rats were injected i.p. with single doses of 5, 10 or 15 mg cisplatin/kg bw at 18 days of gestation and sacrificed 24 h later, Cisplatin-DNA adducts were determined by dissociation-enhanced lanthanide fluoroimmunoassay (DELFIA) using both High (90 pmol/mu g DNA) and Low (0.50 pmol/mu g DNA) Modified cisplatin-DNA standards and atomic absorbance spectrometry (AAS), The adduct quantities determined by the two DELFIAs varied in concert, but the DELFIA with Low Modified standard gave actual values similar to those observed with AAS, In maternal and fetal tissues, with the exception of placenta in one experiment and maternal kidney in another experiment, the extent of cisplatin-DNA adduct formation increased with dose. In maternal kidney, the low adduct levels observed at the 15 mg/kg dose may reflect kidney toxicity, Fetal kidney, liver and lung contained fewer cisplatin-DNA adducts than the

corresponding maternal tissues, In contrast, at 5 and 15 mg/kg, fetal brain DNA contained higher adduct levels than maternal brain DNA, This study demonstrates the presence of DNA damage induced by cisplatin in multiple maternal and fetal rat tissues at tumorigenic doses of drug; the results are therefore consistent with the hypothesis that genotoxic mechanisms play an important role in the drug-induced tumor incidence.

Giusti RM, Iwamoto K, Hatch EE. 1995. Diethylstilbestrol revisited: A review of the long-term health effects. Ann Intern Med 122:778-788.
Abstract: PURPOSE: To review the literature on the long-term health effects of exposure to diethylstilbestrol (DES) among women prescribed DES during pregnancy (DES mothers), among their children exposed inutero to the drug (DES sons and daughters) and among the progeny of these exposed sons and daughters (DES grandchildren). DATA SOURCES: English-language articles were identified through MEDLINE and CANCERLIT searches and through review of the bibliographies of identified articles. STUDY SELECTION: All human studies relevant to long-term health effects of exposure to DES were reviewed. DATA EXTRACTION: Descriptive data on existing DES cohorts were extracted from early publications. Risk estimates for health effects were extracted from published reports. DATA SYNTHESIS: An estimated 5 to 10 million Americans received DES during pregnancy or were exposed to the drug in utero. Exposure to DES has been associated with an increased risk for breast cancer in DES mothers (relative risk, < 2.0) and with a lifetime risk of clear-cell cervicovaginal cancer in DES daughters of 1/1000 to 1/10,000. The association between DES exposure and testicular cancer in DES sons remains controversial. Exposure to DES has also been linked to reproductive tract abnormalities in DES sons and daughters that consist of immune system disorders and psychosexual effects. No evidence for transgenerational effects currently exists. Recommendations for screening persons exposed to DES are reviewed. CONCLUSIONS: Further research is needed to define long-term health effects related to DES exposure. Such research would provide a basis for counseling persons exposed to DES and would further understanding of environmental and pharmacologic compounds similar to DES.

Giwercman A, Andrews PW, Jorgensen N, Muller J, Graem N, Skakkebaek NE. 1993 . Immunohistochemical expression of embryonal marker TRA-1-60 in carcinoma in situ and germ cell tumors of the testis. Cancer 72:1308-1314.
Abstract: BACKGROUND. Testicular cancer is preceded by the noninvasive stage of carcinoma in situ (CIS). According to a recent hypothesis, testicular CIA cells are germ cells transformed in fetal life. The idea of an embryonal origin of testicular germ cell neoplasia would be strengthened by the finding of antigenic similarity between fetal germ cells, CIS cells, and invasive testicular germ cell tumors. METHODS. Monoclonal antibody (MoAb) TRA-1-60 raised against a human embryonal carcinoma cell line was immunohistochemically tested on 21 fetal gonads (11 male gonads and 10 female gonads; 11th-24th week of gestation). In addition, TRA-1-60 was tested on tissue from 27 testes with CIS, 11 testes with invasive testicular cancer, and 24 adult and 4 infant testicular control specimens. RESULTS. Expression of TRA-1-60 was found in germ cells of six female and two male fetal gonads. In addition, 26 of 27 adult human testes with CIS, 7 of 8 seminomas, and 3 of 3 embryonal carcinomas were TRA-1-60 positive. CONCLUSIONS. The study demonstrated an antigenic link between fetal germ cells, cells of CIS and seminomas, and embryonal carcinomas. The results provided additional evidence for the hypothesis that testicular neoplasia arises during early fetal life and CIS cells are malignant fetal gonocytes.

Goerttler K, Loehrke H, Hesse B, Milz A, Schweizer J. 1981. Diaplacental initiation of NMRI mice with 7,12-dimethylbenz[a]anthracene during gestation days 6--20 and postnatal treatment of the F1-generation with the phorbol ester 12-O-tetradecanoylphorbol-13-acetate: tumor incidence in organs other than the skin. Carcinogenesis 2:1087-1094.
Abstract: The tumor spectrum and tumor incidence in organs other than the skin were investigated in the 12-O-tetradecanoylphorbol-13-acetate (TPA) treated F 1-generation of 13 groups of NMRI mice which had been initiated by a single intragastric dose of 7,12-dimethylbenz[a]anthracene during days 6, 8, and 10--20 of pregnancy. Promotion by topical application of TPA to the back skin was carried out twice per week 12 weeks after birth over a period of 26 weeks. The forestomach epithelium represented the only organ in which statistically significant 2-stage carcinogenesis could be demonstrated. A promotion effect could be seen in tumors of the Harderian gland, of the liver of male animals and on the development of both benign and malignant tumors of the lung in both sexes. Promotion treatment therefore led to an activation of

initiated tumor cells in those organs in which a very sensitive, more or less narrowly spaced oncogenic determination period exists.

Gold E, Gordis L, Tonascia J, Szklo M. 1979. Risk factors for brain tumors in children. Am J Epidemiol 109:309-319.
Abstract: An exploratory case-control study was conducted in 15 hospitals in the Baltimore, MD, SMSA of possible etiologic factors associated with brain tumors in children. Eighty-four children with brain tumors were compared to normal children and to children with other malignancies. Parents of these children were interviewed about a variety of possible etiologic factors. The findings included: 1) children with brain tumors as well as children with other cancers had a greater tendency than normal children to have been first births and to have had higher birth weights; 2) more children with brain tumors had a sibling with epilepsy or seizures than did normal children, and several of the mothers of children with brain tumors had themselves had epilepsy or a stroke at a relatively young age; 3) there were no significant differences between the groups with regard to several maternal characteristics, including smoking during pregnancy and prior radiation exposure; 4) more children with brain tumors and children with other cancers were found to have had exposures to insecticides than had normal children; 5) fewer children with brain tumors or with other cancers were reported to have had tonsillectomies than normal children; and 6) more of the children with brain tumors as well as the children with other malignancies were reported to have been exposed to farm animals and to sick pets. This exploratory study is one of the first case-control studies of the epidemiology of brain tumors in children, and the results suggest directions for future epidemiologic studies in this relatively uncharted field.

Gold EB, Diener MD, Szklo M. 1982. Parental occupations and cancer in children--A case-control study and review of the methodologic issues. J Occup Med 24:578-584.
Abstract: The findings of a number of published reports have been conflicting with regard to the role of parental occupation in the occurrence of cancer in children. In the present study, the occupations and occupational exposures of parents before and after the birth of a child who later developed leukemia or a brain tumor (cases) were compared with the occupational experience of parents of children with other cancers and of normal children. Forty-three children diagnosed with leukemia from 1969 through 1974 and 70 children diagnosed with brain tumors from 1965 through 1974 in the Baltimore Standard Metropolitan Statistical Area were ascertained. The findings of the present study do not demonstrate a relationship between parental occupation and occurrence of leukemia or brain tumors in the offspring. The results of this and other studies are evaluated in the context of a number of important but difficult methodologic issues that arise in studies of this potentially significant subject area.

Golden R, Gandy J, Vollmer G. 2005. A review of the endocrine activity of parabens and implications for potential risks to human health. Crit Rev Toxicol 35:435-458.
Abstract: Parabens are a group of the alkyl esters of p-hydroxybenzoic acid and typically include methylparaben, ethylparaben, propylparaben, butylparaben, isobutylparaben, isopropylparaben, and benzylparaben. Parabens (or their salts) are widely used as preservatives in cosmetics, toiletries, and pharmaceuticals due to their relatively low toxicity profile and a long history of safe use. Testing of parabens has revealed to varying degrees that individual paraben compounds have weakly estrogenic activity in some in vitro screening tests, such as ligand binding to the estrogen receptor, regulation of CAT gene expression, and proliferation of MCF-7 cells. Reported in vivo effects include increased uterine weight (i.e., butyl-, isobutyl-, and benzylparaben) and male reproductive-tract effects (i.e., butyl- and propylparaben). However, in relation to estrogen as a control during in vivo studies, the parabens with activity are many orders of magnitude less active than estrogen. While exposure to sufficient doses of exogenous estrogen can increase the risk of certain adverse effects, the presumption that similar risks might also result from exposure to endocrine-active chemicals (EACs) with far weaker activity is still speculative. In assessing the likelihood that exposure to weakly active EACs might be etiologically associated with adverse effects due to an endocrine-mediated mode of action, it is paramount to consider both the doses and the potency of such compounds in comparison with estrogen. In this review, a comparative approach involving both dose and potency is used to assess whether in utero or adult exposure to parabens might be associated with adverse effects mediated via an estrogen-modulating mode of action. In utilizing this approach, the paraben doses required to produce estrogenic effects in vivo are compared with the doses of either 17 beta-estradiol or diethylstilbestrol (DES) that are well established in their ability to affect

endocrine activity. Where possible and appropriate, emphasis is placed on direct comparisons with human data with either 17 beta-estradiol or DES, since this does not require extrapolation from animal data with the uncertainties inherent in such comparisons. Based on these comparisons using worst-case assumptions pertaining to total daily exposures to parabens and dose/potency comparisons with both human and animal no-observed-effect levels (NOELs) and lowest-observed-effect levels (LOELs) for estrogen or DES, it is biologically implausible that parabens could increase the risk of any estrogen-mediated endpoint, including effects on the male reproductive tract or breast cancer. Additional analysis based on the concept of a hygiene-based margin of safety (HBMOS), a comparative approach for assessing the estrogen activities of weakly active EACs, demonstrates that worst-case daily exposure to parabens would present substantially less risk relative to exposure to naturally occurring EACs in the diet such as the phytoestrogen daidzein.

Golding J, Greenwood R, Birmingham K, Mott M. 1992. Childhood-cancer, intramuscular viramin-Ks, and pethidine given during labor. Br Med J 305:341-346.
Abstract: Objective-To assess unexpected associations between childhood cancer and pethidine given in labour and the neonatal administration of vitamin K that had emerged in a study performed in the 1970 national birth cohort. Design and setting-195 children with cancer diagnosed in 1971-March 1991 and born in the two major Bristol maternity hospitals in 1965-87 were compared with 558 controls identified from the delivery books for the use of pethidine during labour and administration of vitamin K. Main outcome measures-Odds ratios for cancer in the presence of administration of pethidine or of intramuscular vitamin K. Both logistic regression and Mantel-Haenszel techniques were used for statistical analyses. Results-Children of mothers given pethidine in labour were not at increased risk of cancer (odds ratio 1.05, 95% confidence interval 0.7 to 1.5) after allowing for year and hospital of delivery, but there was a significant association (p=0.002) with intramuscular vitamin K (odds ratio 1.97, 95% confidence interval 1.3 to 3.0) when compared with oral vitamin K or no vitamin K. There was no significantly increased risk for children who had been given oral vitamin K when compared with no vitamin K (odds ratio 1.15, 95% confidence interval 0.5 to 2.7). These results could not be accounted for by other factors associated with administration of intramuscular vitamin K, such as type of delivery or admission to a special care baby unit. Conclusions-The only two studies so far to have examined the relation between childhood cancer and intramuscular vitamin K have shown similar results, and the relation is biologically plausible. The prophylactic benefits against haemorrhagic disease are unlikely to exceed the potential adverse effects from intramuscular vitamin K. Since oral vitamin K has major benefits but no obvious adverse effects this could be the prophylaxis of choice.

Golenko OL, Ryzhova NI. 1991. Transplacental effect of nicotinamide with N-nitroso-n-ethylurea-induction of preneoplastic changes in epithelium of the organ-cultures of embryonic kidneys in BALB/C mice. Eksperimentalnaya Onkologiya 13:15-19.
Abstract: Transplacental effect of nicotinamide (NA) on carcinogenic action of N-nitroso-N-ethylurea (NEU) was studied in organ cultures of embryonic kidney tissue of mice. NA injected into BALB/C female mice in the prenatal period stimulated hyperplastic epithelial growth induced by transplacental effect of NEU. Frequency of focal proliferation in kidney explantats under combined action of NA and NEU was 1.7 times higher than under isolated action of NEU (54.7 and 32.2 %, respectively $P < 0.001$).

Gondos B. 1993. Ultrastructure of developing and malignant germ cells. Eur Urol 23:68-74; discussion 75.
Abstract: Ultrastructural studies have provided special insights on the growth and differentiation of normal and neoplastic germ cells. Prespermatogenic germ cells in the fetal and postnatal testis are large spherical to ovoid cells characterized by a central symmetrical nucleus, prominent reticular nucleoli and abundant cytoplasm with accumulation of glycogen and paucity of other organelles. Similar findings have been observed in seminoma and intratubular neoplasia. These observations support origin of the tumours from germ cells at early stages of differentiation. Evidence is presented to suggest that the pathogenesis of germ cell neoplasia involves excessive proliferation of precursor germ cells associated with loss of intercellular communication.

Gonzalez A, Oberley TD, Li JJ. 1989. Morphological and immunohistochemical studies of the estrogen-induced Syrian hamster renal tumor: Probable cell of origin. Cancer Res 49:1020-1028.
Abstract: Chronic natural or synthetic estrogen treatment of Syrian golden hamsters leads to the development of malignant renal neoplasms. In the present study, morphological and immunohistochemical

studies were performed to further characterize the estrogen-induced hamster renal tumors. The neoplasms were composed of two distinct cell populations: a large-cell component that appeared highly epithelial, and a poorly differentiated small-cell component. Importantly, both cell types had epithelial characteristics, since they contained desmosomes at their cell surfaces. However, the large-cell component possessed additional epithelial features such as microvilli, intracytoplasmic lumens, and cilia. Comparative studies of renal tumors and developing renal tissue from fetal and newborn hamsters revealed remarkable histological similarities. Morphologically, the large tumor cells resembled early metanephric tubules and the small tumor cells were very similar to the blastemal cells of the developing kidney. The earliest tumor foci were found after 4.5 months of treatment. They were consistently found in the kidney interstitium in proximity to large arteries. Immunohistochemical staining for intermediate filaments in developing fetal and newborn kidneys demonstrated cytokeratin in renal tubules, desmin in blastemal cells, and vimentin in stromal cells. Estrogen-induced renal tumor cells uniquely possessed reactivity for all three intermediate filaments, clearly demonstrating their epithelial and mesenchymal characteristics. Based on their morphological resemblance to developing embryonic kidney cells and the presence of both epithelial and mesenchymal intermediate filaments, our findings provide strong evidence that the cell of origin of this malignant tumor is a precursor cell that is committed to an epithelial differentiation pathway.

Gostjeva EV, Zukerberg L, Chung D, Thilly WG. 2006. Bell-Shaped Nuclei Dividing by Symmetrical and Asymmetrical Nuclear Fission Have Qualities of Stem Cells in Human Colonic Embryogenesis and Carcinogenesis. Cancer Genet Cytogenet 164:16-24.
Abstract: Large cell nuclei with at least eight distinct morphologies have been discovered throughout the fetal gut (5-7 weeks), colonic adenomas, and adenocarcinomas, five of which are not present in the normal adult colon. The most remarkable nuclear forms are hollow bells, approximately 10-15 microns in height and about 7-10 microns in bell mouth diameter. When encased in tubular syncytia, these bell-shaped structures divide symmetrically by an amitotic nuclear fission process resembling the separation of two paper cups. Seven other nuclear morphotypes emerge from the bell-shaped nuclei within the syncytia by asymmetrical amitotic nuclear fission. Cells containing these differentiated nuclear forms subsequently divide extra-syncytially by mitoses that form clonal populations of cells with identical nuclear morphotypes in embryos, adenomas, adenocarcinomas, and metastases. Cells with bell-shaped nuclei thus appear to be responsible for both net growth and differentiation in the embryonic gut, adenomas, and adenocarcinomas, and fulfill the requirements for post-embryonic stem cells in colon organogenesis and carcinogenesis. (c) 2006 Elsevier Inc. All rights reserved.

Gray LE, Ostby J, Furr J, Wolf CJ, Lambright C, Parks L, Veeramachaneni DN, Wilson V, Price M, Hotchkiss A, Orlando E, Guillette L. 2001. Effects of environmental antiandrogens on reproductive development in experimental animals. Hum Reprod Update 7:248-264.
Abstract: Chemicals that act as androgen receptor (AR) agonists and antagonists or inhibit fetal steroidogenesis can induce reproductive malformations in humans and laboratory animals. Several environmental chemicals disrupt development in: rats and/or rabbits at fetal concentrations at, or near, exposure levels seen in some segments of the human population. In rats, fetal tissues concentrations of 10-20 p,p,m. of the DDT metabolite, p,p ' -DDE, are correlated with reproductive abnormalities in male offspring. These concentrations are similar to those measured in first-trimester human fetal tissues in the late 1960s. The pesticides vinclozolin, procymidone, linuron and DDT are AR antagonists;: They reduce male rat anogenital distance, and induce areolas at relatively low dosages, Hypospadias, agenesis of the sex accessory tissues and retained nipples are seen in the middle dosages, while undescended testes and epididymal agenesis are seen in the highest doses. Phthalate esters (PE) inhibit testosterone synthesis during fetal life, but do not appear to be AR antagonists. Prenatal administration of a single low dose of dioxin (50-1000 ng TCDD/kg) alters the differentiation of androgen-dependent tissues at p.p.t. concentrations, but the mechanism of action likely involves interaction with a hormone-like nuclear transcription factor, the hormone-like receptor AhR, rather than AW, p,p ' -DDT and p,p ' -DDE, vinclozolin and di-n-butyl phthalate affect reproductive function in rabbits when administered during prenatal and/or neonatal life. Cryptorchidism and carcinoma in situ-like (CIS) testicular lesions were seen in male rabbits treated during development with p,p ' -DDT or p,p ' -DDE, Extrapolation of effects from rodents to humans would be enhanced if future studies incorporate determination of tissue concentrations of the active metabolites. Knowledge of the tissue concentrations of the active toxicants also would provide an important link to in-vitro studies, which provide more useful mechanistic information when they are

executed at relevant concentrations.

Gray LE, Wolf C, Mann P, Ostby JS. 1997. In utero exposure to low doses of 2,3,7,8-tetrachlorodibenzo-p-dioxin alters reproductive development of female Long Evans Hooded rat offspring. Toxicology & Applied Pharmacology 146:237-244.
Abstract: Prenatal administration of a single dose of 1 mu g TCDD/kg induces malformations of the external genitalia and subfertility in female offspring (L. E. Gray, Jr., and J. S. Ostby (1995) Toxicol. Appl. Pharmacol. 133, 285-294). A cross-fostering study indicated that in utero but not lactational TCDD exposure (1 mu g TCDD/kg on gestational Day 15) induces cleft phallus, vaginal thread formation, and reduced ovarian weight. TCDD treatment on the 15th day of pregnancy at 0, 0.05, 0.20, or 0.80 mu g TCDD/kg delayed vaginal opening at 0.80 mu g/kg in the progeny. A persistent vaginal thread was displayed by 27% of the progeny at 0.20 and 92% at 0.80 mu g TCDD/kg. These effects did not appear to result from abnormal ovarian function during prepubertal development; neither serum estradiol levels nor ovarian estradiol production were reduced in 21- or 28-day-old progeny of darns exposed to 1 mu g TCDD/kg. In addition, partial to complete clefting of the phallus was displayed in TCDD-treated rats (10% at 0.20 and 60% at 0.80 mu g TCDD/kg) and these dosage levels also increased the length of the urethral slit, increased distance from the urethral opening to the tip of the phallus, and decreased distance from the urethral opening to the vaginal orifice. Although fertility rates were normal, time-to-pregnancy was delayed by treatment with 0.80 mu g TCDD/kg. When necropsied at 20 months of age, females from the TCDD-dose groups displayed histopathological alterations of the reproductive tract. In summary, administration of TCDD at dosage levels of 0.2, 0.8, and 1.0 mu g/kg produces morphological reproductive alterations in female rat offspring as a consequence of in utero exposure.

Greaves M. 2005. In utero origins of childhood leukaemia. Early Hum Dev 81:123-129.
Abstract: Chimaeric fusion genes derived by chromosome translocation are common molecular abnormalities in paediatric leukaemia and provide unique markers for the malignant clone. They have been especially informative in studies with twins concordant for leukaemia and in retrospective scrutiny of archived neonatal blood spots. These data have indicated that, in paediatric leukaemia, the majority of chromosome translocations arise in utero during foetal haemopoiesis. Chromosomal translocations and preleukaemic clones arise at a substantially higher frequency (-100x) before birth than the cumulative incidence or risk of disease, reflecting the requirement for complementary and secondary genetic events that occur postnatally. A consequence of the latter is a very variable and occasionally protracted postnatal latency of disease (1-15 years). These natural histories provide an important framework for consideration of key aetiological events in paediatric leukaemia. (C) 2004 Elsevier Ireland Ltd. All rights reserved.

Gressani KM, Leone-Kabler S, O'sullivan MG, Case LD, Malkinson AM, Miller MS. 1999. Strain-dependent lung tumor formation in mice transplacentally exposed to 3-methylcholanthrene and post-natally exposed to butylated hydroxytoluene. Carcinogenesis 20:2159-2165.
Abstract: The carcinogenic effects of in utero exposure to 3-methylcholanthrene (MC) have been demonstrated in the tumor-resistant C57BL/6 (B6) and DBA (D2) strains of mice, In this study, we determined the effects of in utero exposure to MC in BALB/c mice, a strain which demonstrates greater susceptibility to lung tumor induction, and compared our findings with those previously found in [D2 x B6D2F(1)]F-2 mice. In addition, we assessed the molecular pathogenesis of the chemically induced tumors and examined the effects of the putative lung tumor promoter butylated hydroxytoluene (BHT) in BALB/c mice. BALB/c mice were treated on day 17 of gestation with 5, 15 or 45 mg/kg MC and 6 weeks after birth with BHT for 6 consecutive weeks. Mice were killed at 6 months of age. Ki-ras, p16(Ink4a) and p19(ARF) gene loci were amplified from paraffin-embedded lung tumor tissue and screened for the presence of point mutations via allele-specific oligonucleotide hybridization and single strand conformation polymorphism (SSCP) analyses. Ki-ras point mutations were found in 56% (20/36) of BALB/c lung tumors, with 33% (2/6) of the hyperplasias, 58% (10/19) of the adenomas and 73% (8/11) of the carcinomas exhibiting point mutations at this gene locus, Similar incidences of Ki-ras mutations were previously found following transplacental exposure of [D2 X B6D2F(1)]F-2 mice to MC and treatment of adult A/J mice with urethane, Interestingly, a strain-dependent difference was observed in the mutational spectrum, Sixty-two and 38% of the lung lesions in BALB/c mice exhibited G-->C and G-->T transversions, respectively, in contrast to the 13 and 84% incidences previously observed in [D2 X B6D2F(1)]F-2 mice. SSCP analysis of the tumor suppressor gene p16(Ink4a) showed a 6% incidence of point mutations, consistent with that

found in [D2 x B6D2F(1)]F-2 mice. No mutations were found in exon 1 beta of the p19(ARF) gene of either strain. BHT, a lung tumor promoter in adult mice, had no statistically significant effects on either tumor incidence, tumor multiplicity or the mutational spectrum produced in the Ki-ms gene by in utero MC treatment. However, though not significant, there was an observable trend in increased tumor multiplicity in mice co-treated with BHT, These data demonstrate the transplacental carcinogenic effect of MC in BALB/c mice and show that mutagenic damage to Ki-ras is a critical early event mediating murine lung tumorigenesis in both the tumor-sensitive and tumor-resistant strains. Unlike what occurs when adult BALB/c mice are treated with MC, BHT does not appear to significantly promote the formation of lung tumors following transplacental exposure to MC, possibly due to the rapid growth and cell proliferation in the developing organism. Strain-dependent differences in the Ki-ms mutational spectrum may be associated with their differential susceptibility to lung tumor initiation.

Gressani KM, Leone-Kabler S, O'sullivan MG, Townsend AJ, Miller MS. 2000. Prenatal toxicity and lack of carcinogenicity of 2-amino-3-methylimidazo[4,5-f]quinoline (IQ) following transplacental exposure. Toxicol Sci 55:407-414.
Abstract: Accumulating evidence from human and experimental animal studies indicates that consumption of heterocyclic amines (HA), derived from cooked meat and fish, may be associated with an increased incidence of cancer. Experiments were initiated to assess the role of one of these compounds, 2-amino-3-methylimidazo[4,5-f]quinoline (IQ), as a potential transplacental carcinogen, as well as to evaluate whether in utero exposure to IQ results in the induction of fetal cytochrome P4501A1 (Cyp1a1), P4501B1 (Cyp1b1), and/or glutathione S-transferase (GST). Inducible, or responsive, backcrossed fetuses resulting from a cross between congenic C57BL/6 (Ah(d)Ah(d)) nonresponsive female mice and C57BL/6 (Ah(b)Ah(b)) responsive male mice were transplacentally exposed to olive oil or 6.25, 12.5, or 25 mg/kg of IQ on day 17 of gestation. No macroscopically or microscopically visible liver, lung, or colon tumors were found in the transplacentally treated offspring by one year after birth. Em/thoxyresorufin O-deethylase (EROD) and 1-chloro-2,4-dinitrobenzene assays were performed to evaluate whether transplacental exposure to IQ results in the induction of fetal Cyp1a1 and GST, respectively, in lung and liver tissues. Results showed levels of EROD and GST activity in tissues of IQ-treated mice to be very close, if not identical, to those of mice treated with olive oil. Similarly, ribonuclease protection assay data showed that the levels of Cyp1a1 and Cyp1b1 RNA in tissues of IQ-treated mice were not significantly different from those of oil-treated controls. Previous studies have shown that the developing organism expresses very low levels of Cyp1a2. Thus, in utero exposure to IQ does not lead to induction of Cyp1a1, Cyp1a2, or Cyp1b2 in the fetal compartment, thereby maintaining the low levels of these activating enzymes in the developing organism. Taken together, these data imply that, at least under the conditions employed for these experiments, IQ may not play an important role in transplacentally induced tumorigenesis.

Grigor KM, Wylie CC. 1998 . The origin and biology of CIS cells: General discussion. APMIS 106:221-224.
Abstract: Participants at the 4th Copenhagen Workshop on Carcinoma in situ and Cancer of the Testis, representing cell biologists and tumour biologists, met together to discuss the similarities and differences between primordial germ cells (PGCs) of the embryo, and the carcinoma in situ (CIS) stem cell of human testicular germ cell tumours (GCTs). Much has been discovered about PGCs in the last 10 years and we still do not know the exact nature of CIS cells. Knowledge of PGCs comes mainly from mouse experiments and knowledge of CIS comes from the study of human tumours. A mouse model of human GCT would help to investigate the nature of CIS cells. Grafting mouse male genital ridges into mouse fetal testes results in the development of testicular tissue and the formation of teratomatous tumour components. Amplification of PGCs in culture is possible but this results in their transformation into embryonic germ (EG) cells. CIS cells die by apoptosis if they are isolated, and short-term culture is only possible if the CIS cells are cultured in their normal environment within seminiferous tubules. It may be possible for CIS cells to differentiate in culture although they cannot be maintained in culture as isolated cells. Human CIS cells are likely to be formed as a result of in utero factors rather than agents acting on normal adult testicular germ cells. EG cells stimulate feeder cells by paracrine factors but it is not known if these cells produce autocrine factors.

Groce DF, Kimbrough RD. 1984. Stunted growth, increased mortality, and liver tumors in offspring of polybrominated biphenyl (PBB) dosed Sherman rats. J Toxicol Environ Health 14:695-706.
Abstract: Firemaster FF-1, a polybrominated biphenyl (PBB) mixture, was dissolved in corn oil and given

as a dose of 200 mg/kg body weight to Sherman rats on d 7 and 14 of pregnancy. Control rats received equivalent doses of corn oil alone. Selected pups and all dams were killed 1 mo after pups were weaned. A total of 50 male and 50 female offspring per group were followed until they were 2 yr old. The livers of offspring killed at the ages of 2 mo and 2 yr had PBB levels of 2,4 (SD 1.2) and 0.8 (SD 0.65) mg/kg for females and 3.0 (SD 1.6) and 0.6 (SD 0.37) mg/kg for males, respectively. The incidence of hepatocellular carcinomas was 3/51 (5.9%) and 4/41 (9.6%) after 2 yr in females and males, respectively. Hepatocellular carcinomas were not observed among the controls. Neoplastic (hyperplastic) nodules of the liver were present in 9/51 (17.6%) and 2/41 (4.9%) of exposed females and males, respectively, whereas only 2/48 (4.2%) of control females and no control males had neoplastic (hyperplastic) nodules. Body weights were lower in PBB-exposed rats at ages 1, 6, 12, and 24 mo. Survival rates from birth to weaning were lower in PBB-exposed pups (89%) than in controls (98%). Mortality was two times higher in PBB-exposed males (64%) than in control males (32%) after 2 yr. Transplacental PBB exposure and exposure through milk resulted in PBB body burdens in the offspring still measurable at the end of their lifespan. These offspring had increased mortality rates and lower body weights than controls, and they developed hepatocellular carcinomas.

Grotmol T, Weiderpass E, Tretli S. 2006. Conditions in utero and cancer risk. European Journal of Epidemiol 21:561-70.
Abstract: There is increasing recognition that conditions in utero are of importance for later cancer risk in several organs, particularly the testis and breast. A review of the most recent literature on this topic is therefore warranted. The PubMed database was searched for relevant recent literature on intrauterine conditions associated with cancer risk later in life, with particular emphasis on the testis, breast, but also studies pertaining to other organs were included. Epidemiological and experimental data support the hypothesis that factors acting in utero play a role in the development of cancer in the testis and breast. For other organs, such as the prostate, urinary system and colorectum, the results are inconclusive. While conditions during foetal life are associated with later cancer risk in the testis and breast, the biological mechanisms are for the most part elusive. They are, however, likely to involve hormonal disturbances, number of cells at risk, and genetic or epigenetic events.

Grufferman S, Schwartz AG, Ruymann FB, Maurer HM. 1993. Parents use of cocaine and marijuana and increased risk of rhabdomyosarcoma in their children. Cancer Causes & Control 4:217-224.
Abstract: Parents' use of marijuana and cocaine was evaluated in a national (United States) case-control study of childhood rhabdomyosarcoma (RMS). Subjects were 322 RMS cases, aged 0-20 years, from the Intergroup Rhabdomyosarcoma Study, and 322 matched controls identified by random-digit telephone dialing. Parents of subjects were interviewed by telephone using a structured questionnaire. Mothers' marijuana use during the year before their child's birth was associated with a 3.0-fold increased risk of RMS in the child (95% confidence interval [CI] = 1.4-6.5) and maternal cocaine use was associated with a 5.1-fold increased risk (CI = 1.0-25.0). Risk was increased 3.1-fold (CI = 1.4-6.7) with use of any recreational drug. Fathers' marijuana use was associated with a 2.0-fold increased risk (CI = 1.3-3.3), cocaine use with a 2.1-fold increased risk (CI = 0.9-4.9), and use of any recreational drug with a 2.0-fold (CI = 1.3-3.3) increased risk. Case mothers' cocaine use and both parents' marijuana use were associated with their children being diagnosed at a significantly younger age. It was not possible to determine whether cocaine and marijuana have independent effects, since use of the two drugs was materially correlated. Similarly, mothers' and fathers' use of these drugs was highly correlated. In summary, parents' marijuana and cocaine use during the year preceding their child's birth may increase, by twofold to fivefold, the risk of RMS in their children.

Guo MZ, House MG, Akiyama Y, Qi Y, Capagna D, Harmon J, Baylin SB, Brock MV, Herman JG. 2006. Hypermethylation of the GATA gene family in esophageal cancer. Int J Cancer 119:2078-2083.
Abstract: The GATA family of transcription factors promotes the normal development of the gastrointestinal tract during embryogenesis and determines tissue differentiation in adult gut epithelium. Loss of GATA-4 and GATA-5 has been reported in human gastric and colon cancer. We examined GATA-4,-5 and -6 gene expression in established esophageal squamous cancer cell lines and the relationship to DNA methylation in the promoter region of these genes. GATA-4 and GATA-5 expression was absent in most esophageal cancer cell lines, but was restored upon treatment with the demethylating agent 5-aza-2-deoxycytidine. For each of the cell lines without detectable GATA gene expression, aberrant methylation

of the promoter region CpG-island was detected by methylation specific PCR. We confirmed these results with genomic bisulfite sequencing. GATA-6 expression was found in each of the cell lines. GATA-4/-5 promoter methylation was not detected in normal esophageal mucosa, but GATA-4 methylation was present in 27 of 44 (61%) squamous carcinomas and 31 of 44 (71%) adenocarcinoma of the esophagus, while GATA-5 methylation was present in 14 of 44 (32%) squamous carcinomas and 24 of 44 (55%) adenocarcinoma of the esophagus. Our studies demonstrate frequent silencing of GATA-4 and GATA-5, but not GATA-6, in human esophageal neoplasia associated with gene promoter hypermethylation. (c) 2006 Wiley-Liss, Inc.

Gurney JG, Smith MA, Olshan AF, Hecht SS, Kasum CM. 2001. Clues to the etiology of childhood brain cancer: N-nitroso compounds, polyomaviruses, and other factors of interest. Cancer Invest 19:630-640.

Hadjimichael OC, Meigs JW, Falcier FW, Thompson WD, Flannery JT. 1984. Cancer risk among women exposed to exogenous estrogens during pregnancy. J Natl Cancer Inst 73:831-834.
Abstract: A cohort of 3,139 obstetric patients, who delivered children between 1946 and 1965, was followed retrospectively to assess the relationship between exposure to diethylstilbestrol [(DES) CAS: 56-53-1; alpha,alpha'-diethyl-4,4'-stilbenediol] or other estrogenic substances during pregnancy and subsequent cancer incidence. Among the 1,531 women exposed to DES, the relative risk (RR) for all cancers was 1.46 [95% confidence interval (CI), 1.07-2.00]. The RR for cancers of the breast, cervix, and ovary were 1.37 (adjusted), 1.40, and 2.83, respectively, but none of these estimates was statistically significant. For breast cancer an RR in excess of 2.28 can be excluded, with 95% CI for doses averaging 2,100 mg. Within the exposed group there was no evidence for a dose-response relationship.

Hajek RA, King DW, Hernandez-Valero MA, Kaufman RH, Liang JC, Chilton JA, Edwards CL, Wharton JT, Jones LA. 2006. Detection of chromosomal aberrations by fluorescence in situ hybridization in cervicovaginal biopsies from women exposed to diethylstilbestrol in utero. International Journal of Gynecological Cancer 16:318-34.
Abstract: Epidemiologic studies have associated estrogens with human neoplasms such as those in the endometrium, cervix, vagina, breast, and liver. Perinatal exposure to natural (17beta-estradiol [17beta-E(2)]) and synthetic (diethylstilbestrol [DES]) estrogens induces neoplastic changes in humans and rodents. Previous studies demonstrated that neonatal 17beta-E(2) treatment of mice results in increased nuclear DNA content of cervicovaginal epithelium that precedes histologically evident neoplasia. In order to determine whether this effect was associated with chromosomal changes in humans, the frequencies of trisomy of chromosomes 1, 7, 11, and 17 were evaluated by the fluorescence in situ hybridization (FISH) technique in cervicovaginal tissue from 19 DES-exposed and 19 control women. The trisomic frequencies were significantly elevated in 4 of the 19 (21%) DES-exposed patients. One patient presented with trisomy of chromosomes 1, 7, and 11, while trisomy of chromosome 7 was observed in one patient. There were two patients with trisomy of chromosome 1. Trisomy of chromosomes 1, 7, 11, and 17 was not observed in the cervicovaginal tissue taken from control patients. These data suggest that DES-induced chromosomal trisomy may be an early event in the development of cervicovaginal neoplasia in humans.

Hajek RA, Robertson AD, Johnston DA, Van NT, Tcholakian RK, Wagner LA, Conti CJ, Meistrich ML, Contreras N, Edwards CL, Jones LA. 1997. During development, 17 alpha-estradiol is a potent estrogen and carcinogen. Environ Health Perspect 105:577-581.
Abstract: Neonatal administration of estradiol-17 beta (E-2-17 beta) increases the nuclear DNA content in the mouse reproductive tract. Similar responses have been demonstrated for synthetic estrogens such as diethylstilbestrol. One of the questions raised regarding environmental estrogens such as organochlorines is whether they are potent enough to result in abnormal changes such as those demonstrated by both natural and synthetic estrogens. To test this hypothesis, female BALB/c mice were treated neonatally (days 1-5) with either E-2-17 beta or estradiol-17 alpha (E-2-17 alpha), an inactive stereoisomer in adult reproductive tissues. We also proposed whether neonatal administration of (E-2-17 alpha) was tumorigenic and whether the effects were age dependent. To answer these questions, one set each of 10-day-old treated and control mice received short-term secondary administration of E-2-17 beta, E-2-17 alpha, or cholesterol. Cervicovaginal tracts from intact BALB/c mice were examined histologically and by flow cytometry at 70 days of age and by histology alone at 18 to 22 months of age. The results include several important findings: a) like E-2-17 beta, neonatal E-2-17 alpha treatment induced persistent vaginal cornification,

hypospadias, vaginal concreticns, and hyperproliferation in nearly 100% of the animals regardless of the secondary treatment for most groups; b) neonatal E-2-17 alpha treatment increased the nuclear DNA content of cervicovaginal epithelium at one-half both the level (mean DNA index of 1.02 vs 1.04) and incidence (22 vs 46% of the animals) of E-2-17 beta; c) short-term secondary treatment with E-2-17 alpha, unlike E-2-17 beta, did not significantly augment the increase in DNA content (13% for E-2-17 alpha vs 37 and 56% for control and E-2-17 beta, respectively); and d) neonatal administration with E-2-17 alpha induced adenosquamous tumors in the reproductive tract in 25% of the animals. Therefore, the biological effects (estrogenic potency) of E-2-17 alpha may be age dependent.

Hajek RA, Van NT, Johnston DA, Jones LA. 1993. In-vivo induction of increased DNA-ploidy of mouse cervicovaginal epithelium by neonatal estrogen-treatment. Biol Reprod 49:908-917.
Abstract: The purpose of this study was to test the hypothesis that exposure to natural estrogen early in the development of hormone-dependent tissue induces a change in nuclear DNA content. Female BALB/c mice were treated neonatally with daily s.c. injections of either 25 mug of 17beta-estradiol (E2) in 0.02 ml of sesame oil (vehicle) or vehicle alone for 5 days. Treatment was begun either within 15 h of birth or 6 days after birth. One set each of 10-day-old E2-treated and control mice received s.c. pellet implants containing 15 mg of E2 and cholesterol (10% E2 and 90% cholesterol), a second set received implants containing 25 mg of cholesterol alone, and a third set did not receive implants. Cervicovaginal tracts from intact BALB/c mice were examined histologically and by flow cytometry at 21, 40, 70, 180, or 240 days of age. The results obtained include several important findings: 1) neonatal E2 treatment in BALB/c mice causes an increase in nuclear DNA content in cervicovaginal epithelium; 2) short-term administration of secondary exogenous E2 reduces the latency period for the appearance of increased nuclear DNA content in neonatally E2-treated cervicovaginal epithelium; 3) increased nuclear DNA content can indicate abnormal cervicovaginal epithelium before histological abnormalities become evident; and 4) there is a sensitive period for neonatal E2 induction of increased nuclear DNA content in the cervicovaginal epithelium. These findings support other reports of the carcinogenic potential of estrogen in vivo. Therefore, increased DNA ploidy may be an important early detectable event in estrogen-induced carcinogenesis.

Hamrick SEG, Olshan AF, Neglia JP, Pollock BH. 2001. Association of pregnancy history and birth characteristics with neuroblastoma: a report from the Children's Cancer Group and the Pediatric Oncology Group. Paediatric & Perinatal Epidemiology 15:328-337.
Abstract: Previous studies have suggested a relationship between reproductive history, pregnancy and birth factors, and the risk of neuroblastoma. We conducted a case-control telephone interview study that included a total of 504 children under the age of 19 years with newly diagnosed neuroblastoma identified by two national collaborative clinical trials groups, the Children's Cancer Group and the Pediatric Oncology Group. A total of 504 controls, matched to cases on age, were identified by random digit dialling. Conditional logistic regression was used to estimate the matched odds ratio (OR) and 95% confidence interval (CI) with adjustment for household income, and maternal race and education. In addition, case subgroups defined by age at diagnosis, tumour MYCN oncogene amplification status, and stage were evaluated. A suggestive pattern of increased risk was seen for a greater number of prior pregnancies, history of previous miscarriages and induced abortions, with nearly a twofold increase in risk for two or more prior induced abortions (OR = 1.9, 95% CI [1.0,3.7]). No association was found for the following diseases or conditions during pregnancy: hepatitis, rubella, measles, mumps, chickenpox, mononucleosis, vaccinations, morning sickness, pre-eclampsia, bleeding, proteinuria, anaemia, urinary tract infections, heart disease, kidney disease, liver disease and diabetes. A weak association was found for hypertension during pregnancy. Several labour and delivery factors were related to an increased risk, including threatened miscarriage, anaesthetic during labour (specifically epidural) and caesarean delivery. We found associations between premature delivery (<33 weeks: OR = 1.9, 95% CI [0.7,4.8]), very low birthweight (<1500 g: OR 2.6, 95% CI [0.7,10.3]) and risk of neuroblastoma. There was no consistent pattern of increased risk found for most factors within subgroups defined by age at diagnosis, stage or MYCN status.

Hankin C, Lyall H, Peckham C, Tookey P. 2007. Monitoring death and cancer in children born to HIV-infected women in England and Wales: use of HIV surveillance and national routine data. AIDS 21:867-9.
Abstract: There may be long-term adverse health effects of in-utero antiretroviral therapy exposure. Data on children reported through national HIV surveillance were linked to routinely collected cancer and death

data: a process known as "flagging". Ninety-five per cent (2612) of reported children born in 2001-2004 in England or Wales who were uninfected or of indeterminate infection status were flagged. By the end of 2005, no cancers and 14 deaths (three uninfected and 11 indeterminate) had been notified.

Hanselaar A, Vanloosbroek M, Schuurbiers O, Helmerhorst T, Bulten J, Bernheim J. 1997. Clear cell adenocarcinoma of the vagina and cervix - An update of the central Netherlands registry showing twin age incidence peaks. Cancer 79:2229-2236.
Abstract: BACKGROUND. The objective of this study was to update the registry of women in the Netherlands with clear cell adenocarcinoma (CCAC) of the cervix or vagina with or without intrauterine exposure to diethylstilbestrol (DES). METHODS. From a nationwide search in PALGA, the automated pathology registry in the Netherlands, data were gathered on women with CCAC born after 1947. Information obtained from the clinical files of the patients included reported exposure to DES, patterns of complaints previous to diagnosis, the current status of the patients, and the results of cytopathologic examinations previous to histopath ologic diagnosis. After review of the histopathologic slides, the specific pathologic characteristics of CCAC were determined. The age distribution of women born after 1947 was compared with that of women born before 1947. RESULTS. Information about possible exposure to DES during pregnancy was available for 73 of 88 women with CCAC born after 1947. Exposure to DES was reported for 47 (64%) of these women. The DES medication was most often reported as having started before the 18th week of pregnancy. Cytopathologic examination was informative in 81% of the cases of CCAC of the cervix, but only in 41% of the cases of CCAC of the vagina. Most patients had Stage I or II tumors at diagnosis. Tumor Stage III and IV and a high grade of nuclear atypia were related to unfavorable outcome. The age distribution of all patients with CCAC showed two distinct peaks: one at young age, (a mean age of 26 years), and one at older age (a mean age of 71 years). This bimodal age distribution still applied when the cases in which DES exposure was reported had been excluded. CONCLUSIONS. Despite the fact that DES has not been prescribed to pregnant women in the Netherlands in the last 20 years, CCAC is still relevant in our times. It is important to stay alert and periodically to update and evaluate the data of this registry, including data on women born outside the DES exposure period. The bimodal age distribution in this study of women without intrauterine exposure to DES suggests a carcinogenesis-promoting role of menarche and menopause and/or the existence of a subpopulation with genetic risk factors or exogenous risk factors other than exposure to DES. Postmenopausal observation of women exposed to DES must be encouraged for clinical reasons and may help facilitate differentiation between these two hypotheses. If these risk factors of CCAC were better documented and their interrelationships better defined, CCAC could become an important model of multistep carcinogenesis in tissues sensitive to sex hormones. (C) 1997 American Cancer Society.

Hansen C, Sorensen LD, Asmussen I, Autrup H. 1992. Transplacental exposure to tobacco smoke in human-adduct formation in placenta and umbilical cord blood vessels. Teratog Carcinog Mutagen 12:51-60.
Abstract: Smokers are exposed to a large number of genotoxic compounds that react with DNA to form covalently bound carcinogen-DNA adducts after metabolic conversion to their biological active form. Using the P32-postlabeling techniques, tobacco smoke related carcinogen--DNA adducts have been demonstrated in DNA isolated from human placenta and umbilical cord vein and artery obtained from 11 nonsmoking and 8 smoking normal healthy women and foetuses. The adduct level was significantly higher in tissues from smokers than from nonsmokers ($P = 0.021$), when all tissues were combined. Furthermore, the total adduct level was higher in maternal tissue than the level in fetal tissues ($P = 0.030$). The adduct level in umbilical cord vein DNA was significantly lower than in placenta, and marginally lower than in umbilical cord artery from the same donor. This suggests that the foetus can metabolise some of the genotoxic compounds found in tobacco smoke to DNA-binding metabolites. The presence of DNA adducts in foetal tissues is indicative of potential genomic damage, that may result in an increased risk for the development of serious diseases, like cancer in childhood or later during the life span of the individual.

Hardell L, van Bavel B, Lindström G, Carlberg M, Dreifaldt AC, Wijkström H, Starkhammar H, Eriksson M, Hallquist A, Kolmert T. 2003. Increased concentrations of polychlorinated biphenyls, hexachlorobenzene, and chlordanes in mothers of men with testicular cancer. Environ Health Perspect 111:930-934.
Abstract: An increasing incidence of testicular cancer has been reported from several countries in the Western world during the last decades. According to current hypothesis, testicular cancer is initiated during the fetal period, and exposure to endocrine disruptors, i.e., xenoestrogens, has been of concern. In this

investigation we studied the concentrations of the sum of 38 polychlorinated biphenyls (PCBs), *p,p´*-dichlorodiphenyl-dichloroethylene, hexachlorobenzene (HCB), and chlordanes, in 61 cases with testicular cancer and 58 age-matched controls. Furthermore, case and control mothers were also asked to participate, and 44 case mothers and 45 control mothers agreed. They were of similar age. In cases only the concentration on lipid basis of *cis*-nonachlordane was significantly increased, whereas case mothers showed significantly increased concentrations of the sum of PCBs, HCB, *trans*- and *cis*-nonachlordane, and the sum of chlordanes. Among case mothers the sum of PCBs yielded an odds ratio (OR) of 3.8; 95% confidence interval (CI), 1.4-10 was calculated using the median concentration for the control mothers as cutoff value. For HCB, OR = 4.4 (95% CI, 1.7-12); for *trans*-nonachlordane, OR = 4.1 (95% CI, 1.5-11); for *cis*-nonachlordane, OR = 3.1 (95% CI, 1.2-7.8); and for sum of chlordanes, OR = 1.9 (95% CI, 0.7-5.0). No consistent different risk pattern was found for seminoma or nonseminoma testicular cancer.

Hardell L, Van Bavel B, Lindstrom G, Carlberg M, Eriksson M, Dreifaldt AC, Wijkstrom H, Starkhammar H, Hallquist A, Kolmert T. 2004. Concentrations of polychlorinated biphenyls in blood and the risk for testicular cancer. International Journal of &Rology 27:282-290.
Abstract: An increasing incidence of testicular cancer has been reported from several western countries during the last decades. According to current hypothesis testicular cancer is initiated during the foetal period and exposure to endocrine disruptors such as some persistent organic pollutants has been of concern. We have previously reported the results for concentrations of polychlorinated biphenyls (PCBs), p,p'-dichlorodiphenyl-dichloroethylene (pp'-DDE), hexachlorobenzene (HCB) and chlordanes in 58 cases with testicular cancer, 61 age-matched controls and 44 case mothers and 45 control mothers. In that report, significant increase of odds ratio (OR) was found for sum of PCBs, HCB, trans- and cis-nonachlordane in case mothers. These data have now been further analysed for 37 congeners of PCBs. No significant differences were found among cases and controls. However, case mothers had significantly increased concentrations of a number of PCB congeners. A priori decided grouping of PCBs yielded for oestrogenic PCBs OR = 2.4, 95% confidence interval (CI) = 0.95-6.0, enzyme-inducing PCBsOR = 2.6, 95% CI = 1.03-6.5 and toxic equivalents (TEQ) yielded OR = 3.3, 95% CI = 1.3-8.4. These data further elucidate the role of foetal exposure to different PCB congeners in the aetiology of testicular cancer.

Harkonen PL, Makela SI. 2004. Role of estrogens in development of prostate cancer. J Steroid Biochem Mol Biol 92:297-305.
Abstract: Estrogens have previously been extensively used in prostate cancer treatment. Serious side effects, primarily in cardiovascular system have, however, limited their use. The therapeutic effect of estrogen in preventing prostate cancer growth was mainly obtained indirectly by feedback inhibition of the hypothalamic release of LRH leading to lowered serum androgen levels and castration like effects. Prostate tissue is also most probably a target for direct regulation by estrogens. Prostate contains estrogen receptor a (ERalpha) and beta (ERbeta), which are localized characteristically in stroma and epithelium, respectively. The physiological function of these receptors is not known but there is evidence of the role of estrogens in prostatic carcinogenesis. Developing prostate seems particularly sensitive to increased level of endogenous and/or exogenous estrogens. Perinatal or neonatal exposure of rats and mice to estrogens leads to "imprinting" of prostate associated with increased proliferation, inflammation and dysplastic epithelial changes later in life. Prolonged treatment of adult rodents with estrogens along with androgens also leads to epithelial metaplasia, PIN-like lesions and even adenocarcinoma of prostate speaking for the role of estrogen in prostate cancer development. Recent results concerning antiestrogen inhibition of prostate cancer development beyond PIN-type lesions in transgenic mouse models further suggests a role for estrogens in prostate cancer progression. These results also suggest that direct inhibition of estrogen action at the level of prostate tissue may provide an important novel principle of development of prostate cancer therapies. (C) 2004 Elsevier Ltd. All rights reserved.

Hasegawa R, Kimura J, Yaono M, Takahashi S, Kato T , Futakuchi M, Fukutake M, Fukutome K, Wakabayashi K, Sugimura T, Ito N, Shirai T. 1995. Increased risk of mammary-carcinoma development following transplacental and trans-breast milk exposure to a food-derived carcinogen, 2-amino-1-methyl-6-phenylimidaso[4,5-b]pyridine (PhIP), in Sprague-Dawley rats. Cancer Res 55:4333-4338.
Abstract: Effects of transplacental and trans-breast milk exposure to a food-derived mammary and colon carcinogen, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), were investigated in rats, Female Sprague-Dawley rats were administered PhIP in the diet (100 ppm) for 4 weeks before mating with

nontreated males and also during gestation and lactation, As controls, additional females were maintained on the basal diet without PhIP and mated as with the treated animals, The offspring of both groups were subdivided for each sex at weaning into three dietary groups receiving 100, 25, and 0 ppm and were killed at 47 weeks of age. Effects of the transplacental and neonatal exposure to PhIP on mammary carcinogenesis were most evident in females administered 25 ppm PhIP after weaning; the incidence and multiplicity of adenocarcinomas in offspring from the PhIP fed dams (42.9%, 0.62/rat) was significantly higher than the value for offspring from nontreated dams (4.8%, 0.05/rat), Furthermore, in the basal diet groups, the incidence of adenocarcinomas in females was higher, albeit not significantly, in offspring of the PhIP-treated than the nontreated dams (16.7%, 0.22/rat as compared with 3.3%, 0.07/rat). Although the highest incidence of mammary adenocarcinomas was found in the female progeny given 100 ppm PhIP from PhIP-treated dams (70.0%, 1.55/rat), this was only slightly higher than the 61.9% and 0.90/rat of the same dose group from the nontreated dams. In males, no apparent effects of transplacental and neonatal exposures were evident. In a separate experiment, excretion of PhIP into breast milk and transfer of PhIP to fetuses and neonates with resultant hepatic PhIP-DNA adduct formation were demonstrated. Thus, maternal exposure to this food-derived carcinogen may be a critical risk factor for generation of mammary carcinomas.

Hatch EE, Palmer JR, Titus-Ernstoff L, Noller KL, Kaufman RH, Mittendorf R, Robboy SJ, Hyer M, Cowan CM, Adam E, Colton T, Hartge P, Hoover RN. 1998 . Cancer risk in women exposed to diethylstilbestrol in utero. JAMA 280:630-634.
Abstract: CONTEXT: The association between in utero exposure to diethylstilbestrol (DES) and clear cell adenocarcinoma (CCA) of the vagina and cervix is well known, yet there has been no systematic study of DES-exposed daughters to determine whether they have an increased risk of other cancers. As many as 3 million women in the United States may have been exposed to DES in utero. OBJECTIVE: To determine whether women exposed to DES in utero have a higher risk of cancer after an average of 16 years of follow-up. DESIGN: A cohort study with mailed questionnaires and medical record review of reported cancer outcomes. PARTICIPANTS: A cohort of 4536 DES-exposed daughters (of whom 81% responded) and 1544 unexposed daughters (of whom 79% responded) who were first identified in the mid-1970s. MAIN OUTCOME MEASURES: Cancer incidence in DES-exposed daughters compared with population-based rates and compared with cancer incidence in unexposed daughters. RESULTS: To date, DES-exposed daughters have not experienced an increased risk for all cancers (rate ratio, 0.96; 95% confidence interval [CI], 0.58-1.56) or for individual cancer sites, except for CCA. Three cases of vaginal CCA occurred among the exposed daughters, resulting in a standardized incidence ratio of 40.7 (95% CI, 13.1-126.2) in comparison with population-based incidence rates. The rate ratio for breast cancer was 1.18 (95% CI, 0.56-2.49); adjustment for known risk factors did not alter this result. CONCLUSIONS: Thus far, DES-exposed daughters show no increased cancer risk, except for CCA. Nevertheless, because exposed daughters included in our study were, on average, only 38 years old at last follow-up, continued surveillance is warranted to determine whether any increases in cancer risk occur during the menopausal years.

Hattis D, Goble R, Russ A, Chu M, Ericson J. 2004. Age-related differences in susceptibility to carcinogenesis: A quantitative analysis of empirical animal bioassay data. Environ Health Perspect 112:1152-1158.
Abstract: In revising cancer risk assessment guidelines, the U.S. Environmental Protection Agency (EPA) analyzed animal cancer bioassay data over different periods of life. In this article, we report an improved analysis of these data (supplemented with some chemical carcinogenesis observations not included in the U.S. EPA's original analysis) and animal bioassay studies of ionizing radiation. We use likelihood methods to avoid excluding cases where no tumors were observed in specific groups. We express dosage for animals of different weights on a metabolically consistent basis (concentration in air or food, or per unit body weight to the three-quarters power). Finally, we use a system of dummy variables to represent exposures during fetal, preweaning, and weaning-60-day postnatal periods, yielding separate estimates of relative sensitivity per day of dosing in these intervals. Central estimate results indicate a 5- to 60-fold increased carcinogenic sensitivity in the birth-weaning period per dose divided by (body weight(0.75)-day) for mutagenic carcinogens and a somewhat smaller increase-centered about 5-fold-for radiation carcinogenesis per gray. Effects were greater in males than in females. We found a similar increased sensitivity in the fetal period for direct-acting nitrosoureas, but no such increased fetal sensitivity was detected for carcinogens requiring metabolic activation. For the birth-weaning period, we found an increased sensitivity for direct

administration to the pups similar to that found for indirect exposure via lactation. Radiation experiments indicated that carcinogenic sensitivity is not constant through the "adult" period, but the dosage delivered in 12- to 21-month-old animals appears a few-fold less effective than the comparable dosage delivered in young adults (90-105 days of age).

Hawkes CH, Cavanagh JB, Darling JL, Watkins BA, Thomas DGT. 1992. Chronic low-dose exposure of sodium-nitrite in VM-strain mice - Central-nervous-system changes. Human & Experimental Toxicology 11:279-281.
Abstract: 1 There is suggestive evidence that nitrite may be a causative factor in cerebral glioma. 2 To test this hypothesis we selected the VM mouse strain, known for its susceptibility to spontaneous glioma formation, and exposed 300 animals to 0.2% sodium nitrite in their drinking water. One hundred of this group were exposed both in utero and throughout their adult lives. The remaining 200 animals received nitrite from the time of weaning. A further 200 mice were used as controls and received distilled water. 3 All animals were maintained until their natural death and were then subjected to autopsy and routine histological examination. 4 There was no excess of nervous system tumours in the experimental groups.

Heikinheimo K, Sandberg M, Happonen RP, Virtanen I, Bosch FX. 1991 . Cytoskeletal gene expression in normal and neoplastic human odontogenic epithelia. Lab Invest 65:688-701.
Abstract: In situ and Northern hybridization was carried out to study cytokeratin (Ck) 1, 4, 8, 18, and 19 and vimentin (Vim) gene expression in 13- to 24-week-old human fetal tooth germs, including overlying oral epithelium and odontogenic tumors (N = 6) of epithelial (ameloblastoma) and epithelial-ectomesenchymal (ameloblastic fibroma) origin. The results were compared with immunocytochemistry using monoclonal antibodies. A relatively strong expression of simple epithelial Ck 19 mRNA, together with low, but significant expression of Ck 8 and 18 mRNAs, was demonstrated in all normal and neoplastic odontogenic epithelia studied. Transcripts for squamous differentiation marker, Ck 4, and for terminal differentiation marker, Ck 1, were detected suprabasally in the fetal oral epithelium, focally in the dental lamina but not in the enamel organ. Ck 4 mRNA was expressed variably in most odontogenic tumors studied, whereas Ck 1 mRNA was detected in one ameloblastoma only. Vim mRNA was not found in the fetal oral epithelia, dental lamina or the enamel organ, but a distinct immunoreactivity with monoclonal antibodies to Vim was seen in the stellate reticulum cells of the enamel organ. The epithelium of most ameloblastomas showed a focal Vim mRNA and polypeptide expression. In addition to Vim, the neoplastic ectomesenchymal cells of ameloblastic fibroma coexpressed low amounts of simple epithelial Cks 8, 18, and 19. The results indicate that the differentiation and cytoskeletal gene expression programs of odontogenic epithelia upon neoplastic transformation are not fully retained. Most ameloblastomas and ameloblastic fibromas show differentiation parameters reminiscent of dental lamina. Ameloblastomas seem to form a heterogenous group of tumors, which may originate from odontogenic epithelial cells at various differentiation levels. The origin of ameloblastic fibroma is more closely related to the tooth germ proper.

Hemminki E, Gissler M, Toukomaa H. 1999. Exposure to female hormone drugs during pregnancy: Effect on malformations and cancer. Br J Cancer 80:1092-1097.
Abstract: This study aimed to investigate whether the use of female sex hormone drugs during pregnancy is a risk factor for subsequent breast and other oestrogen-dependent cancers among mothers and their children and for genital malformations in the children. A retrospective cohort of 2052 hormone-drug exposed mothers, 2038 control mothers and their 4130 infants was collected from maternity centres in Helsinki from 1954 to 1963. Cancer cases were searched for in national registers through record linkage. Exposures were examined by the type of the drug (oestrogen, progestin only) and by timing (early in pregnancy, only late in pregnancy). There were no statistically significant differences between the groups with regard to mothers' cancer, either in total or in specified hormone-dependent cancers. The total number of malformations recorded, as well as malformations of the genitals in male infants, were higher among exposed children. The number of cancers among the offspring was small and none of the differences between groups were statistically significant. The study supports the hypothesis that oestrogen or progestin drug therapy during pregnancy causes malformations among children who were exposed in utero but does not support the hypothesis that it causes cancer later in life in the mother; the power to study cancers in offspring, however, was very low. Non-existence of the risk, negative confounding, weak exposure or low study-power may explain the negative findings.

Hemminki K, Chen BW. 2006. Familial Risks in Testicular Cancer as Aetiological Clues. Int J Androl 29:205-210.
Abstract: We used the nationwide Swedish Family-Cancer Database to analyse the risk for testicular cancer in offspring through parental and sibling probands. Among 0 to 70-year-old offspring, 4586 patients had testicular cancer. Standardized incidence ratios for familial risk were 3.8-fold when a father and 7.6-fold when a brother had testicular cancer. Testicular cancer was associated with leukaemia, distal colon and kidney cancer, melanoma, connective tissue tumours and lung cancer in families. Non-seminoma was associated with maternal lung cancer but the risk was highest for the late-onset cases, providing no support to the theory of the in utero effect of maternal smoking on the son's risk of testicular cancer. However, the theory cannot be excluded but should be taken up for study when further data are available on maternal smoking. The high familial risk may be the product of shared childhood environment and heritable causes.

Hemminki K, Kyyronen P. 1999. Parental age and risk of sporadic and familial cancer in offspring: Implications for germ cell mutagenesis. Epidemiology 10:747-751.
Abstract: We used the nationwide Swedish Family-Cancer Database to analyze the effect of parental age on cancer in offspring at ages 15-53 years. We studied 13 cancer sites, including 37,877 people. Data on familial and sporadic cancers were analyzed separately. We adjusted for age of spouse, year of diagnosis, and birth order. Rate ratios (RRs) were calculated by Poisson regression. Maternal age was associated with sporadic melanoma and leukemia, causing a 30% excess if mothers were more than 40 years vs less than 20 years of age. A marginal effect of about 10% of both maternal and paternal age was observed for sporadic breast cancer. Paternal age increased the RR of sporadic nervous system cancer by about 15%. Accumulation of chromosomal aberrations and mutations during the maturation of germ cells may be a mechanism for these findings. In familial cancers of colon, melanoma, and thyroid, higher age showed an apparent protective effect, which was also noted for sporadic cervical cancer and melanoma. The results argue against major age-induced mutagenic/carcinogenic effects on germ cells as well as against age induced adverse cancer-related hormonal effects during pregnancy. Because two or more mutations are required for adult cancers, however, these cancers may be an insensitive indicator of germ cell mutagenesis.

Hemminki K, Saloniemi I, Salonen T, Partanen T, Vainio H. 1981 . Childhood cancer and parental occupation in Finland. Journal of Epidemiology & Community Health 35:11-15.
Abstract: A case-control study was conducted of the occupations of parents of children under 15 with diagnosed malignancies. The total series contained all childhood cancers cases reported to the Finnish Cancer Registry during the period 1959-75. The parental occupations, recorded at the time of pregnancy, were collected from maternity welfare centres. The cases were analysed as a singly group or as subgroups according to the diagnoses-brain tumours, leukaemia, and all other malignancies. The maternal occupations found more frequently among cases than controls included farmers' wives (1959-68 only), pharmacists, saleswomen, bakers, and factory work of an vehicle driving, machine repair, painting, and the work of men who gave an academic degree as their occupation. Some of these occupations involve possible exposure to harmful chemicals, although chance correlations cannot be excluded.

Henderson B.E., Benton B, Jing J, Yu MC, Pike MC. 1979. Risk factors for cancer of the testis in young men. Int J Cancer 23:598-602.
Abstract: An individual matched case-control study of testis cancer in 131 men under age 40 was conducted to investigate antecedent risk factors including events during prenatal life. Ten patients were born with an undescended testis compared to only two controls (p less equal to 0.02), a previously reported risk factor. Two new risk factors were uncovered: six patients-mothers received hormones during the index pregnancy compared to only one control-mother, and eight patient-mothers and two control-mothers reported excessive nausea as a complication of the index pregnancy. A hypothesis linking these three factors is presented: viz, that a major risk factor for testis cancer is a relative excess of certain hormones (in particular estrogen) at the time of differentiation of the testes.

Hendry WJ, Weaver BP, Naccarato TR, Khan SA. Apr 2006. Differential Progression of Neonatal Diethylstilbestrol-Induced Disruption of the Hamster Testis and Seminal Vesicle. Reprod Toxicol 21:225-240.
Abstract: The synthetic estrogen diethylstilbestrol (DES) is now recognized as the prototypical endocrine disruptor. Using a hamster experimental system, we performed a detailed temporal assessment of how

neonatal DES-induced disruption progresses in the testis compared to the seminal vesicle. Both morphological and Western blot analyses confirmed that neonatal DES exposure alters androgen responsiveness in the male hamster reproductive tract. We also determined that the disruption phenomenon in the male hamster is manifest much earlier in the seminal vesicle than in the testis and that testis disruption often occurs differently between the pair of organs in a given animal. In the neonatally DES-exposed seminal vesicle, histopathological effects included: (1) general atrophy, (2) lack of exocrine products, (3) epithelial dysplasia, (4) altered organization of stromal cells and extracellular matrix, and (5) striking infiltration with polymorphonuclear leukocytes. Also, the morphological disruption phenomenon in the seminal vesicle was accompanied by a range of up-regulation and down-regulation responses in the whole organ levels of various proteins. (c) 2005 Elsevier Inc. All rights reserved.

Henley DV, Korach KS. 2006. Endocrine-disrupting chemicals use distinct mechanisms of action to modulate endocrine system function. Endocrinology 147:S25-S32.
Abstract: The term endocrine-disrupting chemicals is used to define a structurally diverse class of synthetic and natural compounds that possess the ability to alter various components of the endocrine system and potentially induce adverse health effects in exposed individuals and populations. Research on these compounds has revealed that they use a variety of both nuclear receptor-mediated and non-receptor-mediated mechanisms to modulate different components of the endocrine system. This review will describe in vitro and in vivo studies that highlight the spectrum of unique mechanisms of action and biological effects of four endocrine-disrupting chemicals-diethylstilbestrol, genistein, di(n-butyl)phthalate, and methoxyacetic acid-to illustrate the diverse and complex nature of this class of compounds.

Herbst AL. 1972. Stilbestrol and vaginal cancer in young women. CA Cancer J Clin 22:292-295.

Herbst AL. 2000. Behavior of estrogen-associated female genital tract cancer and its relation to neoplasia following intrauterine exposure to diethylstilbestrol (DES). Gynecol Oncol 76:147-156.

Heussen GAH, Vandenberg JHJ, Dreefvandermeulen HC, Alink GM. 1996. Carcinogenicity study of outdoor airborne particulate matter in newborn male NMRI mice. Toxicol Lett 88:23-28.
Abstract: An organic extract of airborne particulate matter (APM) was tested for carcinogenicity at two dose levels in the newborn mouse bioassay. The samples used were taken under specific polluted conditions. The doses tested corresponded with 0.75 and 1.5 times the amount of air man inhales during lifetime. Benzo(a)pyrene, which was used as a positive control, significantly increased the lung tumor incidence. No evidence was found for a carcinogenic activity of the organic extract of APM. Considering the high dose of APM applied in this animal model and the much lower actual cumulative dose to which man is exposed to in many areas, the conclusion can be drawn that exposure to APM alone probably does not represent an important cancer risk for man.

Higuchi TT, Palmer JS, Gray LE, Veeramachaneni DNR. 2003. Effects of dibutyl phthalate in male rabbits following in utero, adolescent, or postpubertal exposure. Toxicol Sci 72:301-313.
Abstract: We evaluated sequelae in male rabbits following exposure to dibutyl phthalate (DBP) at a dose level known to adversely affect testicular function in rodents without causing systemic toxicity. Because rabbits have a relatively long phase of reproductive development simulating better than rodents the reproductive development of humans, and because the use of rabbits facilitates multiple evaluations of mating ability and seminal quality, we used this animal model. Rabbits were exposed to 0 or 400 mg DBP/kg/day in utero (gestation days [GD] 15-29) or during adolescence (postnatal weeks [PNW] 4-12), and male offspring were examined at 6, 12, and 25 weeks of age. Another group was exposed after puberty (for 12 weeks) and examined at the conclusion of exposure. The most pronounced reproductive effects were in male rabbits exposed in utero. Male offspring in this group exhibited reduction in numbers of ejaculated sperm (down 43 h; $p < 0.01$), in weights of testes (at 12 weeks, down 23%; $p < 0.05$) and in accessory sex glands (at 12 and 25 weeks, down 36%; $p < 0.01$ and down 27%; $p < 0.05$, respectively). Serum testosterone levels were down (at 6 weeks, 32 /c; $p < 0.05$); a slight increase in histological alterations of the testis ($p < 0.05$) and a doubling in the percentage (from 16 to 30%, $p < 0.01$) of abnormal sperm; and 1/17 males manifesting hypospadias, hypoplastic prostate, and cryptorchid testes with carcinoma in situ-like cells. In the DBP group exposed during adolescence, basal serum testosterone levels were reduced at 6 weeks ($p < 0.01$) while at 12 weeks, testosterone production in vivo failed to respond

normally, to a GnRH challenge ($p < 0.01$). In addition, weight of accessory sex glands was reduced at 12 weeks but not at 25 weeks after a recovery period; there was a slight increase in the percentage of abnormal sperm in the ejaculate; and 1/11 males was unilaterally cryptorchid. In both of these DBP-treated groups, daily, sperm production, epididymal sperm counts, mating ability, and weights of body, and nonreproductive organs were unaffected. Thus, DBP induces lesions in the reproductive system of the rabbit, with the intrauterine period being the most sensitive stage of life.

Hilakivi-Clarke L, Cabanes A, De Assis S, Wang M, Khan G, Shoemaker WJ, Stevens RG. 2004. In utero alcohol exposure increases mammary tumorigenesis in rats. Br J Cancer 90:2225-2231.
Abstract: Findings in humans and animal models suggest that in utero hormonal and dietary exposures increase later breast cancer risk. Since alcohol intake by adult women consistently increases their breast cancer risk, we wondered whether maternal alcohol consumption during pregnancy increases female offspring's mammary tumorigenesis. In our study, pregnant female rats were pair-fed isocaloric diets containing either 0 (control), 16 or 25 g alcohol kg(-1) feed between days 7 and 19 of gestation. These alcohol exposures generate blood alcohol levels that correspond to low and moderate alcohol consumption and are lower than those that induce foetal alcohol syndrome. Serum oestradiol levels were elevated in pregnant rats exposed to alcohol ($P < 0.003$). When adult, female offspring of alcohol-exposed dams developed significantly more 7,12-dimethylbenz[a]anthracene-induced mammary tumours, compared to the controls (tumour multiplicity; mean +/- s.e.m., controls: 2.0 +/- 0.3, 16 g alcohol: 2.7 +/- 0.4 and 25 g alcohol: 3.7 +/- 0.4; $P < 0.006$). In addition, the mammary epithelial tree of the alcohol-exposed offspring was denser ($P < 0.004$) and contained more structures that are susceptible for the initiation of breast cancer ($P < 0.001$). Immunohistochemical assessment indicated that the mammary glands of 22-week-old in utero alcohol-exposed rats contained elevated levels of oestrogen receptor-alpha ($P < 0.04$) that is consistent with the changes in mammary gland morphology. In summary, maternal alcohol intake during pregnancy increases female offspring's mammary tumorigenesis, perhaps by programming the foetal mammary gland to exhibit persistent alterations in morphology and gene expression. It remains to be determined whether an increase in pregnancy oestradiol levels mediated alcohol's effects on offspring's mammary tumorigenesis. (C) 2004 Cancer Research UK.

Hilakivi-Clarke L, Cho E, Cabanes A, Deassis S, Olivo S, Helferich W, Lippman ME, Clarke R. 2002. Dietary modulation of pregnancy estrogen levels and breast cancer risk among female rat offspring. Clin Cancer Res 8:3601-3610.
Abstract: Purpose: Against the hypothesis that high estrogen levels in utero increase the risk of developing breast cancer in later life are data showing that pregnancy estrogen levels are significantly higher in Asian women who have low breast cancer risk than in Caucasian women. We investigated whether maternal dietary intake of genistein or n-3 polyunsaturated fatty acids (PUFAs), which are typical to Asian but not Caucasian diet, affect pregnancy estrogen levels and susceptibility to mammary tumorigenesis among offspring. Experimental Design: For that purpose, pregnant female Sprague Dawley rats were fed isocaloric AIN-93-based diets containing either at 15 mg (low), 150 mg (medium), or 300 mg (high)/kg genistein/diet or low- or high-fat (16 versus 39% energy from fat) diet composed either of n-3 PUFA menhaden oil or n-6 PUFA corn oil. All diets were switched to regular AIN-93 diet when pups were born. Results: Maternal intake of n-3 PUFA diets significantly increased pregnancy 17beta-estradiol (E2) levels (48% increase when compared with high n-6 PUFA diet; $P < 0.0045$). High genistein exposure also increased pregnancy estrogen levels, but the increase did not reach statistical significance ($P < 0.14$). The offspring of high-fat n-3 PUFA-consuming dams were significantly less likely to develop 7,12-dimethylbenz[a]anthracene-induced mammary tumors (38% of these rats developed tumors during week 17 versus 64% of high n-6 PUFA offspring; $P < 0.003$). Maternal genistein intake did not affect offspring's tumor incidence. The mammary glands of high fat n-3 PUFA offspring contained more lobules ($P < 0.07$) and were thus more differentiated, whereas the glands of high genistein offspring contained more terminal end buds ($P < 0.0015$), which are the sites of malignant transformation. Conclusions: Our findings indicate that the elevated estrogen levels in the n-3 PUFA mothers were linked to reduced rather than increased breast cancer risk among their offspring, suggesting that other effects of n-3 PUFA may counteract the effects of high fetal estrogenicity on the mammary gland. High maternal genistein intake did not reduce offspring's breast cancer risk, and therefore high maternal soy intake in Asian women may not be associated with daughters' low breast cancer risk.

Hilakivi-Clarke L, Cho E, Clarke R. 1998. Maternal genistein exposure mimics the effects of estrogen on mammary gland development in female mouse offspring. Oncol Rep 5:609-616.
Abstract: Human and animal data indicate that a high maternal estrogen exposure during pregnancy increases breast cancer risk among daughters. This may reflect an increase in the epithelial structures that are the sites for malignant transformation, i.e., terminal end buds (TEBs), and a reduction in epithelial differentiation in the mammary gland. Some phytoestrogens, such as genistein which is a major component in soy- based foods, and zearalenone, a mycotoxin found in agricultural products, have estrogenic effects on the reproductive system, breast and brain. The present study examined whether in utero exposure to genistein or zearalenone influences mammary gland development. Pregnant mice were injected daily with i) 20 ng estradiol (E2); ii) 20 microg genistein; iii) 2 microg zearalenone; iv) 2 microg tamoxifen (TAM), a partial estrogen receptor agonist; or v) oil-vehicle between days 15 and 20 of gestation. E2, genistein, zearalenone, and tamoxifen all increased the density of TEBs in the mammary glands. Genistein reduced, and zearalenone increased, epithelial differentiation. Zearalenone also increased epithelial density, when compared with the vehicle-controls. None of the treatments had permanent effects on circulating E2 levels. Maternal exposure to E2 accelerated body weight gain, physical maturation (eyelid opening), and puberty onset (vaginal opening) in the female offspring. Genistein and tamoxifen had similar effects on puberty onset than E2. Zearalenone caused persistent cornification of the estrus smears. These findings indicate that maternal exposure to physiological doses of genistein mimics the effects of E2 on the mammary gland and reproductive systems in the offspring. Thus, our results suggest that genistein acts as an estrogen in utero, and may increase the incidence of mammary tumors if given through a pregnant mother. The estrogenic effects of zearalenone on the mammary gland, in contrast, are probably counteracted by the permanent changes in estrus cycling.

Hilakivi-Clarke L, Cho E, deAssis S, Olivo S, Ealley E, Bouker KB, Welch JN, Khan G, Clarke R, Cabanes A. 2001. Maternal and prepubertal diet, mammary development and breast cancer risk. J Nutr 131:154S-157S.
Abstract: At present, we do not know what causes sporadic breast cancer. Environmental factors,particularly diet, appear to explain at least 70% of newly diagnosed breast cancers, but it is not clear what these factors are. We propose that the lack of progress in this area is due to a lack of considering the effect of timing of environmental and dietary exposures on the breast. The evidence provided above suggests that an in utero exposure to an estrogenic environment-including that caused by diet [high (n-6) PUFA or genistein]-increases breast cancer risk. This increase may be mediated by an increased presence of TEB in the mammary epithelial tree and increased ER-alpha levels, reduced ER- beta levels or both. Prepubertal estrogenic exposure, in contrast, reduces later risk of developing breast cancer. The protective effect of estrogens may be mediated by early epithelial differentiation, reduced presence of ER-alpha and increased levels of ER-beta in the mammary gland. The challenge we are now facing is to determine whether the data obtained mainly through the use of animal models is relevant to women and if so, how we might be able to modulate pregnancy and childhood estrogenic exposure by appropriate dietary modifications to reduce breast cancer risk in women.

Hilakivi-Clarke L, Cho E, Onojafe I, Liao DJ, Clarke R. 2000. Maternal exposure to tamoxifen during pregnancy increases carcinogen-induced mammary tumorigenesis among female rat offspring. Clin Cancer Res 6:305-308.
Abstract: Tamoxifen is under investigation as a potential chemopreventive agent in women of child-bearing age who are at an increased risk to develop breast cancer. However, because tamoxifen may act as an estrogen in the fetus and high fetal estrogenic activity, in turn, may increase subsequent breast cancer risk, we wanted to determine the effects of a maternal exposure to tamoxifen during pregnancy on offspring's susceptibility to mammary tumorigenesis. Pregnant rats were injected s.c. with 20 microg of tamoxifen or oil vehicle daily during days 15 and 20 of gestation. In utero exposure to tamoxifen caused abnormalities in the development and function of the reproductive track, including a delayed puberty onset and changes in uterine wet weights. The tamoxifen-exposed offspring, treated with 7,12-dimethylbenz[a]antracene (DMBA) at the age of 45 days, developed an increased incidence of mammary tumors. In week 18 after DMBA administration, 50% of the vehicle-controls had developed mammary tumors, whereas tumor incidence in the tamoxifen group was 95%. In addition, a significantly higher number of tumors in the tamoxifen-exposed group kept growing (rather than stopped growing or regressed) than in the control group. Furthermore, histopathological examination revealed that the mammary tumors in the tamoxifen offspring were less differentiated and exhibited a more aggressive phenotype, compared with the tumors

growing in the controls. These results suggest that a maternal exposure to tamoxifen during pregnancy acts as an estrogen in the fetal mammary gland and increases the susceptibility to breast cancer among female offspring.

Hilakivi-Clarke L, Cho E, Onojafe I, Raygada M, Clarke R. 1999. Maternal exposure to genistein during pregnancy increases carcinogen- induced mammary tumorigenesis in female rat offspring. Oncol Rep 6:1089-1095.
Abstract: A high estrogenic environment in utero may increase subsequent breast cancer risk. It was therefore determined whether a maternal exposure during pregnancy to the phytoestrogen genistein or zearalenone, both of which exhibit estrogenic activities in vitro and in vivo, alters breast cancer risk among female offspring. Pregnant rat dams were treated daily with subcutaneous injections of 20, 100 or 300 microgram genistein, 20 microgram zearalenone, or vehicle between days 15 and 20 of gestation. The offspring were given 7, 12-dimethylbenz(a)anthracene (DMBA) at the age of 2 months to induce mammary tumors. The results indicate that in utero exposure to genistein, but not to zearalenone, dose-dependently increased the incidence of DMBA-induced mammary tumors, when compared with the controls. Tumor growth characteristics were not altered. Prior to the carcinogen administration, the number of estrogen receptor (ER) binding sites, determined using a ligand binding assay, were significantly elevated in the mammary glands of genistein offspring. In contrast, the mammary protein kinase C (PKC) activity was significantly reduced in the genistein offspring. Our results suggest that a maternal exposure to subcutaneous administration of genistein can increase mammary tumorigenesis in the offspring, mimicking the effects of in utero estrogenic exposures. Further, increased ER protein levels and reduced PKC activity in the mammary gland may be involved in increasing susceptibility to carcinogen-induced mammary tumorigenesis in rats exposed to genistein in utero.

Hilakivi-Clarke L, Cho E, Raygada M, Kenney N. 1997. Alterations in mammary gland development following neonatal exposure to estradiol, transforming growth factor alpha, and estrogen receptor antagonist ICI 182,780. J Cell Physiol 170:279-289.
Abstract: High fetal/early postnatal levels of estrogen increase breast cancer risk, but the mechanisms remain unknown. Growth factors, such as transforming growth factor alpha (TGF alpha), may participate as secondary modifiers in this process. We characterized a modulatory role of early postnatal exposure to 17 beta-estradiol (E-2) on the developing mammary gland morphology by treating intact female CD-1 mice with physiological doses of E-2 (2-4 mu g), human recombinant TGF alpha (4 mu g), or an estrogen receptor (ER) antagonist ICI 182,780 (20 mu g) during postnatal days 1-3. Early postnatal exposure of E-2 stimulated mammary ductal growth by days 25 and 35, but by day 50 this was inhibited. The level of differentiation from terminal end buds (TEBs) to the lobulo-alveolar units (LAUs) also was reduced by day 50. The number of TEBs was increased throughout most of the development in the female mice exposed to E-2 during early life. An exposure to TGF alpha or ICI 182,780 between postnatal days 1 and 3 stimulated ductal growth, formation of TEBs, and the differentiation of mammary epithelial structures. ICI 182,80 treatment also caused hyperplastic lobular-like structures in 54-day-old females. Thus, neonatal exposure to TGF alpha and ICI 182,780 induced both similar (increase in TEBs) and different (increase/decrease in lobulo-alveolar differentiation) developmental changes in the mouse mammary gland, when compared with an exposure to E-2. A unique feature of the postnatal E-2 treatment was that it inhibited ductal migration by days 50-54. Our data suggest than an exposure to E-2 on postnatal days 1-3, possibly combined with secondary epigenetic alterations, leads to various changes within the developing mammary tree. These changes may be potential prerequisites for mammary tumorigenesis. (C) 1997 Wiley-Liss, Inc.

Hilakivi-Clarke L, Clarke R. 1998. Timing of dietary fat exposure and mammary tumorigenesis: Role of estrogen receptor and protein kinase C activity. Molecular & Cellular Biochemistry 188:5-12.
Abstract: The possible association between a high fat diet and increased breast cancer risk has remained controversial. This largely reflects the conflicting data obtained from migrant, case control and animal studies, which generally support this association, and cohort studies which often fail to show a link between fat and breast cancer. The mammary gland is particularly sensitive to estrogens during fetal development, leading us to hypothesize that dietary fat levels during this period may significantly influence breast cancer risk. Using chemically-induced mammary tumors in rats as our experimental model, we have demonstrated the ability of a maternal diet, high in the polyunsaturated fatty acid (PUFA) linoleic acid, to alter mammary gland differentiation, accelerate the onset of sexual maturation, and increase breast cancer risk. The mammary glands of female rats exposed to a high-fat diet in utero have more of the undifferentiated

structures (terminal end buds) and fewer of the differentiated structures (alveolar buds) than the glands of rats exposed to a low-fat diet in utero. Furthermore, these mammary glands contain lower levels of total estrogen receptors and have reduced total protein kinase C activity. These effects appear to be mediated by an increase in the serum estradiol levels of pregnancy, which are elevated at least 30% in pregnant dams fed a high-fat diet. Furthermore, the administration of estradiol to pregnant dams produces effects on mammary gland development, onset of puberty and sensitivity to chemical carcinogenesis comparable to those seen in the offspring of rats fed a high fat diet during pregnancy. Our results, thus, support the hypothesis based on epidemiological data that high maternal estrogen levels increase daughters' breast cancer risk. The results also suggest that a high-fat diet may be an important factor in increasing pregnancy estrogenic activity.

Hilakivi-Clarke L, Clarke R, Onojafe I, Raygada M, Cho E, Lippman M. 1997. A maternal diet high in n - 6 polyunsaturated fats alters mammary gland development, puberty onset, and breast cancer risk among female rat offspring. Proc Natl Acad Sci U S A 94:9372-9377.
Abstract: We hypothesized that feeding pregnant rats with a high-fat diet would increase both circulating 17beta-estradiol (E2) levels in the dams and the risk of developing carcinogen-induced mammary tumors among their female offspring. Pregnant rats were fed isocaloric diets containing 12% or 16% (low fat) or 43% or 46% (high fat) of calories from corn oil, which primarily contains the n - 6 polyunsaturated fatty acid (PUFA) linoleic acid, throughout pregnancy. The plasma concentrations of E2 were significantly higher in pregnant females fed a high n - 6 PUFA diet. The female offspring of these rats were fed with a laboratory chow from birth onward, and when exposed to 7,12-dimethylbenz(a)anthracene had a significantly higher mammary tumor incidence (60% vs. 30%) and shorter latency for tumor appearance (11.4 +/- 0.5 weeks vs. 14.2 +/- 0.6 weeks) than the offspring of the low-fat mothers. The high-fat offspring also had puberty onset at a younger age, and their mammary glands contained significantly higher numbers of the epithelial structures that are the targets for malignant transformation. Comparable changes in puberty onset, mammary gland morphology, and tumor incidence were observed in the offspring of rats treated daily with 20 ng of E2 during pregnancy. These data, if extrapolated to humans, may explain the link among diet, early puberty onset, mammary parenchymal patterns, and breast cancer risk, and indicate that an in utero exposure to a diet high in n - 6 PUFA and/or estrogenic stimuli may be critical for affecting breast cancer risk.

Hilakivi-Clarke L, De Assis S. 2006. Fetal origins of breast cancer. Trends in Endocrinology and Metabolism 17:340-348.
Abstract: Susceptibility to breast cancer might be pre-determined in utero. Alterations in the fetal hormonal environment, caused by either maternal diet or exposure to environmental factors with endocrine activities, can modify the epigenome, and these modifications are inherited in somatic daughter cells and maintained throughout life. These epigenetic modifications might lead to changes in mammary gland development, such as increased vulnerability of epithelial targets for malignant transformation. According to this hypothesis, on post-pubertal exposure to an initiating factor, such as a carcinogen, high levels of hormones and radiation, the mammary epithelial targets, perhaps stem cells, in terminal end buds/terminal ductal lobular units would be at an increased risk of malignant transformation. The increased susceptibility for cancer initiation might result from high levels of cell proliferation, reduced apoptosis and/or altered stromal regulation. Thus, maternal diet and environmental exposure might increase the risk of breast cancer by inducing permanent epigenetic changes in the fetus that alter the susceptibility to factors that can initiate breast cancer. Identifying the epigenetically altered target genes and their ligands might lead to strategies to prevent this disease in some women.

Hirakawa K, Suzuki K, Ueda S, Handa J. 1986. Fetal origin of the medulloblastoma: Evidence from growth analysis of two cases. Acta Neuropathologica (Berlin) 70:227-234.
Abstract: Growth analysis of medulloblastomas was performed in two children. They initially manifested symptoms at the age of 3 years and 9 months and at the age of 2 months respectively. Computerized tomography (CT) scans were obtained at different points in each case. The growth curves were drawn on a semilogarithmic graph by calculating the tumor volume on CT on the assumptions that the tumor started from a single tumor cell and that the growth rate was constant. By extrapolating the curves back, tumor inception was estimated to have occurred respectively at the 14-23rd week and at the 16-17th week of gestation. Additional cell kinetic data were obtained from DNA analysis of surgical pathology specimens.

Calculated cell-cycle times were 22-32 h for both cases. The S phases comprised 26.3% and 27% and the G0G1 phases 66.8% and 62% of the cell cycle, respectively, for case 1 and 2. Assuming a labelling index of 14%, the cell loss factors were estimated to be 97% and 74% (case 1 and case 2 respectively). The seventeenth week of gestation in humans corresponds to the timing of events occurring postnatally at days 3-18 in the developing cerebella of rodents, i.e., at the time of maximal activity in the migration and differentiation of the cells of the fetal external granular layer. Medulloblastomas have been experimentally induced in rodents by the injection of oncogenic viruses during the neonatal period, and statistical data on the epidemiology of human medulloblastomas have suggested a possible association with the contamination of polio vaccine by the SV 40 virus.(ABSTRACT TRUNCATED AT 250 WORDS)

Hjalgrim LL, Rostgaard K, Hjalgrim H, Westergaard T, Thomassen H, Forestier E, Gustafsson G, Kristinsson J, Melbye M, Schmiegelow K. 2004. Birth weight and risk for childhood leukemia in Denmark, Sweden, Norway, and Iceland. J Natl Cancer Inst 96:1549-1556.
Abstract: BACKGROUND: Compelling evidence suggests that childhood leukemia often originates in utero. Birth weight is one of the few pregnancy-related risk factors that has been associated with leukemia risk, but the association has remained poorly characterized. We conducted a population-based case-control study in Denmark, Sweden, Norway, and Iceland to investigate the association between birth weight (and other birth characteristics) and the risk of childhood leukemia. METHODS: Overall, 1905 children (aged 0-14 years) with acute lymphoblastic leukemia (ALL) and 299 children with acute myeloid leukemia (AML) diagnosed between January 1, 1984, and December 31, 1999, were identified in the Nordic Society of Paediatric Haematology and Oncology acute leukemia database. Each case patient was matched to five population control subjects (n = 10745) on nationality, age, and sex. All live-born siblings of case patients (n = 3812) and control subjects (n = 17,937) were also identified in population registers. Information on birth weight and gestational age at birth was ascertained from the national Medical Birth Registers. The association between various birth characteristics and leukemia risk was assessed by conditional logistic regression. All statistical tests were two-sided. RESULTS: Risk of ALL overall was statistically significantly associated with birth weight (odds ratio [OR] = 1.26 per 1-kg increase in birth weight, 95% confidence interval [CI] = 1.13 to 1.41). The association was similar for B- and T-lineage ALL and across all diagnostic ages (0-14 years). However, children with ALL did not weigh more at birth than their siblings. Statistically significantly reduced risks of B-precursor ALL were observed with increasing position in the birth order (OR = 0.90 per position increase, 95% CI = 0.84 to 0.96) and increasing gestational age (OR = 0.87 per 2-week increase in gestational age, 95% CI = 0.81 to 0.94). Risk of AML did not vary monotonically with birth weight, and low birth weight (<1500 g [i.e., 3.3 pounds]) was associated with the highest risk. CONCLUSION: Our results are compatible with the hypothesis that a high birth weight is associated with an increased risk of ALL.

Ho SM, Leung YK, Chung I. 2006. Estrogens and antiestrogens as etiological factors and therapeutics for prostate cancer. Ann N Y Acad Sci 1089:177-93.
Abstract: Mounting evidence supports a key role played by estrogen or estrogen in synergy with an androgen, in the pathogenesis of prostate cancer (PCa). New experimental data suggest that this process could begin as early as prenatal life. During adulthood, estrogen carcinogenicity is believed to be mediated by the combined effects of hormone-induced, unscheduled cell proliferation and bioactivation of estrogens to genotoxic carcinogens. Increased bioavailability of estrogen through age-dependent increases in conversion from androgen could also be a contributing factor. Individual variations and race-/ethnic-based differences in circulating or locally formed estrogens or in tissue estrogen responsiveness may explain differential PCa risk among individuals or different populations. Estrogen receptor (ER)-alpha and ER-beta are the main mediators of estrogen action in the prostate. However, ER-beta is the first ER subtype expressed in the fetal prostate. During cancer development, ER-beta expression is first lost as tumors progress into high grade in the primary site. Yet, its reexpression occurs in all metastatic cases of PCa. A change in cytosine methylation in a regulatory CpG island located in the proximal promoter of ER-beta may constitute an "on/off" switch for reversible regulation of ER-beta expression. A variety of estrogenic/antiestrogenic/selective estrogen receptor modulator (SERM)-like compounds have been shown to use non-ERE pathways, such as tethering of ER-beta to NF-kappaB binding proteins, Sp2, or Ap1 for gene transactivation. These findings open new avenues for drug design that now focuses on developing a new generation of estrogen-based PCa therapies with maximal proapoptotic action but few or no side effects.

Ho SM, Tang WY. 2007. Techniques used in studies of epigenome dysregulation due to aberrant DNA methylation: an emphasis on fetal-based adult diseases. Reprod Toxicol 23:267-282.
Abstract: Epigenetic changes are heritable modifications that do not involve alterations in the primary DNA sequence. They regulate crucial cellular functions such as genome stability, X-chromosome inactivation, and gene imprinting. Epidemiological and experimental observations now suggest that such changes may also explain the fetal basis of adult diseases such as cancer, obesity, diabetes, cardiovascular disorders, neurological diseases, and behavioral modifications. The main molecular events known to initiate and sustain epigenetic modifications are histone modification and DNA methylation. This review specifically focuses on existing and emerging technologies used in studying DNA methylation, which occurs primarily at CpG dinucleotides in the genome. These include standard exploratory tools used for global profiling of DNA methylation and targeted gene investigation: methylation sensitive restriction fingerprinting (MSRF), restriction landmark genomic scanning (RLGS), methylation CpG island amplification-representational difference analysis (MCA-RDA), differential methylation hybridization (DMH), and cDNA microarrays combined with treatment with demethylating agents and inhibitors of histone deacetylase. The basic operating principals, resource requirements, applications, and benefits and limitations of each methodology are discussed. Validation methodologies and functional assays needed to establish the role of a CpG-rich sequence in regulating the expression of a target or candidate gene are outlined. These include in silico database searches, methylation status studies (bisulfite genomic sequencing, COBRA, MS-PCR, MS-SSCP), gene expression studies, and promoter activity analyses. Our intention is to give readers a starting point for choosing methodologies and to suggest a workflow to follow during their investigations. We believe studies of epigenetic changes such as DNA methylation hold great promise in understanding the early origins of adult diseases and in advancing their diagnosis, prevention, and treatment.

Ho SM, Tang WY, De Frausto JB, Prins GS. 2006. Developmental exposure to estradiol and bisphenol A increases susceptibility to prostate carcinogenesis and epigenetically regulates phosphodiesterase type 4 variant 4. Cancer Res 66:5624-5632.
Abstract: Early developmental perturbations have been linked to adult-onset prostate pathology, including excessive exposure to estrogenic compounds; however, the molecular basis for this imprinting event is not known. An important and controversial health concern is whether low-dose exposures to hormonally active environmental estrogens, such as bisphenol A, can promote human diseases, including prostate cancer. Here, we show that transient developmental exposure of rats to low, environmentally relevant doses of bisphenol A or estradiol increases prostate gland susceptibility to adult-onset precancerous lesions and hormonal carcinogenesis. We found permanent alterations in the DNA methylation patterns of multiple cell signaling genes, suggesting an epigenetic basis for estrogen imprinting. For phosphodiesterase type 4 variant 4 (PDE4D4), an enzyme responsible for cyclic AMP breakdown, a specific methylation cluster was identified in the 5'-flanking CpG island that was gradually hypermethylated with aging in normal prostates, resulting in loss of gene expression. Early and prolonged hypomethylation at this site following neonatal estradiol or bisphenol A exposure resulted in continued, elevated PDE4D4 expression. Cell line studies confirmed that site-specific methylation is involved in transcriptional silencing of the PDE4D4 gene and showed hypomethylation of this gene in prostate cancer cells. Importantly, the PDE4D4 alterations in the estrogen-exposed prostates were distinguishable before histopathologic changes of the gland, making PDE4D4 a candidate molecular marker for prostate cancer risk assessment as a result of endocrine disruptors. In total, these findings indicate that low-dose exposures to ubiquitous environmental estrogens affect the prostate epigenome during development and, in so doing, promote prostate disease with aging.

Hoei-Hansen CE, Almstrup K, Nielsen JE, Brask Sonne S, Graem N, Skakkebaek NE, Leffers H, Rajpert-De Meyts E. 2005. Stem Cell Pluripotency Factor Nanog Is Expressed in Human Fetal Gonocytes, Testicular Carcinoma in Situ and Germ Cell Tumours. Histopathology 47:48-56.
Abstract: Aims: NANOG is a key regulator of embryonic stem cell (ESC) self-renewal and pluripotency. Our recent genome-wide gene expression profiling study of the precursor of testicular germ cell tumours, carcinoma in situ testis (CIS), showed close similarity between ESC and CIS, including high NANOG expression. In the present study we analysed the protein expression of NANOG during normal development of human testis and in a large series of neoplastic/dysgenetic specimens. Methods and results: We detected abundant expression of NANOG in CIS and in CIS-derived testicular tumours with marked differences; seminoma and embryonal carcinoma were strongly positive, differentiated somatic elements of teratoma were negative. We provide evidence for the fetal origin of testicular cancer as we detected strong

expression of NANOG in fetal gonocytes up to gestational week 20, with subsequent down-regulation occurring earlier than for OCT-4. We detected no expression at the protein level in normal testis. Conclusions: NANOG is a new marker for testicular CIS and germ cell tumours and the high level of NANOG along with OCT-4 are determinants of the stem cell-like pluripotency of the preinvasive CIS cell. Timing of NANOG down-regulation in fetal gonocytes suggests that NANOG may act as a regulatory factor up-stream to OCT-4.

Holly EA, Aston DA, Ahn DK, Kristiansen JJ. 1992. Ewing's bone sarcoma, paternal occupational exposure, and other factors. Am J Epidemiol 135:122-129.
Abstract: To determine risk factors for Ewing's bone sarcoma, the authors interviewed mothers of 43 patients diagnosed between January 1978 and August 1986 and 193 controls in the San Francisco Bay Area, California, regarding medical and occupational history of parents and other factors related to the subjects and their immediate families. Controls were selected by using random digit dial telephone methods. Adjusted relative risk estimates suggest that risks were elevated for children whose fathers were engaged in agricultural occupations during the period from 6 months prior to conception of the subject up to the time of diagnosis for the patients or interview for the controls (relative risk (RR) = 8.8, 95% confidence interval (CI) 1.8-42.7) and for children whose fathers had occupational exposure to herbicides, pesticides, or fertilizers (RR = 6.1, 95% CI 1.7-21.9, p = 0.002). Prior ingestion of poison or an overdose of medication was more common in patients than in controls (RR = 4.4, 95% CI 1.4-13.5). These and other findings should be investigated in larger population-based studies to determine specific factors that may account for the associations.

Holly EA, Bracci PM, Hong MK, Mueller BA, Preston-Martin S. 2002. West Coast study of childhood brain tumours and maternal use of hair-colouring products. Paediatr Perinat Epidemiol 16:226-235.
Abstract: The immature nervous system of the fetus is characterised by rapid cell growth and division and is particularly vulnerable to carcinogens and mutagens. Several epidemiological studies have reported an increased risk for childhood brain tumours (CBT) associated with exposure to N-nitroso compounds (NOC). Hair-colouring products (hair 'dyes') that contain NOC-related aromatic amines have shown mutagenicity in vitro and carcinogenic properties in vivo . The potential public health impact of the relationship between hair dye use and carcinogenesis has prompted epidemiological research, given that a large proportion of American women have used hair dyes. A large population-based case-control study was conducted on the west coast of the USA to investigate risk factors for CBT including exposure to NOC. Eligible CBT patients (<20 years of age and diagnosed between 1984 and 1991) were identified from cancer registries in Los Angeles County, the San Francisco Bay Area in California and the Seattle area in Washington state. A total of 540 biological mothers of these children were interviewed, and 801 control subjects who were frequency matched to the CBT patients on birth year and sex were obtained using random digit dialling. Mothers were asked details about personal use of hair dyes during the index pregnancy including frequency of use, trimester of use and type of dye used. Results from age- and sex-adjusted unconditional logistic regression analyses showed no association between risk for CBT and use of hair dyes 1 month before and/or during pregnancy nor during specific trimesters. A nearly twofold increased risk for CBT was associated with single-interval use during the 1 month before pregnancy, but the confidence interval (CI) was imprecise and the estimate was not different from unity (OR = 1.9, 95% CI [0.5, 7.0]). Exclusive use of permanent dye, temporary dye or hair darkeners was not associated with risk for CBT. A twofold increased risk (OR = 2.0, 95% CI [0.83, 4.7]) was observed with exclusive use of semi-permanent dye during the month before or during pregnancy. Exclusive use of semi-permanent dye during the month before pregnancy and/or first trimester also was associated with an elevated risk for CBT, again not different from unity and with an imprecise CI (OR = 2.5, 95% CI = [0.58, 10.3]). There was no evidence of an association between risk for CBT by histological subtypes and use of hair dyes during the index pregnancy or the month before conception. Together with results from previous studies, these results provide no consistent evidence of an association between risk for CBT and use of hair dyes during pregnancy.

Holmberg L, Ekbom A, Calle E, Mokdad A, Byers T. 1995. Parental age and breast-cancer mortality. Epidemiology 6:425-427.
Abstract: Because older ages of both mothers and fathers have been hypothesized by others to increase the subsequent risk of breast cancer in female babies, we analyzed the association between maternal and

paternal age at birth and mortality from breast cancer in a cohort of 384,796 American women. Cox proportional hazards modeling accounted for age, family history of breast cancer in first-degree relatives, age at menarche, age at first pregnancy, and parity. We found little association between paternal age at birth and death from breast cancer. Although there was no clear linear trend for higher risk with increasing age of the mothers at birth, women born to mothers age 45 years or older had a relative hazard of 1.30 (95% confidence interval = 0.85-1.98), compared with women born to mothers under the age of 20 years. Although these findings are of little public health significance, they may indicate a hormonal profile in older mothers that predisposes female offspring to a higher risk of breast cancer in later years.

Hong HHL, Dunnick J, Herbert R, Devereux TR, Kim Y, Sills RC. 2007. Genetic alterations in K-ras and p53 cancer genes in lung neoplasms from Swiss (CD-1) male mice exposed transplacentally to AZT. Environ Mol Mutagen 48:299-306.
Abstract: A transplacental carcinogenicity study was conducted by exposing pregnant Swiss (CD-1) mice to 0, 50, 100, 200, or 300 mg of 3'-azido-3'-deoxythymidine (AZT)/kg bw/day, through a 18 to 19 day gestation [National Toxicology Program, NIH Pub. No. 04-4458, 2004]. The incidences of alveolar/bronchiolar adenomas and carcinomas, in the 200 and 300 mg/kg male treatment groups, were significantly greater than that of the controls. In the present study, we evaluated the benign and malignant lung neoplasms from this bioassay for point mutations, in the K-ras and p53 cancer genes that are often mutated in human lung tumors. K-ros and p53 mutations were detected by cycle sequencing of polymerose chain reaction-amplified DNA, isolated from formalin-fixed, paraffin-embedded neoplasms. K-ros mutations were detected in 25 of 38 (66%) of the AZT-induced lung tumors, and the predominant mutations were codon 12 G-T transversions. p53 mutations were detected in 32 of 38 (84%) of the AZT-induced lung tumors, with the predominant mutations being exon 8, codon 285 A-T transversions, and exon 6, codon 198 T-A transversions. No K-ros or p53 mutations were detected in five tumors, examined from control mice. The patterns of mutations identified in the lung tumors suggest that incorporation of AZT or its metabolites into DNA, oxidative stress, and genomic instability may be the contributing factors to the mutation profile and development of lung cancer in these mice. Environ. Mal. Mutagen. 48:299-306, 2007. Published 2006 Wiley-Liss, Inc.

Hong YC, Kim H, Im MW, Lee KH, Woo BH, Christiani DC. 2001. Maternal genetic effects on neonatal susceptibility to oxidative damage from environmental tobacco smoke. J Natl Cancer Inst 93:645-647.

Hori A, Schmidt D, Kuebber S. 1999 . Immunohistochemical survey of migration of human anterior pituitary cells in developmental, pathological, and clinical aspects: A review. Microscopy Research & Technique 46:59-68.
Abstract: Developmentally pathological conditions of the anterior pituitary cells include failed separation of the primary pituitary gland into sellar and pharyngeal ones, ectopic migration into the subarachnoid space, and basophil invasion into the posterior lobe although the last is a physiological phenomenon with pathological potentiality in certain circumstances. Pituitary primordium appears at about 4 weeks of gestation. One of the causes of the pituitary gland agenesis may be a formation of the primary hypothalamic ganglionic hamartoma just at the time of occurrence of the pituitary primordium, as analyzed in cases of Pallister-Hall syndrome. A double pituitary in a single individual is a rare malformation. Its pathogenesis is considered as a result of notochordal anomaly. In the 8th gestational week, the primary pituitary gland separates into sellar and pharyngeal parts. The disturbance of this histogenesis results in a rare pituitary malformation, a "pharyngosellar pituitary." Despite the failed separation in this case, differentiation of the pituitary cells proceeds and the hormone production of this malformed pituitary gland can be displayed immunohistochemically. In this case, the distribution of the different hormone producing cells was atypical, particularly in those of gonadotropic hormones and ACTH. Life-long existence of the pharyngeal pituitary is a normal anatomical state in humans. Cell differentiation (hormone production) in the pharyngeal pituitary occurs about 4-10 weeks later than in the sellar pituitary. In pharyngeal pituitary, all kinds of adenohypophyseal hormones are produced. Extracranial pituitary adenomas (with intact sellar pituitary), exclusively found in the nasopharynx, sphenoid sinus, and clivus, may occur from the pharyngeal pituitary while another tumorigenesis can develop from the residual tissue fragment in the craniopharyngeal canal. The "overshoot" of the adenohypophyseal cell migration in the distal part of the sellar pituitary is frequently observed in the leptomeninges of the peri-infundibular or peri-hypothalamic region as ectopic pituitary cell clusters that are apparently independent of the pars tuberalis. It is suggested

that these cells, frequently found in "normal" individuals, may be one of the possible origins of the intracranial ectopic pituitary adenomas. However, the reason why a majority of the reported intracranial ectopic pituitary tumors are ACTH-adenomas remains unexplained, since the ectopic cells, found in "normal" individuals, consist of fairly different hormone-producing cells. A further enigmatic phenomenon is a "basophil invasion." ACTH-positive cells invade from the pars intermedia into the posterior lobe of the pituitary. This invasion increases in intensity and frequency according to increase in age. However, the invasion of ACTH cells is observed as early as in the fetal life. The invasive cells display occasionally cell atypia as well as mitotic activity. The origin of extremely rare pituitary adenomas inside the posterior lobe can be explained by the existence and proliferative activity of basophil invasion.

Hovey RC, Asai-Sato M, Warri A, Terry-Koroma B, Colyn N, Ginsburg E, Vonderhaar BK. 2005. Effects of Neonatal Exposure to Diethylstilbestrol, Tamoxifen, and Toremifene on the Balb/C Mouse Mammary Gland. Biol Reprod 72:423-435.
Abstract: In this study, we compared the long-term effects of neonatal exposure to diethylstilbestrol (DES, 0.0125-50 mug), tamoxifen (TAM, 0.0125-50 mug), and toremifene (TOR, 53 mug) on mammary gland development and differentiation. Allometric growth of the mammary ducts was stimulated by neonatal DES exposure (112.5 mug) and impaired by exposure to TAM (25 mug). Neonatal treatment with high doses of DES resulted in mammary ducts that displayed extensive dilatation and precocious lactogenesis in postpubertal, nulliparous females. Initiation of this precocious differentiation coincided with the absence of corpora lutea, increased levels of serum prolactin (PRL), and the induction of Prl mRNA expression within the mammary glands. Neonatal exposure to 1.25 mug TAM increased alveolar development in postpubertal, nulliparous females similar to that recorded in females treated with low doses of DES. Lower doses of TAM did not affect alveolar development, whereas branching morphogenesis and alveolar development were impaired by higher doses. increased alveolar development in females exposed to 1.25 jig TAM was associated with elevated serum progesterone (P) and increased alveolar development in response to exogenous P. Taken together, our findings demonstrate that neonatal exposure to both DES and TAM exerts long-lasting effects on the proliferation and differentiation of the mammary glands in female BALB/c, primarily as the result of endocrine disruption.

Howe GR, Burch JD, Chiarelli AM, Risch HA, Choi BC. 1989. An exploratory case-control study of brain tumors in children. Cancer Res 49:4349-4352.
Abstract: An exploratory case-control study of childhood brain tumors was conducted in southern Ontario between 1977 and 1983, on 74 cases and 138 age- and sex-matched population controls. A significantly elevated risk (perhaps due to early case symptoms) was seen for skull X-rays at least 5 years prior to diagnosis, and for head or neck injuries which required medical attention. However, no evidence of an increased risk appeared for exposure to sick pets or to pesticides, maternal or paternal history of smoking, and various birth characteristics or antenatal exposure of the child, though these have previously been reported to be associated with childhood brain tumors. With respect to the hypothesis that N-nitroso compounds may be involved in the etiology of childhood brain tumors, most exposures of this type were not associated with risk, though a significant positive association was seen for consumption of beer by the mother during pregnancy, and a significant negative association was seen with consumption of fruit juice by the child. Other findings in the present study include an association with developmental problems relating to height and weight and with certain socioeconomic characteristics of the mother. Further investigation of these results in future studies is warranted.

Hsieh CC, Lan SJ, Ekbom A, Petridou E, Adami HO, Trichopoulos D. 1992. Twin membership and breast cancer risk. Am J Epidemiol 136:1321-1326.
Abstract: Pregnancy estrogens are substantially elevated in twin pregnancies and are likely to be more so in the case of dizygotic twins. If levels of pregnancy estrogens were positively related to breast cancer risk in the offspring, female twin members would be expected to be at slightly higher risk. Data from an international case-control study were utilized to assess this hypothesis. The analysis was based on 870 cases with breast cancer and 2,641 hospital controls from two sites: Glamorgan, Wales (1965-1967), and Boston, Massachusetts (1965-1966). Seventeen cases were members of twin pairs, and 8 of them had a twin brother; 33 controls were members of twin pairs and 14 had a twin brother. Among all women, the odds ratios for breast cancer were as follows: for twins with brothers, 1.54 (95% confidence interval (CI) 0.64-3.71); for twins with sisters, 1.30 (95% CI 0.58-2.92); and for all twins, 1.40 (95% CI 0.77-2.55). The odds

ratios were higher among premenopausal women. These findings are not conclusive, but they are compatible with the hypothesis that pregnancy estrogens may affect the risk of breast cancer in the offspring.

Hsieh CC, Tzonou A, Trichopoulos D. 1991. Birth order and breast cancer risk. Cancer Causes & Control 2:95-98.
Abstract: It has been hypothesized that prenatal exposure to maternal estrogens may be a risk factor for breast cancer in the offspring. In two recent studies, maternal estradiol levels in the first pregnancy have been compared to those in the second, and in both studies levels were higher in the first pregnancy. If both the hypothesis and the reported findings were true, women born as their mother's second child would be expected to have lower risk for breast cancer than first-born women. Data from 1,468 cases of breast cancer and 4,175 hospital controls from three previously published studies were modelled through multiple logistic regression to evaluate this possibility. The size of the woman's sibship was not related to breast cancer risk. On the other hand, second-born women had, as predicted, lower breast cancer risk than first-born women, although the difference was nominally significant only among premenopausal women. The relative risk for breast cancer, contrasting second-born to first-born women, and the corresponding 95 per cent confidence intervals, were 0.71 (0.54-0.94) among premenopausal women, 0.94 (0.76-1.17) among postmenopausal women, and 0.86 (0.73-1.02) among all women, controlling for menopausal status.

Hu JF, Mao Y, Ugnat AM. 2000. Parental cigarette smoking, hard liquor consumption and the risk of childhood brain tumors - A case-control study in northeast China. Acta Oncol 39:979-984.
Abstract: In this study we examine the effect of parents' lifestyles on the risk of childhood brain tumors. Parents of 82 children newly diagnosed with primary malignant brain tumors and 246 individually matched hospital controls were interviewed in the hospital wards between September 1991 and December 1996. Data were collected on socioeconomic status, parental lifestyle prior to and during the pregnancy, and Family history. Odds ratios and 95% confidence intervals were derived through conditional logistic regression. The risk of childhood brain tumors was associated with paternal use of hard liquor prior to the pregnancy: the odds ratios were 3.72 (95% CL = 1.91-7.26) for less than or equal to 15 years of hard liquor consumption and 4.06 (95%CI = 1.09-15.21) for greater than or equal to 16 years of hard liquor consumption compared with never consuming hard liquor (test for trend p = 0.0001); the odds ratios increased with increasing lifetime hard liquor consumption. There is little evidence to support an association between childhood brain tumors and parents' smoking prior to or during pregnancy.

Hu M, Shivdasani RA. 2005. Overlapping Gene Expression in Fetal Mouse Intestine Development and Human Colorectal Cancer. Cancer Res 65:8715-8722.
Abstract: Pathways relevant to cancer are well known to overlap with fetal development, as reflected in reactivation of embryonic genes in tumors. However, molecular evidence for this notion has gathered in piecemeal fashion, and systematic approaches have rarely been applied to gauge the extent and global characteristics of the overlap in gene expression between developing tissues and cancer. The fraction of genes that is expressed aberrantly in a given cancer and also developmental in primary function is unknown, and the tissue specificity of recapitulated gene expression remains unexplored. We developed a statistical method to relate expression profiles from human colon cancer and diverse nonintestinal tumors to transcripts that decline in expression with epithelial differentiation in the fetal mouse gut. For genes that are overexpressed in colon cancer, we computed 8% to 19% likelihood that they were expressed transiently during epithelial morphogenesis in intestine development. Among genes dysregulated in other tumors, the corresponding likelihood fell between 1% and 6%. Similarly, low probabilities were obtained when we compared genes not overexpressed in colon cancer with transcriptional profiles in intestine organogenesis. Genes that increase after fetal gut epithelial differentiation were not differentially represented between cancerous and normal colon. Our findings systematically characterize the global extent and tissue specificity of developmental expression programs in colorectal cancer and illustrate the use of such an approach to identify candidate biomarkers and therapeutic targets.

Huang PHT, Catalano A. 1992. N-alkyl-n-nitrosourea induced secondary structural-changes in DNA from rat embryos and fetal brains invivo. Teratogenesis Carcinogenesis & Mutagenesis 12:135-153.
Abstract: N-methyl-N-nitrosourea (MNU) and N-ethyl-N-nitrosourea (ENU) are gestational stage dependent teratogens and transplacental carcinogens capable of inducing neurogenic tumours in rats. Intravenous treatment of gravid Wistar rats showed that MNU is teratogenic but ENU is a transplacental

carcinogen and may be a teratogen when administered on day 12 of gestation. Twenty-four hours after single doses of 2, 5, or 10 mg MNU/kg on day 12, dose dependent decreases in embryonic wet weight and total embryonic DNA were observed. Rats similarly treated with 2 and 5 mg MNU/kg showed dose dependent decreases in fetal brain DNA synthesis, DNA content, and wet weight 9 days later. Administration of single ENU doses of 1. 5, 3, 6, 12, 48, and 80 mg/kg to day 12 embryos resulted in a dose dependent reduction in [methyl-C-14]-thymidine (C-14-TdR) incorporation into DNA after 24 h although total DNA amounts and embryonic wet weights were unaffected. Benzoylated DEAE-cellulose (BD-cellulose) chromatography fractionates DNA on the basis of secondary structure by stepwise elution of double-stranded DNA with 1.0 M NaCl solution (SE-DNA) followed by elution of DNA containing single-stranded regions with caffeine solution (CE-DNA). Day 13 embryonic and day 21 fetal brain DNA was monitored by in vivo labelling with [methyl-H-3]-thymidine on days 6 and 7 of gestation. Significant reduction in percentages of CE-DNA (%CE-DNA) 24 h after treatment of day 12 embryos with 2, 5, or 10 mg MNU/kg were attributed to the necrotic effect of MNU. Day 12 treatment with MNU produced no change in %CE-DNA values of day 21 fetal brains. A teratogenic dose of 80 mg ENU/kg to day 12 embryos resulted in significantly increased %CE-DNA values compared to controls but no changes were observed after 1.5 to 48 mg/kg. Analysis of the distribution of %CE-DNA values from the 80 mg ENU/kg treated litter showed that the increase in %CE-DNA was due to a second distinct population of embryos with higher %CE-DNA values than controls. Incorporation of C-14-TdR into embryonic and fetal brain DNA demonstrated the effects of treatment with these compounds on DNA synthesis in vivo. The relative %CE-DNA is expressed as the ratio of the percentage of caffeine-eluted C-14-labelled DNA to %CE-DNA(i.e., %CE-C-14-DNA:%CE-H-3-DNA). In the majority of control embryos the C-14-specific activity of CE-DNA was higher than the C-14-specific activity of SE-DNA. Treatment with ENU doses between 1.5 and 48 mg/kg on day 12 of gestation resulted in a dose dependent increase in the percentage of embryos from each litter with higher concentrations of newly synthesized DNA in SE-DNA than in CE-DNA. The results of this study suggest that mechanisms of ENU induced teratogenesis and transplacental carcinogenesis may be different although alkylation of embryonic DNA may initiate both phenomena. BD-cellulose fractionation of embryonic DNA showed differences in the DNA secondary structural changes produced by MNU and ENU, suggesting they may not share the same mechanism of teratogenesis. The pertinence of relative %CE-DNA to transplacental carcinogenesis is also discussed.

Huang PHT, Catalano A. 1994. Changes in secondary structure of DNA of rat embryos following treatment with 1,2-diethylhydrazine and dimethylnitrosamine in-vivo. Teratogenesis Carcinogenesis & Mutagenesis 14:53-64.

Abstract: 1,2-Diethylhydrazine (DEH) and dimethylnitrosamine (DMN) are indirect acting carcinogens that require metabolic activation to exert their potency. DEH is a transplacental carcinogen and teratogen in Wistar rats when administered by i.p. injection on day 12 of gestation. DMN is embryotoxic during this period. In this study, gravid Wistar rats were injected i.v. with DEH (10, 15, or 20 mg/kg) or i.p. with DMN (10 or 30 mg/kg) and the effects on the embryos 24 hours later were observed. Controls were similarly injected with saline vehicle. The incidence of resorptions increased after treatment with 20 mg DEH/kg. DEH treatment also resulted in decreases in embryo wet weights and total DNA that were not dose dependent. Treatment with DMN did not affect embryonic wet weights and total embryonic DNA amount when compared to the saline-treated controls. The effects of DEH and DMN on DNA synthesis in vivo were monitored by injecting [methyl-C-14]-thymidine 1 hour prior to embryo death. DEH induced significant increases in thymidine incorporation into embryo DNA but the increases were not proportional to the doses administered. DNA synthesis was significantly decreased in embryos treated with 30 mg DMN/kg. The DNA of treated and control embryos was fractionated by benzoylated DEAE-cellulose (BD-cellulose) chromatography to determine differences in DNA secondary structure following treatment. BD-cellulose chromatography separates double-stranded DNA from DNA containing single-stranded regions by step elution with 1 M NaCl solution and caffeine solution, respectively. Embryonic DNA was monitored by in vivo labelling with [methyl-H-3]-thymidine on days 6 and 7 of gestation. Significant dose dependent increases in percentages of caffeine-eluted DNA (%CE-DNA) compared to controls were detected after treatment with 10, 15, and 20 mg DEH/kg and 10 and 30 mg DMN/kg. The relative %CE-DNA is expressed as the ratio of %CE-C-14-labelled DNA to %CE-H-3-labelled DNA. Litters treated with 10, 15, and 20 mg DEH/kg had relative %CE-DNA values significantly lower than controls. The results support the hypothesis that initiation mechanisms of transplacental carcinogenesis and teratogenesis are different. The pertinence of %CE-DNA and relative %CE-DNA values to the study of transplacental carcinogenesis

and teratogenesis is discussed. (C) 1994 Wiley-Liss, Inc.

Huff V, Meadows A, Riccardi VM, Strong LC, Saunders GF. 1990. Parental origin of de novo constitutional deletions of chromosomal band 11p13. Am J Hum Genet 47:155-160.
Abstract: One-half of all cases of Wilms tumor (WT), a childhood kidney tumor, show loss of heterozygosity at chromosomal band 11p13 loci, suggesting that mutation of one allele and subsequent mutation or loss of the homologous allele are important events in the development of these tumors. The previously reported nonrandom loss of maternal alleles in these tumors implied that the primary mutation occurred on the paternally derived chromosome and that it was "unmasked" by loss of the normal maternal allele. This, in turn, suggests that the paternally derived allele is more mutable than the maternal one. To investigate whether germinal mutations are seen with equal frequency in maternally versus paternally inherited chromosomes, we determined the parental origin of the de novo germinal 11p13 deletions in eight children by typing lymphocyte DNA from these children and from their parents for 11p13 RFLPs. In seven of the eight cases, the de novo deletion was of paternal origin. The one case of maternal origin was unremarkable in terms of the size or extent of the 11p13 deletion, and the child did develop WT. Transmission of 11p13 deletions by both maternal and paternal carriers of balanced translocations has been reported, although maternal inheritance predominates. These data, in addition to the general preponderance of paternally derived, de novo mutations at other loci, suggest that the increased frequency of paternal deletions we observed is due to an increased germinal mutation rate in males.

Huncharek M, Kupelnick B. 2004. A meta-analysis of maternal cured meat consumption during pregnancy and the risk of childhood brain tumors. Neuroepidemiology 23:78-84.
Abstract: Objective: N-Nitroso compounds (NOCs) are recognized neural carcinogens in animal models and are suspected human carcinogens. A meta-analysis was performed examining the possible association of maternal intake of cured meat (an important source of dietary NOCs) during pregnancy and the risk of pediatric brain tumors. Methods: Data from epidemiological studies were pooled using a general variance-based meta-analytic method employing confidence intervals described by Greenland in 1986. The outcome of interest was a summary relative risk (RR) reflecting the risk of childhood brain tumor (CBT) development associated with maternal intake of cured meats during pregnancy. Sensitivity analyses were performed when necessary to explain any observed statistical heterogeneity. Results: Seven observational studies were found that met the protocol-specified inclusion criteria. Analysis for heterogeneity demonstrated a lack of statistical heterogeneity (p = 0.59), indicating that the data could be statistically combined. Pooling data from the 6 reports containing data on maternal cured meat intake of all types yielded an RR of 1.68 (1.30 2.17), being a statistically significant result. Analyzing CBT risk by type of cured meat ingested showed that hot dog consumption increased CBT risk by 33% (1.08 - 1.66), with a similar increase shown by frequent ingestion of sausage, i.e. 44%. Conclusion: The data provide support for the suspected causal association between ingestion of NOCs from cured meats during pregnancy and subsequent CBT in offspring. Limitations in study design preclude definitive conclusions, but the relationship warrants exploration via additional observational and laboratory-based studies. Copyright (C) 2004 S. Karger AG, Basel.

Huncharek M, Kupelnick B, Klassen H. 2001. Paternal smoking during pregnancy and the risk of childhood brain tumors: Results of a meta-analysis. In Vivo 15:535-541.
Abstract: Objective: Prior epidemiological studies suggest a possible association between patemal smoking during pregnancy and risk of childhood brain tumors (CBT). A meta-analysis was performed statistically pooling all available observational studies on this topic in order to evaluate this suspected association. Methods: Using previously described methods, a protocol was developed for a meta-analysis examining the association between patemal smoking during pregnancy and subsequent development of primary brain tumors in their offspring. Literature search techniques study inclusion criteria and statistical procedures were prospectively defined. Data from epidemiological studies were pooled using a general variance based meta-analytic method employing confidence interval; previously described by Greenland. The outcome of interest was a summary relative risk (RRs) reflecting the risk of childhood brain tumor development associated with father's smoking during the index pregnancy. Sensitivity analyses were performed when necessary to explain any, observed statistical heterogeneity and/or to evaluate the impact of demographic or study characteristics on the summary estimate of effect. Results: Seven observational studies meeting protocol specified inclusion criteria were obtained via a comprehensive literature search. These studies

enrolled a total of 3,600 patients. Analysis for homogeneity demonstrated that the data were homogeneous (P=0.52) and could be statistically combined. Pooling all seven reports yielded a RRS of 1.29 (1.07-1.53), a statistically significant result suggesting a 29% increased risk of brain tumor development associated with Paternal smoking during pregnancy. An analysis of father's smoking impact on CBT risk based on "ever" versus "never" smoking history gave a RRs of 1.14 (0.98-1.34), a marginally non-statistically significant result. Conclusion: The available epidemiological data suggest an association between paternal smoking during pregnancy and pediatric brain tumor development. Although this association is biologically plausible, limitations in study designs limit definitive conclusions based on available data.

Huncharek M, Kupelnick B, Klassen H. 2002. Maternal smoking during pregnancy and the risk of childhood brain tumors: A meta-analysis of 6566 subjects from twelve epidemiological studies. J Neurooncol 57:51-57.
Abstract: OBJECTIVE: Prior epidemiological studies suggest a possible association between maternal smoking during pregnancy and risk of childhood brain tumors. A meta-analysis was performed statistically pooling all available observational studies on this topic in order to evaluate this suspected association. METHODS: Using previously described methods, a protocol was developed for a meta-analysis examining the association between maternal smoking during pregnancy and subsequent development of primary brain tumors in their offspring. Literature search techniques, study inclusion criteria and statistical procedures were prospectively defined. Data from epidemiological studies were pooled using a general variance-based meta-analytic method employing confidence intervals previously described by Greenland. The outcome of interest was a summary relative risk (RRs) reflecting the risk of childhood brain tumor development associated with mother's smoking during the index pregnancy. Sensitivity analyses were performed when necessary to explain any observed statistical heterogeneity and/or to evaluate the impact of demographic or study characteristics on the summary estimate of effect. RESULTS: Twelve observational studies meeting protocol specified inclusion criteria were obtained via a comprehensive literature search. These studies enrolled a total of 6566 patients. Analysis for homogeneity demonstrated that the data were homogeneous (P > 0.50) and could be statistically combined. Pooling all twelve reports yielded an RRs of 1.05 (0.90-1.21), a non-statistically significant result suggesting no clear association between maternal smoking during pregnancy and risk of childhood brain tumor development. Numerous sensitivity analyses examining the possible effect of study design and various patient characteristics failed to show any influence on the RRs further supporting the observed lack of association. CONCLUSION: The available epidemiological data do not support a clear association between maternal smoking during pregnancy and pediatric brain tumor development. Although it appears likely that no association exists, limitations in study designs limit definitive conclusions based on available data.

Ichihara T, Wanibuchi H, Totsuka Y, Morimura K, Wei M, Nakae D, Fukushima S. 2004. Induction of DNA-adducts and increase of 8-hydroxy-2-deoxyguanosine, but no development of preneoplastic lesions in offspring liver with transplacental and trans-breast milk exposure to 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MelQx) in rats. Cancer Science 95:943-948.
Abstract: Humans may be exposed to 2-amino-3,8-dimethylimidazo[4,5f]quinoxaline (MeIQx) at low doses during the period of gestation and lactation, and thereafter throughout life. The current study was designed to examine the possibility that early exposure may increase the risk of liver tumor development and related genetic changes. Male and female F344 rats were therefore administered MeIQx in diet (1, 10 and 100 ppm) for 4 weeks before mating and also during gestation and lactation. We also examined the carcinogenic risk of low-dose maternal and post-weaning exposure (MeIQx at doses of 1 and 10 ppm). Surviving male F1 rats were sacrificed under ether anesthesia at 19 weeks of age for analyses of glutathione S-transferase placental form-positive foci in the liver and aberrant crypt foci in the colon, as putative preneoplastic lesions. Transplacental and trans-breast milk exposure to MeIQx did not enhance development of the lesions, and levels of cell proliferation in the liver also did not differ from control values. However, excretion of MeIQx into breast milk and transfer to the fetus and offspring were observed with resultant hepatic MeIQx-DNA adducts and 8-hydroxy-2'-deoxyguanosine formation. Thus, our data suggest that maternal exposure to MeIQx during the period of pregnancy and lactation may not increase the risk of hepatocarcinogenesis in male offspring, despite causing genetic damage. If this result can be extrapolated to humans, exposure to MeIQx may not increase carcinogenic risk in offspring at usual human exposure levels.

Ichihara T, Yoshino H, Imai N, Tsutsumi T, Kawabe M, Tamano S, Inaguma S, Suzuki S, Shirai T. 2003. Lack of

carcinogenic risk in the prostate with transplacental and lactational exposure to bisphenol A in rats. J Toxicol Sci 28:165-171.
Abstract: The current study was designed to examine the modulating effects of bisphenol A (BPA) on prostate cancer risk in male offspring exposed transplacentally and lactationally. BPA was administered to F344 female rats by gavage at 0, 0.05, 7.5, 30, 120 mg/kg/day during pregnancy and lactation periods. When F1 males reached 5 weeks old, they were given 10 subcutaneous injections of 3,2'-dimethyl-4-aminobiphenyl (DMAB) or corn oil vehicle and rats were then sacrificed under ether anesthesia at week 60. There were no observable effects on the accessory sex organ weights of male offspring. Transplacental and lactational exposure to BPA did not affect the incidences of preneoplastic and neoplastic lesions in the accessory sex organs (prostate and seminal vesicle) of F1 rats and did not induce any proliferating lesions without DMAB. Our data suggest that maternal exposure to BPA during the period of pregnancy and lactation does not affect the risk of prostate carcinogenesis in male offspring.

Ikezuki Y, Tsutsumi O, Takai Y, Kamei Y, Taketani Y. 2002. Determination of bisphenol A concentrations in human biological fluids reveals significant early prenatal exposure. Hum Reprod 17:2839-2841.
Abstract: BACKGROUND: There is broad human exposure to bisphenol A (BPA), an estrogenic endocrine-disrupting chemical widely used for the production of plastic products. BPA is reported to affect preimplantation embryos or fetuses and alter their postnatal development at doses typically found in the environment. We measured contamination of BPA in various kinds of human biological fluids by a novel enzyme-linked immunosorbent assay. METHODS: Blood samples were obtained from healthy premenopausal women, women with early and full-term pregnancy, and umbilical cord at full-term delivery. Ovarian follicular fluids obtained during IVF procedures and amniotic fluids obtained at mid-term and full-term pregnancy were also subject to BPA measurements. RESULTS: BPA was present in serum and follicular fluid at approximately 1-2 ng/ml, as well as in fetal serum and full-term amniotic fluid, confirming passage through the placenta. Surprisingly, an approximately 5-fold higher concentration, 8.3 +/- 8.7 ng/ml, was revealed in amniotic fluid at 15- 18 weeks gestation, compared with other fluids. CONCLUSION: These results suggest accumulation of BPA in early fetuses and significant exposure during the prenatal period, which must be considered in evaluating the potential for human exposure to endocrine-disrupting chemicals.

Imajima T, Shono T, Zakaria O, Suita S. 1997. Prenatal phthalate causes cryptorchidism postnatally by inducing transabdominal ascent of the testis in fetal rats. J Pediatr Surg 32:18-21.
Abstract: Phthalate esters, which are commonly used as plasticizers for polyvinyl chloride, are also well known to disturb Sertoli cells. This study aims to show the effect of prenatally administered phthalate on testicular descent in pre- and postnatal rats. Pregnant rats were exposed to mono-n-butyl phthalate (MBP) by gavage from the 15th to the 18th gestational days. Rats administered with solvent only were used as controls. In 20-day-old fetuses (n = 15), the degree of transabdominal testicular ascent in relation to the bladder neck was thus found to be significantly higher in MBP-treated rats than that of the controls (n = 19). In addition, in MBP-treated male offspring (n = 26), 22 rats showed either bilateral or unilateral cryptorchidism at the age of 30 to 40 days old, and the occurrence of cryptorchidism was 84.6%. By contrast, the occurrence of cryptorchidism was 0% in the control rats (n = 15, P < .001). It is therefore suggested that prenatal exposure to MBP may disturb the Sertoli cells and elevate the fetal testes relative to the bladder neck while also inducing cryptorchidism postnatally. Sertoli cells may thus play an important role in the transabdominal descent of the testis by secreting Mullerian-inhibiting substance (MIS), which is known to act as a putative mediator of the transabdominal p1997hase. Copyright (C) 1997 by W.B. Saunders Company

Infante-Rivard C. 1995. Electromagnetic-field exposure during pregnancy and childhood leukemia. Lancet 346:177.

Infante-Rivard C, Amre D, Sinnett D. 2002. GSTT1 and CYP2E1 polymorphisms and trihalomethanes in drinking water: Effect on childhood leukemia. Environ Health Perspect 110:591-593.
Abstract: The purpose of the study was to determine whether the risk of childhood acute lymphoblastic leukemia (ALL) associated with drinking water disinfection by-products was modified in the presence of variants in genes involved in the metabolism of trihalomethanes (THMS). We included a subset of cases from a population-based case-control study in a case-only study to estimate the interaction odds ratios (IORs) between prenatal and postnatal exposure to THMs and polymorphisms in the GSTT1 and CYP2E1

genes. We compared cases with and without a given variant regarding their exposure to THMs using unconditional logistic regression. The IOR for a postnatal average of total THM above the 95th percentile with GSTT1 null genotype was 9.1 [95% confidence interval (95% CI), 1.4-57.8]. With CYP2E1 (variant G-1259C, known as the allele CYP2E1*5), the effect of exposure during pregnancy for an average exposure to total THM at or above the 75th percentile was 9.7 (95% CI, 1.1-86.0). These results contrast strongly with those from our case-control analysis, in which we considered the exposure to THMs only in relation with ALL, and observed no increase in risk or very moderate ones. The present preliminary study shows suggestive but imprecise results. We found no similar results in the literature, underscoring the need for other studies as well as the potential usefulness of combining exposure and relevant genetic information in such studies.

Infante-Rivard C, Deadman JE. 2003. Maternal occupational exposure to extremely low frequency magnetic fields during pregnancy and childhood leukemia. Epidemiology 14:437-441.
Abstract: Background: Pregnancy is a target period for events that could induce childhood leukemia. There has been little attention to possible effects of maternal occupational exposure to extremely low frequency magnetic fields (ELF-MF) during pregnancy. Methods: We conducted a population-based, case-control study of 491 incident cases of acute lymphoblastic leukemia in children 0-9 years of age, matched on age and sex to 491 healthy controls. Cases were diagnosed in the Province of Quebec between 1980 and 1993. Mothers were interviewed to obtain detailed prenatal occupational history; individual exposure to ELF-MF was estimated based on a method we recently developed. We used 3 metrics for analyzing exposure: cumulative, average and maximum levels. Analyses were carried out among all study women and among working women only. Results: Comparing the highest 10% of exposed mothers to the others, the risk of leukemia among offspring was moderately increased by using any metric, in all women and among working women only. The highest odds ratio of 2.5 (95% confidence interval = 1.2-5.0) was found for maximum exposure attained in an occupation (greater than or equal to0.4 microtesla). Conclusions: Our results are compatible with an increased risk of childhood leukemia among children whose mothers were exposed to the highest occupational levels of ELF-MF during pregnancy.

Infante-Rivard C, El-Zein M. 2007. Parental alcohol consumption and childhood cancers: A review. J Toxicol Environ Health B Crit Rev 10:101-129.
Abstract: The etiology of childhood cancers remains generally unknown. Given that the metabolites of alcohol are likely carcinogens and that leukemia, the most frequent childhood cancer, can arise in utero, the study of alcohol consumption as a potential risk factor for the development of childhood cancer is justified. This article summarizes the epidemiological evidence on the association between parental exposure to alcohol and the risk of childhood cancers. To do this, a thorough search of the literature from 1960 to 2003 using the PubMed database was carried out. It yielded 33 case-control studies published between 1982 and 2003, including 13 studies that considered paternal exposure in the preconceptional period. In 10 of the 33 studies at least 1 statistically significant risk increase was reported in relation with parental alcohol consumption; in 7 of these studies the increase was related to maternal consumption, whereas in 3 studies, it was related to paternal consumption. The cancers most often found associated with parental drinking were leukemia, brain tumors, and neuroblastoma. A few studies also reported a protective effect with maternal exposure at modest levels. Inconsistencies in the results and the low risks reported do not suggest an association between childhood cancer and parental consumption of alcohol. However, before reaching any definitive conclusions, methodological issues need to be addressed in future studies, as well as the role of genetic susceptibility. Moreover, subtypes of specific cancers need to be studied separately.

Infante-Rivard C, Krajinovic M, Labuda D, Sinnett D. 2000. Parental smoking, CYP1A1 genetic polymorphisms and childhood leukemia (Quebec, Canada). Cancer Causes & Control 11:547-553.
Abstract: Objective: To evaluate the effect of parental smoking on childhood acute lymphoblastic leukemia and to determine if it is modified by child genetic polymorphisms. Methods: We carried out a case-control study in Quebec, Canada, including 491 incident cases aged 0-9 years and as many healthy controls matched on age and sex. Each parent was interviewed separately with respect to smoking habits during and after pregnancy. In addition, we carried out a case-only substudy with 158 cases classified according to presence or absence of the alleles *2A, *2B, and *4 in the CYP1A1 gene. Results: There were small risk increases with maternal smoking during the later trimesters. Interaction odds ratios were increased (although often not significantly) for the CYP1A1*4 allele at high levels of maternal smoking in the last

trimesters and at low level of paternal postnatal smoking, and decreased for the CYP1A1*2B allele. The latter appeared to confer a protective advantage at low levels for maternal prenatal smoking and at high levels for paternal postnatal smoking. Conclusions: Reported smoking habits showed no association with leukemia; risks for genetic polymorphisms lacked precision but indicated that the effect of parental smoking could be modified by variant alleles in the CYP1A1 gene.

Infante-Rivard C, Krajinovic M, Labuda D, Sinnett D. 2002. Childhood acute lymphoblastic leukemia associated with parental alcohol consumption and polymorphisms of carcinogen-metabolizing genes. Epidemiology 13:277-281.
Abstract: Background. Limited information is available on the association of parental consumption of alcohol prior to and during pregnancy with the risk of childhood leukemia, as well as for the potentially modifying role of genetic polymorphisms. Methods. We conducted a population-based, case-control study of 491 incident cases of acute lymphoblastic leukemia age 0-9 years and matched on age and sex to 491 healthy controls. Cases were identified at tertiary care centers in the Province of Quebec between 1980 and 1993. Each parent was interviewed separately about alcohol consumption habits. We also used a case-only design with 186 cases to estimate interaction odds ratios between prenatal exposure and child DNA variants in the GSTM1 and CYP2E1 genes. Results. The adjusted odds ratio for any maternal consumption during pregnancy was 0.7 (95% confidence interval = 0.5-0.9). The interaction odds ratios for the GSTM1 null genotype during third pregnancy trimester was 2.4 (95% confidence interval = 1.1-5-4); the interaction odds ratio for CYP2E1 variant G-1295C (or allele *5) during the nursing period was 4.9 (95% confidence interval = 1.5-16.7). Conclusions. The observed association with maternal alcohol consumption during pregnancy could be due to the potential chemopreventive effects of flavonoids found in wine and beer. These possible effects of alcohol may be at least partially genetically determined, although data are preliminary.

Infante-Rivard C, Labuda D, Krajinovic M, Sinnett D. 1999. Risk of childhood leukemia associated with exposure to pesticides and with gene polymorphisms. Epidemiology 10:481-487.
Abstract: We conducted a population-based case-control study of childhood acute lymphoblastic leukemia (ALL) to evaluate the risk posed by reported exposure to pesticides used in and around the home. We compared 491 cases 0-9 years of age to as many controls. We also conducted a case-only study on a subsample of 123 cases to evaluate gene-environment interaction be tween child genotype and maternal exposure during pregnancy as well as child exposure after birth. We used the polymerase chain reaction (PCR) approach to analyze polymorphisms in CYP1A1, CYP2D6, GSTT1, and GSTM1 genes, which encode enzymes involved in carcinogen metabolism. Indoor use of some insecticides by the owners and pesticide use in the garden and on interior plants, in particular frequent prenatal use, was associated with increased risks up to severalfold in magnitude. Interaction odds ratios were increased among carriers of the CYP1A1m1 and CYP1a1m2 mutations when mother during pregnancy or the child had been exposed to certain indoor insecticides. No such effects were observed in the presence of other tested polymorphisms.

Infante-Rivard C, Mur P, Armstrong B, Alvarez-Dardet C, Bolumar F. 1991. Acute lymphoblastic leukaemia among Spanish children and mothers' occupation: a case-control study. J Epidemiol Community Health 45:11-15.
Abstract: STUDY OBJECTIVE--The aim was to investigate the association between mothers' occupational exposure during pregnancy and the incidence of acute lymphoblastic leukaemia in children. DESIGN--The study was a case-control investigation. A face to face interview was used to assess exposures at work and relevant confounding variables. SETTING--The study was community based and was carried out in five provinces of Spain. SUBJECTS--128 cases less than 15 years of age were interviewed (91% of those eligible). Controls (one for each case) were chosen from the census lists and were matched on year of birth, sex and municipality. MEASUREMENTS AND MAIN RESULTS--Children of mothers working at home had a relative risk (RR) of 7.0 (95% CI = 1.59-30.79) of developing acute lymphoblastic leukaemia. Exposure to organic dust was associated with a RR of 5.5 (95% CI = 1.21-24.8). There was a statistically significant interaction between exposure to organic dust and working at home. The majority of women working at home were hired by local industries to sew different types of tissues (cotton, wool, synthetic fibres) on a machine. CONCLUSION--A similar association has not been reported before: if confirmed, this finding may suggest a new health concern.

Infante-Rivard C, Olson E, Jacques L, Ayotte P. 2001. Drinking water contaminants and childhood leukemia.

Epidemiology 12:13-19.
Abstract: We conducted a population-based case-control study to evaluate the relation between exposure to drinking water contaminants (total and specific trihalomethanes and certain metals and nitrates) and childhood acute lymphoblastic leukemia. We compared 491 cases 0-9 years of age with 491 controls. We developed a municipality-exposure matrix based on municipal and provincial historical data, a tapwater survey in 227 homes, and information about residential history. We used average level of exposure and cumulative average over the period as exposure indices, and we measured risk for the pregnancy period as well as for the postnatal period. We show that risks were generally not increased for the prenatal period nor with average levels of exposure. Postnatal cumulative exposure for total trihalomethanes at above the 95th percentile of the distribution for cases and controls was associated with an odds ratio of 1.54 (95% confidence interval = 0.78-3.03); for that same period, risk associated with exposure to chloroform was increased (odds ratio = 1.63; 95% confidence interval = 0.84-3.19) as well as that for exposure to zinc (odds ratio = 2.48; 95% confidence interval = 0.99-6.24), Risks were also increased for exposure to cadmium and arsenic, but not for other metals nor for nitrates.

Infante-Rivard C, Siemiatycki J, Lakhani R, Nadon L. 2005. Maternal exposure to occupational solvents and childhood leukemia. Environ Health Perspect 113:787-792.
Abstract: Many organic solvents are considered probable carcinogens. We carried out a population-based case-control study including 790 incident cases of childhood acute lymphoblastic leukemia and as many healthy controls, matched on age and sex. Maternal occupational exposure to solvents before and during pregnancy was estimated using the expert method, which involves chemists coding each individual's job for specific contaminants. Home exposure to solvents was also evaluated. The frequency of exposure to specific agents or mixtures was generally low. Results were generally similar for the period ranging from 2 years before pregnancy up to birth and for the pregnancy period alone. For the former period, the odds ratio (OR), adjusted for maternal age and sex, for any exposure to all solvents together was 1.11 [95% confidence interval (CI), 0.88-1.40]. Increased risks were observed for specific exposures, such as to 1,1,1-trichloroethane (OR = 7.55; 95% CI, 0.92-61.97), toluene (OR = 1.88; 95% CI, 1.01-3.47), and mineral spirits (OR = 1.82; 95% CI, 1.05-3.14). There were stronger indications of moderately increased risks associated with exposure to alkanes (C5-C17; OR = 1.78; 95% CI, 1.11-2.86) and mononuclear aromatic hydrocarbons (OR = 1.64; 95% CI, 1.12-2.41). Risk did not increase with increasing exposure, except for alkanes, where a significant trend (p = 0.04) was observed. Home exposure was not associated with increased risk. Using an elaborate exposure coding method, this study shows that maternal exposure to solvents in the workplace does not seem to play a major role in childhood leukemia.

Innes K, Byers T, Schymura M. 2000. Birth characteristics and subsequent risk for breast cancer in very young women. Am J Epidemiol 152:1121-1128.
Abstract: There is growing evidence that prenatal exposures may influence later breast cancer risk. This matched case-control study used linked New York State birth and tumor registry data to examine the association between birth characteristics and breast cancer risk among women aged 14-37 years. Cases were women diagnosed with breast cancer between 1978 and 1995 who were also born in New York after 1957 (n = 484). For each case, selected controls were the next six liveborn females with the same maternal county of residence. The authors found a J-shaped association between birth weight and breast cancer risk, and very high birth weight (> or =4,500 g) was associated with the greatest elevation in risk (adjusted odds ratio (OR) = 3.10, 95% confidence interval (CI): 1.18, 7.97). The association of maternal age with breast cancer risk was also J-shaped, with maternal age of more than 24 years showing a positive, linear association (adjusted OR = 1.94, 95% CI: 1.18, 3.18 for maternal age > or =35 vs. 20-24 years; p for trend = 0.02). In contrast, women born very preterm had a lower risk (adjusted OR = 0.11, 95% CI: 0.02, 0.79 for gestational age <33 vs. > or =37 weeks). These findings support a role for early life factors in the development of breast cancer in very young women.

Innes KE, Byers TE. 1999. Preeclampsia and breast cancer risk. Epidemiology 10:722-732.
Abstract: Breast cancer is associated with endogenous hormone levels, but the exact relation and underlying mechanisms remain unclear. Data from several recent epidemiologic studies suggest that a woman who experiences preeclampsia in her own pregnancy, or who was herself born to a preeclamptic pregnancy, is at reduced risk for breast cancer later in life. This paper reviews the evidence for a connection between preeclampsia and breast cancer risk, and discusses the hormonal mechanisms that might explain

this association. Preeclampsia is characterized by reduced levels of estrogens and insulin-like growth factor-1, and by elevated levels of progesterone, androgens, human chorionic gonadotropin, IGF-1 binding protein, corticotropin-releasing factor, cortisol, and insulin. These factors may act both individually and synergistically to decrease breast cancer risk. The occurrence of preeclampsia during a woman's pregnancy may reflect an underlying hormonal profile that both predisposes her to preeclampsia and reduces her risk for breast cancer. In addition, the major hormonal alterations associated with preeclampsia during gestation may have lasting effects on subsequent breast cancer risk. Finally, the hormonal and nutritional environment of the womb, for which preeclampsia is a marker, may play an important role in programming lifelong risk for breast cancer in the female offspring.

Ito N, Hasegawa R, Imaida K, Tamano S, Hagiwara A, Hirose M, Shirai T. 1997. Carcinogenicity of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) in the rat. Mutat Res 376:107-114.
Abstract: A total of 10 highly-mutagenic heterocyclic amines have been identified to be carcinogenic in rodents. Among these, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), generally the most abundant with normal cooking procedures, induces mammary and colon carcinomas in rats in a clear dose-dependent manner. In a two-generation exposure (transplacental and trans-breast milk) experiment using Sprague-Dawley rats, an increased risk of mammary adenocarcinoma development was found in the second generation. Excretion of PhIP into the milk and transfer of PhIP to fetuses and neonates with resultant hepatic PhIP-DNA adduct formation were also confirmed. On the other hand, PhIP mammary carcinogenesis was significantly inhibited by coadministration of chlorophyllin or a synthetic antioxidant, 1-O-hexyl-2,3,5-trimethylhydroquinone, in long-term experiments using female F344 rats. The available findings strongly suggest that this food-derived carcinogen might be of importance as an environmental factor in the production of human cancers and that its carcinogenicity could be largely avoided by reducing intake of such compounds or by adoption of appropriate chemopreventive measures.

Ivankovic S. 1979. Teratogenic and carcinogenic effects of some chemicals during perinatal life in rats, Syrian golden hamsters, and minipigs. Natl Cancer Inst Monogr :103-115.
Abstract: Teratogenic effects of ENU have been observed in the rat, Syrian golden hamster, and minipig. In BD and Wistar rats, as well as in hamsters, ENU is a potent carcinogen when administered prenatally. Other members of the homologous series of alkylnitrosoureas, except n-propylnitrosourea, have been shown to be less active or totally inactive as carcinogens in experiments on prenatal animals. Simultaneous oral administration of L-citrulline and sodium nitrite induced adenosarcomas of the kidney (Wilm's tumors) in 6 of 22 offspring. The importance of prophylactic measures in man during prenatal development is emphasized.

Ivnitsky I, Torchinsky A, Gorivodsky M, Zemliak I, Orenstein H, Savion S, Shepshelovich J, Carp H, Fein A, Toder V. 1998. TNF-alpha expression in embryos exposed to a teratogen. Am J Reprod Immunol 40:431-440.
Abstract: PROBLEM: The role of tumor necrosis factor (TNF)-alpha produced by embryonic cells in normal and abnormal development is poorly understood. To assess to what extent TNF-alpha may be involved in the process of induced dysmorphogenesis, the expression of TNF-alpha and TNF-alpha receptor (TNFRI) mRNA as well as TNF-alpha protein was evaluated in embryos responding to a cyclophosphamide (CP)-induced teratogenic insult. The effect of maternal immunostimulation increasing the embryo's tolerance to CP on TNF-alpha expression was also investigated. METHOD OF STUDY: ICR female mice were treated intraperitoneally with 40 mg/kg CP on day 12 of pregnancy. The immunostimulator, xenogeneic rat splenocytes, was injected intrauterine 21 days before mating. Embryos were collected on days 13, 14, or 15 of pregnancy. TNF-alpha mRNA, TNFRI mRNA, and TNF-a protein expression were evaluated by in situ hybridization and immunostaining techniques in control, teratogen-treated, and immunostimulated teratogen-treated embryos. RESULTS: CP-treated embryos showed severe external brain and craniofacial anomalies already visible on day 14 of pregnancy. TNF-alpha mRNA transcripts were detected in cells of the brain and the head of 13-day embryos, which preceded the occurrence of CP-induced external craniofacial anomalies. On day 15 of pregnancy, when severe craniofacial anomalies increased, a significant increase in the intensity of TNF-alpha, TNFR1 mRNA transcripts, and TNF-alpha protein expression were observed in cells of the malformed regions of the head and the brain. In other nonmalformed organs of CP-treated embryos such as the liver (not macroscopically different from controls), neither TNF-alpha nor TNFR1 transcripts were detected. Immunostimulation substantially diminished the severity of CP-induced brain and craniofacial anomalies, decreased the

resorption rate, and was associated with decreased intensity of TNF-alpha mRNA transcripts detected on day 15 of pregnancy in the head and the brain of CP-treated embryos. CONCLUSIONS: TNF-alpha expressed in the embryo may be one of the molecules promoting the formation of CP-induced brain and craniofacial anomalies. The decrease of TNF-alpha expression in embryos of immunostimulated females may be one of the mechanisms responsible for the increased tolerance to the teratogenic insult.

Izraeli S. 2006. Perspective: chromosomal aneuploidy in leukemia - lessons from down syndrome. Hematol Oncol 24:3-6.
Abstract: Abnormal number of chromosomes, aneuploidy, is the most common abnormality in leukemia and cancer. However, the casual relationship between aneuploidy and cancer is unclear. Additional copies of chromosome 21 are frequently found in leukemic cells. Constitutional trisomy 21 that characterizes Down Syndrome is associated with markedly increased risk for childhood leukemia. In this perspective I review recent studies that suggest that constitutional trisomy 21 promotes leukemic transformation during fetal hematopoiesis. As most of childhood leukemias arise in-utero, these studies are of general relevance to sporadic childhood leukemias. Copyright (c) 2005 John Wiley & Sons, Ltd.

Izzotti A, Balansky RM, Cartiglia C, Camoirano A, Longobardi M, De Flora S. 2003. Genomic and transcriptional alterations in mouse fetus liver after transplacental exposure to cigarette smoke. FASEB J 17:1127-1129.
Abstract: The transplacental exposure of fetuses to maternal cigarette smoke may increase the risk of developmental impairments, congenital diseases, and childhood cancer. The whole-body exposure of Swiss mice to environmental cigarette smoke (ECS) during pregnancy decreased the number of fetuses per dam, placenta weight, and fetus weight. ECS increased DNA adducts, oxidative nucleotide alterations, and cytogenetic damage in fetus liver. Evaluation by cDNA array of 746 genes showed that 61 of them were expressed in fetus liver under basal conditions. The oral administration of N-acetylcysteine (NAC) during pregnancy enhanced the expression of three genes only, including two glutathione S-transferases and alpha1-antitrypsin precursor, whose deficiency plays a pathogenetic role in congenital emphysema. Transplacental ECS upregulated the expression of 116 genes involved in metabolism, response to oxidative stress, DNA and protein repair, and signal transduction. NAC inhibited the ECS-related genetic damage and upregulation of most genes. ECS stimulated pro-apoptotic genes and genes downregulating the cell cycle, which may justify growth impairments in the developing fetus. Thus, both genetic and epigenetic mechanisms were modulated by ECS. Moreover, hypoxia-related genes and several oncogenes and receptors involved in proliferation and differentiation of leukocytes were induced in the fetal liver, which also bears hematopoietic functions.

Jackson AA. 2005. Integrating the Ideas of Life Course Across Cellular, Individual, and Population Levels in Cancer Causation. J Nutr 135:2927S-2933S.
Abstract: Cells, individuals, and societies are complex systems in which the integrity of structure and function is protected through tight regulation and control. For each level of organization, health represents the ability to maintain integrity in response to the wider environment. Critical stages during growth and development act as checkpoints, where choice is exercised, and help determine future direction. Important among factors influencing the checkpoints include the availability of nutrients or foods within the immediate environment. At the cellular and whole-body levels, this information can be communicated to future generations. Recent work on the developmental origins of adult disease indicate specific factors that set limits on structure and function and potentially limit the capacity of the cell and individual to respond to environmental stressors that represent potential risk factors for neoplastic change. Epigenetic mechanisms modulate structure and function at the cellular and tissue levels, reflecting the potential for the growth and development of individuals, and reflect the food and nutrients available to the body as a whole and within the wider society. Understanding the nature and the interaction of the critical factors that determine and regulate variable stable and unstable gene expression will be increasingly important in characterizing abnormal cellular function and risk of disease for individuals and populations. This will require the ability to synthesize large data sets within and between different levels of organization to develop and refine a deeper understanding of how the systems are effectively integrated and regulated within and across generations and where this fails in the genesis of cancer.

Jacquet P. 2004. Sensitivity of germ cells and embryos to ionizing radiation. Journal of Biological Regulators & Homeostatic Agents 18:106-114.

Abstract: Experiments performed in laboratory animals suggest that ionizing radiation can induce DNA damage in the germ cells of exposed individuals and lead to various deleterious effects in their progeny, including miscarriage, low birth weight, congenital abnormalities and perhaps cancer. However, no clear evidence for such effects has been found in epidemiological studies of people exposed to radiation. The predicted risks of hereditary effects of any kinds, resulting from parental exposure to relatively low doses of ionizing radiation remain very low, compared to the spontaneous risks in the absence of irradiation. Irradiation of the mouse embryo can lead to various effects (lethality, growth retardation, congenital abnormalities), depending on the period of gestation at which irradiation occurs. In humans, prenatal irradiation has only been exceptionally associated with congenital abnormalities, but irradiation between weeks 8-25 has been shown to be able to induce severe mental retardation. Although being not proven, the risk of developing a childhood cancer following prenatal irradiation may also not be excluded. Like for genetic effects, the risk of adverse effects following exposure of the embryo to relatively low doses remains quite low compared to the natural risks.

Jang TC, Savarese T, Low HP, Kim S, Vogel H, Lapointe D, Duong T, Litofsky NS, Weimann JM, Ross AH, Recht L. 2006. Osteopontin expression in intratumoral astrocytes marks tumor progression in gliomas induced by prenatal exposure to N-ethyl-N-nitrosourea. Am J Pathol 168:1676-1685.
Abstract: To better study early events in glioma genesis, markers that reliably denote landmarks in glioma development are needed. In the present study, we used microarray analysis to compare the gene expression patterns of magnetic resonance imaging (MRI)-localized N-ethyl-N-nitrosourea (ENU)-induced tumors in rat brains with those of uninvolved contralateral side and normal brains. Our analysis identified osteopontin (OPN) as the most up-regulated gene in glioma. Using immunohistochemistry we then confirmed OPN expression in every tumor examined (n = 17), including those with diameters as small as 300 mu m. By contrast, no OPN immunostaining was seen in normal brain or in brains removed from ENU-exposed rats before the development of glioma. Further studies confirmed that OPN was co-localized exclusively in intratumoral glial fibrillary acidic protein-expressing cells and was notably absent from nestin-expressing ones. In conjunction with this, we confirmed that both normal neurosphere cells and ENU-immortalized subventricular zone/striatal cells produced negligible amounts of OPN compared to the established rat glioma cell line C6. Furthermore, inducing OPN expression in an immortalized cell line increased cell proliferation. Based on these findings, we conclude that OPN overexpression in ENU-induced gliomas occurs within a specific subset of intratumoral glial fibrillary acidic protein-positive cells and becomes evident at the stage of tumor progression.

Janosek J, Hilscherova K, Blaha L, Holoubek I. 2006. Environmental xenobiotics and nuclear receptors - Interactions, effects and in vitro assessment. Toxicology in Vitro 20:18-37.
Abstract: A group of intracellular nuclear receptors is a protein superfamily including arylhydrocarbon AhR, estrogen ER, androgen AR, thyroid TR and retinoid receptors RAR/RXR as well as molecules with unknown function known as orphan receptors. These proteins play an important role in a wide range of physiological as well as toxicological processes acting as transcription factors (ligand-dependent signalling macromolecules modulating expression of various genes in a positive or negative manner). A large number of environmental pollutants and other xenobiotics negatively affect signaling pathways, in which nuclear receptors are involved, and these modulations were related to important in vivo toxic effects such as immunosuppression, carcinogenesis, reproduction or developmental toxicity, and embryotoxicity. Presented review summarizes current knowledge on major nuclear receptors (AhR, ER, AR, RAR/RXR, TR) and their relationship to known in vivo toxic effects. Special attention is focused on priority organic environmental contaminants and experimental approaches for determination and studies of specific toxicity mechanisms. (c) 2005 Elsevier Ltd. All rights reserved.

Jansen Mwjc, Corral L, Van Der Velden VHJ, Panzer-Grumayer R, Schrappe M, Schrauder A, Marschalek R, Meyer C, Den Boer ML, Hop WJC, Valsecchi MG, Basso G, Biondi A, Pieters R, Van Dongen JJM. 2007. Immunobiological diversity in infant acute lymphoblastic leukemia is related to the occurrence and type of MLL gene rearragement. Leukemia 21:633-641.
Abstract: The aim of this study was to identify immunobiological subgroups in 133 infant acute lymphoblastic leukemia (ALL) cases as assessed by their immunophenotype, immunoglobulin (Ig) and T-cell receptor (TCR) gene rearrangement pattern, and the presence of mixed lineage leukemia (MLL) rearrangements. About 70% of cases showed the pro-B-ALL immunophenotype, whereas the remaining

cases were common ALL and pre-B-ALL. MLL translocations were found in 79% of infants, involving MLL-AF4 (41%), MLL-ENL (18%), MLL-AF9 (11%) or another MLL partner gene (10%). Detailed analysis of Ig/TCR rearrangement patterns revealed IGH, IGK and IGL rearrangements in 91, 21 and 13% of infants, respectively. Cross-lineage TCRD, TCRG and TCRB rearrangements were found in 46, 17 and 10% of cases, respectively. As compared to childhood precursor-B-ALL, Ig/TCR rearrangements in infant ALL were less frequent and more oligoclonal. MLL-AF4 and MLL-ENL-positive infants demonstrated immature rearrangements, whereas in MLL-AF9-positive leukemias more mature rearrangements predominated. The immature Ig/ TCR pattern in infant ALL correlated with young age at diagnosis, CD10 negativity and predominantly with the presence and the type of MLL translocation. The high frequency of immature and oligoclonal Ig/TCR rearrangements is probably caused by early (prenatal) oncogenic transformation in immature B-lineage progenitor cells with germline Ig/TCR genes combined with a short latency period.

Jasienska G, Ziomkiewcz A, Lipson SF, Thune I, Ellison PT. 2006. High Ponderal Index at Birth Predicts High Estradiol Levels in Adult Women. American Journal of Human Biology 18:133-140.
Abstract: Inter-individual variation in levels of sex hormones results from differences in genetic, developmental, and environmental factors. We tested a hypothesis that programming of the fetal neuroendocrine axis may predispose some women to produce higher levels of steroid hormones during their menstrual cycles as adults. One hundred forty-five regularly menstruating 24- to 36-year-old women collected daily saliva samples for one menstrual cycle. Data on women's birth weights and birth lengths were obtained from medical records. A positive relationship was observed between ponderal index at birth (an indicator of nutritional status, calculated as birth weight/(birth length)(3)) and levels of estradiol (E2) in menstrual cycles, after controlling for potential confounding factors. Mean E2 was 16.4 pmol/l in the low ponderal index tertile, 17.3 pmol/l in the moderate ponderal index tertile, and 19.6 pmol/l in the high ponderal index tertile (the high ponderal index group had significantly higher E2 than both low and moderate ponderal index groups, P = 0.0001). This study shows a positive association between ponderal index recorded for women at birth and levels of E2 measured during their menstrual cycles as adults. This suggests that conditions during fetal life influence adult production of reproductive hormones and may contribute to inter-individual variation in reproductive function. In addition, because large size at birth is one of the factors linked with an increased risk of breast cancer, our findings provide a physiological link for the observed positive relationship between indicators of energetic conditions during fetal growth and breast cancer in women.

Jauchem JR, Merritt JH. 1991. The epidemiology of exposure to electromagnetic-fields - An overview of the recent literature. J Clin Epidemiol 44:895-906.
Abstract: Epidemiologic studies of exposure to electromagnetic fields (EMF) have been reviewed. Possible links to incidences of cancer and abnormal fetal development have been suggested by some investigators. In general, the results have been inconsistent. There are many deficiencies in the studies, and many questions have been raised about the validity of some of the conclusions proposed. There is currently no definitive evidence of an association between exposure to EMF and the alleged risks. Due to problems and limitations inherent in future studies (misconceptions about exposure levels, uncertainty about field variability, criticisms of surrogate measures), this question is unlikely to ever be answered with certainty. Unfortunately, many highly-publicized accounts of speculative and unsubstantiated claims have caused undue concern among the general public.

Jenkins S, Rowell C, Wang J, Lamartiniere CA. 2007. Prenatal TCDD exposure predisposes for mammary cancer in rats. Reprod Toxicol 23:391-396.
Abstract: Epidemiological data are conflicting in the link between 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure and breast cancer causation. We have hypothesized that timing of exposure to endocrine disruptors, such as TCDD, will alter breast cancer susceptibility. Using a carcinogen induced rat mammary cancer model, we have shown that prenatal exposure to TCDD alters mammary gland differentiation and increases susceptibility for mammary cancer. Investigations into imprinting via DNA methylation mechanisms showed that there were no changes in protein expression in DNA methyltransferases, ER-alpha, ER-beta, GST-pi, or MDGI. Using 2D gels and mass spectrometry, we have found seven proteins to be differentially regulated, including a decrease in superoxide dismutase 1 (SOD1). Down-regulation of SOD1 could provide an environment ill equipped to deal with subsequent free radical exposure. We

conclude that prenatal TCDD can predispose for mammary cancer susceptibility in the adult offspring by altering the mammary proteome.

Jennings-Gee JE, Moore JE, Xu M, Dance ST, Kock ND, McCoy TP, Carr JJ, Miller MS. 2006. Strain-specific induction of murine lung tumors following in utero exposure to 3-methylcholanthrene. Molecular Carcinog 45:676-84.
Abstract: Fetal mice are more sensitive to chemical carcinogens than are adults. We previously demonstrated that resistant offspring of a DBA/2 x (C57BL/6 x DBA2) backcross exhibited a high incidence of lung tumors 12-13 mo after transplacental exposure to 3-methylcholanthrene (MC). We compared the effects of in utero treatment with MC on lung tumor incidence in the offspring of intermediately susceptible BALB/c (C), resistant C57BL/6 (B6), and reciprocal crosses between these strains. Pregnant mice were treated with 45 mg/kg of MC on day 17 of gestation and tumor incidence, multiplicity, and the Ki-ras mutational spectrum determined in the offspring 12-18 mo after birth. Tumor incidences in C mice and reciprocal crosses were 86% and 100%, respectively, while B6 mice demonstrated resistance to tumorigenesis, with a tumor incidence of 11%. Tumor multiplicities in C, B6C, CB6, and B6 mice were 3.3 +/- 3.2, 5.8 +/- 3.2, 5.0 +/- 2.7, and <0.1, respectively. Ki-ras mutations, which occurred chiefly in the K(s) allele (96%), were found in 79-81% of reciprocally crossed F1 mice, 64% of C mice, and 50% of B6 mice, with the Val(12), Asp(12), and Arg(13) mutations associated with more aggressive tumors. A subset of these mice was used to demonstrate the utility of computer tomography (CT) for the visualization and measurement of lung tumors in the submillimeter range in vivo. Based on known genetic differences in murine strains for lung cancer, our results suggest the presence of a previously unidentified genetic factor(s) which appears to specifically influence lung tumorigenesis following exposure to carcinogens during fetal development.

Jensen CD, Block G, Buffler P, Ma X, Selvin S, Month S. 2004. Maternal dietary risk factors in childhood acute lymphoblastic leukemia (United States). Cancer Causes & Control 15:559-570.
Abstract: OBJECTIVE: Acute lymphoblastic leukemia (ALL) is the most common childhood cancer, and the second most common cause of mortality in children aged 1-14 years. Recent research has established that the disease can originate in utero, and thus maternal diet may be an important risk factor for ALL. METHODS: The Northern California Childhood Leukemia Study is a population-based case-control study of risk factors for childhood leukemia, including maternal diet. Cases (n = 138) and controls (n = 138) were matched on sex, date of birth, mother's race, Hispanicity, and county of residence at birth. Maternal dietary intake in the 12 months prior to pregnancy was obtained by a 76-item food frequency questionnaire. RESULTS: Consumption of the vegetables (OR = 0.53; 95% CI, 0.33-0.85; p = 0.008), protein sources (OR = 0.40; 95% CI, 0.18-0.90, p = 0.03), and fruits (OR = 0.71; 95% CI, 0.49-1.04; p = 0.08) food groups were inversely associated with ALL. Among nutrients, consumption of provitamin A carotenoids (OR = 0.65, 95% CI, 0.42-1.01; p = 0.05), and the antioxidant glutathione (OR = 0.42; 95% CI, 0.16-1.10; p = 0.08) were inversely associated with ALL. CONCLUSION: Maternal dietary factors, specifically the consumption of vegetables, fruits, protein sources and related nutrients, may play a role in the etiology of ALL. Dietary carotenoids and glutathione appear to be important contributors to this effect.

Jensen MS, Toft G, Thulstrup AM, Bonde JP, Olsen J. 2007. Cryptorchidism according to maternal gestational smoking. Epidemiology 18:220-225.
Abstract: BACKGROUND: It has been suggested that maternal smoking during pregnancy is a risk factor for low sperm counts and testicular cancer in the offspring. Cryptorchidism is associated with both of these disorders and might share causal mechanisms. METHODS: We used prospective information on prenatal exposures and obstetric information on the birth of 5716 boys, collected from 1984 to 1987. During the 16-19 years of follow-up, 270 cases of cryptorchidism were diagnosed, and 185 of these boys underwent orchiopexy. RESULTS: Compared with nonsmokers, the adjusted risk ratio for being diagnosed with cryptorchidism was 1.1 (95% confidence interval = 0.8-1.6) if the mothers smoked 10-19 cigarettes/day and 2.3 (1.1-5.0) if they smoked > or = 20 cigarettes/day. The risk ratios for orchiopexy were 1.4 (0.9-2.1) and 1.8 (0.6-5.0), respectively. CONCLUSION: An excess risk of cryptorchidism was observed among sons of mothers who smoked 10 cigarettes or more per day during pregnancy. In recognition of the limited power of this study, the findings should be replicated in larger cohorts.

Ji BT, Shu XO, Linet MS, Zheng W, Wacholder S, Gao YT, Ying DM, Jin F. 1997. Paternal cigarette smoking and

the risk of childhood cancer among offspring of nonsmoking mothers. J Natl Cancer Inst 89:238-244.
Abstract: BACKGROUND: Cigarette smoking has been shown to increase oxidative DNA damage in human sperm cells. Assessment of the role of cigarette smoking in the etiology of childhood cancer has focused primarily on the effect of maternal smoking. Similar studies in relation to paternal smoking, however, have been inconclusive. Few studies have evaluated the effect of paternal smoking in the preconception period, and most of these could not disentangle the effects of paternal from maternal smoking. PURPOSE: We investigated the relationship of paternal smoking, particularly in the preconception period, with childhood cancer among offspring of the nonsmoking mothers. METHODS: We conducted a population-based, case-control study in Shanghai, People's Republic of China, where the prevalence of smoking is high among men but extremely low among women. The study included 642 childhood cancer case patients (<15 years of age) and their individually matched control subjects. Information concerning parental smoking, alcohol drinking, and other exposures of the index child was obtained by direct interview of both parents of the study subjects. Odds ratios (ORs), derived from conditional logistic regression models, were used to measure the association between paternal smoking and risk of childhood cancers. RESULTS AND CONCLUSIONS: Paternal preconception smoking was related to a significantly elevated risk of childhood cancers, particularly acute leukemia and lymphoma. The risks rose with increasing pack-years of paternal preconception smoking for acute lymphocytic leukemia (ALL) (P for trend = .01), lymphoma (P for trend = .07), and total cancer (P for trend = .006). Compared with children whose fathers had never smoked cigarettes, children whose fathers smoked more than five pack-years prior to their conception had adjusted ORs of 3.8 (95% confidence interval [CI] = 1.3-12.3) for ALL, 4.5 (95% CI = 1.2-16.8) for lymphoma, 2.7 (95% CI = 0.8-9.9) for brain tumors, and 1.7 (95% CI = 1.2-2.5) for all cancers combined. Statistically significant increased risks of cancer were restricted to children under the age of 5 years at diagnosis or those whose fathers had smoked during all of the 5 years prior to conception. IMPLICATIONS: Further studies are needed to confirm the association of paternal smoking with increased risk of cancer in offspring, to clarify the pattern of risks in relation to the timing of cigarette smoking, and to elucidate the biologic mechanism involved in predisposing the offspring to cancer. For example, it may be that paternal smoking induces prezygotic genetic damage that, in turn, acts as the predisposing factor.

Johnson CC, Annegers JF, Frankowski RF, Spitz MR, Buffler PA. 1987. Childhood nervous system tumors--An evaluation of the association with paternal occupational exposure to hydrocarbons. Am J Epidemiol 126:605-613.
Abstract: Paternal occupational exposures to hydrocarbons have been associated with childhood nervous system cancer, but study results have not been consistent. This population-based case-control study was designed to examine this association using a large sample size to increase the precision of risk estimates. The birth certificates of 499 children who died in Texas from intracranial and spinal cord tumors were compared with 998 control certificates randomly selected from all Texas live births. Information on parental job title and industry at the time of birth was obtained from the birth certificates. No significant associations were identified for the dichotomized variable of all hydrocarbon-related occupations combined, as variously defined in previous studies, or for most of the specific jobs affiliated with exposures to hydrocarbons. Significant, relatively stable odds ratios (OR) were found for printers and graphics arts workers (OR = 4.5; 95% confidence interval (CI) = 1.4-14.7) and chemical and petroleum workers with high exposure levels (OR = 3.0; CI = 1.1-8.5). A discussion of the biases involved in this type of study design is presented.

Johnson MD, Kenney N, Stoica A, Hilakivi-Clarke L, Singh B, Chepko G, Clarke R, Sholler PF, Lirio AA, Foss C, Reiter R, Trock B, Paik S, Martin MB. 2003. Cadmium mimics the in vivo effects of estrogen in the uterus and mammary gland. Nat Med 9:1081-1084.
Abstract: It has been suggested that environmental contaminants that mimic the effects of estrogen contribute to disruption of the reproductive systems of animals in the wild, and to the high incidence of hormone-related cancers and diseases in Western populations. Previous studies have shown that functionally, cadmium acts like steroidal estrogens in breast cancer cells as a result of its ability to form a high-affinity complex with the hormone binding domain of the estrogen receptor. The results of the present study show that cadmium also has potent estrogen-like activity in vivo. Exposure to cadmium increased uterine wet weight, promoted growth and development of the mammary glands and induced hormone-regulated genes in ovariectomized animals. In the uterus, the increase in wet weight was accompanied by

proliferation of the endometrium and induction of progesterone receptor (PgR) and complement component C3. In the mammary gland, cadmium promoted an increase in the formation of side branches and alveolar buds and the induction of casein, whey acidic protein, PgR and C3. In utero exposure to the metal also mimicked the effects of estrogens. Female offspring experienced an earlier onset of puberty and an increase in the epithelial area and the number of terminal end buds in the mammary gland.

Jorquera R, Castonguay A, Schuller HM. 1992. Effects of pregnancy and ethanol treatment on the metabolism of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone by hamster liver and lung microsomes. Drug Metabolism & Disposition 20:510-517.
Abstract: The tobacco-specific N-nitrosamino 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) is a potent carcinogen in adult Syrian golden hamsters and causes a high incidence of tumors in the offspring of hamsters after in utero exposure. We have investigated how pregnancy and/or ethanol treatment modulates the microsomal metabolism of NNK. Pregnancy decreased the alpha-carbon hydroxylation (activation) of NNK, whereas it increased both the pyridine N-oxidation and carbonyl reduction of NNK in liver microsomes, but not in the lung. Ethanol treatment of nonpregnant hamsters induced both the hepatic microsomal alpha-carbon hydroxylation and pyridine N-oxidation of NNK, but it increased only the formation of NNAL, the N-nitroso alcohol NNAL, in the lung. Ethanol-consuming pregnant hamsters showed no changes in the hepatic or pulmonary metabolism of NNK. In contrast, fetal hamsters exposed in utero to ethanol showed a general increase in the rate of metabolism of NNK. Immunoblot analyses demonstrated a reduction in the P-450IIE1 and total P450IIB1/IIB2 protein levels in the liver of pregnant hamsters, whereas a moderate increase of P-450IIB1 was observed in the lung. Moreover, ethanol treatment increased the amount of immunodetectable P-450IIE1 and total P-450IIB1/IIB2 in the liver of nonpregnant hamsters, but only the hepatic P-450IIE1 was induced by ethanol in pregnant hamsters. The P-450IIB1 protein levels were not affected by ethanol treatment in the lung of nonpregnant, pregnant, or fetal hamsters. In contrast, the fetal hepatic P-450IIE1 and P-450IIB1/IIB2 protein levels were increased by transplacental ethanol exposure. These results demonstrate that pregnancy and/or ethanol treatment may significantly alter the adult and fetal metabolism of NNK. The observed effects, such as suppression and/or induction of specific P-450 enzymes, could play important roles in the modulation of the transplacental carcinogenesis of NNK.

Jorquera R, Castonguay A, Schuller HM. 1993. Effect of tobacco-smoke condensate on the metabolism of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone by adult and fetal hamster microsomes. Drug Metabolism & Disposition 21:318-324.
Abstract: The tobacco-specific N-nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) is a potent carcinogen in Syrian golden hamsters exposed pre- or postnatally to NNK. NNK requires metabolic activation, mainly by the cytochrome P-450 monooxygenase system, to exert its carcinogenic activity. Along with carcinogens, tobacco smoke contains other biologically active substances such as enzyme inducers and inhibitors. In this study, we have investigated the effects of tobacco smoke condensate (TSC) on microsomal metabolism of NNK in hamsters. TSC was instilled intratracheally to nonpregnant and pregnant hamsters on days 12, 13, and 14 of gestation. Following euthanasia on day 15 of gestation, liver and lung microsomes from adult and fetal hamsters were prepared, and the metabolism of NNK was analyzed by HPLC. Although TSC tended to increase the formation of some alpha-carbon hydroxylation metabolites with liver microsomes from adult hamsters, none of the metabolic pathways of NNK showed a statistically significant increase or decrease caused by TSC exposure. Similarly, no significant alterations of NNK metabolism were observed with lung microsomes from TSC-treated adult hamsters, as well as with liver or lung microsomes from fetal hamsters exposed in utero to TSC. As shown by Western blotting analyses, the protein levels of the P-450 enzymes most likely involved in NNK metabolism (i.e. P-4S0IIB1 and P-450IIE1) remained almost unchanged in liver or lung microsomes from TSC-exposed hamsters. Interestingly, the P-450IIB1 protein content was increased in lung microsomes from TSC-treated pregnant hamsters, an effect likely related to the altered hormonal status of these animals. Although these results suggest a low or noninducing potential of crude TSC on enzymes involved in NNK metabolism, failure to cause a more significant induction could also arise from the relatively short exposure of hamsters to TSC. An insufficient placental transfer of enzyme inducers (or inhibitors) present in TSC into the fetal compartment might account for the lack of effect of TSC at the fetal hamster level.

Juckett DA, Rosenberg B. 1997. Time series analysis supporting the hypothesis that enhanced cosmic radiation

during germ cell formation can increase breast cancer mortality in germ cell cohorts. Int J Biometeorol 40:206-221.
Abstract: Techniques from cancer epidemiology and time series analysis were used to explore the hypothesis that cosmic radiation can induce germ cell changes leading to increases in future breast cancer mortality. A birth cohort time series for female breast cancer mortality was obtained using a model-independent, age-period-cohort analysis on age-specific mortality data for 1940-1990. The birth cohort series contained several oscillatory components, which were isolated and compared to the corresponding frequency components of a cosmic ray surrogate time series - Greenland ice-core Be-10 concentrations. A technique, referred to as component wavetrain alignment, was used to show that the breast cancer and cosmic ray oscillations were phase-locked approx. 25 years before the time of birth. This is consistent with the time of germ cell formation, which occurs during the fetal development stage of the preceding generation. Evidence is presented that the observable oscillations in the birth cohort series were residues of oscillations of much larger amplitude in the germ cell cohort, which were attenuated by the effect of the broad maternal age distribution. It is predicted that a minimum of 50% of breast cancer risk is associated with germ cell damage by cosmic radiation (priming event), which leads to the development of individuals with a higher risk of breast cancer. It is proposed that the priming event, by preceding other steps of carcinogenesis, works in concert with risk factor exposure during life. The priming event is consistent with epigenetic changes such as imprinting.

Kaatsch P, Kaletsch U, Meinert R, Miesner A, Hoisl M, Schuz J, Michaelis J. 1998. German case control study on childhood leukaemia - Basic considerations, methodology and summary of the results. Klin Padiatr 210:185-191.
Abstract: In order to explore potential risk factors of childhood leukaemia, a case control study was performed including all incident cases from 1992 to 1994. The study was based on the German Childhood Cancer Registry. It was restricted to cases from West Germany and extended retrospectively until 1980 for children who were living in regions covered by a previous incidence study on nuclear installations (21). The study was conducted in close correspondence with a preceding case control study in Lower Saxony (13). Results of this study and of others published in the literature were used to define explicit hypotheses for the present study. This paper presents the methodology of the study and gives an overview of some basic results. More detailed analyses of the investigated potential risk factors will be published elsewhere. The study comprised a total of 2358 cases (leukaemias, lymphomas, selected tumours) and 2588 controls. Response rates were 81% for cases and 67% for controls. For leukaemias, the main results regarding maternal factors, pregnancy, birth, immune system, ionising radiation, parental occupation and environmental factors were as follows: Positive associations were observed between childhood leukaemias and young maternal age at birth, high birth weight, tonsillectomy and use of pesticides. Some results suggest a protective effect for allergies and vaccinations. A negative association was observed with maternal smoking and childhood leukaemia. No associations were found with frequency of stillbirths, maternal alcohol consumption, parental exposure to benzene and use of wood preservatives. X-ray examinations in early childhood and parental radiation exposure did not show any consistent associations with leukaemia. Potential risk factors were not reported more frequently by cases and controls living in 114 communities with increased incidence rates. The strength of our study lies in the large number of participating families and in the population-based approach.

Kadan-Lottick NS, Kawashima T, Tomlinson G, Friedman DL, Yasui Y, Mertens AC, Robison LL, Strong LC. 2006. The Risk of Cancer in Twins: a Report From the Childhood Cancer Survivor Study. Pediatric Blood & Cancer 46:476-481.
Abstract: Background Twin concordance studies help evaluate the contribution of genetic factors in childhood cancers, but previous reports have primarily focused on leukemia because of the rarity of other malignancies. In the current report, a large cohort of childhood cancer survivors was used to: (1) describe twin concordance patterns for a range of cancers, (2) calculate the standardized incidence rates of cancers in twins, and (3) describe clinical features and outcomes of concordant twins. Procedure. Cancer family history was obtained on the 211 twins participating in the Childhood Cancer Survivor Study (CCSS) (14,352 participants surviving >= 5 years after a malignancy diagnosed at < 21 years during January 1, 1970-December 31, 1986) to calculate probandwise twin concordance rates and standardized incidence ratios (SIRs) using Surveillance, Epidemiology, and End-Results data. Results. Seven monozygotic twin pairs were concordant for cancer (six for leukemia, one for non-Hodgkin lymphoma), yielding probandwise

concordance rates of 9.5%, 20.7%, and 20.0% for all cancer, leukemia, and non-Hodgkin lymphoma (NHL), respectively. No concordance was observed among clizygotic twins or for dissimilar cancers. The SIR in monozygotic twins was 23.3 (95% CI-11.1-48.9) for all cancer, 112.4 (95% Cl - 50.5-250.1) for leukemia, and 40.5 (5.7-287.5) for NHL. Concordant twins were similar in age at diagnosis and vital status. Conclusions. Twin concordance for cancer is largely restricted to monozygotic twins and hematological malignancies, consistent with in utero malignancy transmission demonstrated by others. Our data support clinical monitoring of the twins of cases with hematological malignancies, and does not contribute evidence for genetic factors in other cancers. Pediatr Blood Cancer 2006;46:476-481. (c) 2005 Wiley-Liss, Inc.

Kaijser M, Akre O, Cnattingius S, Ekbom A. 2005. Preterm Birth, Low Birth Weight, and Risk for Esophageal Adenocarcinoma. Gastroenterology 128:607-609.
Abstract: Background & Aims: Gastroesophageal reflux is common among preterm infants and those who are small for gestational age, and it is a strong risk factor for adenocarcinoma of the esophagus. Methods: In a cohort of 3364 individuals born preterm and/or small for gestational age between 1925 and 1949, we assessed the long-term risk for esophageal cancer. Results: The standardized incidence rate ratio for esophageal adenocarcinoma was increased more than 7-fold in the cohort (standardized incidence rate ratio, 7.27; 95% confidence interval, 1.98-18.62), and a birth weight <2000 g was associated with a more than 11-fold increase in risk (standardized incidence rate ratio, 115; 95% confidence interval, 1.39-41.5). Conclusions: The associations may be spurious, but if not, they may be explained by increased gastroesophageal reflux during infancy among infants born preterm and/or small for gestational age.

Kaijser M, Granath F, Jacobsen G, Cnattingius S, Ekbom A. 2000. Maternal pregnancy estriol levels in relation to anamnestic and fetal anthropometric data. Epidemiology 11:315-319.
Abstract: In epidemiologic studies of perinatal exposures, birth weight has been proposed as a proxy variable for intrauterine estrogen exposure. To assess the validity of this assumption, we performed analyses of the association between estriol levels in 188 women in the 17th, 25th, 33rd, and 37th weeks of pregnancy and the birth weights of their infants. We found a general increase in mean cumulative estriol dose with increasing birth weight category throughout pregnancy. In late pregnancy, mean pregnancy estriol level of mothers of infants in the highest birth weight category (>4,500 gm) was twice as high as that of mothers of infants in the lowest category (<2,500 gm), 775 nmol/liter and 392 nmol/liter, respectively. Smoking lowered the maternal estriol levels by 20% or more throughout pregnancy. With smoking and birth weight included in a regression analysis, maternal age, placental weight, and infant ponderal index did not add any explanatory power to the model. Our data suggest that, on an aggregate level, birth weight can be used as a proxy variable of intrauterine estriol exposure.

Kajantie E, Osmond C, Barker DJP, Forsen T, Phillips DIW, Eriksson JG. 2005. Size at Birth as a Predictor of Mortality in Adulthood: a Follow-up of 350 000 Person-Years. Int J Epidemiol 34:655-663.
Abstract: Background Small body size at birth, as a marker of an adverse intrauterine environment, has recently emerged as an important risk factor for death from cardiovascular disease. Our aim was to study the relationship between small size at birth and all-cause and non-cardiovascular mortality, which has been poorly documented. Methods We studied 13 830 individuals born between 1924 and 1944 in Helsinki, Finland, at term as singletons. Dates and primary causes of death between 1971 and 1998 were obtained from the Finnish National Death Register. Results 1668 men and 671 women died during the follow-up at the mean age of 56.0 (range 26.7-74.9) years. Lower birthweight was associated with increased all-cause mortality in females (Odds ratio (OR) for 1 kg decrease in birthweight 1.25, 95% CI 1.05-1.49; P = 0.01) but not in males (OR 1.08; 0.96-1.19; P = 0.2; P for sex-birthweight interaction = 0.09). Similarly, short length at birth was a predictor of all-cause mortality in females (OR for I cm decrease 1.10; 1.05-1.15; P < 0.0001) but not in males (OR 1.01; 0.98-1.02; P = 0.4; P for sex-length at birth interaction = 0.002). Low birthweight and short length at birth predicted premature death in adulthood (< 55 years) in both sexes. In males, death from cardiovascular disease (n = 654) was associated with lower birthweight (OR for I kg decrease 1.33; 1.12-1.59; P = 0.001), and length (OR 1.05; 1.00-1.10; P = 0.03), and in females death from cardiovascular disease (n = 179) was associated with short length at birth (OR 1.11; 1.02-1.20; P = 0.02). In females death from non-cardiovascular diseases was predicted by low birthweight (OR 1.25; 1.01-1.54; P = 0.04) and short length at birth (OR 1.09; 1.03-1.15; P = 0.003) (n = 475), but not in males (n = 975; P for interaction = 0.02 and 0.004, respectively). Cancer-related death was associated with higher birthweight (OR for I kg decrease 0.76; 0.61-0.95; P = 0.02) and ponderal index (OR for I kg/m(3) increase 0.95; 0.91-

0.99; P = 0.01) in males (n = 361) but not in females (n = 269). Conclusions Small size at birth is associated with increased all-cause mortality at all ages among adult women but only with premature death in adult men. Among women death from both cardiovascular and non-cardiovascular causes is associated with small body size at birth. Among men an association between small birthsize and later cardiovascular disease is counterbalanced by an association between large body size at birth and later cancer.

Kaleva M, Toppari J. 2005. Cryptorchidism: an Indicator of Testicular Dysgenesis? Cell Tissue Res 322:167-172.
Abstract: Cryptorchidism is a common ailment of new-born boys, affecting 1-9% of full term boys at birth. Cryptorchidism has been associated with an increased risk of testicular cancer and reduced fertility. Aetiology of cryptorchidism remains obscure in most cases. Familial occurrence suggests a heritable susceptibility to cryptorchidism; however, seasonal variation in the incidence of cryptorchidism suggests that environmental factors also contribute. Testicular descent is characterised by androgen-dependent regression of cranial suspensory ligament and androgen + insulin-like hormone 3 (Insl3)-dependent gubernacular outgrowth. Even though hormonal defects are rarely detected in patients, both hypo-and hypergonadotropic hormonal patterns have been associated with cryptorchidism. Moreover, cryptorchid boys have significantly reduced serum androgen bioactivity at 3 months of age when normal boys have a strong surge of reproductive hormones. Defects in Ins13 action cause cryptorchidism in male mice, and over-expression in female mice causes ovarian descent. Defects in leucine-rich repeat-containing G-protein-coupled receptor 8/G-protein-coupled receptor affecting testis descent (LGR8/GREAT), the receptor for lnsl3, manifest the same phenotype as Ins13 knockout mutants. Even though mutations found in Ins13 and LGR8/GREAT genes are not a common cause of cryptorchidism in patients, it remains to be resolved whether low Ins13 levels during development are associated with cryptorchidism. Cryptorchidism may reflect foetal testicular dysgenesis that may later manifest as subfertility or testicular cancer.

Kardaun JWPF, Hayes RB, Pottern LM, Brown LM, Hoover RN. 1991. Testicular cancer in young men and parental occupation exposure . Am J Ind Med 20:219-227.
Abstract: To investigate whether parental occupation, especially during the 12 month period before birth, could be responsible for elevated rates of testicular cancer in young men, we used data from a case-control study of 223 cases and 212 controls conducted in the Washington, DC area. For all histologic types of testicular cancer combined, no significant associations were found for specific occupations, nor for the broad occupational categories of professional, other white collar, or blue collar workers. However, for cases with seminomas, excess risks were seen for those with parents employed in the following occupations: mothers in health-related occupations, O.R. = 4.6 (1.1-19.1), and fathers working in automobile service stations, O.R. = 4.0 (0.6-24.5), manufacturing industries, O.R. = 2.2 (1.0-4.2), and aircraft production and maintenance, O.R. = 5.3 (0.7-24.1). Although these findings for seminoma are intriguing, they do not explain the increase of testicular cancer in young men.

Kasprzak KS, Diwan BA, Rice JM, Misra M, Riggs CW, Olinski R, Dizdaroglu M. 1992. Nickel(II)-mediated oxidative DNA-base damage in renal and hepatic chromatin of pregnant rats and their fetuses - Possible relevance to carcinogenesis. Chem Res Toxicol 5:809-815.
Abstract: DNA base damage was studied in renal and hepatic chromatin of nickel(II)-injected pregnant female F344/NCr rats and their fetuses under conditions leading to initiation of sodium barbital-promotable renal tumors, but not liver tumors, in the male offspring. Pregnant rats were given a total of 90 or 180 mumol of nickel(II) acetate/kg body wt in a single ip dose on day 17 or in 2 or 4 ip doses between days 12 and 18 of gestation. Control rats received 180 mumol of sodium acetate/kg body wt. The animals were killed 24 or 48 h after the last injection. Chromatin was isolated from livers and kidneys from both adults and fetuses and analyzed by gas chromatography/mass spectrometry with selected ion monitoring. Eleven products derived from the purine and pyrimidine bases in DNA bases were identified and quantified. These were the following: 5-hydroxy-5-methylhydantoin,5-hydroxyhydantoin,5-(hydroxymethyl)uracil,c ytosine glycol, thymine glycol, 5,6-dihydroxycytosine, 4,6-diamino-5-formamidopyrimidine, 2,6-diamino-4-hydroxy-5-formamidopyrimidine,8-hydroxyadenine, 2-hydroxyadenine, and 8-hydroxyguanine (8-OH-Gua). Nickel(II) exposure increased the content of these products, especially those derived from purines, in both renal and hepatic chromatin of pregnant rats. The major difference between these two organs was the content of 8-OH-Gua, which increased greatly in the kidney but remained unchanged in the liver. In the corresponding fetal organs, the relative increases in 8-OH-Gua were comparable to the findings in adults. Fetal kidney DNA was relatively higher in pyrimidine-derived products (especially thymine glycol and 5-

hydroxyhydantoin) and lower in purine-derived products (except for 8-OH-Gua) than fetal hepatic DNA. No consistent dose effect of nickel(II) on the amounts of the DNA base products recovered from either organ was observed in either the dams or their fetuses. The products determined were typical hydroxyl radical-produced derivatives of DNA bases, suggesting a role for hydroxyl radical in the induction of their formation by nickel(II). Some of these base products have been shown previously to be promutagenic. Therefore, the present results indicate possible involvement of oxidative DNA base damage in the mechanism of nickel(II) carcinogenesis in the rat kidney. The prevalence of 8-OH-Gua in the kidney but not in the liver is consistent with the hypothesis that 8-OH-Gua is a tumor-initiating lesion in that organ. However, the complexity of the observed response to nickel(II) does not exclude possible roles for other DNA base products elevated by nickel(II) treatment, especially thymine glycol and 5-hydroxyhydantoin, in nickel(II)-induced carcinogenesis in the kidney.

Kato H, Yoshimoto Y, Schull WJ. 1989. Risk of cancer among children exposed to atomic bomb radiation in utero: a review. IARC Sci Publ :365-374.
Abstract: We have examined the risk for cancer (incidence) over a period of 40 years, 1945-1984, among 1829 persons exposed in utero to the atomic bombing of Hiroshima and Nagasaki. This report adds eight years of follow-up to a previous report which was confined to mortality. Only two cases of childhood cancer were observed among these survivors in the first 14 years of life; both had been heavily exposed. Subsequent cancers have all been of the adult type. Not only did these latter cancers occur earlier in persons exposed to greater than 0.30 Gy than in unexposed (0 Gy) but the incidence continues to increase, and the crude cumulative incidence rate 40 years after the bombing is 3.9-fold greater in persons exposed to greater than 0.30 Gy. In the observation period 1950-1984, the relative risk for cancer at 1 Gy, based on the absorbed dose to the mother's uterus as estimated by the Dosimetry System 1986 (DS86), is 3.77 with a 95% confidence interval of 1.14-13.48. For all persons exposed to greater than 0.01 Gy, the average excess risk per 10(4) person-year-Gy is 6.57 (0.07-14.49), and the estimated attributable risk is 40.9% (2.9-90.2%). These results, when viewed in the perspective of fetal doses, suggest that susceptibility to radiation-induced cancers is higher in survivors exposed prenatally than in those exposed postnatally (at least, those exposed as adults). However, definitive conclusions must await further follow-up studies.

Kato N, Shibuya H, Fukase M, Tamura G, Motoyama T. 2006. Involvement of adenomatous polyposis coli (APC) gene in testicular yolk sac tumor of infants. Hum Pathol 37:48-53.
Abstract: The pathogenesis of testicular yolk sac tumor (YST) of infants is still unclear. Infantile YSTs rarely show isochromosome 12p or aneuploidy, which are common in adult germ cell tumors. On the other hand, recent epigenetic studies suggest the involvement of some tumor suppressor genes, including the adenomatous polyposis coli (APC) gene. In the present study, we examined 10 infantile pure YSTs for mutation, allelic loss, promoter methylation, and protein expression status of the APC gene to evaluate whether the APC gene plays a significant role in the pathogenesis of infantile YSTs. Loss of heterozygosity at 5q21, where the APC gene is localized, was detected in at least 3 (30%) of the 9 YSTs examined. None of the 10 YSTs showed mutations. Promoter methylation was detected in 7 (70%) of the 10 YSTs; among 7 YSTs showing methylation, 3 YSTs also harbored loss of heterozygosity at 5q21. Immunohistochemically, 8 infantile YSTs did not express the APC protein, whereas 2 YSTs without showing APC methylation, as well as germ cells of normal infantile testes, expressed this protein in the cytoplasm. These data indicate that inactivation of the APC gene, by allelic loss and/or promoter methylation, is related to the occurrence of infantile YSTs. (c) 2006 Elsevier Inc. All rights reserved.

Kauffman SL. 1981 . Histogenesis of the papillary Clara cell adenoma. Am J Pathol 103: 174-180.
Abstract: Mouse lung adenomas have two characteristic histologic patterns, alveolar and bronchiolar or papillary. Differences in biologic behavior have been noted in tumors of different histologic form, in that papillary tumors were said to grow faster and become larger and possibly malignant. Progressive development from the alveolar to the papillary tumors has been proposed, involving a step-wise transformation from benign to malignant tumors. The author recently presented evidence from ultrastructural studies that the different histologic patterns were related to the cell of origin; the bronchiolar tumors consisted of Clara cells, while the alveolar tumors were made up of Type II alveolar epithelium. In the present study, designed to evaluate the histologic patterns of tumors during their development, multiple lung adenomas were induced in fetal Bagg-Webster mice on the sixteenth day of gestation by a single transplacental exposure to ethyl-nitrosourea. The animals were killed from the seventh postnatal day to 185

days of age; their tumors were counted and categorized histologically. Analysis of serial-step sections of the right lower lobes of young postnatal mice showed tumors with either an alveolar (37%) or a bronchiolar pattern (63%). Two forms of the latter were recognized, tubular and papillary. Between Day 80 and Day 186 papillary adenomas increased, tubular tumors decreased, and alveolar adenomas remained relatively constant in number. At the end of the 6-month observation period the overall proportion of alveolar and Clara cell tumors was similar to that found in the first 3 weeks of life. These data support the concept that alveolar and papillary tumors arise from different cell lines, the papillary tumors exclusively from Clara cells.

Kaye SA, Robison LL, Smithson WA, Gunderson P, King FL, Neglia JP. 1991. Maternal reproductive history and birth characteristics in childhood acute lymphoblastic-leukemia. Cancer 68:1351-1355.
Abstract: Using birth-registration data, a case-control study was done to investigate the possible associations of childhood acute lymphoblastic leukemia (ALL) with birth characteristics and maternal reproductive history. The data included cases born and diagnosed in Minnesota since 1969. Matched analyses were conducted using 337 cases and 1336 birth year-matched controls. There was a statistically significant increased odds of ALL for births to older (> 35 years) mothers (odds ratio (OR) = 2.14, 95% confidence interval (CI) = 1.28, 3.58), older fathers (OR = 1.62, 95% CI = 1.14, 2.30), mothers with at least a high school education (OR = 1.61, 95% Cl = 1.05, 2.48), and larger intervals (> 5 years) between the birth of the proband and the preceding sibling (OR = 1.86, 95% CI = 1.12, 3.09). The increased odds of ALL for birth by Caesarean section approached significance (OR = 1.42, P = 0.06). No overall association was found for: gender, race, paternal education, fetal-loss history, birth order, prenatal care history, pregnancy complications, inducement of labor, multiple birth, gestational age, or birth weight. Age at diagnosis was an important effect modifier of some analyses. For cases diagnosed before age 2 years, there was a 2.7-fold increased odds of ALL if the last pregnancy had resulted in a fetal loss (P = 0.03). For cases diagnosed before age 4 years, birth weight greater than 3800 g was associated with a significant 2.05-fold increased odds of ALL. These data strengthen the hypothesis that prenatal events may play a causative role in childhood ALL, particularly in those cases diagnosed at a younger age.

Keil DE, Warren DA, Jenny MJ, Eudaly JG, Smythe J , Peden-Adams MM. 2003. Immunological function in mice exposed to JP-8 jet fuel in utero. Toxicol Sci 76:347-356.
Abstract: Immunological parameters, host resistance, and thyroid hormones were evaluated in F1, mice exposed in utero to jet propulsion fuel-8 (JP-8). C57BL/6 pregnant dams (mated with C3H/HeJ males) were gavaged daily on gestation days 6-15 with JP-8 in a vehicle of olive oil at 0, 1000, or 2000 mg/kg. At weaning (3 weeks of age), no significant differences were observed in body, liver, spleen, or thymus weight, splenic and thymic cellularity, splenic CD4/CD8 lymphocyte subpopulations, or T-cell proliferation. Yet, lymphocytic proliferative responses to B-cell mitogens were suppressed in the 2000 mg/kg treatment group. In addition, thymic CD4-/CD8+ cells were significantly increased. By adulthood (8 weeks of age), lymphocyte proliferative responses and the alteration in thymic CD4-/CD8+ cells had returned to normal. However, splenic weight and thymic cellularity were altered, and the IgM plaque forming cell response was suppressed by 46% and 81% in the 1000 and 2000 mg/kg treatment groups, respectively. Furthermore, a 38% decrease was detected in the total T4 serum hormone level at 2000 mg/kg. In F-1 adults, no significant alterations were observed in natural killer cell activity, T-cell lymphocyte proliferation, bone marrow cellularity and proliferative responses, complete blood counts, peritoneal and splenic cellularity, liver, kidney, or thymus weight, macrophage phagocytosis or nitric oxide production, splenic CD4/CD8 lymphocyte subpopulations, or total T3 serum hormone levels. Host resistance models in treated F-1 adults demonstrated that immunological responses were normal after challenge with Listeria monocytogenes, but heightened susceptibility to B16F10 tumor challenge was seen at both treatment levels. This study demonstrates that prenatal exposure to JP-8 can target the developing murine fetus and result in impaired immune function and altered T-4 levels in adulthood.

Kelleher FC, Fennelly D, Rafferty M. 2006. Common critical pathways in embryogenesis and cancer. Acta Oncol 45:375-388.
Abstract: Cancer may arise because the developmental programs that create the dramatic alterations in form and structure in embryonic development are potentially corrupted. The cells in our bodies retain memories of these processes and cancer can occur later in life if imperfections occur in the fidelity of these pathways. This article is particularly interested in the phenomenon of epithelial to mesenchymal transition, which

occurs in embryogenesis. Also reviewed are the small molecules and pathways that are involved both in homeostasis in adult epithelium and embryogenesis in utero. There are five such pathways in particular selected for review in this article: the Wnt pathway, Hedgehog, Notch, PAR and Bone morphogenetic peptide/TGF beta. These are usually conserved throughout mammalian evolution. Though they have been arbitrarily separated in this article they are not exclusive from one another. Their pathologically altered expression is found especially frequently in childhood tumours where they may recapitulate their developmental role, and in tumours that resemble primitive precursor cells. These pathways are important for selecting cell fates, cellular rearrangements, cytological context and morphologic design in embryology as well as participating in epithelial function in adults.

Keller C, Nanda R, Shannon RL, Amit A, Kaplan AL. 2001. Concurrent primaries of vaginal clear cell adenocarcinoma and endometrial adenocarcinoma in a 39-year old woman with in utero diethylstilbestrol exposure. International Journal of Gynecological Cancer 11:247-250.
Abstract: Diethylstilbestrol (DES) was used widely in the late 1940s in an attempt to prevent adverse pregnancy outcomes. In 1971 the US Food and Drug Administration proscribed its use for pregnancy support secondary to its association with clear cell adenocarcinoma of the vagina. Several studies in animal models demonstrated an association with endometrial cancer among offspring following in utero DES exposure. To date, there is only one case report of endometrial cancer in women exposed to DES in utero. We present the first case, to our knowledge, of a woman exposed to DES in utero who presented with double primaries of clear cell cancer of the vagina concomitant with endometrial cancer.

Khan G, Penttinen P, Cabanes A, Foxworth A, Chezek A, Mastropole K, Yu B, Smeds A, Halttunen T, Good C, Makela S, Hilakivi-Clarke L. 2007. Maternal flaxseed diet during pregnancy or lactation increases female rat offspring's susceptibility to carcinogen-induced mammary tumorigenesis. Reprod Toxicol 23:397-406.
Abstract: Flaxseed contains several dietary components that have been linked to low breast cancer risk; i.e., n-3 polyunsaturated fatty acids (PUFAs), lignans and fiber, but it also contains detectable levels of cadmium, a heavy metal that activates the estrogen receptor (ER). Since estrogenic exposures early in life modify susceptibility to develop breast cancer, we wondered whether maternal dietary intake of 5% or 10% flaxseed during pregnancy or lactation (between postpartum days 5 and 25) might affect 7,12-dimethylbenz[a]anthracene (DMBA)-induced mammary tumorigenesis in the rat offspring. Our data indicated that both in utero and postnatal 5% and 10% flaxseed exposures shortened mammary tumor latency, and 10% flaxseed exposure increased tumor multiplicity, compared to the controls. Further, when assessed in 8-week-old rats, in utero 10% flaxseed exposure increased lobular ER-alpha protein levels, and both in utero and postnatal flaxseed exposures dose-dependently reduced ER-beta protein levels in the terminal end buds (TEBs) lobules and ducts. Exposures to flaxseed did not alter the number of TEBs or affect cell proliferation within the epithelial structures. In a separate group of immature rats that were fed 5% defatted flaxseed diet (flaxseed source different than in the diets fed to pregnant or lactating rats) for 7 days, cadmium exposure through the diet was six-fold higher than allowed for humans by World Health Organization, and cadmium significantly accumulated in the liver and kidneys of the rats. It remains to be determined whether the increased mammary cancer in rats exposed to flaxseed through a maternal diet in utero or lactation was caused by cadmium present in flaxseed, and whether the reduced mammary ER-beta content was causally linked to increased mammary cancer risk among the offspring.

Kheifets LI. 2001. Electric and magnetic field exposure and brain cancer: A review. Bioelectromagnetics :S120-S131.
Abstract: A number of epidemiologic studies have investigated exposure to electric and magnetic fields as a possible risk factor for brain cancer. Studies of residential exposure and childhood brain tumors have produced inconsistent results, regardless of the exposure metrics used; this outcome holds for both current and past estimates of magnetic fields, whether based on wire codes, distance, or measured or calculated fields. Most recent studies provide little evidence of an association. Studies examining use of appliances by children or by their mothers during pregnancy have also found an inconsistent pattern of risk, and recent studies of parental occupational exposure and childhood brain tumors suggest a lack of an association. Methodological issues may weaken these conclusions. In adults. residential studies have found little or no association between electric and magnetic field exposure and brain cancer. However, meta-analysis of occupational studies indicates a slightly higher risk for electrical workers. A comparative analysis of major studies of electric utility workers also suggests a small increase in brain cancer risk. Of note in these

analyses are large exposure misclassifications and the lack of a clear dose-response relationship in most individual studies. Bioelectromagnetics Supplement 5:S120-S131, 2001. (C) 2001 Wiley-Liss, Inc.

Kikuchi-Horie K, Kawakami E, Kamata M, Wada M, Hu JG, Nakagawa H, Ohara K, Watabe K, Oyanagi K. 2004. Distinctive expression of midkine in the repair period of rat brain during neurogenesis: Immunohistochemical and immunoelectron microscopic observations. J Neurosci Res 75:678-687.
Abstract: Distinctive expression of midkine (MK) was observed during the repair period of fetal brain neuroepithelium. MK is a heparin-binding growth factor that occurs as a product of a retinoic acid-inducible gene, and has a molecular mass of 13 kDa. MK expression was examined immunohistochemically and by immunoelectron microscopy during a period of repair in developing rat brain at the neurogenesis stage. Injury was induced in rat fetuses by transplacental administration of ethylnitrosourea (ENU) on embryonic Day (E) 16, and histological changes were examined up to 48 hr thereafter (i.e., up to E 18). In normal rat fetuses, MK immunostaining was observed in the cytoplasm and radial and horizontal processes of all cells in the neuroepithelium (NE), subventricular zone (SV), and intermediate zone (IMZ). In EN U-ad ministered brains, cells in the NE, SV, and IMZ were damaged severely, especially 16-24 hr after ENU administration. The remaining neuroepithelial cells, with the exception of those in M-phase and the tips of processes at the ventricular surface, were negative for MK immunohistochemistry 16-24 hr after the administration of ENU. Forty-eight hours after the administration, the cytoplasm and processes of cells in the NE, SV, and IMZ were MK immunopositive. Our previous data reported that the cell cycle of most NE cells is synchronized to the S-phase 16 hr after ENU administration and to the M-phase at 24 hr, and many NE cells were recovered 48 hr after ENU administration. The previous results taken together with the present results indicate that: (1) MK expression does not increase during the repair period of the NE, being different from adults; (2) MK expression is likely to be suppressed at S-phase according to the condition of the NE; and (3) MK expression is not essential for every cell cycle phase of NE cells; but (4) is necessary to maintain the M-phase of NE cells. (C) 2004 Wiley-Liss, Inc.

Kim AS, Eastmond DA, Preston RJ. 2006. Childhood acute lymphocytic leukemia and perspectives on risk assessment of early-life stage exposures. Mutation Research-Reviews in Mutation Research 613:138-160.
Abstract: Recognition that children are a potentially susceptible subpopulation has led to the development of child-specific sensitivity factors. Establishing reliable sensitivity factors in support of risk assessment of early-life stage exposures can be aided by evaluating studies that enhance our understanding both of the biological basis of disease processes and the potential role of environmental exposures in disease etiology. For these reasons, we evaluated childhood acute lymphocytic leukemia (ALL) studies from the point of view of mechanism and etiology. ALL is the most common form of childhood cancer proposed to result from a prenatal primary event and a postnatal second event. This multi-stage model is supported by the observation that chromosomal translocations/fusion genes (e.g., TEL-AML 1) involved in producing ALL are detected at birth (prenatal event), and a postnatal event (e.g., TEL deletion) is required for disease manifestation. It appears that a proportion of ALL cases are the result of environmental exposures, in which case preconceptional, prenatal, and postnatal stages are likely to be critical exposure windows. To this end, we recognized postnatal infection-related risk factors as potential candidates associated with the ALL second event. Additionally, we discuss use of ALL-associated fusion genes and genetic polymorphisms, together or separately, as indicators of ALL susceptibility and increased risk. The possibility of using fusion genes alone as biomarkers of response is also discussed because they can serve as predictors of key events in the development of a mode of action (a sequence of key events, starting with interaction of an agent with a cell, ultimately resulting in cancer formation) for particular environmental exposures. Furthermore, we discuss use of an initiated animal model for ALL, namely transgenic mice with TEL-AML 1 expression, for exploring mechanisms by which different classes of environmental exposures could be involved in inducing the postnatal step in ALL formation. (c) 2006 Elsevier B.V. All rights reserved.

Kish PE, Blaivas M, Strawderman M, Muraszko KM, Ross DA, Ross BD, Mcmahon G. 2001. Magnetic resonance imaging of ethyl-nitrosourea-induced rat gliomas: A model for experimental therapeutics of low-grade gliomas. J Neurooncol 53:243-257.
Abstract: Human low-grade gliomas represent a population of brain tumors that remain a therapeutic challenge. Preclinical evaluation of agents, to test their preventive or therapeutic efficacy in these tumors, requires the use of animal nobreak models. Spontaneous gliomas develop in models of chemically induced

carcinogenesis, such as in the transplacental N-ethyl-N-nitrosourea (ENU) rat model. However, without the ability to detect initial tumor formation, multiplicity or to measure growth rates, it is difficult to test compounds for their interventional or preventional capabilities. In this study Fisher-334 rats, treated transplacentally with ENU, underwent magnetic resonance imaging (MRI) examination in order to evaluate this approach for detection of tumor formation and growth. ENU-induced intracranial cerebral tumors were first observable in T2-weighted images beginning at 4 months of age and grew with a mean doubling time of 0.487 +/- 0.112 months. These tumors were found histologically to be predominately mixed gliomas. Two therapeutic interventions were evaluated using MRI, vitamin A (all-trans retinol palmitate, RP), as a chemopreventative agent and the anti-angiogenic drug SU-5416. RP was found to significantly delay the time to first tumor observation by one month (P = 0.05). No differences in rates of tumor formation or growth rates were observed between control and RP-treated groups. MRI studies of rats treated with SU-5416 resulted in reduction in tumor growth rates compared to matched controls. These results show that MRI can be used to provide novel information relating to the therapeutic efficacy of agents against the ENU-induced tumor model.

Kitamura T, Nishimura S, Sasahara K, Yoshida M, Ando J, Takahashi M, Shirai T, Maekawa A. 1999. Transplacental administration of diethylstilbestrol (DES) causes lesions in female reproductive organs of Donryu rats, including endometrial neoplasia. Cancer Lett 141:219-228.
Abstract: The effects of transplacental administration of diethylstilbestrol (DES) on female reproductive organs were investigated using Donryu rats. The animals were given subcutaneous injections of DES dissolved in olive oil at doses of 0.01 or 0.1 mg/kg on days 17 and 19 of gestation. In female offspring, clinical signs, body weights and estrous cycles were continuously assessed until all survivors were killed at month 18, A low mean litter size and shortening of period of pregnancy were recognized in the 0.1 mg/kg group. Disorder and/or suspension of the estrous cycle (so called persistent estrus) also appeared very early in the 0.1 mg/kg group. Macroscopically, the incidences of hypoplasia of the oviduct, cystic dilatation of the uterus and small size of the uterine cervix were higher in the 0.1 mg/kg group than those in the control group. Histologically, in the ovary, the incidence and degree of atrophy were increased in both 0.01 and 0.1 mg/kg groups. Ln the uterus, total incidences of endometrial hyperplasias were about the same in all groups. However, endometrial adenocarcinomas were dose-dependently increased in the treated groups, the incidence in the 0.1 mg/kg group being significant, compared to that in the control. In the vagina, mucification was more prominent in the treated animals, especially at the higher dose, but no tumors were observed. The present results indicate that prenatal exposure to DES can produce uterine adenocarcinomas in rats, as reported earlier for mice, although its carcinogenic activity is not so strong. Increase of endometrial adenocarcinoma incidence might depend on hormonal imbalance resulting from the ovarian atrophy due to transplacental treatment of DES. (C) 1999 Elsevier Science Ireland Ltd. All rights reserved.

Kneale GW, Stewart AM. 1980. Pre-conception X-rays and childhood cancers. Br J Cancer 41:222-226.
Abstract: An analysis of data collected during the course of the Oxford Survey of Childhood Cancer has shown that it is possible to recognize different facets of memory bias without systematic checking of individuals' records, and to make use of the biased data. The position of foetal irradiation in the aetiology of childhood cancers has been re-affirmed, but there is no support for the idea that exposure of parental gonads to diagnostic X-rays is conducive to cancer in the next generation.

Knight CH, Sorensen A. 2001. Windows in early mammary development: critical or not? Reproduction 122:337-45.
Abstract: Two critical windows in mammary development have been proposed. The first arises from observations in rodents that nutrition during fetal and neonatal periods can affect mammary ductular outgrowth, subsequent proliferative activity and, eventually, tumorigenesis, that is, potentially it could have a long-term effect on pathological outcome (breast cancer) in women. The second similarly involves early diet, but in this case the outcome is phenotypic, in that dairy heifers reared too quickly during the peripubertal period subsequently show impaired udder development and reduced milk yield persisting throughout life. Most mammary development occurs during pregnancy, but this period is usually thought of only in terms of the immediate outcome for the subsequent lactation; it is not believed to be a critical window, at least in terms of lifetime mammary productivity. This review examines the evidence underlying these various claims and attempts to define the mechanisms involved, and also considers whether derangements occurring earlier in life (prenatally) could also have long-term consequences for physiological or pathological mammary development.

Knight JA, Marrett LD. 1997. Parental occupational exposure and the risk of testicular cancer in Ontario. Journal of Occupational & Environmental Medicine 39:333-338.
Abstract: The incidence of germ cell testicular cancer is increasing, but its etiology remains largely unknown. Initiation may occur in a parental germ cell. In a case-control study in Ontario, jobs and industries of mothers (before and during pregnancy) and fathers (before pregnancy) of 343 case subjects and 524 control subjects were analyzed. Significantly increased risk was associated with fathers who were wood processors (odds ratio [OR] = 10.46; 95% confidence interval [CI], 1.20 to 91.14), metalworkers (OR = 3.28; 95% CI, 1.03 to 10.52), stationary engineers (OR = 1.05; 95% CI, 1.05 to 11.87), or employees of the food products (OR = 2.79; 95% CI, 1.34 to 5.79), metal products (OR = 5.77, 95% CI; 1.53 to 21.77), or food and beverage services (OR = 4.36; 95% CI, 1.50 to 12.63) industries. There was little evidence of risk associated with maternal employment. Paternal employment before conception in jobs related particularly to metal or food and beverages may be related to testicular cancer risk in sons.

Knox EG. 2005. Childhood cancers and atmospheric carcinogens. Journal of Epidemiology Community Health 59:101-105.
Abstract: STUDY OBJECTIVES: To retest previous findings that childhood cancers are probably initiated by prenatal exposures to combustion process gases and to volatile organic compounds (VOCs); and to identify specific chemical hazards. DESIGN: Birth and death addresses of fatal child cancers in Great Britain between 1966 and 1980, were linked with high local atmospheric emissions of different chemical species. Among migrant children, distances from each address to the nearest emissions "hotspot" were compared. Excesses of outward over inward migrations show an increased prenatal or early infancy risk. SETTING AND SUBJECTS: Maps of emissions of many different substances were published on the internet by the National Atmospheric Emissions Inventory and "hotspots" for 2001 were translated to map coordinates. Child cancer addresses were extracted from an earlier inquiry into the carcinogenic effects of obstetric radiographs; and their postcodes translated to map references. MAIN RESULTS: Significant birth proximity relative risks were found within 1.0 km of hotspots for carbon monoxide, PM10 particles, VOCs, nitrogen oxides, benzene, dioxins, 1,3-butadiene, and benz(a)pyrene. Calculated attributable risks showed that most child cancers and leukaemias are probably initiated by such exposures. CONCLUSIONS: Reported associations of cancer birth places with sites of industrial combustion, VOCs uses, and associated engine exhausts, are confirmed. Newly identified specific hazards include the known carcinogens 1,3-butadiene, dioxins, and benz(a)pyrene. The mother probably inhales these or related materials and passes them to the fetus across the placenta.

Knox EG. 2005. Oil combustion and childhood cancers. J Epidemiol Community Health 59:755-760.
Abstract: Study OBJECTIVES: To identify specific toxic atmospheric emissions and their industrial sources in Great Britain. To link them with each other and with the birth addresses of children dying from cancer. To identify specific causal agents and sources. DESIGN: Birth and death addresses of children dying from cancer were linked to emissions hotspots for specific chemicals: and to related source installations. Among those who moved house, distances from each address to the nearest hazard were compared. Relative excesses of close-to-hazard birth addresses showed high prenatal or early postnatal risks. Relative risks for individual and for combined exposures were measured.Setting and SUBJECTS: Atmospheric emissions hotspots (UK, 2001) published as maps on the internet, were converted to coordinates. Industrial sites were identified through trade directories and map inspections. Child cancer addresses for 1955-80 births were extracted from an earlier inquiry and their postcodes converted to map references. MAIN RESULTS: There were excess relative risks (RR) within 0.3 km of hotspots for carbon monoxide, PM10 particles, nitrogen oxides, 1,3-butadiene, benzene, dioxins, benzo(a)pyrene, and volatiles; and within 1.0 km of bus stations, hospitals, heavy transport centres, railways, and oil installations. Some excesses were attributable to mutual confounding, but 1,3-butadiene and carbon monoxide, mainly derived from engine exhausts, were powerful independent predictors. They were strongly reinforced when associated with bus stations, hospitals, railways, oil installations, and industrial transport centres; RR = 12.6 for joint <0.5 km exposure to bus stations and 1,3-butadiene. CONCLUSIONS: Childhood cancers are strongly determined by prenatal or early postnatal exposures to oil based combustion gases, especially from engine exhausts. 1,3-butadiene, a known carcinogen, may be directly causal.

Knox EG. Feb 2006. Roads, Railways, and Childhood Cancers. J Epidemiol Community Health 60:136-141.
Abstract: Study objectives: To locate geographical sources of engine exhaust emissions in Great Britain

and to link them with the birth addresses of children dying from cancer. To estimate the cancer initiating roles of nearby roads and railways and to measure effective ranges. Design: Birth and death addresses of all children born between 1955 and 1980 in Great Britain, and dying from leukaemia or other cancer during those years, were linked to locations of railway stations, bus stations, ferry terminals, railways, roads, canals, and rivers. Nearest distances to births and deaths were measured, and migration data relating to children who had moved house were analysed. Excesses of close to hazard birth addresses, compared with close to hazard death addresses, indicate a high prenatal or early postnatal risk of cancer initiation. Setting and subjects: Child cancer birth and death addresses and their map references were extracted from an earlier inquiry. Map references of putative hazards were downloaded from the Ordnance Survey national digital map of Great Britain. These data are recorded to a precision of one metre and have ground accuracies around 20 metres. Main results: Significant birth excesses were found within short distances of bus stations, railway stations, ferries, railways, and A, B class roads, with a relative risk of 2.1 within 100 m, tapering to neutral after 3.0 km. About 24% of child cancers were attributable to these joint birth proximities. Roads exerted the major effect. Conclusions: Child cancer initiations are strongly determined by prenatal or early postnatal exposures to engine exhaust gases, probably through maternal inhalation and accumulation of carcinogens over many months. The main active substance is probably 1,3-butadiene.

Kondo Y, Homma Y, Aso Y, Kakizoe T. 1994. Promotional effect of 2-generation exposure to a high-fat diet on prostate carcinogenesis in ACI/Seg rats. Cancer Res 54:6129-6132.
Abstract: Epidemiological studies have shown an association between a high-fat diet and a high mortality rate from breast, colon, and prostate cancer. However, the promotional effect of a high-fat diet on experimental carcinogenesis has not been fully established for the prostate. In this study, the effect on prostatic carcinogenesis of two-generation exposure to a high-fat diet was investigated using ACI/Seg rats, a strain with high incidence of spontaneous prostate cancer. A high-fat diet (20% corn oil) or a low-fat diet (5% corn oil) was given to mother rats during pregnancy and the newborn male rats were fed the same diets for 60 or 100 weeks after weaning. At 100 weeks, atypical hyperplasia and adenocarcinoma of the prostate were respectively found in 73.3% (11/15) and 20.0% (3/15) of the high-fat diet group and in 20.0% (3/15) acid 0% (0/15) of the low-fat diet group. There was a significant increase of atypical hyperplasia in the high-fat diet group ($P < 0.05$). The serum concentrations of sex hormones and the prostatic proliferative activity as measured by flow cytometry or bromodeoxyuridine labeling were not significantly affected by diet. These results showed that feeding a high-fat diet before conception and from the beginning of organogenesis had a marked promotional effect on the early stage of prostate carcinogenesis in rats.

Kossenko MM, Ostroumova Y, Akleyev A, Startsev N, Degteva M, Granath F, Hall P. 2000. Mortality in the offspring of individuals living along the radioactively contaminated Techa River: A descriptive analysis. Radiation & Environmental Biophysics 39:219-225.
Abstract: From 1949 onwards, radioactive waste was released into the Techa River in the southern Urals and the population living along the river was exposed to ionising radiation. Relocation of these people did not start until several years later, causing many individuals to be exposed to substantial doses from internal and external radiation. The identification and follow-up of the exposed individuals started more than 40 years ago and is still continuing. The Techa River offspring cohort (TROC) that has recently been established, comprises 10,459 children born to at least one parent living along the Techa River during the period 1950-1992. Of these children, 3,897 were born during the period of highest release, i.e. between 1950 and 1956 and might thus have been exposed in utero. A total of 1,103 individuals have since died mainly due to infectious and respiratory diseases, injury and poisoning. Only 25 cases were identified as having died of a malignant condition. The radioactive contamination of the Techa River in the southern Urals gives a unique possibility to study the adverse effects of protracted exposure to ionising radiation in a large well-described cohort. The Techa River offspring cohort will make it possible to study the effects on those exposed in utero or early in life and the follow-up of the cohort in the future is, therefore, of great importance. Comparisons with other cohorts of humans exposed early in life, will increase our knowledge in this field of research.

Kossoy G, Yarden G, Benhur H, Stark A, Madar Z, Zusman I. 2001. Effects of maternal feeding with different high fat diets on cellular composition of lymphoid compartments in the spleen and lymphoid infiltrates of mammary gland tumors in rat offspring. Experimental Oncology 23:114-118.
Abstract: We studied whether feeding pregnant female rats a 15% olive-oil diet affects the splenic

lymphoid system and synthesis of apoptosis-related proteins in offspring with chemically induced mammary glands tumors. Rat mothers were fed either a 7% corn-oil or a 15% olive-oil diet. Five-week-old offspring were exposed twice to the carcinogen, dimethylbenz(a)antracene, (10 mg/rat) and divided into 3 groups. Control group fed the 7% corn-oil control diet as their mothers. The first experimental group was fed a control diet (7% corn-oil) whereas their mothers were fed 15% olive-oil diet. The second experimental group was fed the same 15% olive-oil diet as their mothers. Results of experiments were studied 4 months later. The activity of lymphoid elements of the spleen and of tumors were studied using immunohistochemical methods for evaluating different types of lymphocytes (B and T cells) and the synthesis of apoptosis-related proteins (Fas ligand, p53, Bcl-2). Maternal feeding a diet rich in olive oil before and throughout pregnancy resulted in different manners in their offspring, and results were dependent on diets fed their progeny. In the spleen, feeding mothers the 15% olive-oil diet inhibited the reaction of zones producing the B and T lymphocytes in offspring fed a control diet. In offspring fed the 15% olive-oil diet, the activation of the lymphoid, system was seen. In tumors, activity of T cell killers/suppressors, macrophages and of the synthesis of Bcl-2 protein was found to manifest on their border. The positive correlation was found between the most parameters studied. The effect of maternal feeding a high-fat diet was manifested in a different manner in different parts of the spleen. In the white pulp, the effect was manifested only in an increase in the size of the germinal center due to the activation of production of B cells and was seen even in offspring fed a regular diet. In the red pulp, such effect was exhibited in an increase in the number of T cell killers and macrophages in both groups of progeny. The findings indicate that feeding mothers a diet high in olive oil concentrations retains its cancer-modulating role in offspring, but such a role is manifested in different manners, mostly at a cellular level.

Kozlowski R, Bouffler SD, Haines JW, Harrison JD, Cox R. 2001. In utero haemopoietic sensitivity to alpha, beta or X-irradiation in CBA/H mice. Int J Radiat Biol 77:805-815.
Abstract: Purpose: To assess in utero sensitivity to x-rays, alpha -emissions from plutonium-239 and beta -emissions from tritium in terms of induction of chromosomal aberration sin bone marrow cells. Materials and methods: CBA/H mice were exposed to a single dose of X-rays (0.5 Gy) on either day 7 or day 14 of pregnancy or given Pu-239 (100 kBq kg(-1)) by intraperitoneal injection on either day 6 or day 13. Tritium was administered to mice throughout pregnancy as either tritiated water, ad libitum in drinking ater (total intake averaged 130 MBq), or as homogenized tritiated cress, administered by gastric intubation (total 60 MBq). Irradiated and unexposed control mice and their offspring were sacrificed at 2-8 weeks after birth. Direct metaphase preparations from femoral bone marrow cells from mothers and offspring were used for G-band analysis. Results: The incidence of stable aberrations was significantly and similarly increased in neonatal and maternal marrow samples after exposure to X-rays, 239Pu or H-3. The estimated average bone absorbed doses from 239Pu in pregnant females were similar to the X-ray dose of 0.5 Gy, suggesting a low RBE for alpha -irradiation in adults. The similar levels of damage observed in neonates after X-irradiation and Pu-239 exposure are indicative of greater in utero sensitivity to alpha -irradiation since the overall estimated in utero alpha -particle doses to haemopoietic tissue were much lower. In utero doses from H-3 and corresponding maternal doses were around 0.5 Gy, showing no evidence of greater in utero sensitivity, no significant difference between the effects of the two forms of tritium, and were consistent with an RBE value of 1-2. Conclusions: Comparison of stable aberration yields in haemopoetic cells suggests a greater sensitivity to alpha -particles from Pu-239 than X-rays or beta -particles from H-3 for irradiation in utero but a low RBE value in adults.

Kristensen P, Andersen A, Irgens LM, Bye AS, Sundheim L. 1996 . Cancer in offspring of parents engaged in agricultural activities in Norway: incidence and risk factors in the farm environment. Int J Cancer 65:39-50.
Abstract: In this study of cancer in offspring we demonstrate that factors linked to horticulture and use of pesticides are associated with cancer at an early age, whereas factors in animal husbandry, in particular poultry farming, are associated with cancers in later childhood and young adulthood. Incident cancer was investigated in offspring born in 1952-1991 to parents identified as farm holders in agricultural censuses in Norway in 1969-1989. In the follow-up of 323,292 offspring for 5.7 million person-years, 1,275 incident cancers were identified in the Cancer Registry for 1965-1991. The standardized incidence for all cancers was equal to the total rural population of Norway, but cohort subjects had an excess incidence of nervous-system tumours and testicular cancers in certain regions and strata of time that could imply that specific risk factors were of importance. Classification of exposure indicators was based on information given at the agricultural censuses. Risk factors were found for brain tumours, in particular non-astrocytic

neuroepithelial tumours: for all ages, pig farming tripled the risk [rate ratio (RR), 3.11; 95% confidence interval (CI), 1.89-5.13]; indicators of pesticide use had an independent effect of the same magnitude in a dose-response fashion, strongest in children aged 0 to 14 years (RR, 3.37; 95% CI, 1.63-6.94). Horticulture and pesticide indicators were associated with all cancers at ages 0 to 4 years, Wilms' tumour, non-Hodgkin's lymphoma, eye cancer and neuroblastoma. Chicken farming was associated with some common cancers of adolescence, and was strongest for osteosarcoma and mixed cellular type of Hodgkin's disease. The main problem in this large cohort study is the crude exposure indicators available; the resulting misclassification is likely to bias any true association towards unity.

Kuijten RR, Bunin GR, Nass CC, Meadows AT. 1990. Gestational and familial risk factors for childhood astrocytoma: Results of a case-control study. Cancer Res 50:2608-2612.
Abstract: Gestational and familial risk factors were investigated for their association with astrocytoma, the most frequently occurring brain tumor in children. A case-control study of 163 matched pairs was performed. Cases under 15 years of age at diagnosis in 1980-1986 were identified through the tumor registries of 8 hospitals in Pennsylvania, New Jersey, and Delaware. Controls were selected by random digit dialing and were matched to cases for age, race, and telephone area code and exchange. Maternal antinausea medications increased the risk of childhood astrocytoma [OR (odds ratio) = 2.0, P = 0.04]. Cured meat consumption during pregnancy was more common among cases (OR = 1.9, P = 0.07), and a significant trend with increasing frequency of consumption was observed (P = 0.04). Results for gestational exposure to marijuana (OR = 2.8, P = 0.07) were of borderline significance. Gestational exposure to neurally active medications, alcohol, and tobacco were not risk factors. There was a significant trend for cases to be of higher birth weight (P = 0.03). Mental retardation (OR = 3.0, P = 0.04) and cancer (OR = 1.7, P = 0.02) in a relative of the child significantly increased the risk of astrocytoma. Significantly increased risks were observed for brain tumors in relatives of children 0-4 years of age at diagnosis (OR = 6/0, P = 0.04). A significant protective effect was observed for maternal history of miscarriage or stillbirth (OR = 0.5, P = 0.01). The results of this study suggest that some gestational and familial factors may increase the risk of childhood astrocytoma.

Kuijten RR, Bunin GR, Nass CC, Meadows AT. 1992. Parental occupation and childhood astrocytoma - Results of a case-control study. Cancer Res 52:782-786.
Abstract: Parental occupations were investigated as possible risk factors for astrocytoma, the most frequently occurring brain tumor in children. A case-control study of 163 pairs was performed. Cases under 15 years of age at diagnosis in 1980-1986 were identified through the tumor registries of eight hospitals in Pennsylvania, New Jersey, and Delaware. Controls were selected by random-digit dialing and were matched to cases on age, race, and telephone area code. Occupations before the child's conception, during the pregnancy, and after the child's birth were studied separately. We did not observe any strong associations. Significantly more fathers of cases were electrical or electronic repairmen, a subgroup of an occupational category previously associated with increased risk. An excess of case mothers employed as nurses was observed, which was significant for mothers of children diagnosed before 5 years of age. Elevated although not significant odds ratios were observed for some white collar and professional occupations in case parents; for paternal exposure to paint and paternal occupation in the paper and pulp mill industry, both in the period after the child's birth; and for maternal occupation as a hairdresser. The lack of strong associations may have resulted from low statistical power for some job groupings. Our study, unlike previous studies, focused on a single type of brain tumor: childhood astrocytoma. Thus our results suggest that some parental occupations associated with childhood brain tumors in previous studies may not be risk factors for childhood astrocytoma.

Kurmasheva RT, Peterson CA, Parham DM, Chen B, Mcdonald RE, Cooney CA. 2005. Upstream Cpg Island Methylation of the Pax3 Gene in Human Rhabdomyosarcomas. Pediatric Blood & Cancer 44:328-337.
Abstract: Background. Adult tumors can be characterized by hypermethylation of CpG islands associated with 5'-upstream and coding regions of specific genes. This hypermethylation can also be part of the aging process. In contrast, much less is known about gene hypermethylation in childhood cancers, where methylation changes are not part of the aging process but likely represent developmental dysregulation. PAX3 is an important gene in muscle development and muscle-producing neoplasms such as rhabdomyosarcomas. Procedures. We examined the methylation status of a PAX3 5'-CpG island in rhabdomyosarcoma subtypes and in normal fetal skeletal muscle. PAX3 methylation was analyzed in 15

embryonal rhabdomyosarcomas, 12 alveolar rhabdomyosarcomas, and in six normal skeletal muscle samples, using semiquantitative PCR analysis of DNA digested with methyl-sensitive restriction enzymes. Results.The CpG island in the upstream region of the human PAX3 gene was hypermethylated in the majority of ERMS examined (13 of 15 tumors, mean of 52% methylation), whereas most ARMS (9 of 12 tumors) and all normal muscle samples showed relative hypomethylation (both 18% mean methylation). Various CpG sites differ in contribution to overall PAX3 CpG island methylation, with methylation at a Haell site being inversely correlated with PAX3 expression. Conclusions. PAX3 CpG island methylation appears to distinguish embryonal subtype of rhabdomyosarcoma from alveolar, and methylation at certain sites within this CpG island is inversely correlated with PAX3 expression. In addition to exemplifying developmental dysregulation, methylation of PAX3 has potential in the development of an epigenetic profile for the diagnosis of rhabdomyosarcoma. (C) 2004 Wiley-Liss, Inc.

Kwan ML, Metayer C, Crouse V, Buffler PA. 2007. Maternal illness and drug/medication use during the period surrounding pregnancy and risk of childhood leukemia among offspring. Am J Epidemiol 165:27-35.
Abstract: Maternal illness and drug/medication use (prescription, over-the-counter, and illicit) during pregnancy might be related to childhood leukemia risk. These issues were evaluated using data (1995-2002) from the Northern California Childhood Leukemia Study. The authors selected 365 children under age 15 years who had been diagnosed with incident leukemia and birth certificate controls who were matched to them on age, sex, Hispanic ethnicity, and maternal race. Data on maternal illnesses and drug use from before pregnancy through breastfeeding were obtained by interview with the biologic mother and were analyzed by conditional logistic regression. Maternal history of influenza/pneumonia was associated with a statistically significant increased risk of acute lymphoblastic leukemia (ALL) in the offspring (odds ratio (OR) = 1.89, 95% confidence interval (CI): 1.24, 2.89), although the risk was nonsignificant for common ALL (OR = 1.41, 95% CI: 0.75, 2.63). A similar pattern of increased risk was found for history of sexually transmitted disease. Use of iron supplements was indicative of decreased ALL risk (OR = 0.67, 95% CI: 0.47, 0.94). Observing an increased risk of leukemia in children of mothers reporting a history of influenza/pneumonia and sexually transmitted disease around the time of pregnancy suggests that maternal infection might contribute to the etiology of leukemia. Furthermore, maternal iron supplement use may be protective against childhood leukemia.

Lacayo NJ, Di Martino JF, Wei MC, Dahl GV. 2006. CpG island methylator phenotype and childhood leukemia. Clin Cancer Res 12:4787-4789.

Lagiou P, Adami HO, Trichopoulos D. 2006. Early life diet and the risk for adult breast cancer. Nutrition and Cancer-an International Journal 56:158-161.
Abstract: A hypothesis postulating intrauterine and early life influences on the occurrence of breast cancer in adult life has received considerable support in the literature. We present alternative or complementary ways through which diet could affect breast cancer risk in this context. Emphasis is placed on evidence that reduced energy intake in early life is associated with smaller body size, which, in turn, constrains birth weight and subsequent development of offspring and is associated with reduced breast cancer risk.

Lagueux J, Pereg D, Ayotte P, Dewailly E, Poirier GG. 1999. Cytochrome p450 CYP1A1 enzyme activity and DNA adducts in placenta of women environmentally exposed to organochlorines. Environ Res 80:369-382.
Abstract: Organochlorine compounds bioaccumulate in fishing and hunting products included in the daily diet of many coastal populations. Prenatal and perinatal exposure to large doses of PCBs and PCDFs was shown to be deleterious on fetal and neonatal development, but information is scarce regarding possible effects of chronic low-dose exposure. This study investigates biomarkers of early effects in newborns from women exposed to organochlorines through the consumption of species from marine food chains, in two remote coastal regions of the province of Quebec (Canada). A CYP1A1-dependent enzyme activity (EROD) and DNA adducts were measured in placenta samples obtained from 30 women living on the Lower-North-Shore of the St. Lawrence River and 22 Inuit women from Nunavik (Arctic Quebec). These biomarkers were also assessed in 30 women from a Quebec urban center (Sept-Iles) as a reference group. Prenatal organochlorine exposure was determined by measuring these compounds in umbilical cord plasma. The amount of bulky polycyclic aromatic hydrocarbon (PAH)-related DNA adducts was significantly greater in the Lower-North-Shore group than in the reference group. Placental EROD activity and the amount of less bulky (OC-related) DNA adducts were significantly higher in the Nunavik group

than in the reference group. For both biomarkers, smoking was found to be an important confounding factor. Organochlorine exposure was significantly associated with EROD activity and DNA adduct levels when stratifying for smoking. This study confirms that CYP1A1 enzyme induction and DNA adducts in placental tissue constitute useful biomarkers of early effects induced by environmental exposure to organochlorines. (C) 1999 Academic Press.

Laitman CJ. 2002. DES exposure and the aging woman: mothers and daughters. Current Women's Health Reports 2:390-393.
Abstract: Diethylstilbestrol (DES), the first orally active artificial estrogen ever developed, was prescribed to several million pregnant women during the 1940s through the 1960s in the mistaken belief that it reduced the risk of miscarriage. In 1971, the US Food and Drug Administration contraindicated its use in pregnancy when DES was associated with the development of vaginal clear cell adenocarcinoma (CCA) in daughters exposed in utero. In daughters whose mothers took DES during pregnancy, the drug has been associated with congenital malformations of the reproductive tract, fertility problems, a possible increased risk of cervical carcinoma in situ, and a presumed lifetime risk of vaginal and cervical CCA. DES mothers have an increased risk of breast cancer (RR = 1.3). DES sons have an increased prevalence of urogenital anomalies, and a possible increased risk of testicular cancer.

Lamartiniere CA, Zhao YX, Fritz WA. 2000. Genistein: Mammary cancer chemoprevention, *in vivo* mechanisms of action, potential for toxicity, and bioavailability in rats. Journal of Women's Cancer 2:11-19.
Abstract: Asian women consuming a traditional diet high in soy have a low incidence of breast cancer. However, when Asians emigrate to the U.S., future generations of Asians lose this protection. We have hypothesized that early exposure to genistein, a major component of soy, could have a permanent protective effect against breast cancer. To test this hypothesis, we have exposed Sprague-Dawley CD rats to neonatal and prepubertal injection of pharmacological doses of genistein, and perinatally to physiological doses of genistein in the diet. These treatments resulted in reduced number of dimethylbenz[a]antracene (DMBA)- induced mammary tumors in the adults. The initial effect of early exposure to genistein was to up-regulate the EGF-signaling pathway and to down-regulate TGF-beta expression. These actions enhanced cell differentiation, resulting in terminal ductal structures and cells that in adulthood are now characterized as having a reduced EGF-signaling pathway. These differentiated cells are less proliferative and less susceptible to carcinogenesis. Bioavailability studies revealed that 24 and 250 mg genistein/kg diet resulted in blood total genistein concentrations of 54 to 1810 pmol/ml in prepubertal rats. These "frame" the 276 pmol total genistein/ml concentration found in Asians eating a traditional diet high in soy, and are lower than blood genistein concentrations in babies fed soy infant formula. Genistein is demonstrated to be bioavailable to the mammary gland in postnatal rats. Prenatal genistein in the diet (250 mg/kg) did not protect against DMBA-induced mammary cancer or result in significant toxicity to the F1 female reproductive tract. Prenatal exposure to genistein via the diet yielded only th e43-pmol total genistein/ml blood in the fetus. We conclude that in utero exposure to genistein via the diet did not protect against mammary cancer or cause toxicity because conjugated genistein does not cross the placental barrier. Our results demonstrate that postnatal exposure of rats to physiological concentrations of genistein in the diet is a safe and effective means of programming against chemically induced mammary cancer.

Landrigan P, Garg A, Droller DBJ. 2003. Assessing the effects of endocrine disruptors in the National Children's Study. Environ Health Perspect 111:1678-1682.
Abstract: Children are uniquely vulnerable to toxic chemicals in the environment. Among the environmental toxicants to which children are at risk of exposure are endocrine disruptors (EDs), chemicals that have the capacity to interfere with hormonal signaling systems. EDs may alter feedback loops in the brain, pituitary, gonads, thyroid and other components of the endocrine system. They can affect development. Effects of EDs have been described in wildlife populations, in animals exposed experimentally, and to a more limited extent in humans. Mechanisms of action of EDs are increasingly being elucidated, and genetic polymorphisms that convey differential susceptibility to EDs are beginning to be explored. It is hypothesized that *in utero* and early childhood exposures to EDs may be responsible, at least in part, for decreases in semen quality; increasing incidence of congenital malformations of the reproductive organs, such as hypospadias; increasing incidence of testicular cancer; and acceleration of onset of puberty in females. The National Children’s Study (NCS) will provide a unique opportunity to test

the validity of these hypotheses in the context of a large prospective multi-year epidemiologic investigation. It will be essential in the NCS to assess exposures to a range of putative natural and synthetic EDs, to assess outcomes possibly due to ED exposure, to examine the potential interplay between EDs and genetic polymorphisms, and to seek links between ED exposures in early life and endocrine, reproductive, neurobehavioral and other outcomes throughout the life-span.

Lantos PL. 1972 . The fine structure of periventricular pleomorphic gliomas induced transplacentally by N-ethyl-N-nitrosourea in BD-IX rats. With a note on their origin. J Neurol Sci 17:443-460.

Lantos PL, Cox DJ. 1976 . The origin of experimental brain tumours: a sequential study. Experientia 32:1467-1468.
Abstract: A sequential study of rat brains treated transplacetally with the neurotropic carcinogen ethylnitrosourea reveals small foci of cell proliferations from the age of 8 weeks. These lesions consist mainly of undifferentiated cells of the subependymal plate type. They occur in those areas in which gliomas develop and represent the earliest, histologically detectable, changes in the development of brain tumours.

Larsen E, Reite K, Nesse G, Gran C, Seeberg E, Klungland A. 2006. Repair and mutagenesis at oxidized DNA lesions in the developing brain of wild-type and Ogg1(-/-) mice. Oncogene 25:2425-2432.
Abstract: OGG1 (8-oxoguanine DNA glycosylase-1) is one of the main DNA glycosylases present in mammalian cells. The enzyme removes 7,8-dihydro-8-oxoguanine (8-oxoG) lesions, believed to be the most important oxidized lesions due to their relatively high incidence and their miscoding properties. This study shows that in prenatal mice brains the repair capacity for 8-oxoG is 5-10-fold higher than in adult mice brains. Western blot analysis and repair activity in extracts from Ogg1(-/-) mice revealed that OGG1 was responsible for the efficient 8-oxoG removal from prenatal mice. To investigate how OGG1 protects against oxidative stress-induced mutagenesis, pregnant Big Blue/wild-type and Big Blue/Ogg1(-/-) mice were exposed to nontoxic doses of gamma radiation. A 2.5-fold increase in the mutation frequency in Ogg1(-/-) mouse brains was obtained by exposure to 3.5 Gy at day 19 postfertilization. This was largely due to GC to TA transversions, believed to originate from 8-oxoG mispairing with A during replication. Furthermore, rapid cell divisions seemed to be required for fixation of mutations, as a similar dose of radiation did not increase the mutation frequency, or the frequency of GC to TA transversion, in the adult brain.

Larson PS, Ungarelli RA, De Las Morenas A, Cupples LA, Rowlings K, Palmer JR, Rosenberg CL. 2006. In utero exposure to diethylstilbestrol (DES) does not increase genomic instability in normal or neoplastic breast epithelium. Cancer 107:2122-2126.
Abstract: BACKGROUND. in 1992, the National Cancer Institute (NCI) established the Continuation of Follow-Up of DES-Exposed Cohorts to study the long-term health effects of exposure to diethylstilbestrol (DES). Genetic effects on human breast tissue have not been examined. The authors investigated whether breast tissue of women exposed in utero to DES might exhibit the genetic abnormalities that characterize other DES-associated tumors. METHODS. Subjects enrolled in the NCI Cohort were queried about breast biopsies or breast cancer diagnoses. Available tissue blocks were obtained for invasive cancers (IC), in situ cancers (CIS), or atypical hyperplasia (AH). Exposure status was blinded, lesions were microdissected, and their DNA was analyzed for microsatellite instability (MI) and loss of heterozygosity (LOH), or allele imbalance (AI), at 20 markers on 9 chromosome arms. RESULTS. From 31 subjects (22 exposed, 9 unexposed), 273 samples were analyzed (167 normal epithelium, 16 AH, 30 CIS, 60 IC). Exposed and unexposed subjects exhibited no differences in breast cancer risk factors or demographic characteristics, except for age at diagnosis (exposed vs. unexposed: 43.2 vs. 48.8 years of age, P = .02). The authors found that MI was rare and that AI was common, with frequencies consistent with previous reports. The global age-adjusted relative rate (RR) of AI was 1.3, 95% CI = 0.8-2.4. No statistically significant associations were observed after adjustment for risk factors or after stratification by histology or by chromosome arm. CONCLUSION. In utero DES exposure does not appear to significantly increase genomic instability in breast epithelium, as measured by MI and AI. Breast tissue may respond differently from that of the reproductive tract to in utero DES exposure. Consequences of in utero DES exposure on the breast may be mediated by proliferative effects of estrogen.

Laska MJ, Nexo BA, Vistisen K, Poulsen HE, Loft S, Vogel U. 2005. Polymorphisms in Rai and in Genes of Nucleotide and Base Excision Repair Are Not Associated With Risk of Testicular Cancer. Cancer Lett

225:245-251.
Abstract: Testicular cancer has been suggested to be primed in utero and there is familiar occurrence, particularly brothers and sons of men with testicular cancer have increased risk. Although no specific causative genotoxic agents have been identified, variations in DNA repair capacity could be associated with the risk of testicular cancer. A case-control study of 184 testicular cancer cases and 194 population-based controls living in the Copenhagen Greater Area in Denmark was performed. We found that neither polymorphisms in several DNA repair genes nor alleles of several polymorphisms in the chromosomal of region 19q13.2-3, encompassing the genes ASE, ERCC1, RAI and XPD, were associated with risk of testicular cancer in Danish patients. This is in contrast to other cancers, where we reported strong associations between polymorphisms in ERCC1, ASE and RAI and occurrence of basal cell carcinoma, breast cancer and lung. To our knowledge this is the first study of DNA repair gene polymorphisms and risk of testicular cancer. (c) 2005 Elsevier Ireland Ltd. All rights reserved.

Lauver D, Nelles KK, Hanson K. 2005. The Health Effects of Diethylstilbestrol Revisited. Jognn-Journal of Obstetric Gynecologic and Neonatal Nursing 34:494-499.
Abstract: Although diethylstilbestrol has not been prescribed commonly for more than 25 years, its effects on the health of exposed persons are still important. In this article, we summarize current information about the major health effects of diethylstilbestrol exposure and delineate implications for nurses. Nurses can help to identify persons at risk from prior diethylstilbestrol exposure, facilitate comprehensive assessments of persons exposed to diethylstilbestrol, and share current information about diethylstilbestrol.

Lee K, Johnson VJ, Blakley BR. 2000. The effect of exposure to a commercial 2,4-D herbicide formulation during gestation on urethan-induced lung adenoma formation in CD-1 mice. Veterinary & Human Toxicology 42:129-132.
Abstract: Female CD-1 mice were exposed to a commercial amine Formulation of 2.4-dichlorophenoxyacetic acid (2,4-D) on days 6-16 of gestation in drinking water at concentrations ranging from 0 to 1.0% of the formulated product, equivalent to approximately 0 650 mg/kg/d expressed as the amine derivative. The effect of 2,4-D on urethan-induced pulmonary adenoma formation was evaluated in female offspring 19 w after birth. Urethan-induced sleeping times observed following ip injection of 1.5 mg urethran/g bw 7 w after birth were not altered by 2,4-D (0 = 0.10), indicating that 2,4-D did not affect the rate of urethan elimination. 2,4-D exposure did not affect the number of tumors produced (0 = 0.58), but did reduce the mean tumor diameter in the highest dose group ($p < 0.01$). This minor antineoplastic activity of 2,4-D may be related, in part, to inhibitory effects of 2.4-D on various enzymatic or metabolic pathways, essential for cellular growth and tissue development. Since exposure to 2,4-D during pregnancy had little impact of tumor production, it is unlikely that persistent alteration to developing immune cells involved in the cell-mediated immunosurveillance mechanisms occurred. The subtle alteration in tumor size and the mild impairment of growth in the offspring were observed almost exclusively in the highest treatment group. Since this level of exposure is well in excess of those associated with normal application of 2,4-D, the hazard to non-target mammalian populations appears minimal.

Lee Y, Miller HL, Russell HR, Boyd K, Curran T, Mckinnon PJ. 2006. Patched2 modulates tumorigenesis in Patched1 heterozygous mice. Cancer Res 66:6964-6971.
Abstract: The sonic hedgehog (SHH) receptor Patched 1 (Ptch1) is critical for embryonic development, and its loss is linked to tumorigenesis. Germ line inactivation of one copy of Ptch1 predisposes to basal cell carcinoma and medulloblastoma in mouse and man. In many cases, medulloblastoma arising from perturbations of Ptch1 function leads to a concomitant up-regulation of a highly similar gene, Patched2 (Ptch2). As increased expression of Ptch2 is associated with medulloblastoma and other tumors, we investigated the role of Ptch2 in tumor suppression by generating Ptch2-deficient mice. In striking contrast to Ptch1(-/-) mice, Ptch2(-/-) animals were born alive and showed no obvious defects and were not cancer prone. However, loss of Ptch2 markedly affected tumor formation in combination with Ptch1 haploinsufficiency. Ptch1(+/-)Ptch2(-/-) and Ptch(+/1)Ptch2(+/-) animals showed a higher incidence of tumors and a broader spectrum of tumor types compared with Ptch1(+/-) animals. Therefore, Ptch2 modulates tumorigenesis associated with Ptch1 haploinsufficiency.

Lepourcelet M, Tou LQ, Cai L, Sawada J, Lazar AJF , Glickman JN, Williamson JA, Everett AD, Redston M, Fox EA, Nakatani Y, Shivdasani RA. 2005. Insights Into Developmental Mechanisms and Cancers in the

Mammalian Intestine Derived From Serial Analysis of Gene Expression and Study of the Hepatoma-Derived Growth Factor (Hdgf). Development 132:415-427.
Abstract: The vertebrate intestine is a model for investigating inductive cellular interactions and the roles of epithelial stem cells in tissue regeneration, and for understanding parallels between development and cancer. We have used serial analysis of gene expression to measure transcript levels across stages in mouse intestine development. The data (http://genome.dfci.harvard.edu/GutSAGE) identify novel differentiation products, potential effectors of epithelial-mesenchymal interactions, and candidate markers and regulators of intestinal epithelium. Transcripts that decline significantly during intestine development frequently are absent from the adult gut. We show that a significant proportion of such genes may be reactivated in human colon cancers. As an example, hepatoma-derived growth factor (HDGF) mRNA is expressed prominently in early gut tissue, with substantially reduced levels after villous epithelial differentiation. HDGF expression is dramatically increased in human colorectal cancers, especially in tumors proficient in DNA mismatch repair, and thus represents a novel marker for a distinctive tumor subtype. HDGF overexpression in fetal intestine explants inhibits maturation, suggesting a role in epithelial differentiation. To investigate the molecular basis for HDGF functions, we isolated components of a nuclear HDGF complex, including heterogeneous nuclear ribonucleoproteins implicated in processing RNA. These genes are regulated in tandem with HDGF during intestine development and one factor, TLS/Fus, is commonly overexpressed in colon cancers. Tumor expression of fetal genes may underlie similarities between developing and malignant tissues, such as self-renewal, invasion and angiogenesis. Our findings also advance understanding of HDGF functions and implicate this developmentally regulated gene in RNA metabolic pathways that may influence malignant behaviors in colorectal cancer.

Lightfoot T. 2005. Aetiology of Childhood Leukemia. Bioelectromagnetics 26:S5-S11.
Abstract: Leukemia is the most common cancer to affect children, accounting for approximately a third of all childhood cancers. The major morphological subtypes of leukemia, acute lymphoblastic leukemia (ALL), and acute myeloblastic leukemia (AML), are characterized by chromosomal translocations involving over 200 genes including mixed lineage leukemia (MLL), TEL, and AML1. Chromosomal translocations involving the MLL gene at 11q23 are a common feature of infant acute leukemia, found in up to 80% of all cases, and there is strong evidence that rearrangements involving the MLL gene or the TEL-AML1 gene fusion can originate in utero. As with most other cancers, the mechanism by which leukemia arises is likely to involve gene-environment interactions. Accordingly, it is important to identify exposures that cause DNA damage and induce chromosome breaks which are inadequately repaired, ultimately leading to the initiation and disease progression. Exposures acting before birth and early in life has long been thought to be important determinants of leukemia, and the list of suspected chemical, physical, and biological agents continues to increase. Unfortunately, the evidence regarding the majority of suggested exposures is limited and often contradictory, and there are areas, which clearly warrant further investigation in order to further our understanding of the aetiology of childhood leukemia.

Lightfoot T, Bunch K, Ansell P, Murphy M. 2005. Ovulation Induction, Assisted Conception and Childhood Cancer. Eur J Cancer 41:715-724.
Abstract: Rapid advances have been made in the treatment of infertility over the last 30 years following the introduction of in vitro fertilisation and intracytoplasmic sperm injection. Whilst effects of assisted reproductive technology (ART) on birth outcomes are well documented little is known about effects on child health after the neonatal period. Childhood cancer is one area warranting further examination. The hypothesis that cancer in children may be initiated during early fetal development means that events leading up to and around conception may be important. Whilst the few large-scale epidemiological studies that have looked at childhood cancer incidence following ART have failed to find any significant increased risk, some case-control studies have reported an increased risk of specific cancers. However, it is important not to over interpret these findings as the reason for the infertility may be the predisposing factor, rather than the procedure itself. Recent recommendations by the UK's National Health Service to offer intra-uterine insemination and one free treatment cycle for infertile couples will result in increasing numbers of children born following ART. More detailed investigations that include larger numbers plus sufficient follow-up periods and information on the underlying causes of the infertility are needed since long term outcomes for these children, in particular the risk of developing cancer, remain largely unknown. (c) 2004 Elsevier Ltd. All rights reserved.

Lightfoot TJ, Roman E. 2004. Causes of childhood leukaemia and lymphoma. Toxicology & Applied Pharmacology 199:104-17.
Abstract: Childhood cancer is rare comprising less than 1% of all malignancies diagnosed each year in developed countries. Leukaemia is the commonest form of cancer in children accounting for around a third of all childhood cancer, with acute lymphoblastic leukaemia (ALL) being the most prevalent. Biologically specific subtypes of ALL and acute myeloblastic leukaemia (AML), the other major morphological type of childhood leukaemia, are characterised by chromosomal changes. Whilst over 200 genes have been associated with chromosomal translocations, to date, only MLL, TEL, and AML1 have been linked with childhood leukaemia. Interestingly, there is increasing evidence to support the theory that gene rearrangements such as these may originate in utero. As with many other human diseases, both genetic and environmental factors have been implicated in the aetiology of the disease. Although much has been documented with regard to diet, smoking, alcohol consumption and recreational and prescription drug use during pregnancy, there is no consistent evidence to support a link with any of these factors and childhood leukaemia. However, findings from studies investigating prenatal and early life exposures are often based on small numbers of cases as both the type of cancer and exposure are rare. Furthermore, accurate information relating to past exposures can be difficult to obtain and is often reliant on self-reporting. To further our understanding of the aetiology of childhood leukaemia and lymphoma, there are areas which clearly warrant investigation. These include collection of parental dietary folate data combined with genetic analysis of the folate related genes, in utero exposure to DNA topoisomerase II inhibitors, and the possible effects of assisted reproduction technology on disease susceptibility.

Likhachev A, Anisimov V, Loktionov A, Zabezhinski M, Napalkov N, Tomatis L. 1989. Increased tumour incidence and skin tumour promotion in two generations of descendants of 7,12-dimethylbenz[a]anthracene-treated pregnant mice. IARC Scientific Publications Publ :81-92.
Abstract: Many experiments suggest the possibility of hereditary transmission of a predisposition to developing cancer. If this is the case, the progeny of animals exposed to carcinogens during embryogenesis should bear initiated cells. In order to examine this possibility, offspring of mice exposed to 7,12-dimethyl-benz[a]anthracene in utero were treated cutaneously with a tumour promoter, 12-O-tetradecanoylphorbol-13-acetate. This treatment resulted in the development of skin tumours, i.e., papillomas and carcinomas. Moreover, various tumours also developed in many internal organs, and particularly in the lung. These findings suggest that exposure to carcinogens may not only increase cancer risk in subsequent generations, but also considerably reinforce sensitivity to tumour-promoting factors, which by themselves may pose no threat to an unexposed population.

Lin LM, Sciubba DM, Gallia GL, Sosnowski J, Weingart JD. 2007. Diethylstilbestrol (DES)-induced clear cell adenocarcinoma of the vagina metastasizing to the brain. Gynecol Oncol 105:273-276.
Abstract: Background. Primary vaginal clear cell adenocarcinoma (CCA) is a rare gynecological malignancy occurring predominantly in young females with a history of diethylstilbestrol exposure in utero. Vaginal CCA commonly metastasizes to the lungs and the supraclavicular lymph nodes; however we present a rare case of diethylstilbestrol-induced vaginal CCA with cerebral metastases. Case description. A 43-year-old woman with prenatal diethylstilbestrol exposure and history of vaginal CCA treatment 8 years prior to current presentation noted new onset headache and dizziness. MRI showed an enhancing mass in the right frontal lobe. Histopathology was consistent with CCA. Conclusions. This case report highlights the necessity of close extended follow-up in patients with a history of vaginal CCA and demonstrates the potential for spread of primary vaginal CCA to the brain. (c) 2007 Elsevier Inc. All rights reserved.

Linet MS, Gridley G, Cnattingius S, Nicholson HS, Martinsson U, Glimelius B, Adami HO, Zack M. 1996. Maternal and perinatal risk factors for childhood brain tumors (Sweden). Cancer Causes & Control 7:437-448.
Abstract: Childhood brain tumors (CBT) include a diversity of rare neoplasms of largely unknown etiology. To assess possible maternal and perinatal risk factors for CBT according to subtype, we carried out a nested (within Swedish birth-cohorts, 1973-89) case-control study, utilizing data from the nationwide Birth Registry. We ascertained incident brain tumor cases through linkage of the nationwide Birth and Cancer Registries and randomly selected five living controls from the former, matching each case on gender and birthdate. There were 570 CBT cases, including 205 low grade astrocytomas, 58 high grade astrocytomas, 93 medulloblastomas, 54 ependymomas, and 160 'others.' Risks for all brain tumors combined were

elevated in relation to: (i) three maternal exposures-oral contraceptives prior to conception (odds ratios [OR] = 1.6, 95 percent confidence interval [CI] = 1.0-2.8), use of narcotics (OR = 1.3, CI = 1.0-1.6), or penthrane (OR = 1.5, CI = 1.1-2.0) during delivery); (ii) characteristics of neonatal distress (a combined variable including low one-minute Apgar score, asphyxia [OR = 1.5, CI = 1.1-2.0]) or treatments for neonatal distress (use of supplemental oxygen, ventilated on mask, use of incubator, scalp vein infusion, feeding with a jejunal tube [OR = 1.6, CI = 0.9-2.6]); and (iii) neonatal infections (OR = 2.4, CI = 1.5-4.0). Higher subtype-specific risks, observed for a few risk factors, did not differ significantly from the risk estimates for all subtypes combined for the corresponding risk factors. Childhood brain tumors were not associated significantly with other maternal reproductive, lifestyle, or disease factors; perinatal pain, anesthetic medications, birth-related complications; or with birthweight, birth defects, or early neonatal diseases. These findings suggest several new leads, but only weak evidence of brain tumor subtype-specific differences.

Linos A, Kardara M, Kosmidis H, Katriou D, Hatzis C, Kontzoglou M, Koumandakis E, Tzartzatou-Stathopoulou F. 1998. Reported influenza in pregnancy and childhood tumour. Eur J Epidemiol 14:471-475.
Abstract: The present study was conducted to test the hypothesis that exposure to influenza in pregnancy increases the risk of tumour of certain type in childhood. Children ages 17 years or less diagnosed in Greece with brain tumours or neuroblastomas from 1982 to 1993 (n = 94) were contrasted to 210 controls selected from the same hospitals. Mothers of these children were interviewed about a variety of possible etiologic factors. The prevalence of influenza in Greece for each year during the period 1984-1992 was also compared with the number of children born during the same year who subsequently developed brain tumour or neuroblastoma. The results indicate a significant association between influenza in pregnant women and occurrence of tumour in index child (OR: 3.15, 95% CI: 1.13-8.77). These results persisted when adjustment for potential confounding factors was made. The findings should be interpreted cautiously because of lack of serologic documentation of information about infection obtained in interviews. A positive correlation (r = 0.74) of the number of tumour births by year of birth with the prevalence of influenza during the same year was also noted. This exploratory study is one of the few case-control studies of the epidemiology of childhood tumours in children, and the results suggest directions for future epidemiologic studies in this relatively uncharted field.

Liu J, Xie YX, Ducharme DMK, Shen J, Diwan BA, Merrick BA, Grissom SF, Tucker CJ, Paules RS, Tennant R, Waalkes MP. 2006. Global Gene Expression Associated With Hepatocarcinogenesis in Adult Male Mice Induced by in Utero Arsenic Exposure. Environ Health Perspect 114:404-411.
Abstract: Our previous work has shown that exposure to inorganic arsenic in utero produces hepatocellular carcinoma (HCC) in adult male mice. To explore further the molecular mechanisms of transplacental arsenic hepatocarcinogenesis, we conducted a second arsenic transplacental carcinogenesis study and used a genomewide microarray to profile arsenic-induced aberrant gene expression more extensively. Briefly, pregnant C3H mice were given drinking water containing 85 ppm arsenic as sodium arsenite or unaltered water from days 8 to 18 of gestation. The incidence of HCC in adult male offspring was increased 4-fold and tumor multiplicity 3-fold after transplacental arsenic exposure. Samples of normal liver and liver tumors were taken at autopsy for genomic analysis. Arsenic exposure in utero resulted in significant alterations ($p<0.001$) in the expression of 2,010 genes in arsenic-exposed liver samples and in the expression of 2,540 genes in arsenic-induced HCC. Ingenuity Pathway Analysis revealed that significant alterations in gene expression occurred in a number of biological networks, and Myc plays a critical role in one of the primary networks. Real-ltime reverse transcriptase-polymerase chain reaction and Western blot analysis of selected genes/proteins showed, 90% concordance. Arsenic-altered gene expression included activation of oncogenes and HCC biomarkers, and increased expression of cell proliferation-related genes, stress proteins, and insulin-like growth factors and genes involved in cell-cell communications. Liver feminization was evidenced by increased expression of estrogen-linked genes and altered expression of genes that encode gender-related metabolic enzymes. These novel findings are in agreement with the biology and histology of arsenic-induced HCC, thereby indicating that multiple genetic events are associated with transplacental arsenic hepatocarcinogenesis.

Liu J, Xie YX, Merrick BA, Shen J, Ducharme DMK, Collins J, Diwan BA, Logsdon D, Waalkes MP. 2006. Transplacental arsenic plus postnatal 12-O-teradecanoyl phorbol-13-acetate exposures associated with hepatocarcinogenesis induce similar aberrant gene expression patterns in male and female mouse liver.

Toxicology & Applied Pharmacology 213:216-223.
Abstract: Our prior work shows that in utero arsenic exposure alone is a complete transplacental carcinogen, producing hepatocellular carcinoma in adult male offspring but not in females. In a follow-up study to potentially promote arsenic-initiated tumors, mice were exposed to arsenic (85 ppm) from gestation day 8 to 18 and then exposed to 12-O-teradecanoyl phorbol-13-acetate (TPA), a well-known tumor promoter after weaning. The dermal application of TPA (2 mu g/0.1 ml acetone, twice/week for 21 weeks) after transplacental arsenic did not further increase arsenic-induced liver tumor formation in adult males but significantly increased liver tumor formation in adult females. Thus, for comparison, liver tumors and normal liver samples taken from adult male and female mice at necropsy were analyzed for aberrant gene/protein expression by microarray, real-time RT-PCR and Western blot analysis. Arsenic/TPA treatment resulted in increased expression of alpha-fetoprotein, k-ras, c-myc, estrogen receptor-alpha., cyclin D 1, cdk2na, plasminogen activator inhibitor-1, cytokeratin-8, cytokeratin-18, glutathione S-transferases and insulin-like growth factor binding proteins in liver and liver tumors from both male and female mice. Arsenic/TPA also decreased the expression of BRCA1, betaine-homocysteine methyltransferase, CYP7B1, CYP2F2 and insulin-like growth factor-1 in normal and cancerous livers. Alterations in these gene products were associated with arsenic/TPA-induced liver tumors, regardless of sex. Thus, transplacental arsenic plus postnatal TPA exposure induced similar aberrant gene expression patterns in male and female mouse liver, which are persistent and potentially important to the mechanism of arsenic initiation of hepatocarcinogenesis. Published by Elsevier Inc.

Lowengart RA, Peters JM, Cicioni C, Buckley J, Bernstein L, Preston-Martin S, Rappaport E. 1987. Childhood leukemia and parents' occupational and home exposures. J Natl Cancer Inst 79:39-46.
Abstract: A case-control study of children of ages 10 years and under in Los Angeles County was conducted to investigate the causes of leukemia. The mothers and fathers of acute leukemia cases and their individually matched controls were interviewed regarding specific occupational and home exposures as well as other potential risk factors associated with leukemia. Analysis of the information from the 123 matched pairs showed an increased risk of leukemia for children whose fathers had occupational exposure after the birth of the child to chlorinated solvents [odds ratio (OR) = 3.5, P = .01], spray paint (OR = 2.0, P = .02), dyes or pigments (OR = 4.5, P = .03), methyl ethyl ketone (CAS: 78-93-3; OR = 3.0, P = .05), and cutting oil (OR = 1.7, P = .05) or whose fathers were exposed during the mother's pregnancy with the child to spray paint (OR = 2.2, P = .03). For all of these, the risk associated with frequent use was greater than for infrequent use. There was an increased risk of leukemia for the child if the father worked in industries manufacturing transportation equipment (mostly aircraft) (OR = 2.5, P = .03) or machinery (OR = 3.0, P = .02). An increased risk was found for children whose parents used pesticides in the home (OR = 3.8, P = .004) or garden (OR = 6.5, P = .007) or who burned incense in the home (OR = 2.7, P = .007). The risk was greater for frequent use. Risk of leukemia was related to mothers' employment in personal service industries (OR = 2.7, P = .04) but not to specified occupational exposures. Risk related to fathers' exposure to chlorinated solvents, employment in the transportation equipment-manufacturing industry, and parents' exposure to household or garden pesticides and incense remains statistically significant after adjusting for the other significant findings.

Lu LJW, Anderson LM, Jones AB, Moskal TJ, Salazar JJ, Hokanson JA, Rice JM. 1993. Persistence, gestation stage-dependent formation and interrelationship of benzo[a]pyrene-induced DNA adducts in mothers, placentae and fetuses of Erythrocebus patas monkeys. Carcinogenesis 14:1805-1813.
Abstract: Since DNA adducts have been detected in the placentae of pregnant women who smoke cigarettes, the importance of these adducts as biomarkers of fetal exposure and risk has been evaluated using a non-human primate as a model. Pregnant Erythrocebus patas monkeys on days 50, 100 or 150 of gestation (term = 160 +/- 5 days) were treated once with 5-50 mg/kg benzo[a]pyrene (B[a]P), p.o. Fetuses were removed by Cesarean section 1 - 50 days after treatment and analyzed for DNA adducts by the nuclease P1 version of the P-32-postlabeling method. B[a]P induced high levels of DNA adducts in all fetal organs, placentae and maternal livers in all three trimesters of gestation. DNA adduct levels were higher in mid-gestation compared to early and late gestation. The major adduct detected was 10beta-(deoxyguanosin)-N2-yl-7beta,8alpha,9alpha-trihydroxy-7,8,9,10-tet rahydro-B[a]P. The adduct levels in fetal tissues increased with B[a]P dose, but at a much lower rate than in placentae or maternal livers. Preference in binding to DNA of various fetal organs was more apparent in early gestation compared to late gestation and at lower doses compared to higher doses. During early gestation and at low doses, B[a]P

produced a similar level of DNA adducts in fetal lung, fetal liver, maternal liver and placenta. Individual fetal organ adduct levels correlated significantly with placental adduct levels, indicating placental and/or maternal contribution to genotoxic injuries in fetuses. However, the slopes of linear regression lines of correlation analyses varied among organs and among gestation stages at treatment, indicating fetal contribution to its own genotoxic injuries. DNA adduct levels in fetal skin were the lowest of all fetal organs tested and less affected by gestational stages at time of treatment. In contrast, DNA adduct levels in fetal liver exhibited distinct gestation stage specificity with higher adduct levels attained during mid-gestation compared to other stages of gestation. Adduct levels decreased at a much faster rate during the first 10-15 days compared to 15-50 days after B[a]P treatment. However, 10% of DNA adducts persisted 50 days after treatment in all organs studied. Together, the results suggest that placental adduction accurately indicates fetal exposure. Toxicokinetics of B[a]P and its metabolites as well as maternal, placental and fetal competence in activation and deactivation of B[a]P may be critical determinants in overall fetal risk to genetic damage. Importantly, maximal sensitivity to transplacental DNA damage may be during mid-gestation.

Lubin F, Farbstein H, Chetrit A, Farbstein M, Freedman L, Alfandary E, Modan B. 2000. The role of nutritional habits during gestation and child life in pediatric brain tumor etiology. Int J Cancer 86:139-143.
Abstract: Our aim was to evaluate the role of maternal nutritional habits during the period of gestation and of children subsequent diet in the etiology of pediatric brain tumors. All cases of incident nervous system tumors under age 18, diagnosed between 1984 and 1993 (n = 300) in Israel were identified, Two matched population controls per case were selected (n = 574). Personal interviews, using a semi-quantified three-step food frequency questionnaire, were performed. Univariate analysis showed that increased child consumption of vegetable fat [p trend 0.01; 95% confidence interval (CI) 1.1-3.2], carbohydrates (p trend 0.05; CI 1.0-5.9), and vitamin E (p trend 0.05; CI 1.0-3.3), were significantly associated with brain tumor risk. No associations were found with nitrate, nitrite or vitamin C. A significant positive association with potassium consumption (p trend 0.01; CI 1.1-3.7) was noted during gestation. Results of multivariate analysis showed that the only persisting associations were with vegetable fat (OR = 1.36; CI 1.06-1.73) in the child diet and potassium intake during gestation (OR = 1.44; CI 1.04-1.99). In conclusion, nutritional associations with pediatric brain tumor etiology, remain unsubstantiated. Int. J. Cancer 86: 139-143, 2000, (C) 2000 Wiley-Liss, Inc.

Luijten M, Thomsen AR, van den Berg JA, Wester PW, Verhoef A, Nagelkerke NJ, Adlercreutz H, van Kranen HJ, Piersma AH, Sorensen IK, Rao GN, van Kreijl CF. 2004. Effects of soy-derived isoflavones and a high-fat diet on spontaneous mammary tumor development in Tg.NK (MMTV/c-neu) mice. Nutrition & Cancer 50:46-54.
Abstract: Phytoestrogens such as isoflavonoids and lignans have been postulated as breast cancer protective constituents in soy and whole-grain cereals. We investigated the ability of isoflavones (IFs) and flaxseed to modulate spontaneous mammary tumor development in female heterozygous Tg.NK (MMTV/c-neu) mice. Two different exposure protocols were applied, either from 4 wk of age onward (postweaning) or during gestation and lactation (perinatal). In the postweaning exposure study, mice were fed IFs or flaxseed in a high-fat diet. In addition, flaxseed in a low-fat diet was tested. Postweaning exposure to IFs and flaxseed tended to accelerate the onset of mammary adenocarcinoma development, although tumor burden at necropsy was not changed significantly. Perinatal IF exposure resulted in enhanced mammary gland differentiation, but palpable mammary tumor onset was not affected. However, tumor burden at necropsy in the perinatal exposure study was significantly increased in the medium- and high-IF dose groups. Comparison of both exposure scenarios revealed a strongly accelerated onset of tumor growth after perinatal high-fat diet exposure compared with the low-fat diet. This study shows that breast cancer-modulating effects of phytoestrogens are dependent both on the background diet and on the timing of exposure in the life cycle.

Luke B, Hediger M, Min SJ, Brown MB, Misiunas RB, Gonzalez-Quintero VH, Nugent C, Witter FR, Newman RBHGD, Grainger DA, Macones GA. 2005. Gender mix in twins and fetal growth, length of gestation and adult cancer risk. Paediatric & Perinatal Epidemiology 19 Suppl 1:41-47.
Abstract: This study evaluated the effect of gender mix (the gender combinations of twin pairs) on fetal growth and length of gestation, and reviewed the literature on the long-term effects of this altered fetal milieu on cancer risk. In singletons, it is well established that females weigh less than males at all

gestations, averaging 125-135 g less at full term. This gender difference is generally believed to be the result of the effect of androgens on fetal growth. The gender difference in fetal growth is greater before the third trimester and less towards term, with males growing not only more, but also earlier than females. Plurality is a known risk factor for reduced fetal growth and birthweight. Compared with singletons, the mean birthweight percentiles of twins fall substantially (by 10% or more) below the singleton 10th percentile by 28 weeks, below the singleton 50th percentile by 30 weeks, and below the singleton 90th percentile by 34 weeks. In unlike-gender twin pairs, it has been reported that the female prolongs gestation for her brother, resulting in a higher birthweight for the male twin than that of like-gender male twins. Other researchers have demonstrated that females in unlike-gender pairs had higher birthweights than females in like-gender pairs. Analyses from our consortium on 2491 twin pregnancies with known chorionicity showed longer gestations and faster rates of fetal growth in both males and females in unlike-gender pairs compared with like-gender male or female pairs, although these differences were not statistically significant. The post-natal effects for females growing in an androgenic-anabolic environment include increased sensation-seeking behaviour and aggression, lowered visual acuity, more masculine attitudes and masculinising effects of the auditory system and craniofacial growth. In contrast, there is no evidence to suggest that there might be a similar feminising effect on males from unlike-gender pairs. This hormonal exposure in utero may influence adult body size and susceptability to breast cancer.

Lummus ZL, Henningsen G. 1995. Modulation of T-cell ontogeny by transplacental benzo(a)pyrene. Int J Immunopharmacol 17:339-350.

Abstract: Transplacental exposure to the carcinogen, benzo(a)pyrene BaP, leads to depressed immune function and increased tumor incidence in mice. This paper reports ontogenetic T-cell changes in BALB/c mice after exposure to BaP in utero. Monoclonal antibodies (MAbs) were produced to fetal liver T-cells (FLT) and newborn spleen (NBS) lymphocytes purified from offspring of pregnant BALB/c mice that were given one injection of BaP (150 mg/kg body weight) in mid-gestation (day 11-13). The MAbs reacted with two T-cell membrane antigens (FLT and NBS) found in fetal liver, neonatal and adult thymus and spleen. Lymphocytes of BaP-exposed 19-day fetuses showed decreased subpopulation frequencies ($P<0.05$) in fetal liver total T-cells (from 56% to 16%), Lyl cells (from 33% to 9%), and Ly2 cells (from 56% to 1%) compared with untreated controls. In contrast, BaP increased the subpopulation frequencies ($P<0.05$) in FLT cells in fetal liver (from 20% to 52%) and in newborn spleen (from 21% to 51%), and increased NBS cells in newborn spleen (from 24% to 59%). The increased frequency in FLT and NBS cells was due to their relative resistance to BaP toxicity and/or BaP-enhanced proliferation in the neonatal period. Compared with untreated controls, BaP treatment resulted in reduced numbers of T-cells in fetal liver and showed a selective toxicity for Lyl cells (89% reduction) and Ly2 cells (99% reduction), whereas FLT cells were not reduced and NBS cells were reduced by 60%. Six-week-old juvenile mice exposed to BaP in utero showed recovery of total T-cells to control levels in spleen and thymus, but showed depletion ($P<0.01$) in thymic FLT cells (from 81% to 12%) and in splenic NBS cells (from 55% to 16%). The monoclonal antibodies developed for this study recognize novel cellular changes in the murine immune system that are associated with transplacental BaP. The FLT and NBS antigens may be useful biomarkers for developmental immune dysfunctions in progeny exposed to BaP in utero.

Lumniczky K, Antal S, Unger E, Wunderlich L, Hidvegi EJ, Safrany G. 1998. Carcinogenic alterations in murine liver, lung, and uterine tumors induced by in utero exposure to ionizing radiation. Mol Carcinog 21:100-110.

Abstract: The atomic bombing of Hiroshima and Nagasaki and the nuclear accident at Chernobyl raised the question of prenatal sensitivity to ionizing radiation-induced cancer. In this study, mice were exposed to single doses of gamma-radiation (0.2-2.0 Gy) at different embryonic stages. The tumor incidence increased with dose from 15% in in control mice to 35% in mice irradiated with 2.0 Gy on 18 d of prenatal life. Various oncogenic events were investigated in lymphoid, liver, lung, and uterine tumors. We observed threefold to fivefold increases in myc expression in 25% of the lymphomas, and the expression of Ha-ras and p53 genes decreased in 40% and 60% of the lung tumors by twofold to fivefold. Point mutations were tissue specific: Ha-ras codon 61 mutations were found in about 40% of the liver adenocarcinomas, Ki-ras codon 12 mutations in about 17% of lung tumors, and p53 mutations in about 15% of the lymphomas. Amplification and rearrangement of the p53, myc, and Ha-, Ki- and N-ras genes were not detected. Loss of heterozygosity on chromosome 4 at the multiple tumor suppressor 1 and 2 genes was observed in all types of malignancies. Allelic losses on chromosome 11 at the p53 locus were found in lymphoid, liver, and lung

tumors, but they were absent from uterine tumors. Multiple oncogenic changes were often detected. The frequency of carcinogenic alterations was similar in spontaneous and radiation-induced lymphoid, liver, and uterine tumors. In radiation-induced lung adenocarcinomas, however, the incidences of many oncogenic changes were different from those found in their spontaneous counterparts. This suggests that different oncogenic pathways are activated during spontaneous and in utero gamma-radiation-induced murine lung carcinogenesis. (C) 1998 Wiley-Liss, Inc.

Ma XM, Buffler PA, Gunier RB, Dahl G, Smith MT, Reinier K, Reynolds P. 2002. Critical windows of exposure to household pesticides and risk of childhood leukemia. Environ Health Perspect 110:955-960.
Abstract: (T)he potential etiologic role of household pesticide exposures was examined in the Northern California Childhood Leukemia Study. A total of 162 patients (0-14 years old) with newly diagnosed leukemia were rapidly ascertained during 1995-1999, and 162 matched control subjects were randomly selected from the birth registry. The use of professional pest control services at any time from 1 year before birth to 3 years after was associated with a significantly increased risk of childhood leukemia [odds ratio (OR)=2.8; 95% confidence interval (CI), 1.4-5.7], and the exposure during year 2 was associated with the highest risk (OR=3.6; 95% CI, 1.6-8.3). The ORs for exposure to insecticides during the 3 months before pregnancy, pregnancy, and years 1, 2, and 3 were 1.8 (95% CI, 1.1-3.1), 2.1 (95% CI, 1.3-3.5), 1.7 (95% CI, 1.0-2.9), 1.6 (95% CI, 1.0-2.7), and 1.2 (95% CI, 0.7-2.1), respectively. Insecticide exposures early in life appear to be more significant than later exposures, and the highest risk was observed for exposure during pregnancy. Additionally, more frequent exposure to insecticides was associated with a higher risk. In contrast to insecticides, the association between herbicides and leukemia was weak and nonsignificant. Pesticides were also grouped based on where they were applied. Exposure to indoor pesticides was associated with an increased risk, whereas no significant association was observed for exposure to outdoor pesticides. The findings suggest that exposure to household pesticides is associated with an elevated risk of childhood leukemia and further indicate the importance of the timing and location of exposure.

Maciag A, Bialkowska A, Espiritu I, Powell D, Alvord WG, Kasprzak KS, Anderson LM, Witschi HR. 2003. Gestation stage-specific oxidative deoxyribonucleic acid damage from sidestream smoke in pregnant rats and their fetuses. Arch Environ Health 58:238-244.
Abstract: Transplacental exposure to environmental tobacco smoke (ETS) is a possible cancer risk factor in offspring. The authors exposed pregnant Sprague-Dawley rats to a relevant dose of ETS (1 mg/m(3)) from gestation day 4 to days 16 or 21. They then assayed tissues for levels of 8-oxo-2'-deoxyguanosine (8-oxo-dG), a marker of oxidative deoxyribonucleic acid damage. ETS exposure ending on gestation day 16 resulted in statistically significant increases in 8-oxo-dG in maternal liver and kidney and in fetal kidney. On gestation day 21, there were significant 8-oxo-dG increases in fetal liver and brain. These gestational stage- and tissue-specific increases of 1.2- to 1.4-fold are similar to the putative relative increases in risk of human cancers related to ETS.

Maffini MV, Rubin BS, Sonnenschein C, Soto AM. 2006. Endocrine disruptors and reproductive health: The case of bisphenol-A. Molecular & Cellular Endocrinology 254:179-186.
Abstract: Epidemiological studies have reported that during the last 60 years the quantity and quality of human sperm has decreased and the incidence of male genital tract defects, testicular, prostate and breast cancer has increased. During the same time period, developmental, reproductive and endocrine effects have also been documented in wildlife species. The last six decades have witnessed a massive introduction of hormonally active synthetic chemicals into the environment leading some to postulate that the diverse outcomes documented in human and wildlife populations might be the result of extemporaneous exposure to xenoestrogens during development. The estrogen-mimic bisphenol-A (BPA) is used as a model agent for endocrine disruption. BPA is used in the manufacture of polycarbonate plastics and epoxy resins from which food and beverage containers and dental materials are made. Perinatal exposure to environmentally relevant BPA doses results in morphological and functional alterations of the male and female genital tract and mammary glands that may predispose the tissue to earlier onset of disease, reduced fertility and mammary and prostate cancer. (c) 2006 Elsevier Ireland Ltd. All rights reserved.

Magnani C, Pastore G, Luzzatto L, Carli M, Lubrano P, Terracini B. 1989. Risk factors for soft tissue sarcomas in childhood: A case-control study. Tumori 75:396-400.
Abstract: A hospital-based case-control study on soft tissue sarcomas (STS) was conducted in 1983-84 in

Torino and in Padova (Italy). Cases (36 children with rhabdomyosarcoma (RMS) and 16 non RMS-STS) were compared to 326 controls. Histories of parental smoking habits and occupations, parental and children's exposure to ionizing radiation, children's diseases and some other variables were collected through interviews to the relatives attending the child in the hospital. A non statistically significant association was observed with both maternal age above 30 at child's birth (STS: OR = 1.5, C.I. = 0.8-2.9; RMS: OR = 1.9, C.I. = 0.9-4.0) and "in utero" exposure to diagnostic radiation (STS: OR = 1.9, C.I. = 0.5-6.5, based on 4 cases). No association was found with children's previous diseases. Paternal and maternal smoking habits were similar for RMS and STS cases and controls. Some positive associations with either maternal or paternal occupational histories were identified. They are difficult to interpret in view of the large number of comparisons and small absolute figures. They included maternal employment as medical doctor and nurse, farmer, textile worker and machine tool operator. An association was also observed with paternal occupation as butcher, building worker or employment in the production of domestic appliances. One case and no controls reported a maternal aunt affected by breast cancer.

Maher ER. 2005. Imprinting and Assisted Reproductive Technology. Hum Mol Genet 14:R133-R138.
Abstract: In the past 25 years, the frequency of assisted reproductive technology (ART) births has increased rapidly to account for 1-2% of all births in many developed countries. ART procedures such as in vitro fertilization and intracytoplasmic sperm injection are generally considered to be safe, but recent studies suggest a small excess of birth defects and low-birth weight in ART children. In addition, several clinical studies have reported an increased frequency of ART conceptions among children with Beckwith-Wiedemann syndrome or Angelman syndrome caused by an imprinting defect. Although these studies require further confirmation, they are consistent with animal studies reporting disordered expression and epigenetic changes in imprinted genes following in vitro embryo culture. The absolute risk of an imprinting disorder after ART appears to be very small, but further data are required to determine whether the association between ART and human imprinting disorders reflects the effect of embryo culture (or some other aspect of ART) and/or a common mechanism for infertility and imprinting disorders. Retinoblastoma and neurodevelopmental defects have been only tentatively linked to ART, but in view of the role of epigenetic processes in the regulation of gene expression in development and cancer, further research is required into long-term health outcomes for ART children and the epigenetic consequences of ART protocols.

Mandel M, Toren A, Rechavi G, Dor J, Benbassat I, Neumann Y. 1994. Hormonal treatment in pregnancy - A possible risk factor for neuroblastoma. Medical & Pediatric Oncology 23:133-135.
Abstract: In the last 4 years, 24 cases of neuroblastoma were treated in the Pediatric Hematology-Oncology Unit at the Chaim Sheba Medical Center, 8 of whom were under 1 year of age. Four of them were the product of a pregnancy-induced or preserved by gonadotropins, clomiphene citrate, or progestational hormones. These drugs are known to produce a higher than normal level of estradiol or progestrone in the early stages of pregnancy. Our observation led to the hypothesis that high levels of progestational hormones given during pregnancy are a risk factor for neuroblastoma in infancy. (C) 1994 Wiley-Liss, Inc.

Mandeville R, Franco E, Sidrac-Ghali S, Paris-Nadon L, Rocheleau N, Mercier G, Desy M, Devaux C, Gaboury L. 2000. Evaluation of the potential promoting effect of 60 Hz magnetic fields on N-ethyl-N-nitrosourea induced neurogenic tumors in female F344 rats. Bioelectromagnetics 21:84-93.
Abstract: The present study investigated the possible effect of 60 Hz magnetic fields (MFs) as promoters of neurogenic tumors initiated transplacentally by a chemical carcinogen, N-ethyl-N-nitrasourea (ENU). In a preliminary study, 5 mg of ENU was shown to induce 30 to 40% neurogenic tumors in F344 rats offspring after 420 days of observation. In the present study, 400 female rats were divided into eight different groups (50 animals/group) and exposed in utero (on day 18 of gestation) to a single intravenous dose of either Saline (Group I), or ENU, 5 mg/kg (Group II to VIII). Dams in group II were given no further treatment while dams in Groups III to VII were exposed to 5 different intensities of MFs forty eight hours later. Animals in group III were sham exposed (< 0.02 mu T) while groups IV to VII were exposed to 2, 20, 200 and 2000 mu T, respectively. Dams in Group VIII were injected intraperitoneally with 12-O-tetradecanoylphrobol-13-acetate (TPA; 10 mu g/kg) from day 19 until delivery, and then their female offspring continued to be injected every 15 days, starting at day 14 after birth until sacrifice (positive controls). Accordingly, this study included three different types of controls: Internal controls (Groups II and III and positive control (Group VIII). Body weight, mortality and clinical observations were evaluated

in all groups of animals during in-life exposure. Necropsy was performed on all exposed and central animals that died, were found moribund or sacrificed at termination of the study. Histopathological evaluation was done for all brains, spinal cords, cranial nerves, major organs (lungs, liver, spleen, kidneys, pituitary, thyroid and adrenals) and all gross lesions observed during necropsy. All clinical observations and pathological evaluations were conducted under "blinded" conditions. The findings from this ENU/MFs promotion study clearly demonstrate that, under our defined experimental conditions, exposure to 60 Hz linear (single axis) sinusoidal, continuous wave MFs had no effect on the survival of female F344 rats or on the number of animals bearing neurogenic tumors. These results suggest that MFs have no promoting effect on neurogenic tumors in the female F344 rats exposed transplacentally to ENU. (C) 2000,Wiley-Liss, Inc.

Mann PC. 1997. Selected lesions of dioxin in laboratory rodents. Toxicol Pathol 25:72-79.
Abstract: Dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin) has been the subject of intensive investigations in laboratory animals during the last 2 decades. Toxicity studies have been conducted in several species of rodents and include several carcinogenicity studies as well as numerous mechanistic studies initiated to elucidate dioxin's mode of action, as both a carcinogen and a toxicant. Hepatotoxicity is a primary effect of dioxin. There has been an increase in hepatocellular tumors reported in both rats and mice exposed to dioxin. In addition to neoplastic changes, dioxin causes a spectrum of toxic changes in the liver. Additional neoplastic changes include subcutaneous fibrosarcomas and thyroid follicular cell tumors in both rats and mice and histiocytic sarcomas in mice. Dioxin causes developmental effects in the palate and kidney of mice. Changes in the female reproductive tract include ovarian atrophy, sertoliform hyperplasia, and Sertoli cell tumors. Dosing in utero results in gross malformations of the external genetalia. The effects of dioxin on the rodent model of endometriosis are described. In males, there are lowered sperm counts in the epididymis and minor testicular effects following gestational administration of dioxin. Both estrogenic and antiestrogenic-like effects have been ascribed to dioxin in laboratory animals; these activities are the result of dioxin-specific pathways resulting in the same end points as classic reproductive toxicants.

Markey CM, Coombs MA, Sonnenschein C, Soto AM. 2003. Mammalian development in a changing environment: exposure to endocrine disruptors reveals the developmental plasticity of steroid-hormone target organs . Evolution & Development 5:67-75.
Abstract: Recent findings in the field of environmental endocrine disruption have revealed that developmental exposure to estrogenic chemicals induces morphological, functional, and behavioral anomalies associated with reproduction. The aim of the present study was to determine the effects of in utero exposure to low doses of the estrogenic chemical bisphenol A (BPA) on the development of the female reproductive tissues and mammary glands in CD-1 mice. Humans are exposed to BPA, which leaches from dental materials and plastic food and beverage containers. Here we report that prenatal exposure to BPA induces alterations in tissue organization within the ovaries and mammary glands and disrupts estrous cyclicity in adulthood. Because estrogen receptors are expressed developmentally in these estrogen-target organs, we propose that BPA may directly affect the expression of genes involved in their morphogenesis. In addition, alterations in the sexual differentiation of the brain, and thus the hypothalamic-pituitary-gonadal axis, may further contribute to the observed phenotype. The emerging field of endocrine disruptors promises to provide new insights into the mechanisms underlying the development of hormone-target organs and demonstrates that the environment plays important roles in the making of phenotypes.

Markey CM, Luque EH, Munoz de Toro M, Sonnenschein C, Soto AM. 2001. *In utero* exposure to bisphenol A alters the development and tissue organization of the mouse mammary gland. Biol Reprod 65:1215-1223.
Abstract: Exposure to estrogens throughout a woman's life, including the period of intrauterine development, is a risk factor for the development of breast cancer. The increased incidence of breast cancer noted during the last 50 years may have been caused, in part, by exposure of women to estrogen-mimicking chemicals that are released into the environment. Here, we investigated the effects of fetal exposure to one such chemical, bisphenol A (BPA), on development of the mammary gland. CD-1 mice were exposed in utero to low, presumably environmentally relevant doses of BPA (25 and 250 microg/kg body weight), and their mammary glands were assessed at 10 days, 1 mo, and 6 mo of age. Mammary glands of BPA-exposed mice showed differences in the rate of ductal migration into the stroma at 1 mo of age and a significant increase in the percentage of ducts, terminal ducts, terminal end buds, and alveolar buds at 6 mo of age. The percentage of cells that incorporated BrdU was significantly decreased within the epithelium at 10 days of age and increased within the stroma at 6 mo of age. These changes in histoarchitecture, coupled with an

increased presence of secretory product within alveoli, resemble those of early pregnancy, and they suggest a disruption of the hypothalamic-pituitary-ovarian axis and/or misexpression of developmental genes. The altered relationship in DNA synthesis between the epithelium and stroma and the increase in terminal ducts and terminal end buds are striking, because these changes are associated with carcinogenesis in both rodents and humans.

Markey CM, Wadia PR, Rubin BS, Sonnenschein C, Soto AM. 2005. Long-term effects of fetal exposure to low doses of the xenoestrogen bisphenol-A in the female mouse genital tract. Biol Reprod 72:1344-1351.
Abstract: Developmental exposure to estrogenic chemicals induces morphological, functional and behavioral anomalies associated with reproduction. Humans are routinely exposed to bisphenol-A (BPA), an estrogenic compound that leaches from dental materials and plastic food and beverage containers. The aim of the present study was to determine the effects of in utero exposure to low, environmentally relevant doses of BPA on the development of female reproductive tissues in CD-1 mice. In previous publications, we have shown that this treatment alters the morphology of the mammary gland and affects estrous cyclicity. Here we report that in utero exposure to 25 and 250 ng BPA/kg body weight/day via osmotic pumps implanted into pregnant dams at gestational day 9 induces alterations in the genital tract of female offspring that are revealed during adulthood. They include: decreased wet weight of the vagina, decreased volume of the endometrial lamina propria, increased incorporation of bromodeoxyuridine into the DNA of endometrial gland epithelial cells, and increased expression of estrogen receptor-alpha (ER alpha) and progesterone receptor in the luminal epithelium of the endometrium and subepithelial stroma. Since ER alpha is known to be expressed in these estrogen-target organs at the time of BPA exposure, it is plausible that BPA may directly affect the expression of ER controlled genes involved in the morphogenesis of these organs. In addition, BPA-induced alterations that specifically affect hypothalamic-pituitary-gonadal axis function may further contribute to the anomalies observed at three months of age, long after the cessation of BPA exposure.

Marselos M, Tomatis L. 1992. Diethylstilboestrol: I, Pharmacology, Toxicology and carcinogenicity in humans. Eur J Cancer 28A:1182-1189.
Abstract: Diethylstilboestrol is still used as an adjunct palliative treatment in certain patients with breast and prostate cancer. Its pharmacological, toxicological and carcinogenic properties are reviewed. In addition to the usual untoward effects following subacute or chronic administration of oestrogens, treatment with diethylstilboestrol has been associated with serious cardiovascular sequelae. Most characteristic are, however, the carcinogenic properties of this drug. Many epidemiological data provide evidence that prenatal exposure to diethylstilboestrol is causally associated with vaginal and cervical clear-cell adenocarcinomas, a very rare type of cancer in the unexposed female population. The intrauterine exposure of males leads to an increased risk of testicular cancer, although the data are less conclusive in this respect. There is some evidence that administration of diethylstilboestrol in large doses to adult women during pregnancy increases the risk of subsequent breast cancer and it probably increases the incidence of endometrial carcinoma, as has been shown with other similar oestrogens given chronically for menopausal symptoms.

Massaad C, Entezami F, Massade L, Benahmed M, Olivennes F, Barouki R, Hamamah S. 2002. How can chemical compounds alter human fertility? European Journal of Obstetrics Gynecology & Reproductive Biology 100:127-137.
Abstract: The effects of environmental toxins, such as pesticides, solvents and industrial waste, on human and animal health have caused much public fear. The suggested mechanism of action for these xenobiotics is their capacity to interact with steroid hormones receptors, in particular those for estrogens and androgens. Concern was reinforced by the "historical" example of diethylstilbestrol, an estradiol mimetic causing genital cancer in girls exposed in utero. The real harm of these environmental xenobiotics is controversial. Some authors estimate that they do not reach sufficiently high concentrations to do damage and much experimental work has been done. In this review, we summarise the latest findings on the molecular mechanisms of action of three environmental toxicants, xenohormones, dioxin and glycol ethers and compare animal and cell experimental model data with epidemiological studies.

Maule MM, Merletti F, Pastore G, Magnani C, Richiardi L. 2007. Effects of maternal age and cohort of birth on incidence time trends of childhood acute lymphoblastic leukemia. Cancer Epidemiol Biomarkers Prev

16:347-51.
Abstract: Several studies report increasing trends in the incidence of childhood acute lymphoblastic leukemia (ALL). Because ALL may generate in utero, this study investigated if maternal age and birth cohort influence ALL temporal trends. Data on 252 ALL cases in children ages 1 to 5 years were extracted from the population-based Childhood Cancer Registry of Piedmont, Italy. Information on cases' maternal age and year of birth was obtained from the registry, whereas population data were obtained for children born in 1980 to 1997. Incidence rates were analyzed using an age-period-cohort approach, in which the period effect was represented by the child year of birth, the age effect by the maternal age at the time of delivery, and the cohort effect by the maternal birth cohort. ALL incidence increased over the study period [annual percentage change 2.49%; 95% confidence interval (95% CI), 0.09-4.93]. A linear effect of the maternal time variables (P = 0.012) was found, which was equally described by maternal age (direct association) and maternal birth cohort (inverse association). The annual percentage change was 1.83% (95% CI, -0.59-4.31), when maternal age was included in the model, and 5.72% (95% CI, 2.29-9.27), when maternal year of birth was included. In conclusion, maternal characteristics substantially affect temporal trends in childhood ALL incidence.

McBride ML, Vandensteen N, Lamb CW, Gallagher RP. 1991. Maternal and gestational factors in cryptorchidism. Int J Epidemiol 20: 964-970.
Abstract: Previous epidemiological studies of cryptorchidism have led to the hypothesis that the risk of undescended testis is associated with excess oestrogen exposure during pregnancy. A case-control study was undertaken to test this hypothesis, comparing mothers of affected boys (244) and normal male births (488) born within six months of a case selected randomly from the British Columbia population. Information was collected on the mother's reproductive history, family history, and past medical history, and events surrounding all pregnancies ending in a birth. The results were analysed using both the population-based sample of male births and the male sibs of cases as control groups. Neither exogenous oestrogen exposure, nor any of the pregnancy-related variables hypothesized to be indirect indicators of endogenous oestrogen exposure, including bleeding and nausea and/or vomiting, were found to be significantly associated with risk of undescended testes in either comparison. More mothers with later index births reported menstrual irregularity greater than half the time, and smoking, thought to have a protective effect, was more prevalent among case mothers than control mothers. No other variables were significantly different between case and control mothers. The results of this study do not support the hypothesis that elevated exogenous or endogenous oestrogen exposure during pregnancy increases the risk of undescended testis in male children.

McCormack VA, dos Santos Silva I, De Stavola BL, Mohsen R, Leon DA, Lithell HO. 2003. Fetal growth and subsequent risk of breast cancer: Results from long term follow up of Swedish cohort. BMJ 326:248-253.
Abstract: OBJECTIVE: To investigate whether size at birth and rate of fetal growth influence the risk of breast cancer in adulthood. DESIGN: Cohort identified from detailed birth records, with 97% follow up. SETTING: Uppsala Academic Hospital, Sweden. PARTICIPANTS: 5358 singleton females born during 1915-29, alive and traced to the 1960 census. MAIN OUTCOME MEASURES: Incidence of breast cancer before (at age <50 years) and after (> or = 50 years) the menopause. RESULTS: Size at birth was positively associated with rates of breast cancer in premenopausal women. In women who weighed > or =4000 g at birth rates of breast cancer were 3.5 times (95% confidence interval 1.3 to 9.3) those in women of similar gestational age who weighed <3000 g at birth. Rates in women in the top fifths of the distributions of birth length and head circumference were 3.4 (1.5 to 7.9) and 4.0 (1.6 to 10.0) times those in the lowest fifths (adjusted for gestational age). The effect of birth weight disappeared after adjustment for birth length or head circumference, whereas the effects of birth length and head circumference remained significant after adjustment for birth weight. For a given size at birth, gestational age was inversely associated with risk (P=0.03 for linear trend). Adjustment for markers of adult risk factors did not affect these findings. Birth size was not associated with rates of breast cancer in postmenopausal women. CONCLUSIONS: Size at birth, particularly length and head circumference, is associated with risk of breast cancer in women aged <50 years. Fetal growth rate, as measured by birth size adjusted for gestational age, rather than size at birth may be the aetiologically relevant factor in premenopausal breast cancer.

McCormack VA, Silva ID, Koupil I, Leon DA, Lithell HO. 2005. Birth Characteristics and Adult Cancer Incidence: Swedish Cohort of Over 11,000 Men and Women. Int J Cancer 115:611-617.

Abstract: Associations between larger size at birth and increased rates of adult cancer have been proposed but few empirical studies have examined this hypothesis. We investigated overall and site-specific cancer incidence in relation to birth characteristics in a Swedish population-based cohort of 11,166 singletons born in 1915-1929 for whom we have detailed obstetric data and who were alive in 1960. A total of 2,685 first primary cancers were registered during follow-up from 1960 to 2001. A standard deviation (SD) increase in birth weight for gestational age (GA) was associated with (sex-adjusted) increases of 13% (95% CI = 0.03-0.23) in the rates of digestive cancers and of 17% (95% CI = 0.01-0.35) in the rates of lymphatic cancers. Women who had higher birth weights also had increased rates of breast cancer under age 50 years (by 39% per SD increase: 95% CI = 0.09-0.79), but reduced rates (by 24%; 95% CI = 6.07-0.38) of endometrial (corpus uteri) cancer at all ages. There was no evidence of associations with other cancer sites. For overall cancer incidence, men had an 8% increased risk at all ages per SD increase in birth weight for GA while women only had an increased risk under age 50 years (mainly driven by the association with breast cancer). These findings provide evidence of a modest association of birth size and adult cancer risk, resulting front positive associations with a few cancer sites and a possible inverse association with endometrial cancer. © 2005 Wiley-Liss. Inc.

McCormick DL, Kavet R. 2004. Animal models for the study of childhood leukemia: Considerations for model identification and optimization to identify potential risk factors. International Journal of Toxicology 23:149-161.
Abstract: Leukemias are the most common pediatric malignancies diagnosed in western industrialized societies. In spite of the substantial incidence of childhood leukemia in the United States and other countries, neither epidemiology studies conducted in human populations nor hazard identification studies conducted using traditional animal models have identified environmental or other factors that are directly linked to increased risk of disease. Molecular biology data and mathematical modeling of incidence patterns suggest that pediatric leukemogenesis may occur through a multistage or "multihit" mechanism that involves both in utero and postnatal events. The authors propose that pediatric leukemias can be modeled experimentally using a "multihit" paradigm analogous to the "initiation-promotion" and "complete carcinogenesis" models developed for tumor induction in mouse skin and rat liver. In this model for childhood leukemia, an initial genetic alteration occurs during in utero or early postnatal development, but clinical disease develops only upon additional genetic or nongenetic events that occur during the postnatal period. Application of this multistage or "multihit" model to hazard assessment studies conducted in transgenic or knockout mice carrying relevant molecular lesions may provide a sensitive approach to the identification of environmental agents that are important risk factors for childhood leukemia.

McCredie M, Little J, Cotton S, Mueller B, Peris-Bonet R, Choi NW, Cordier S, Filippini G, Holly EA, Modan B, Arslan A, Preston-Martin S. 1999. SEARCH international case-control study of childhood brain tumours: role of index pregnancy and birth, and mother's reproductive history. Paediatric & Perinatal Epidemiology 13:325-341.
Abstract: A series of co-ordinated population-based case-control studies of childhood brain rumours (CBT) was undertaken under the auspices of the Surveillance of Environmental Aspects Related to Cancer in Humans (SEARCH) programme of the International Agency for Research on Cancer (IARC) to evaluate, inter alia, the risk in relation to characteristics of the index pregnancy and birth, and maternal reproductive history. Subjects comprised 1218 cases aged 0-19 years and 2223 controls. Risk estimates were calculated by unconditional logistic regression, adjusted for age, sex, centre and mother's years of schooling, for all lyres of CBT combined as well as for four groups defined by histopathology (astroglial tumours, primitive neuroectodermal rumours of the brain, 'other glial' tumours and 'other histological types') and for five age groups (0-1, 0-4, 5-9, 10-14, 15-19 years). Use of anaesthetic 'gas' was associated with an increased risk of CBT (OR=1.5, 95% CI [1.1, 2.0]), apparent in children aged 0-4 years (OR=2.4, 95% CI [1.4, 4.1]) and for astroglial tumours (OR = 1.6, 95% CI [1.1, 2.2]) with non-significantly increased relative risks for each of the other histological groups. However, not all centre-specific relative risks were elevated. No other aspect of the index pregnancy, delivery and early neonatal period or of the mother's previous reproductive history was associated with risk for CBT.

McCredie M, Maisonneuve P, Boyle P. 1994. Antenatal risk factors for malignant brain tumours in New South Wales children. Int J Cancer 56:6-10.
Abstract: A population-based case-control study of incident primary malignant brain tumours diagnosed

during 1985 to 1989 in children aged 0 to 14 years was carried out in the coastal conurbation of New South Wales comprising Sydney, Wollongong and Newcastle in the period 1988 to 1990. Personal interviews were conducted using a structured questionnaire with mothers of 82 cases and 164 control children individually matched to the cases by sex and age. Among the hypotheses being examined were those related to exposure to parental tobacco smoke, N-nitroso compounds and possible protection from sources of vitamin C. No link was found with tobacco smoking by the mother before or during pregnancy. While exposure during pregnancy of the mother to tobacco smoke of the father appeared to double the risk of childhood brain tumours and a similar risk was found for father (but not mother) smoking before the index pregnancy, there was no "dose-response" and the increased risk was confined to data supplied by the mother (rather than the father himself). The risk of childhood brain tumours rose with reported increasing consumption, during pregnancy, of cured meats, which have high levels of N-nitroso compounds (or their precursors), and fell with rising consumption of vegetables. No association was found between the risk of childhood brain tumours and family history of epilepsy, cancer, or tumours of the nervous system, parental irradiation, previous miscarriage or procedures carried out during pregnancy, maternal consumption of antihistamines, barbiturates or diuretics, or maternal contact with cats or farm-life during pregnancy.

McGlynn KA, Zhang YW, Sakoda LC, Rubertone MV, Erickson RL, Graubard BI. 2006. Maternal smoking and testicular germ cell tumors. Cancer Epidemiology Biomarkers & Prevention 15:1820-1824.
Abstract: Testicular germ cell tumors (TGCT) are the most common cancer among men ages 15 to 35 years in the United States. The well-established TGCT risk factors cryptorchism, prior diagnosis of TGCT, and family history of testicular cancer indicate that exposures in early life and/or in the familial setting may be critical to determining risk. Previous reports of familial clustering of lung cancer in mothers and testicular cancers in sons suggest that passive smoking in childhood may be such an exposure. To clarify the relationship of passive smoking exposure to TGCT risk, data from 754 cases and 928 controls enrolled in the Servicemen's Testicular Tumor Environmental and Endocrine Determinants study were analyzed. Data from 1,086 mothers of the cases and controls were also examined. Overall, there was no relationship between maternal [odds ratio (OR), 1.1; 95% confidence interval (95% CI), 0.9-1.3] or paternal smoking (OR, 1.0; 95% CI, 0.8-1.3) and TGCT risk. Although living with a nonparent smoker was marginally related to risk (OR, 1.4; 95% CI, 1.0-2.1), there was no relationship with number of smokers, amount smoked, or duration of smoking. Responses from both case-control participants and mothers also revealed no relationship between either maternal smoking while pregnant or while breast-feeding. Results did not differ by TGCT histology (seminoma, nonseminoma). These results do not support the hypothesis that passive smoking, either in utero or in childhood, is related to risk of TGCT. Other early life exposures, however, may explain the familial clustering of lung cancer in mothers and TGCT in sons.

McHale CM, Smith MT. 2004 . Prenatal origin of chromosomal translocations in acute childhood leukemia: implications and future directions. Am J Hematol 75:254-257.
Abstract: We, and others, have demonstrated an **in utero origin for translocations associated with childhood leukemia**, with latency periods in some cases exceeding 10 years. The **mechanism of generation of most of the translocations is thought to be aberrant repair following abortive apoptosis**, rather than V(D)J recombination or exposure to topoisomerase II inhibitors. Folate supplementation may prevent some of the chromosome breakage leading to translocation formation. Translocations t(8;21) and t(12;21) have been shown to occur in the normal population (before birth) at a frequency that is 100-fold greater than the risk of developing the corresponding leukemia. In most instances, additional genetic changes are required for progression to leukemia. Tyrosine kinase receptor (RTK) mutations, which give cells a survival/proliferative advantage, are proposed to act cooperatively with fusion genes, leading to transformation. However, translocations and cooperating RTK mutations have not been identified for all leukemia subtypes, particularly in acute myeloid leukemia. The core binding transcriptional pathway is frequently targeted by translocation in utero. We propose that this pathway is highly sensitive during fetal hematopoiesis and may be targeted by mechanisms other than translocation. For each leukemia subtype it is important to characterize the corresponding leukemic stem cell, which is thought to be the initial target for translocation. This would help to elucidate the molecular pathways involved in the progression from preleukemic clone harboring a translocation to fully disseminated leukemia.

McHale CM, Wiemels JL, Zhang L, Ma X, Buffler PA, Feusner J, Matthay K, Dahl G, Smith MT. 2003 . Prenatal origin of childhood acute myeloid leukemias harboring chromosomal rearrangements t(15;17) and inv(16).

Blood 101:4640-4641.

McHale CM, Wiemels JL, Zhang L, Ma X, Buffler PA, Guo W, Loh ML, Smith MT. 2003 . Prenatal origin of TEL-AML1-positive acute lymphoblastic leukemia in children born in California. Genes Chromosomes & Cancer 37:36-43.
Abstract: Acute lymphoblastic leukemia (ALL) is the most common form of childhood cancer. The peak incidence of ALL between ages 2 and 5 is accounted for by one subtype, referred to as common acute lymphoblastic leukemia (cALL). About 25% of cALL patients have the TEL-AML1 gene fusion derived from the t(12;21) chromosomal translocation. Recent evidence from retrospective analysis of neonatal blood spots (Guthrie cards) in Europe has demonstrated that this chromosome translocation may arise prenatally. The aim of our study was to determine whether TEL-AML1 fusions arise prenatally in a U.S. population of cALL patients. TEL-AML1-positive cALL cases (n = 14) were identified by fluorescence in situ hybridization, and the genomic breakpoints were identified by a streamlined long-distance PCR approach and sequenced. Clonotypic primers were designed for each patient breakpoint, and a nested PCR assay was used to determine the presence of the TEL-AML1 fusion sequence in neonatal Guthrie cards. Seven of 14 cases demonstrated clonotypic sequences on the archival Guthrie cards. The oldest patient that was positive was 6.7 years old at the time of diagnosis of leukemia. These results confirm previously published findings of a prenatal origin of TEL-AML1 in Europe by demonstrating its occurrence in a California-born population. Secondary changes were also similar to those described previously, with deletion of the second TEL allele being the most common. Other secondary changes included duplication of the fusion gene, trisomy 21, and monosomy X.

Mckay JA, Williams EA, Mathers JC. 2004. Foliate and Dna Methylation During in Utero Development and Aging. Biochem Soc Trans 32:1006-1007.
Abstract: DNA methylation is one of several epigenetic mechanisms that play a regulatory role in genome programming and imprinting during embryogenesis. Aberrant DNA methylation has been implicated in the pathogenesis of a number of diseases associated with aging, including cancer and cardiovascular and neurological diseases. Evidence is accumulating that dietary factors in utero modulate disease risk in later life. Although folic acid is a key component of DNA methylation, the impact of folic acid availability in utero on DNA methylation patterns and disease risk in adulthood is at present poorly characterized. This review describes the relationship between folic acid and DNA methylation, and the association between DNA methylation during in utero development and aging.

Mckean-Cowdin R, Pogoda JM, Lijinsky W, Holly EA, Mueller BA, Preston-Martin S. 2003. Maternal prenatal exposure to nitrosatable drugs and childhood brain tumours. Int J Epidemiol 32:211-217.
Abstract: **Background** A compelling hypothesis was proposed that childhood brain tumours are associated with maternal exposure to N-nitroso compounds during the prenatal period. Many common drugs, such as antihistamines, aspirin, and antibiotics, are nitrosatable and depending upon the product, potentially carcinogenic. We hypothesized that maternal ingestion of certain subgroups of nitrosatable drug products during pregnancy increases the risk of brain tumour development in offspring. **Methods** Data were collected as part of a population-based case-control study of childhood brain tumours and mothers' self-reported exposure to therapeutic drugs and dietary nitrites. Cases were enrolled from three US West Coast SEER tumour registries: Seattle-Puget sound, Los Angeles County, and the San Francisco-Oakland Bay Area. Tumours were grouped into three major histological tumour subtypes: astroglial, primitive neural ectodermal tumours, and all remaining glial tumours ('other glial'). Therapeutic drugs reported by mothers were translated into active chemical compounds and classified as secondary amines, tertiary amines, amides, or none of the three. Risk estimates were computed according to classes of nitrosatability, potential carcinogenicity, teratogenicity, and predicted end product. **Results** We found no significant association between maternal use of nitrosatable drugs, either overall or within any of the nitrosatable drug classifications, and subsequent development of brain tumours in children. Nitrite consumption from cured meats was not an effect modifier. However, exposure to nitrosoephedrine during pregnancy was associated with significantly increased risk of 'other glial' tumours (OR = 3.1; 95% CI: 1.1-9.2). Conclusions These findings do not support an association between maternal use of nitrosatable drugs during pregnancy and brain tumour risk in offspring. While exposure to the nitrosation end product nitrosoephedrine was associated with increased risk for other glial tumours, the finding was not specific to any one type of tumour.

McKinney PA, Alexander FE, Cartwright RA, Parker L. 1991. Parental occupations of children with leukemia in West Cumbria, North-Humberside, and Gateshead. Br Med J 302:681-687.
Abstract: Objective-To determine whether parental occupations and chemical and other specific exposures are risk factors for childhood leukaemia. Design-Case-control study. Information on parents was obtained by home interview. Setting-Three areas in north England: Copeland and South Lakeland (west Cumbria); Kingston upon Hull, Beverley, East Yorkshire, and Holderness (north Humberside), and Gateshead. Subjects-109 children aged 0-14 born and diagnosed as having leukaemia or non-Hodgkin's lymphoma in study areas during 1974-88. Two controls matched for sex and date and district of birth were obtained for each child. Main outcome measures-Occupations of parents and specific exposure of parents before the children's conception, during gestation, and after birth. Other adults living with the children were included in the postnatal analysis. Results-Few risk factors were identified for mothers, although preconceptional association with the food industry was significantly increased in case mothers (odds ratio 2.56; 95% confidence interval 1.32 to 5.00). Significant associations were found between childhood leukaemia and reported preconceptional exposure of fathers to wood dust (2.73, 1.44 to 5.16), radiation (3.23, 1.36 to 7.72), and benzene (5.81, 1.67 to 26.44); ionising radiation alone gave an odds ratio of 2.35 (0.92 to 6.22). Raised odds ratios were found for paternal exposure during gestation, but no independent postnatal effect was evident. Conclusion-These results should be interpreted cautiously because of the small numbers, overlap with another study, and multiple exposure of some parents. It is important to distinguish periods of parental exposures; identified risk factors were almost exclusively restricted to the time before the child's birth.

McKinney PA, Juszczak E, Findlay E, Smith K, Thomson CS. 1999. Pre- and perinatal risk factors for childhood leukaemia and other malignancies: A Scottish case control study. Br J Cancer 80:1844-1851.
Abstract: A case control study of Scottish children aimed to identify risk factors for leukaemia and other cancers operating in the prenatal environment, during delivery and neonatally. Cases (0-14 years) were age- and sex- matched to two population-based controls and details abstracted from the mother's hospital obstetric notes. Analyses of 144 leukaemias (124 acute lymphoblastic leukaemias (ALL)), 45 lymphomas, 75 central nervous system (CNS) tumours and 126 'other solid tumours' were conducted using conditional logistic regression. The presence of a neonatal infection significantly reduced the risk of ALL (odds ratio (OR) 0.49, 95% confidence interval (CI) 0.26-0.95), particularly in 0- to 4-year-olds. Positive swab tests confirmed 47% of ALL cases with any infection and 46% of controls. This is consistent with the hypothesis that early exposure to infections may reduce the risk of childhood ALL. Asphyxia at birth significantly increased the risk of leukaemia, which was accounted for by ALL. For the 'other solid tumours' higher levels of maternal education were inversely associated with risk (OR 0.59, 95% CI 0.37-0.94) but positively associated with antibiotics (OR 2.16 95% CI 1.10-4.25) and respiratory tract infections (OR 14.1, 95% CI 1.76-113.7) in pregnancy. No obvious plausible patterns of risk were detected either within or across disease subgroups.

McLachlan JA. 1977. Prenatal exposure to diethylstilbestrol in mice: Toxicological studies. Journal of Toxicology & Environmental Health 2:527-537.
Abstract: The effect of prenatal exposure to diethylstilbestrol (DES) on the postnatal development of male and female genital tract function was studied. The placental transfer or radiolabeled (3H or 14C) DES was studied in pregnant mice. DES-associated radioactivity in the fetal plasma approximated that in maternal plasma 1/2 hr after intravenous administration of [3H]DES; 3H activity corresponding to DES in the fetal genital tract was about threefold higher. The decrease in reproductive capacity of female offspring from mice treated with DES during gestation was dose-related; a low incidence (10% or less) of cancer of the vagina, cervix, and/or uterus was also observed in these mice. Male offspring exposed prenatally to the highest dose (100 microng/kg) of DES in this study also had lower reproductive capacities. Lesions in the genital tract of these mice included epididymal cysts, inflammation, cryptorchidism, and nodular masses in the seminal vesicles and/or prostate gland. Such lesions and sterility were not observed at the lower DES doses. Histological studies with neonatal mice raise the possibility that Mullerian duct tissue may represent a site for the transplacental toxicity of DES in both the male and female fetus.

McLachlan JA, Newbold RR, Li S, Negishi M. 1998. Are estrogens carcinogenic during development of the testes? APMIS 106:240-2; discussion 243-4.
Abstract: Many chemicals in the environment mimic the female sex hormone, estrogen. Exposure to

environmental estrogens during early fetal development was proposed by Sharpe & Skakkebaek as a potential risk factor for subsequent testicular disease, including neoplasia and poor semen quality. To understand the mechanisms of action of estrogenic chemicals during differentiation of the male genital tract, we have studied developmental exposure to the synthetic estrogen, diethylstilboestrol (DES). While DES is a much more potent estrogen than most environmental chemicals examined, several of these compounds share some of the same properties as DES, such as a relative lack of binding to serum estrogen carrying proteins. Prenatal exposure to DES is associated with poor semen quality, prostatic disease, cryptorchidism and testicular neoplasia in mice. A rare form of testicular cancer, rete testis carcinoma, was observed in five percent of male mice treated in utero with DES. We also demonstrated altered regulation of an estrogen responsive gene, lactotransferrin (LTF) in the seminal vesicles of treated mice, but not the controls. Likewise, LTF was irreversibly altered in the uteri of developmentally treated females; at the molecular level altered methylation of the gene appears to be involved, thus, providing a potential marker for hormonal effects during development. The induction of permanent or "imprinted" responses during the development of a relatively estrogen-free reproductive tract cell suggests that undifferentiated targets for estrogen action may be sites for subsequent growth and differentiation defects associated with neoplasia.

McLaughlin CC, Baptiste MS, Schymura MJ, Nasca PC, Zdeb MS. 2006. Birth weight, maternal weight and childhood leukaemia. Br J Cancer 94:1738-1744.
Abstract: There is mounting evidence that childhood leukaemia is associated with high birth weight, but few studies have examined the relationship between leukaemia and other perinatal factors that influence birth weight, such as maternal weight or gestational weight gain. This case-cohort study included 916 acute lymphocytic leukaemia (ALL) and 154 acute myeloid leukaemia (AML) cases diagnosed prior to age 10 years between 1985 and 2001 and born in New York State excluding New York City between 1978 and 2001. Controls (n = 9686) were selected from the birth cohorts for the same years. Moderate increased risk of both ALL and AML was associated with birth weight 3500 g or more. For ALL, however, there was evidence of effect modification with birth weight and maternal prepregnancy weight. High birth weight was associated with ALL only when the mother was not overweight while heavier maternal weight was associated with ALL only when the infant was not high birth weight. Increased pregnancy-related weight gain was associated with ALL. For AML, birth weight under 3000 g and higher prepregnancy weight were both associated with increased risk. These findings suggest childhood leukaemia may be related to factors influencing abnormal fetal growth patterns.

Meinert R, Kaletsch U, Kaatsch P, Schuz J, Michaelis J. 1999. Associations between childhood cancer and ionizing radiation: Results of a population-based case-control study in Germany. Cancer Epidemiology Biomarkers & Prevention 8:793-799.
Abstract: In order to investigate the associations between sources of exposure to ionizing radiation and childhood cancer in Germany, a matched case-control study including children under the age of 15 years was conducted. Cases were identified from the German Childhood Cancer Registry; controls came from population registration offices. Exposure was assessed via questionnaires and parental interviews. The study comprises 1184 leukemia cases, 234 non-Hodgkin's lymphomas, 940 solid tumors, and 2588 controls. Preconception parental occupational exposures were positively but not statistically significantly related to all of the cancer types in the study. Maternal occupational exposure during pregnancy was a risk factor for childhood lymphomas [odds ratio (OR) = 3.87, 95% confidence interval (CI): 1.54-9.75] but not for leukemia or solid tumors. ORs for parental occupational exposures were noticeably more pronounced in leukemia cases who were diagnosed in their first 18 months of life. A preconception paternal occupation in the nuclear industry under dosimetric surveillance yielded an OR of 1.80 (95% CI: 0.71-4.58), However, radiation doses of these fathers were often unknown or below the level of detection, and no dose exceeded 30 mSv, Prenatal X-ray examinations of the father (but not of the mother) were significantly related to childhood leukemia (OR = 1.33; 95% CI: 1.10-1.61), No effects were observed for postnatal X-ray examinations of the child, The results suggest that, in Germany at present, exposures to ionizing radiation do not play a noticeable role in the development of childhood cancers. The major strengths of the study are its size and the population basis. The validity of the data from parental questionnaires and the possibility of residual confounding by socioeconomic factors are potential drawbacks.

Meinert R, Schuz J, Kaletsch U, Kaatsch P, Michaelis J. 2000. Leukemia and non-Hodgkin's lymphoma in

childhood and exposure to pesticides: Results of a register-based case-control study in Germany. Am J Epidemiol 151:639-46; discussion 647-50.
Abstract: Previous studies have suggested an association between exposure to pesticides and different types of childhood cancer. This paper presents results from a population-based case-control interview study of parents of children less than 15 years of age, which was conducted in the states of West Germany from 1993 to 1997. Cases were 1,184 children with leukemia, 234 with non-Hodgkin's lymphoma, and 940 with a solid tumor; 2,588 controls were also included. Parental occupational exposures were found to be related to childhood cancer regardless of the time period of exposure and the type of cancer. This finding might partially be explained by different recall of past exposures by the parents of cases and controls. Residential use of insecticides was associated with childhood lymphoma: both extermination of insects by professional pest controllers (odds ratio (OR) = 2.6, 95% confidence interval (CI): 1.2, 5.7) and frequency of parental use of household insecticides (p for trend = 0.02) were significant risk factors for this diagnosis. The use of pesticides on farms was weakly related to childhood leukemia (OR = 1.5, 95% CI: 1.0, 2.2), while their use in gardens was not associated with childhood leukemia (OR = 1.0, 95% CI: 0.8, 1.2). The major strengths of this study were the population base and the large number of cases and controls included; a drawback was assessment of exposure on the basis of parental interviews. The data provide some evidence for an increased leukemia risk for children living on farms and for an association between use of household pesticides and risk of childhood leukemia or lymphoma.

Mellemkjaer L, Olsen ML, Sorensen HT, Thulstrup AM, Olsen J, Olsen JH. 2003. Birth weight and risk of early-onset breast cancer (Denmark). Cancer Causes & Control 14:61-64.
Abstract: OBJECTIVE: To investigate if birth weight is associated with early-onset breast cancer. The mechanism behind an association with high birth weight could be the link between fetal growth and estrogens in utero. METHODS: We conducted a population-based case-control study in Denmark including 881 women with breast cancer diagnosed before the age of 40 years and 3,423 age-matched controls. Information concerning birth weight and other birth-related variables was obtained from midwife reports. RESULTS: The risk of early-onset breast cancer was increased 1.25 times (95% CI 1.00-2.51) for birth weights above 4,000 g and 1.59 times (95% CI 1.00-1.55) for birth weights below 2,500 g in comparison with birthweights of 3,000-3,499 g. CONCLUSIONS: The finding that high birth weight is associated with breast cancer is compatible with the hypothesis that level of estrogen during pregnancy is related to breast cancer in early adult life. The finding that low birth weight is also associated with breast cancer may indicate that other characteristics of the fetal environment may be important for breast cancer in early adult life.

Menegaux F, Baruchel A, Bertrand Y, Lescoeur B, Leverger G, Nelken B, Sommelet D, Hémon D, Clavel J. 2006. Household exposure to pesticides and risk of childhood acute leukaemia. Occupational & Environmental Medicine 63:131-134.
Abstract: OBJECTIVES: To investigate the relation between childhood acute leukaemia and household exposure to pesticides. METHODS: The study included 280 incident cases of acute leukaemia and 288 controls frequency matched on gender, age, hospital, and ethnic origin. The data were obtained from standardised face to face interviews of the mothers with detailed questions on parental occupational history, home and garden insecticide use, and insecticidal treatment of pediculosis. Odds ratios were estimated using unconditional regression models including the stratification variables parental socioeconomic status and housing characteristics. RESULTS: Acute leukaemia was observed to be significantly associated with maternal home insecticide use during pregnancy (OR = 1.8, 95% CI 1.2 to 2.8) and during childhood (OR = 1.7, 95% CI 1.1 to 2.4), with garden insecticide use (OR = 2.4, 95% CI 1.3 to 4.3), and fungicide use (OR = 2.5, 95% CI 1.0 to 6.2) during childhood. Insecticidal shampoo treatment of pediculosis was also associated with childhood acute leukaemia (OR = 1.9, 95% CI 1.2 to 3.3). CONCLUSION: The results reported herein support the hypothesis that various types of insecticide exposure may be a risk factor for childhood acute leukaemia. The observed association with insecticidal shampoo treatment of pediculosis, which has never been investigated before, requires further study.

Mericskay M, Carta L, Sassoon D. 2005. Diethylstilbestrol exposure in utero: A paradigm for mechanisms leading to adult disease. Birth Defects Research Part a-Clinical & Molecular Teratology 73:133-135.
Abstract: The synthetic estrogen diethylstilbestrol (DES) was administered to pregnant women between the 1940s and the mid-1970s and is believed to be responsible for numerous uterine/cervical/vaginal

malformations and cancers that appeared after birth and in young adult life. This medical tragedy has served as one of the prototypical examples of a phenomenon known as "endocrine disruption," in which either environmental agents or other compounds disrupt normal hormonal signaling in the body. Whereas DES signals through estrogen receptors, the subsequent molecular targets were largely unknown. We had identified Wnt7a as a target in this pathway and have used genetic analyses of mutant mice to demonstrate that disruption of Wnt7a is the key event leading to the DES phenotypes and cancers. We find that Wnt7a expression is only transiently deregulated in response to DES exposure, leading to the conclusion that critical events during early reproductive tract development results in a permanent change or "reprogramming" in subsequent development.

Michaelis J, Kaletsch U, Kaatsch P. 2000. Epidelmiology of childhood brain tumours. Zentralbl Neurochir 61:80-87.
Abstract: The German Childhood Cancer Registry (GCCR) was established in 1980. From 1980 to 1997 5.447 CNS tumours in children below 15 years of age have been reported to the registry. From 1980 to 1997 the average annual incidence was 2.5/100,000 children. This corresponds to 19.2% of the registered diseases. Compared with incidence rates reported from other developed countries one can estimate that there is about 25% underreporting of CNS tumours in the GCCR. This is in contrast to the relatively complete ascertainment of other childhood malignancies (above 95%). Based on 3012 incident cases from 1988 to 1997 the Kaplan-Meier-estimate of 5-year-survival probability is 65% for all CNS tumours and 54% for PNETs and gliomas. An active Long-term-follow-up shows that 30% of 142 children with secondary neoplasms following primary lymphoid leukaemias developed a CNS tumour. Following any primary childhood malignancies 45 CNS tumours were recorded, amongst these were one third leukaemias. The paper reports first results from a population based case control study which included 466 children with CNS tumours and 2,458 healthy controls. These indicate an increased risk for children with low birth weight and for children whose mothers smoked during pregnancy Additional data can be found in the Internet (http:info.imsd.uni-mainz.de/ K_Krebsregister).

Michaelis J, Schuz J, Meinert R, Zemann E, Grigat JP, Kaatsch P, Kaletsch U, Miesner A, Brinkmann K, Kalkner W, Karner H. 1998. Combined risk estimates for two German population-based case-control studies on residential magnetic fields and childhood acute leukemia. Epidemiology 9:92-94.
Abstract: From 1992 to 1996, we obtained electromagnetic field measurements in two population-based case-control studies on childhood leukemia in the northwestern part of Germany and in Berlin. Exposure assessment comprised residential 24-hour measurements and short-term measurements. We obtained 24-hour measurements for a fetal of 176 cases and 414 controls. We compared subjects exposed to median 24-hour measurements of 0.2 mu T or more with those exposed to lower amounts. Multivariate regression analysis revealed an odds ratio of 2.3(95% confidence interval = 0.8-6.7).

Michels KB, Trichopoulos D, Robins JM, Rosner BA, Manson JE, Hunter DJ, Colditz GA, Hankinson SE, Speizer FE, Willett WC. 1996. Birthweight as a risk factor for breast cancer. Lancet 348:1542-1546.
Abstract: Background The mammary gland is largely undifferentiated before birth and may be particularly susceptible to intrauterine influences that could increase the risk of cancer through acceleration of cell proliferation or other pregnancy-related processes. Studies of migrant populations, animal data, and limited epidemiological evidence suggest that breast cancer may originate in utero. In a nested case-control study we assessed whether birthweight and other perinatal factors are associated with risk of breast cancer. Methods This case-control study was nested within the cohorts of the two Nurses' Health Studies. We used self-administered questionnaires to obtain information from the mothers of 582 nurses with. invasive breast cancer and the mothers of 1569 nurses who did not have breast cancer (controls). Information on risk factors for breast cancer during adulthood were obtained from the nurses; multiple logistic regression analysis adjusted for these risk factors. Findings Birthweight was a significant predictor of breast-cancer risk. With women who weighed 4000 g or more at birth as the reference category, the adjusted odds ratios for breast cancer were 0.86 (95% CI 0.59-1.25) for birthweights of 3500-3999 g, 0.68 (0.48-0.97) for birthweights of 3000-3499 g, 0.66 (0.45-0.98) for birthweights of 2500-2999 g, and 0.55 (0.33-0.93) for birthweights below 2500 g (p for trend 0.004). Prematurity was not significantly associated with risk of breast cancer. Interpretation Birthweight is significantly associated with breast-cancer risk, which suggests that intrauterine factors or processes affect the risk of breast cancer in the offspring, High concentrations of pregnancy oestrogens may have an important role in breast carcinogenesis, but other pregnancy hormones or intrauterine factors may also be involved.

Michels KB, Xue F. 2006. Role of birthweight in the etiology of breast cancer. Int J Cancer 119:2007-25.
Abstract: Breast cancer may originate in utero. We reviewed the available evidence on the association between birthweight and the risk of breast cancer. To date, 26 research papers addressing this issue have been published. The majority of studies identified a positive link between birthweight and premenopausal, but not postmenopausal, breast cancer. The relative risk estimate for breast cancer comparing women with high birthweight to women with low birthweight combining all studies including both pre- and postmenopausal breast cancer was 1.23 (95% confidence interval 1.13-1.34). The mechanisms underlying this association likely include elevated levels of growth factors that may increase the number of susceptible stem cells in the mammary gland or initiate tumors through DNA mutations. Loss of imprinting (LOI) of growth hormone genes relevant for intrauterine growth, such as insulin-like growth factor 2 (IGF2), leads to abnormally high levels of these hormones evidenced by high birthweight. LOI of IGF2 has also been found in mammary tumor tissue. The role of environmental factors that stimulate such epigenetic regulation of gene expression remains to be elucidated.

Milham S, Ossiander EM. 2001. Historical evidence that residential electrification caused the emergence of the childhood leukemia peak. Med Hypotheses 56:290-295.
Abstract: A peak in childhood leukemia, ages two through four, emerged de novo in the 1920s in the United Kingdom and slightly later in the United States (US). Electrification in US farm and rural areas lagged behind urban areas until 1956. In recent years, childhood leukemia has been associated with residential electromagnetic fields. During 1928-1932, in states with above 75% of residences served by electricity, leukemia mortality increased with age for single years 0-4, while states with electrification levels below 75% showed a decreasing trend with age (P = 0.009). During 1949-1951, all states showed a peak in leukemia mortality at ages 2-4. At ages 0-1, leukemia mortality was not related to electrification levels. At ages 2-4, there was a 24% (95% confidence interval (CI), 8%-41%) increase in leukemia mortality for a 10% increase in percent of homes served by electricity. The childhood leukemia peak of common acute lymphoblastic leukemia may be attributable to electrification.

Miller KP, Borgeest C, Greenfeld C, Tomic D, Flaws JA. 2004. In utero effects of chemicals on reproductive tissues in females. Toxicology & Applied Pharmacology 198:111-131.
Abstract: Chemicals found in the environment as industrial byproducts or pollutants as well as those that are prescribed or part of our daily lives can have multiple effects on the human body. The manner in which we are exposed, and the levels we are exposed to are significant contributing factors. Adults have the bodily defense mechanisms in place to combat exposures to adverse toxicants and general pollution at a variety of levels. However, developing organisms may not have adequate defense mechanisms, and toxicants can have a significant effect on their health and development. In this review, we take particular note of the toxicities of chemicals on the developing female reproductive system as a result of in utero exposure. Environmental and prescribed chemicals such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), polychlorinated biphen, Is (PCBs), polycyclic aromatic hydrocarbons (PAHs), diethylstilbestrol, and genistein, as well as others, will be reviewed for their in utero toxicity in the neuroendocrine system, the ovary, oviduct, placenta, uterus, vagina, cervix, and mammary gland. (C) 2004 Elsevier Inc. All rights reserved.

Minke JM, Weijer K, Misdorp W. 1991 . Allotransplantation of K248 feline mammary carcinoma cell line in cats. A model for monoclonal antibody guided detection and therapy of human breast cancer. Lab Invest 65:421-432.
Abstract: In response to the need for appropriate models for monoclonal antibody guided detection and therapy of human breast cancer, we developed an allogeneic host-tumor model by injecting K248C and K248P cells into cats. A comparison between the K248C- and K248P-induced tumors with respect to biological behavior and histological appearance was made throughout the study. Allotransplantation of tumor cells was performed both in newborn cats and fetal cats between days 42 and 51 of gestation, but only tumor cells injected by the latter approach resulted in tumor growth in all animals injected. Both tumor cell lines gave rise to progressively growing tumors at the site of injection, metastatic spread of tumor cells to various organs, and death from progression 2-4 months after birth. The predominant histological appearance of the K248C and K248P allografts resembled the cribriform and tubulo-papillary growth patterns, respectively, of the original tumor from which the two cell lines were derived. Autopsy of 1-day kittens showed that metastasis started already in the fetus in the short period between injection of tumor

cells and birth. Three predominant patterns of metastases were identified: the pulmonary/pleural type, the abdominal type, and the soft tissue type. A lower incidence of metastases was found in bones and brain. The K248C allografts formed significantly more metastases of the abdominal type than K248P tumors (p less than 0.05). No difference in survival was observed between animals with K248C or K248P allografts. The difference in take rate and latency period between K248C and K248P in athymic mice does not seem to be present in the feline host. The similarity of the present model to spontaneous feline and human mammary carcinoma is discussed.

Mittendorf R. 1995. Teratogen update: Carcinogenesis and teratogenesis associated with exposure to diethylstilbestrol (DES) in utero. Teratology 51:435-445.
Abstract: Exposure of the human fetus to physician-prescribed diethylstilbestrol and other synthetic estrogens (collectively referred to as "DES") led to an important iatrogenic epidemic. In the United States alone, at least four million fetuses and their mothers had a substantial exposure to these estrogens now known to be mild carcinogens and potent teratogens. Mothers exposed to DES may have a somewhat higher risk of breast cancer than women who were not exposed. The sequelae of in utero exposure of daughters include clear cell adenocarcinoma of the vagina and cervix, various gross anomalies of the genital tract that are associated with adverse outcomes of pregnancy, vaginal adenosis and other vaginal epithelial changes, and other possible health effects that have not yet been fully evaluated. Among sons exposed in utero to DES, no increase in the incidence of any cancer has been reported, but several anomalies of the genital tract have been described, and it is possible that some social behaviors are modified. Although the grandchildren of the DES-exposed daughters and sons have not been shown to have any abnormalities, some of them have been the products of short gestations. Future research, being funded by the National Cancer Institute, will permit monitoring of the DES-exposed population to determine whether any other abnormalities will become apparent in them.

Miura M, Yachie A, Hashimoto I, Okabe T, Murata N, Fukuda A, Koizumi S. 2000 . Coexistence of lymphoblastic and monoblastic populations with identical mixed lineage leukemia gene rearrangements and shared immunoglobulin heavy chain rearrangements in leukemia developed in utero. J Pediatr Hematol Oncol 22:81-85.
Abstract: Congenital leukemia often provides insight into mechanisms of in utero leukemogenesis. A 10-day-old boy with clinical features of skin nodules, marked hepatosplenomegaly, and subcutaneous bleeding received a diagnosis of congenital leukemia. This patient initially had a dominant B progenitor lymphoblast population and minor monocyte component. Treatment with prednisolone, vincristine, and doxorubicin resulted in a loss of lymphoblast population and a rapid increase and dominance of the monocyte component within 10 days. Complete remission initially was obtained with additional combination chemotherapy with epipodophyllotoxin (VP-16) and cytosine arabinoside (Ara-C), but relapse characterized by a lymphoblastic population in the bone marrow was subsequently observed. The authors hypothesize that the leukemic cells originated from a common B-monocyte lineage stem cell during fetal hematopoiesis.

Mogren I, Malmer B, Tavelin B, Damber L. 2003. Reproductive factors have low impact on the risk of different primary brain tumours in offspring. Neuroepidemiology 22:249-254.
Abstract: Objectives: The aim of our study was to investigate whether reproductive factors influence the risk of primary brain tumours (PBT) in offspring. Methods: Data on all deliveries in two Swedish counties from 1955 to 1990 were extracted from two birth registries. The follow-up period closed at the end of 1994, with subjects followed up to early middle age. Incidence rates of malignancy for 1958-1994 were obtained from the Swedish Cancer Registry. Standardised incidence ratios (SIR) and relative risks were calculated for astrocytomas, primitive neuroectodermal tumour, ependymoma and menepiiomas in offspring. Results: Few associations were detected. High birth weight indicated an increased risk for astrocytomas grade I and II for all primary brain tumours, and the risk was close to significance for astrocytomas grade I-II (SIR = 3.64; CI = 0.98-9.31). For children under 15 years of age the risk for astrocytomas grade I and II was further increased (SIR = 4.44; Cl = 1.19-11.38). Conclusions:A consistent pattern of non-association indicated a low impact of intrauterine environment on the future development of primary brain tumours in offspring up to early middle age. Copyright (C) 2003 S. Karger AG, Basel.

Mohr U, Dasenbrock C, Tillmann T, Kohler M, Kamino K, Hagemann G, Morawietz G, Campo E, Cazorla M,

Fernandez P, Hernandez L, Cardesa A, Tomatis L. 1999 . Possible carcinogenic effects of X-rays in a transgenerational study with CBA mice. Carcinogenesis 20:325-332.
Abstract: A lifetime experiment using 4279 CBA/J mice was carried out to investigate whether the pre-conceptual exposure of sperm cells to X-ray radiation or urethane would result in an increased cancer risk in the untreated progeny, and/or increased susceptibility to cancer following exposure to a promoting agent. The study consisted of four main groups, namely a control group (saline), a urethane group (1 mg/g body wt) and two X-ray radiation groups (1 Gy, 2 Gy). At 1, 3 and 9 weeks after treatment, the males of these four parental groups were mated with untreated virgin females. The offspring of each parental group was divided into two subgroups: one received s.c. urethane (0.1 mg/g body wt once) as a promoter, the other saline, at the age of 6 weeks. All animals were evaluated for the occurrence of tumours. K-ras oncogene and p53 tumour suppressor gene mutations were investigated in frozen lung tumour samples. The female offspring of male parents exposed to X-rays 1 week before their mating showed a trend towards a higher tumour incidence of the haematopoietic system than the F1 controls. In addition, a higher percentage of bronchioloalveolar adenocarcinomas in male offspring born to irradiated paternals mated 1 week after X-ray treatment points to a plausible increased sensitivity of post-meiotic germ cell stages towards transgenerational carcinogenic effects. On the other hand, no increased tumour incidence and malignancy were observed in the offspring born to irradiated paternals mated 3 and 9 weeks after X-ray treatment. Paternal urethane treatment 1, 3 and 9 weeks prior to conception did not result in significantly altered incidence or malignancy of tumours of the lung, liver and haematopoietic tissue in the offspring. K-ras mutations increased during tumour progression from bronchioloalveolar hyperplasia to adenoma. Codon 61 K-ras mutations were more frequent in lung tumours of urethane-promoted progeny from irradiated parents than from control parents. P53 mutations were absent from these lung alterations.

Mohr U, Emura M, Kamino K, Steinmann J, Kohler M, Morawietz G, Dasenbrock C, Tomatis L. 1995. Increased risk of cancer in the descendants of Syrian hamsters exposed prenatally to diethylnitrosamine (DEN). Int J Cancer 63:86-91.
Abstract: Transmission of site-specific tumorigenicity (papillomas in larynx and trachea) of diethylnitrosamine (DEN) to the 2 subsequent generations (F1 and F2) was studied using an outbred strain (Han:AURA) of pregnant Syrian golden hamsters (P generation), which were treated i.p. with 10 mg/kg b.w. of DEN on day 12, 13 or 14 of gestation. Laryngotracheal papillomas were induced by DEN in the P and F1 generations only, while these tumours did not occur in the F2 generation. Spontaneously occurring tumours, including uterine adenocarcinomas, lymphomas, and laryngotracheal neuro-endocrine cell tumours, were observed at higher incidences among the F2 animals derived from the P generation hamsters treated with DEN only on day 13 or 14 of gestation. In the same animals, the ratio of malignant to benign tumours was considerably higher than in controls. In addition, the F2 hamsters derived from the DEN-treated P generation showed more frequent multiple organ involvement in tumorigenesis than the F2 controls. Several uncommon malignant tumours were detected in the F2 offspring, possibly the result of damage caused to germ cells by the prenatal exposure of F1 Syrian hamsters to DEN.

Mohr U, Reznik-Schuller H, Emura M. 1979 . Tissue differentiation as a prerequisite for transplacental carcinogenesis in the hamster respiratory system, with specific respect to the trachea. Natl Cancer Inst Monogr :117-122.
Abstract: The significance of tissue differentiation for the transplacental carcinogenicity of DEN was examined. In one experiment, pregnant Syrian golden hamsters received a single sc injection of DEN on one of the different days of pregnancy. Approximately 95% of the offspring of those mothers treated on one of the last 4 days (days 12--15) of gestation developed respiratory tract tumors. Transplacental DEN treatment before the 12th prenatal day failed to induce any neoplastic response in the young. In the second experiment, the differentiation of the prenatal Syrian golden hamster tracheal epithelium was examined histologically and by electron microscopy. We found that on the 12th prenatal day the ER occurred for the first time in its functionally competent form. On earlier prenatal days, the epithelial cells lacked this organelle. We conclude that this development of ER is a prerequisite for transplacental DEN carcinogenesis, since this organelle contains the nonspecific enzyme systems necessary for the transformation of DEN to its ultimate carcinogen.

Mohr U, Reznik-Schuller H, Reznik G, Hilfrich J. 1975. Transplacental effects of diethylnitrosamine in Syrian hamsters as related to different days of administration during pregnancy. J Natl Cancer Inst 55:681-683.

Abstract: Female Syrian hamsters were given a single sc dose of 45 mg diethylnitrosamine (DEN)/kg body weight on 1 of the 15 days of pregnancy. In the offspring of females treated on 1 of the first 11 days of pregnancy, no respiratory tract tumors were found. The offspring of mothers given DEN on 1 of the last 4 days (12-15) of pregnancy developed respiratory tract neoplasms at a rate of up to 95%. A lower incidence of tumors in other organs seemed independent of the day of DEN treatment.

Moller H, Skakkebaek NE. 1997. Testicular cancer and cryptorchidism in relation to prenatal factors: case-control studies in Denmark. Cancer Causes & Control 8:904-912.
Abstract: To explore prenatal risk factors that are common to testicular cancer and cryptorchidism, two parallel case-control studies were conducted in Denmark. Information about characteristics of the mother, the pregnancy, and the birth were obtained from the mothers of cases and controls, using a mailed self-administered questionnaire. A maternal age above 30 years was associated with odds ratios (OR) of 1.9 (95 % CI=1.2-3.0) for cryptorchidism and 2.0 (CI= 1.2-3.6) for testicular seminoma; the latter effect was particularly high when the boy was the first child of the mother (OR = 4.1, CI=1.1-14.6). Birthweights below 3,000 g or above 4,000 g were associated with increased risks of testicular cancer, with ORs up to 2.6 (CI = 1.1-5.9) for birthweight below 2,500 g. For cryptorchidism, there was a monotonous trend in the OR from 0.4 birthweights above 4,500 g to 2.3 in birthweights below 2,500 g. The association between cryptorchidism and testicular cancer was not attenuated by adjustment for maternal age and birthweight, indicating that all three variables are independent risk factor for testicular cancer. With the exception of high maternal age, which consistently is associated more strongly with seminoma than with non-seminoma, it remains most likely that seminoma and non-seminoma have similar causes.

Monis B, Valentich MA, Urrutia R, Rivolta M. 1991. Multicentric focal acinar cell hyperplasia and hepatocyte-like cell metaplasia are induced by nitrosomethylurea in rat pancreas. Int J Pancreatol 8:119-131.
Abstract: The present report is a study of the effect of the carcinogen nitrosomethylurea (NMU) on pancreas of rats receiving during lifetime a lipid-poor diet, that is essential fatty acid deficient or control diets. Rats fed a commercial stock chow were mated. At day 10 of pregnancy, dams were divided into three groups, that were respectively supplied with the commercial chow, the essential fatty acid deficient or the sufficient diet. Each litter was separated at random in two groups that received at day one of life one intraperitoneal injection of NMU (50 mg/kg b.w.) or saline. After weaning, they were maintained for life with the diet that was supplied to their mothers. The pancreas of NMU-treated rats presented diffuse proliferative changes, focal acinar cell hyperplasias (FACH), and focal hepatocyte-like metaplasia (FHLCM). FACH were expansive presumably preneoplastic growths, showing abnormal differentiation. The number of NMU-treated rats bearing FACH and FHLCM did not significantly differ in the three nutritional conditions.

Monk D, Sanches R, Arnaud P, Apostolidou S, Hills FA, Abu-Amero S, Murrell A, Friess H, Reik W, Stanier P, Constancia M, Moore GE. 2006. Imprinting of IGF2 P0 transcript and novel alternatively spliced INS-IGF2 isoforms show differences between mouse and human. Hum Mol Genet 15:1259-1269.
Abstract: Genomic imprinting is limited to a subset of genes that play critical roles in fetal growth, development and behaviour. One of the most studied imprinted genes encodes insulin-like growth factor 2, and aberrant imprinting and DNA methylation of this gene is associated with the growth disorders Beckwith-Wiedemann and Silver-Russell syndromes and many human cancers. Specific isoforms of this gene have been shown to be essential for normal placental function, as mice carrying paternal null alleles for the Igf2-P0 transcript are growth restricted at birth. We report here the identification of three novel human transcripts from the IGF2 locus. One is equivalent to the mouse Igf2-P0 transcript, whereas the two others (INSIGF long and short) originate from the upstream INS gene that alternatively splices to downstream IGF2 exons. In order to elucidate the molecular mechanisms involved in the complex imprinting of these novel IGF2 transcripts, both the allele-specific expression and methylation for all the IGF2 promoters including P0 and the INSIGF transcripts were analysed in human tissues. Similar to the mouse, the human IGF2-P0 transcript is paternally expressed; however, its expression is not limited to placenta. This expression correlates with tissue-specific promoter methylation on the maternal allele. The two novel INSIGF transcripts reported here use the INS promoter and show highly restricted tissue expression profiles including the pancreas. As previously reported for INS in the yolk sac, we demonstrate complex, tissue-specific imprinting of these transcripts. The finding of additional transcripts within this locus will have important implications for IGF2 regulation in both cancer and metabolism.

Moore LE, Gold L, Stewart PA, Gridley G, Prince JR, Zahm SH. 2005. Parental occupational exposures and Ewing's sarcoma. Int J Cancer 114:472-478.
Abstract: A case-control study of Ewing's sarcoma (ES) was conducted to search for occupational exposures associated with ES. The study consisted of 196 cases and 196 random-digit controls matched on geographical region, gender, ethnic origin and birth date. A questionnaire was administered to mothers of participants to obtain information on medical conditions, medications, and parental occupations during and after the index pregnancy. An occupational exposure expert coded jobs and industries for possible and probable exposure to selected occupational hazards. Risk of ES was increased with probable parental exposure to wood dusts during their usual occupation post pregnancy (odds ration [OR] = 3.2; 95% confidence interval [CI] = 1.1-9.2). Other exposures, including a priori suspected risk factors such as exposure to pesticides and farm animals, were not significantly associated with ES. A history of household pesticide extermination was associated with ES among boys aged 15 or younger (OR = 3.0; 95% CI = 1.1-8.1), but not among girls or older boys. Our results suggest that earlier reports of associations of ES with parental farm employment may have been describing risks associated with organic dusts encountered when working on a farm, rather than agricultural exposures or other farming related exposures. (C) 2004 Wiley-Liss, Inc.

Moore SW, Satge D, Sasco AJ, Zimmermann A, Plaschkes J. 2003. The epidemiology of neonatal tumours - Report of an international working group. Pediatr Surg Int 19:509-519.
Abstract: Neonatal tumours occur every 12,500-27,500 live births and comprise 2% of childhood malignancies, but there is little clarity as to their real prevalence, sites of origin and pathological nature as reported series vary. As an entity, neonatal tumours provide a unique window of opportunity to study tumours in which minimal environmental interference has occurred. The majority of tumours present with a mass at birth (e.g., teratomas, neuroblastomas, mesoblastic nephroma, fibromatosis), which are not infrequently identified on antenatal ultrasound. Histologically, teratoma and neuroblastoma remain the two main tumour types encountered with soft tissue sarcoma, renal tumours, CNS tumours and leukaemia being the next most common tumour types identified. Malignant tumours are uncommon in the neonatal period per se and benign tumours may have malignant potential. A particular problem exists in clinical classification, as histological features of malignancy do not always correlate with clinical behaviour. Benign tumours may also be life threatening because of their size and location. Other tumours may demonstrate local invasiveness, but no metastatic potential, and tumours that are clearly malignant may demonstrate unpredictable or uncertain behaviour. Screening programmes have brought more tumours to light, but do not appear to affect the overall prognosis. They may provide clues to the stage at which tumours develop in foetu. The aetiology of cancer in children is multifactorial and includes both genetic and environmental factors. The association between congenital abnormalities and tumours is well established (15% of neonatal tumours). Genetic defects are highly likely in neonatal tumours and include those with a high risk of malignancy (e.g., retinoblastoma), but also genetically determined syndromes with an increased risk of malignancy and complex genetic rearrangements. Tumours are mostly genetically related at a cellular level and factors influencing cellular maturation or apoptosis within the developing foetus may continue to operate in the neonatal period. Cytogenetics of neonatal neoplasms appear to differ from neoplasms in older children, thus possibly explaining some of the observed differences in clinical behaviour. Certain constitutional chromosome anomalies, however, specifically favour tumuors occurring in the foetal and neonatal period. In support of this hypothesis, certain cytogenetic anomalies appear to be specific to neonates, and a number of examples are explored. Other environmental associations include ionizing radiation, drugs taken during pregnancy, infections, tumours in the mother and environmental exposure.

Morrison SJ, White PM, Zock C, Anderson DJ. 1999 . Prospective identification, isolation by flow cytometry, and in vivo self-renewal of multipotent mammalian neural crest stem cells. Cell 96:737-749.
Abstract: Multipotent and self-renewing neural stem cells have been isolated in culture, but equivalent cells have not yet been prospectively identified in neural tissue. Using cell surface markers and flow cytometry, we have isolated neural crest stem cells (NCSCs) from mammalian fetal peripheral nerve. These cells are phenotypically and functionally indistinguishable from NCSCs previously isolated by culturing embryonic neural tube explants. Moreover, in vivo BrdU labeling indicates that these stem cells self-renew in vivo. NCSCs freshly isolated from nerve tissue can be directly transplanted in vivo, where they generate both neurons and glia. These data indicate that neural stem cells persist in peripheral nerve into late gestation by

undergoing self-renewal. Such persistence may explain the origins of some PNS tumors in humans.

Moss AR, Osmond D, Bacchetti P, Torti FM, Gurgin V. 1986. Hormonal risk factors in testicular cancer: A case-control study. Am J Epidemiol 124:39-52.
Abstract: The authors interviewed 273 northern California testicular cancer cases aged 40 and under diagnosed between 1976 and 1981, their mothers, and matched peer controls and their mothers on prenatal hormone exposure and other variables. Included was a population-based substudy (1979-1981) of all interviewable cases reported to the San Francisco Bay Area Surveillance, Epidemiology, and End Results registry. They found odds ratios (OR) of from 8.3 (sons'report) to 4.5 (mothers' report) associated with cryptorchidism, but found no association with mothers' hormone exposure or diethylstilbestrol exposure in pregnancy. They also found a significant association with lower age at puberty (OR = 2.0); a marginally significant association with mothers' breast cancer (OR =2.9, p=0.054); and a significant protective effect of reported mononucleosis (OR=0.6). These associations remained strong in the population-based substudy. When cases were divided by histology, strong and specific associations of earlier puberty (OR = 2.3) and mothers' breast cancer (OR =4.4) with nonseminomatous cancer, and of reported mononucleosis (OR 0.3) with seminomatous cancer, were found. These observations suggest that 1) prenatal exogenous hormone exposure does not account for a significant fraction of testicular cancer, 2) a cluster of "breast-cancer-like" risk factors are associated with nonseminomas, and 3) there is some genetic risk of nonseminomas.

Mueller BA, Newton K, Holly EA, Preston-Martin S. 2001. Residential water source and the risk of childhood brain tumors. Environ Health Perspect 109:551-556.
Abstract: Gestation may represent a window of susceptibility to transplacental effects of environmental exposures, including chemicals in water. The N-nitroso compounds (NNC), a class of chemicals with demonstrated neurocarcinogenic potential, include substances detected in drinking water. We used data from a study of possible risk factors for childhood brain tumors (CBT) to investigate the association of source of residential drinking water during pregnancy and CBT occurrence among offspring. In addition, dipstick measurements were made of nitrates and nitrites in tap water for the subset of women living in the same home they had lived in during their pregnancies. Population-based CBT cases (n = 540) and controls (n = 801) were identified in three regions including Los Angeles County, and the San Francisco Bay Area of California, and the Seattle-Puget Sound area of western Washington State, Overall, we observed no increased risk of CBT in offspring associated with wells as the source of residential water. However, an increased risk of CBT [odds ratio (OR) = 2.6; 95% confidence interval (CI), = 1.3-5.2] was observed in western Washington among offspring of women who relied exclusively on well water, and a decreased risk of CBT (OR = 0.2; 95% CI, 0.1-0.8) was observed in Los Angeles County, Among the small subset of subjects for whom dipstick measurements of tap water were available, the risk of CBT associated with the presence of either measurable nitrite and/or nitrate was 1.1 (95% CI, 0.7-2.0). Given the crude measurement method employed and because measurements often were obtained years after these pregnancies occurred, the relevance of the dipstick findings is unclear. The lack of consistency in our findings related to residential water source does not support the hypothesis of increased risk related to consumption of well water; however, regional differences in well water content may exist, and the increased risk observed in western Washington deserves further evaluation.

Mueller BA, Nielsen SS, Preston-Martin S, Holly EA, Cordier S, Filippini G, Peris-Bonet R, Choi NW. 2004. Household water source and the risk of childhood brain tumours: results of the SEARCH International Brain Tumor Study. Int J Epidemiol 33:1209-1216.
Abstract: Background The period in utero is a time of increased vulnerability. Offspring of pregnant women exposed to carcinogenic substances in drinking water may be more likely to develop cancer. We examined whether household water source and the presence of nitrates or nitrites in residential water were associated with increased risks of childhood brain tumours (CBT). Methods We used data from a multicentre, case-control study with maternal information on residential water source, and nitrate/nitrite levels of tap water measured by dipstick. Subjects included 836 CBT cases and 1485 controls from five countries. Results The risks of CBT associated with reliance on well water (versus public water) during pregnancy varied widely, with significantly increased risks noted in two (of seven) regions and a decreased risk observed in one region. CBT risk did not increase with increasing nitrate levels. However, our results based on tap water tested in the pregnancy residences suggest the risk of astrocytoma may be associated

with increasing levels of nitrite (odds ratio [OR] = 4.3, 95% CI: 1.4, 12.6 for nitrite levels of 1-<5 mg/l nitrite ion; OR = 5.7, 95% CI: 1.2, 27.2 of nitrite greater than or equal to5 mg/l). Conclusions These results should be interpreted with caution because women's recollection of water sources may have contained inaccuracies, and nitrate and nitrite measurements, available for only a portion of subjects, were often obtained years after the pregnancies occurred. However, our results suggest a need for closer evaluation of well water content in some regions and the possibility that a nitrite-related water exposure may be associated with CBT.

Muller R, Rajewsky MF. 1983. Elimination of O6-ethylguanine from the DNA of brain, liver, and other rat tissues exposed to ethylnitrosourea at different stages of prenatal development. Cancer Res 43:2897-2904.
Abstract: The magnitude of the neurooncogenic effect of N-ethyl-N-nitrosourea (EtNU) in the BD IX rat is strongly dependent on the developmental stage of the nervous system at the time of carcinogen exposure, with a maximum during late prenatal and early postnatal development. Both with increasing postnatal age and in the direction of early embryonic development (prior to Postnatal Day 15), the yield of neuroectodermal tumors in the brain and peripheral nervous system declines sharply. Using a competitive radioimmunoassay for O6-ethyldeoxyguanosine (O6-EtdGuo), we have ascertained that the initial degree of DNA ethylation in BD IX rat tissues (including brain) is independent of the developmental stage at the time of transplacental (i.v.) exposure to a constant single dose of EtNU over a time range from Prenatal Day 11 to a postnatal age of 102 days. O6-EtdGuo is highly persistent in the DNA of peri- and postnatal rat brain but enzymatically removed from the DNA of other tissues, notably liver. The present analyses by radioimmunoassay indicate that O6-EtdGuo is equally persistent in the DNA of prenatal BD IX rats exposed to EtNU (50 micrograms/g body weight) on the 11th, 13th, or 16th day of gestation but removed enzymatically from other prenatal tissues. The rate of removal from the DNA of liver (Prenatal Day 16) is higher than the corresponding rate in 10-day-old (postnatal) BD IX rats. On Prenatal Day 11 to 12 (when a neurooncogenic effect first became apparent after transplacental exposure of BD IX rats to EtNU; S. Ivankovic and H. Druckrey, Z. Krebsforsch., 71: 320-360, 1968), the number of cells per brain is approximately 2 X 10(5). When a limited number of experimental animals are used, and regardless of the incapacity of neural precursor cells to remove O6-EtdGuo from their DNA, this target population size may be incompatible with the manifestation of a rare event such as malignant transformation.

Munoz-de-Toro M, Markey C, Wadia PR, Luque EH, Rubin BS, Sonnenschein C, Soto AM. 2005. Perinatal exposure to Bisphenol A alters peripubertal mammary gland development in mice. Endocrinology .
Abstract: Developmental exposure to estrogenic chemicals induces morphological, functional and behavioral anomalies associated with reproduction. Humans are exposed to bisphenol-A (BPA), an estrogenic compound that leaches from dental materials and plastic food and beverage containers. The aim of the present study was to determine the effects of perinatal exposure to low, environmentally relevant doses of BPA (25 and 250 ng BPA/kg body weight (bw)/day) on the peripubertal development of the mammary gland. BPA exposure enhanced the mammary glands' sensitivity to estradiol in ovariectomized CD-1 mice. In their intact 30-day-old littermates, the area and numbers of terminal end buds relative to the gland ductal area increased while their apoptotic activity decreased. There was a positive correlation between ductal length and the age at first proestrus; that was reduced as the BPA dose increased, suggesting that BPA exposure slows down ductal invasion of the stroma. There was also a significant increase of progesterone receptor-positive ductal epithelial cells that were localized in clusters, suggesting future branching points. Indeed, lateral branching was significantly enhanced at 4 months of age in mice exposed to 25 ng BPA /kg bw/day. In conclusion, perinatal exposure to environmentally relevant BPA doses results in persistent alterations in mammary gland morphogenesis. Of special concern is the increased terminal end bud density at puberty as well as the increased number of terminal ends reported previously in adult animals, since these two structures are the sites where cancer arises in humans and rodents.

Murray TJ, Maffini MV, Ucci AA, Sonnenschein C, Soto AM. 2006. Induction of mammary gland ductal hyperplasias and carcinoma in situ following fetal bisphenol A exposure. Reprod Toxicol :doi:10.1016/j.reprotox.2006.10.002 .
Abstract: Exposure of the fetus to excess estrogen is believed to increase the risk of developing breast cancer during adult life. Fetal exposure to low doses of the xenoestrogen bisphenol A resulted in long-lasting effects in the mouse mammary gland that were manifested during adult life. It enhanced sensitivity to estradiol, decreased apoptosis, increased the number of progesterone receptor-positive epithelial cells at

puberty and increased lateral branching at 4 months of age. We now report that fetal exposure to 2.5, 25, 250 and 1000mug bisphenol A/kg body weight/day induces the development of ductal hyperplasias and carcinoma in situ at postnatal day 50 and 95 in rats. These highly proliferative lesions have an increased number of estrogen receptor-alpha positive cells. Thus, fetal bisphenol A exposure is sufficient to induce the development of preneoplastic and neoplastic lesions in the mammary gland in the absence of any additional treatment aimed at increasing tumor development.

Muto T, Wakui S, Imano N, Nakaaki K, Takahashi H, Hano H, Furusato M, Masaoka T. 2001. *In-utero* and lactational exposure of 3,3',4,4',5-pentachlorobiphenyl modulate dimethlbanz[a]anthracene-induced rat mammary carcinogenesis. Journal of Toxicologic Pathology 14:213-224.
Abstract: While polychlorinated biphenyls (PCB) are fat soluble environmental pollutants stored breast fatty tissue and secreted in milk; the precise evidence of breast carcinoma from exposure to PCBs remains unclear. The aim of this study was to investigate the dose-response relationshp *in-utero* and lactational exposure of PCBs congener to dimethlbanz[a]anthracene (DMBA)-induced rat mammary carcinogenesis. Female SD rats were injected (i.g.) with 25 pg, 2.5 ng, 250 ng, 7.5μg of 3,3',4,4',5-pentachlorobiphenyl (PCB126)/kg, or the vehicle, on days 13 to 19 post-conception. Fifty-day-old female offspring were injected (i.g.) with 20 mg DMBA. The concentration of PCB in the liver of the 50-day-old was compared to the vehicle-group, found to be 530-fold higher in the 7.5 μg group, nearly 21-fold higher in the 250 ng group, neary 2.4-fold higher in the 2.5 ng group, and nearly 1.2-fold in the 25 pg group. The expression of CYP1A1 in the liver of the 50-day-old was intensive in the 7.5 μg and 250 ng groups, and slight in the 2.5 ng group and not observed in the other groups. The observation was terminated when the pups were 170-day-old or the tumor size reached 20 mm in diameter. The 7.5 μg group showed a reduction of mammary carinogenesis, but the 250 ng and 2.5 ng groups revealed increases incidence of carcinoma, while the 25 pg group showed a similar incidence of the vehicle group. The time course of tumor development of the 7.5 μg group was significantly lower than that of the other groups, but that of the 250 ng group was significantly higher, and that of the 2.5 ng and 25 pg groups was similar to that of the vehicle group. Moreover, the tumors of the 250 ng group showed the highest cell proliferation, anuploid tumor index, and nuclear grade when compared to those of the other groups. The present studies inidcate that *in-utero* and lactational exposure of relatively low dose PCB acts as an enhancing agent toward DMBA-induced rat mammary carcinogenesis, but that of high dose PCB acts as an inhibiting agent. This effect partly may be due to the *in vivo* difference at the day of DMBA exposure (50-day-old); between the concentration of PCB and the expression of phase I drug-metabolizing enzymes (CYP1A1) converting DMBA into the ultimate carcinogen.

Muto T, Wakui S, Imano N, Nakaaki K, Takahashi H, Hano H, Furusato M, Masaoka T. 2002. Mammary gland differentiation in female rats after prenatal exposure to 3,3 ',4,4 ',5-pentachlorobiphenyl. Toxicology 177:197-205.
Abstract: Recently we reported finding that prenatal exposure to a relatively low dose of 3,3',4,4',5-pentachlorobiphenyl (PCB126) increases the rate of 7,12-dimethylbenz(a)antltracene (DMBA)-induced rat mammary carcinoma, while a high dose decreases it. One of the most important factors determining sensitivity of the mammary gland to neoplastic stimuli is its stage of differentiation at the time of exposure to the carcinogenic agent. Hence, to verify a biphasic dose-response relationship (enhancement of carcinogenesis at low dose, and inhibition at high dose), we investigated the effects of prenatal exposure to PCB126 on mammary gland differentiation. Female SD rats were injected (i.g.) with 25 pg, 2.5 ng, 250 ng, 7.5 pg of PCB126/kg, or the vehicle, on days 13-19 postconception. In 50-day-old offspring, regardless of the day of exposure to DMBA, only the 7.5 pg group showed statistically significant high levels of PCB126 in the fatty tissue of their mammary glands. Fifty-day-old female offspring of the 250 ng group showed apparent inhibition of the normal differentiation of terminal end buds (TEB) to alveolar buds and lobules (ABL), while those of the 7.5 mug group showed mammary gland hypoplasia. Expression levels of the estrogen receptor-alpha (ER) in TEBs and the ER mRNA in mammary glands were higher in the 7.5 mug, 250 ng, 2.5 ng groups. Proliferating cell nuclear antigen (PCNA) expression in TEBs of 50-day-old rats was statistically significantly higher in the 250 ng group and lower in the 7.5 pg group. In the developing mammary gland, TEBs are considered the most susceptible to mammary carcinogenesis, while ABLs are relatively protected from mammary carcinogenesis. Thus, prenatal exposure to a relatively low dose of PCB126 induced an alteration of mammary gland differentiation that might potentially increase the risk of

DMBA-induced mammary carcinoma. (C) 2002 Elsevier Science Ireland Ltd. All rights reserved.

Myers SR, Spinnato JA, Pinorini-Godly MT. 2000. Tobacco smoke hemoglobin adducts in maternal and fetal blood. Polycyclic Aromatic Compounds 21:151-166.
Abstract: The maternal-fetal exchange of the potent tobacco related human carcinogen, 4-aminobiphenyl, was studied in women smokers during pregnancy. Maternal and fetal blood samples were classified as coming from nonsmokers (n=74), individuals smoking less than 1 pack of cigarettes per day (n=16), individuals smoking 1 pack of cigarettes per day (n=19), individuals smoking 1-2 packs of cigarettes per day (n=19), and individuals smoking greater than 2 packs of cigarettes per day (n=20). 4-aminobiphenyl was extracted from both maternal and fetal blood samples using organic extractions and the released amine was qualitatively and quantitatively characterized by analysis of the samples by gas chromatographic and mass spectrometric analysis. Increasing levels of Caminobiphenyl hemoglobin adducts were found as the smoking status of the women increased ranging from 144 +/- 22.2 (<1 pack per day) to 633 +/- 87.9 (>2 packs per day). A corresponding increase in the presence of fetal 4-aminobiphenyl hemoglobin adducts was also detected (74.3 +/- 17.8; <1 pack/day to 319 +/- 50.5; >2 packs/day).

Myers SR, Spinnato JA, Pinorinigodly MT, Cook C, Boles B, Rodgers GC. 1996. Characterization of 4-aminobiphenyl-hemoglobin adducts in maternal and fetal blood samples. Journal of Toxicology & Environmental Health 47:553-566.
Abstract: The maternal-fetal exchange of the potent tobacco-related human carcinogen 4-aminobiphenyl was studied in women smokers during pregnancy. The number of cigarettes smoked per day by each of the women in the study was assessed via questionnaire and by measurement by immunoassay of serum and urine cotinine in maternal and fetal blood samples. Maternal and fetal blood samples were classified as coming from nonsmokers (n = 74), individuals smoking less than I pack of cigarettes per day (n = 16), individuals smoking I pack of cigarettes per day (n = 19), individuals smoking 1-2 packs of cigarettes per day (n = 19), and individuals smoking greater than 2 packs of cigarettes per day (n = 20). Both maternal and fetal blood samples were obtained at the rime of delivery. 4-Aminobiphenyl was extracted from both maternal and fetal blood samples using organic extractions and the released amine was qualitatively and quantitatively characterized by analysis of the samples by gas chromatographic and mass spectrometric analysis. Background levels of 4-aminobiphenyl-hemoglobin adducts were detected in maternal nonsmokers (18.3 +/- 12.7 pg 4-aminobiphenyl/g hemoglobin, mean +/- SD) and in fetal samples (8.88 +/- 5.8 pg/g hemoglobin). Increasing levels of 4-aminobiphenyl-hemoglobin adducts were found as the smoking status of the women increased, ranging from 144 +/- 22.2 (<1 pack/d) to 633 +/- 87.9 (>2 packs/d). A corresponding increase in the presence of fetal 4-aminobiphenyl-hemoglobin adducts was also detected (74.3 +/- 17.8, <1 pack/d, to 319 +/- 50.5, >2 packs/d). This study confirms that the potent tobacco-related carcinogen 4-aminobiphenyl crosses the human placenta and binds to fetal hemoglobin in significantly higher concentrations in smokers when compared to nonsmokers.

Naito M, Naito Y, Ito A. 1981 . Effect of age at treatment on the incidence and location of neurogenic tumors induced in Wistar rats by a single dose of N-ethyl-N-nitrosourea. Gann 72:569-577.
Abstract: The effect of age at treatment on the incidence and location of neurogenic tumors induced by N-ethyl-N-nitrosourea (ENU) was investigated in 232 Wistar rats of both sexes. Rats were given 40 ng/kg of ENU on the 16th day of gestation (group I), on the day of birth (group II), and on the 1st week (group III), 2nd week (group IV), 3rd week (group V) and 4th week (group VI) after birth. Up to 6 months of observation, the brain consistently showed the highest susceptibility ranging from group I (93%) to group VI (36%), followed by the spinal cord (group I, 34%; group II, 64%; group III, 43%). However, the trigeminal nerve was only susceptible in group I (27%) and group II (36%) and the spinal root was susceptible exclusively in group II (46%). Most of the tumors obtained were oligodendrogliomas or mixed gliomas. Glioependymomas of the spinal cord were predominant only in group II. The temporal and paraventricular regions and hippocampus were the preferred sites of brain tumors in group I and II, but in groups III and IV frontal tumors were predominant. Mesenchymal tumors of the kidney were also induced, mainly in groups III (16%) and IV (16%).

Nakamura T, Ushijima T, Ishizaka Y, Nagao M, Nemoto T, Hara M, Ishikawa T. 1994. neu proto-oncogene mutation is specific for the neurofibromas in a N-nitroso-N-ethylurea-induced hamster neurofibromatosis model but not for hamster melanomas and human Schwann cell tumors. Cancer Res 54:976-980.

Abstract: Point mutations of the transmembrane domain coding region of the neu proto-oncogene in N-nitroso-N-ethylurea-induced hamster neurofibromas were found at high frequency (93%; 14 or 15). They involved codons 659 as well as 658, the latter not having been reported previously in rat tumors. The mutational change was seen even in the early stage neurofibroma. On the other hand, no mutations were defected in melanomas or Wilms' tumors induced in the same N-nitroso-N-ethylurea-treated animals, even when the melanomas demonstrated extensive schwannian differentiation. Moreover, any human Schwann cell tumors including neurofibroma, schwannoma, and malignant schwannoma did not show the mutation of c-erbB-2 gene (0 of 34), which is homologous to the hamster neu. Since high expression of neu mRNA is evident in the hamster Schwann cell at the late gestational and neonatal stages, transplacental administration of N-nitroso-N-ethylurea is considered to interact directly to carcinogenesis of the hamster Schwann cell through neu gene mutation.

Napalkov NP. 1986. Cancer Detect Prev 9:1-7.
Abstract: Transplacental carcinogenic effects have been demonstrated for about 60 chemicals in eight animal species and even in the human. Many carcinogens are much more active in the fetus than in the adult animal. The stage specificity of transplacental carcinogenesis is characterized by the possibility of inducing tumors only at certain stages of embryogenesis (at the end of organogenesis and during the whole period of histogenesis). Risk of transplacental carcinogenesis is owing to the passage of carcinogens or their active metabolites into embryonic tissue and the possibility of metabolic activation of substances within the fetus. In this connection, four main pathways can be hypothesized for the carcinogenic effect of a substance on the fetus. Organotropism with transplacental carcinogenesis is determined by genetic predisposition, differentiation, and proliferative activity in the target tissues. For indirect carcinogens the level of metabolizing enzymes is also important. Teratogenesis and carcinogenesis can be either independent processes or pathogenetically related to each other (eg, DES action). Experimental data can readily be applied to the discussion of prophylaxis of prenatal tumors in the human.

Nathanielsz PW. 2006. Animal models that elucidate basic principles of the developmental origins of adult diseases. ILAR J 47:73-82.
Abstract: Human epidemiological and animal laboratory studies show that suboptimal environments in the womb and during early neonatal life alter development and predispose the individual to lifelong health problems. The concept of the developmental origins of adult diseases has become well accepted because of the compelling animal studies that have precisely defined the outcomes of specific exposures such as nutrient restriction, overfeeding during pregnancy, maternal stress, and exogenously administered glucocorticoids. This review focuses on the use of animal models to evaluate exposures, mechanisms, and outcomes involved in developmental programming of hypertension, diabetes, obesity, and altered pituitary-adrenal function in offspring in later life. Ten principles of developmental programming are described as fundamental, regardless of the exposure during development and the physiological system involved in the altered outcome. The 10 principles are discussed in the context of the physiological systems involved and the animal model studies that have been conducted to evaluate exposures, mechanisms, and outcomes. For example, the fetus responds to challenges such as hypoxia and nutrient restriction in ways that help to ensure its survival, but this "developmental plasticity" may have long-term consequences that may not be beneficial in adult life. To understand developmental programming, which represents the interaction of nature and nurture, it is necessary to integrate whole animal systems physiology, in vitro cellular biology, and genomic and proteomic approaches, and to use animal models that are carefully characterized and appropriate for the questions under study. Animal models play an important role in this evaluation because they permit combined in vivo and in vitro study at different critical time windows during the exposure and the ensuing developmental responses.

Naumburg E, Bellocco R, Cnattingius S, Hall P, Boice JD, Ekbom A. 2001. Intrauterine exposure to diagnostic X rays and risk of childhood leukemia subtypes. Radiat Res 156:718-723.
Abstract: The relationship between childhood leukemia and prenatal exposure to low-dose ionizing radiation remains debatable. This population-based case-control study investigated the association between prenatal exposure to diagnostic X-ray examinations (for different types of examinations and at different stages of pregnancy) and the risk of childhood lymphatic and myeloid leukemia. All children born and diagnosed with leukemia between 1973-1989 in Sweden (578 lymphatic and 74 myeloid) were selected as cases, and each was matched (by sex and year of birth) to a healthy control child (excluding Down's

syndrome). Exposure data were abstracted blindly from all available medical records. Odds ratios (OR) and 95% confidence intervals (CI) were calculated by conditional logistic regression. It was found that prenatal X-ray examinations resulting in direct fetal exposure were not associated with a significant overall increased risk for childhood leukemia (OR = 1.11, 95% CI 0.83-1.47), for lymphatic leukemia (OR = 1.04, 95% CI 0.77-1.40), or for myeloid leukemia (OR = 1.49, 95% CI 0.48-4.72). There was little evidence of a dose response or variation in risk by trimester of exposure or age at diagnosis. Thus X-ray examinations performed during pregnancy in the 1970s and 1980s in Sweden did not affect the risk of childhood leukemia discernibly. (C) 2001 by Radiation Research Society.

Neri M, Ugolini D, Bonassi S, Fucic A, Holland N, Knudsen LE, Sram RJ, Ceppi M, Bocchini V, Merlo DF. 2006. Children's exposure to environmental pollutants and biomarkers of genetic damage. II. Results of a comprehensive literature search and meta-analysis. Mutation Research-Reviews in Mutation Research 612:14-39.
Abstract: The present review is based on findings from 178 publications retrieved through an extensive search of the MedLine/PubMed database for a 25 years time period (1980-2004) and 10 manually identified papers, Among the cytogenetic biomarkers that are frequently used in field studies, chromosome aberrations (CA) and micronuclei (MN) but not sister chromatid exchanges (SCE) were found consistently increased in children exposed to environmental Pollutants, Meta-analysis of the studies reporting SCE in cord blood showed similar levels of SCE in exposed and in non-exposed newborns. Exposure to airborne pollutants, soil and drinking water contaminants, mostly increased CA and, to a lesser extent, MN levels in children. The effect of exposure to airborne urban pollutants was consistently reported by field studies measuring DNA, albumin and hemoglobin adducts. prenatal (in utero) and postnatal exposure (environmental tobacco smoke, ETS) to tobacco smoke compounds were associated with increased frequencies of DNA and hemoglobin adducts and CA. The limited number of field studies measuring DNA fragmentation (Comet assay), hypoxanthine-guanine phosphoribosyltransferase (HPRT) and the glycophorinA (GPA) mutation frequency in environmentally exposed children precluded a meaningful evaluation of the usefulness of these assays. Meta-analyses performed in children exposed to ETS and in newborns exposed in utero to their mothers' smoke showed 1.3 and 7 times higher levels of hemoglobin adducts compared to referent subjects, respectively. These increases are consistent with the epidemiological evidence of higher lung cancer risks reported in adults who had never smoked and were exposed to ETS during childhood and with 7-15 times higher lung cancer risks reported in smokers than in non-smokers. Higher levels of PAH-DNA adducts were found in fetal than in maternal tissue, suggesting a specific susceptibility of the fetus to this class of ubiquitous environmental pollutants. According to these findings, future research and biomonitoring programs on children would greatly benefit from the inclusion of selected biomarkers that could provide biologically based evidence for the identification of intervention priorities in environmental health.

Newbold R. 1995. Cellular and molecular effects of developmental exposure to diethylstilbestrol - Implications for other environmental estrogens. Environ Health Perspect 103 (suppl 7):83-87.
Abstract: Concerns have been raised regarding the role of environmental and dietary estrogens as possible contributors to an increased incidence of various abnormalities in estrogen-target tissues of both sexes. These abnormalities include breast cancer, endometriosis, fibroids, and uterine adenocarcinoma in females, as well as alterations in sex differentiation, decreased sperm concentrations, benign prostatic hyperplasia, prostatic cancer, testicular cancer, and reproductive problems in males. Whether these concerns are valid remains to be determined; however, studies with the potent synthetic estrogen diethylstilbestrol (DES) suggest that exogenous estrogen exposure during critical stages of development can result in permanent cellular and molecular alterations in the exposed organism. These alterations manifest themselves in the female and male as structural, functional, or long-term pathological changes including neoplasia. Although DES has potent estrogenic activity, it may be used as a model compound to study the effects of weaker environmental estrogens, many of which may fit into the category of endocrine disruptors.

Newbold RR, Banks EP, Bullock B, Jefferson WN. 2001. Uterine adenocarcinoma in mice treated neonatally with genistein. Cancer Res 61:4325-4328.
Abstract: The developing fetus is uniquely sensitive to perturbation with estrogenic chemicals. The carcinogenic effect of prenatal exposure to diethylstilbestrol (DES) is the classic example. Because phytoestrogen use in nutritional and pharmaceutical applications for infants and children is increasing, we

investigated the carcinogenic potential of genistein, a naturally occurring plant estrogen in soy, in an experimental animal model previously reported to result in a high incidence of uterine adenocarcinoma after neonatal DES exposure. Outbred female CD-1 mice were treated on days 1-5 with equivalent estrogenic doses of DES (0.001 mg/kg/day) or genistein (50 mg/kg/day). At 18 months, the incidence of uterine adenocarcinoma was 35% for genistein and 31% for DES. These data suggest that genistein is carcinogenic if exposure occurs during critical periods of differentiation. Thus, the use of soy-based infant formulas in the absence of medical necessity and the marketing of soy products designed to appeal to children should be closely examined.

Newbold RR, Bullock BC, McLachlan JA. 1985. Lesions of the rete testis in mice exposed prenatally to diethylstilbestrol. Cancer Res 45:5145-5150.
Abstract: Adenocarcinoma of the rete testis is an exceptionally rare and malignant testicular neoplasm. Although treatment of pregnant women with diethylstilbestrol (DES) results in reproductive tract abnormalities in their male offspring, increased incidence of testicular tumors has not been verified. However, recently three cases of seminoma have been described in men prenatally exposed to DES, suggesting an association of prenatal DES treatment and the subsequent development of testicular tumors. This report describes the treatment of outbred pregnant CD-1 mice with DES (100 micrograms/kg) on Days 9 through 16 of gestation and its effects on their male offspring. In addition to nonmalignant abnormalities such as retained testes which have been reported in men exposed prenatally to DES, lesions resembling adenocarcinoma of the rete testis were seen in prenatally DES-treated mice at 10 to 18 mo of age (11 of 233; 5%). No comparable lesions were seen in 96 age-matched control male mice. These results suggest an association of prenatal DES exposure and the subsequent development of testicular lesions in the rete testis of mice.

Newbold RR, Bullock BC, McLachlan JA. 1987. Testicular tumors in mice exposed in utero to diethylstilbestrol. J Urol 138:1446-1450.
Abstract: Treatment of pregnant women with diethylstilbestrol (DES) is associated with the subsequent development of reproductive tract abnormalities such as epididymal cysts, retained hypotrophic testes and sperm abnormalities in their male offspring. It recently has been suggested that prenatal DES exposure is associated with development of testicular seminoma in humans. Studies of in utero exposure of laboratory animals to DES are few, but previous reports from our laboratory have described several abnormalities in the reproductive tract of the mouse following prenatal DES exposure. To study the possible association of testicular tumors and prenatal DES exposure in mice, pregnant outbred CD-1 mice were injected subcutaneously with daily doses of DES (100 micrograms./kg.) on days nine through 16 of gestation. DES-exposed and age-matched control male mice were sacrificed at 10 to 18 months of age and examined for testicular lesions. In addition to the nonmalignant abnormalities reported in previous studies such as 91% cryptorchidism and degenerative changes, interstitial cell tumors were observed in nine mice among 277 mice treated prenatally with DES. Two of these lesions were benign tumors and five were interstitial cell carcinomas. Rete testis adenocarcinoma was seen also in 5% of these DES-treated animals and is described in another report. The overall incidence of testicular tumors is 8% in DES-exposed male mice. No comparable lesions were seen in 122 control male mice. These results suggest that the testicular lesions that can occur following prenatal DES exposure include neoplasia. The combined prevalence of DES-induced tumors of the corpus testis and rete testis in mice suggests the male offspring may be more at risk for developing carcinoma of the reproductive tract than the female offspring.

Newbold RR, Bullock BC, McLachlan JA. 1990 . Uterine adenocarcinoma in mice following developmental treatment with estrogens: A model for hormonal carcinogenesis. Cancer Res 50:7677-7681.
Abstract: In order to study the effects of perinatal exposure to estrogens on the developing reproductive tract, outbred female mice were treated neonatally (days 1 to 5) with varying doses of diethylstilbestrol (DES) and sacrificed from 1 to 18 months of age. Uterine adenocarcinoma was observed in a time- and dose-related manner after DES treatment; at 18 months, neoplastic lesions were seen in 90% of the mice exposed neonatally to 2 micrograms/pup of DES/day, while none was observed in the corresponding control mice. These DES-induced uterine tumors were estrogen dependent; when DES-treated mice were ovariectomized before puberty, no uterine tumors developed. As a marker for neoplasia, uterine tumors were transplanted and carried as serial transplants in nude mice. The transplanted tissue retained some differentiated uterine gland structure and function and also required estrogen supplementation for

maintenance. Additional groups of neonatal mice were treated with various DES analogues (hexestrol and tetrafluorodiethylstilbestrol) and steroidal estrogens. The compounds were ranked according to developmental estrogenic potency (hexestrol greater than trifluorodiethylstilbestrol greater than DES greater than 17 beta-estradiol). The combined prevalence of uterine atypical hyperplasia and adenocarcinoma follows the order of estrogenic potency. The experimental induction of these tumors will provide the basis for additional studies in mechanisms of hormonal carcinogenesis.

Newbold RR, Hanson RB, Jefferson WN, Bullock BC, Haseman J, McLachlan JA. 1998. Increased tumors but uncompromised fertility in the female descendants of mice exposed developmentally to diethylstilbestrol. Carcinogenesis 19:1655-1663.
Abstract: Prenatal exposure to diethylstilbestrol (DES) has been associated with the subsequent development of reproductive tract abnormalities, including poor reproductive outcome and neoplasia, in experimental animals and humans. Experimental animal studies with chemical carcinogens have raised the possibility that adverse effects of DES may be transmitted to succeeding generations. To evaluate this possibility and to determine if there is a sensitive window of developmental exposure, outbred CD-1 mice were treated with DES during three stages of development: group 1 was treated on days 9-16 of gestation (2.5, 5 or 10 microg/kg maternal body wt), the time of major organogenesis; group II was treated once on day 18 of gestation (1000 microg/kg maternal body wt) just prior to birth; group III was treated on days 1-5 of neonatal life (0.002 microg/pup/day). Female mice (F1) in each group were raised to sexual maturity and bred to control males. As previously reported, fertility of the F1 DES-exposed females was decreased in all groups. Female offspring (DES lineage or F2) from these matings were raised to maturity and housed with control males for 20 weeks. The fertility of these DES lineage female mice was not affected by DES exposure of their 'grandmothers'. DES lineage mice were killed at 17-19 and 22-24 months of age. An increased incidence of malignant reproductive tract tumors, including uterine adenocarcinoma, was seen in DES lineage mice but not in corresponding controls; the range and prevalence of tumors increased with age. Because uterine adenocarcinomas were seen in all three DES groups, all developmental exposure periods were considered susceptible to the adverse effects of DES. These data suggest that the reduced fertility observed in the DES F1 female mice was not transmitted to their descendants; however, increased susceptibility to tumor formation is apparently transmitted to subsequent generations.

Newbold RR, Hanson RB, Jefferson WN, Bullock BC, Haseman J, McLachlan JA. 2000. Proliferative lesions and reproductive tract tumors in male descendants of mice exposed developmentally to diethylstilbestrol. Carcinogenesis 21:1355-1363.
Abstract: Prenatal exposure to diethylstilbestrol (DES) is associated with reproductive tract abnormalities, subfertility and neoplasia in experimental animals and humans. Studies using experimental animals suggest that the carcinogenic effects of DES may be transmitted to succeeding generations. To further evaluate this possibility and to determine if there is a sensitive window of exposure, outbred CD-1 mice were treated with DES during three developmental stages: group 1 was treated on days 9-16 of gestation (2.5, 5 or 10 microg/kg maternal body weight) during major organogenesis; group II was treated once on day 18 of gestation (1000 microg/kg maternal body weight) just prior to birth; and group III was treated on days 1-5 of neonatal life (0.002 microg/pup/day). DES-exposed female mice (F(1)) were raised to maturity and bred to control males to generate DES-lineage (F(2)) descendants. The F(2) males obtained from these matings are the subjects of this report; results in F(2) females have been reported previously [Newbold et al. (1998) CARCINOGENESIS:, 19, 1655-1663]. Reproductive performance of F(2) males when bred to control females was not different from control males. However, in DES F(2) males killed at 17-24 months, an increased incidence of proliferative lesions of the rete testis and tumors of the reproductive tract was observed. Since these increases were seen in all DES treatment groups, all exposure periods were considered susceptible to perturbation by DES. These data suggest that, while fertility of the DES F(2) mice appeared unaltered, increased susceptibility for tumors is transmitted from the DES 'grandmothers' to subsequent generations.

Newbold RR, Liehr JB. 2000. Induction of uterine adenocarcinoma in CD-1 mice by catechol estrogens. Cancer Res 60:235-237.
Abstract: Catechol estrogens may mediate estrogen-induced carcinogenesis because 4-hydroxyestradiol induces DNA damage and renal tumors in hamsters, and this metabolite is formed in the kidney and estrogen target tissues by a specific estrogen 4-hydroxylase, We examined the carcinogenic potential of

catechol estrogen in an experimental model previously reported to result in a high incidence of uterine adenocarcinoma after neonatal exposure to diethylstilbestrol, Outbred female CD-1 mice were treated with 2- or 4-hydroxyestradiol, 17 beta-estradiol, or 17 alpha-ethinyl estradiol on days 1-5 of neonatal life (2 mu g/pup/day) and sacrificed at 12 or 18 months of age. Mice treated with 17 beta-estradiol or 17 alpha-ethinyl estradiol had a total uterine tumor incidence of 7% or 43%, respectively. 2-Hydroxyestradiol induced tumors in 12% of the mice, but 4-hydroxyestradiol was the most carcinogenic estrogen, with a 66% incidence of uterine adenocarcinoma, Both 2- and 4-hydroxylated catechols were estrogenic and increased uterine wet weights in these neonates. These data demonstrate that both 2- and 4-hydroxyestradiol are carcinogenic metabolites. The high tumor incidence induced by 4-hydroxyestradiol supports the postulated role of this metabolite in hormone-associated cancers.

Newbold RR, McLachlan JA. 1982. Vaginal adenosis and adenocarcinoma in mice exposed prenatally or neonatally to diethylstilbestrol. Cancer Res 42:2003-2011.
Abstract: The association of intrauterine exposure to diethylstilbestrol (DES) and the subsequent development of reproductive tract abnormalities in young women has been well documented. Although the incidence of vaginal adenocarcinoma was low in the exposed population, vaginal adenosis, a nonmalignant abnormality, was quite common. In order to study the pathogenesis of adenocarcinoma and to determine the frequency of adenosis following prenatal exposure to DES, timed pregnant CD-1 mice were treated s.c. with DES (dose range, 5 to 100 micrograms/kg/day) on Days 9 though 16 of gestation. This period corresponds to major organogenesis of the reproductive tract in the mouse. Female offspring were sacrificed between 1 and 18 months of age. In addition to nonmalignant abnormalities, some of which have been described in women exposed prenatally to DES, two cases of vaginal adenocarcinoma (2%) were observed in 91 prenatally DES-treated animals. No comparable epithelial lesions were seen in 158 control female mice. One other case of adenocarcinoma of the vagina was reported previously by this laboratory using the prenatally exposed animal model. In another series of mice treated prenatally with DES, 100 micrograms/kg/day, 3 of 20 (15%) 1-month-old animals and one of 10 (10%) 18-month-old treated offspring had glandular epithelium abnormally located in the vaginal fornices (adenosis). Other cervicovaginal abnormalities observed after prenatal DES exposure included structural alterations, cervical enlargement, squamous metaplasia in the endocervical canal, excess keratinization of the ectocervix and vagina, transverse folds and basal cell hyperplasia in the upper vagina, and prominent Wolffian duct remnants. Thus, vaginal adenosis in the mouse does not appear to be a common abnormality following treatment with DES in utero. Neonatal exposure to DES on Days 1 to 5, on the other hand, resulted in six of eight (75%) animals with adenosis at 35 days of age. Since perinatal mouse studies have reported high incidences of vaginal adenosis, but, to our knowledge, no cases of vaginal adenocarcinoma, the results presented in this report suggest that the stage of cellular differentiation at the time of DES exposure may be critical in the final expression of these abnormalities.

Newbold RR, Padilla-Banks E, Jefferson WN. 2006. Adverse effects of the model environmental estrogen diethylstilbestrol are transmitted to subsequent generations. Endocrinology 147:S11-S17.
Abstract: The synthetic estrogen diethylstilbestrol (DES) is a potent perinatal endocrine disruptor. In humans and experimental animals, exposure to DES during critical periods of reproductive tract differentiation permanently alters estrogen target tissues and results in long-term abnormalities such as uterine neoplasia that are not manifested until later in life. Using the developmentally exposed DES mouse, multiple mechanisms have been identified that play a role in its carcinogenic and toxic effects. Analysis of the DES murine uterus reveals altered gene expression pathways that include an estrogen-regulated component. Thus, perinatal DES exposure, especially at low doses, offers the opportunity to study effects caused by weaker environmental estrogens and provides an example of the emerging scientific field termed the developmental origin of adult disease. As a model endocrine disruptor, it is of particular interest that even low doses of DES increase uterine tumor incidence. Additional studies have verified that DES is not unique; when other environmental estrogens are tested at equal estrogenic doses, developmental exposure results in increased incidence of uterine neoplasia similar to that caused by DES. Interestingly, our data suggest that this increased susceptibility for tumors is passed on from the maternal lineage to subsequent generations of male and female descendants; the mechanisms involved in these trans-generational events include genetic and epigenetic events. Together, our data point out the unique sensitivity of the developing organism to endocrine-disrupting chemicals, the occurrence of long-term effects after developmental exposure, and the possibility for adverse effects to be transmitted to subsequent generations.

Ng SP, Silverstone AE, Lai ZW, Zelikoff JT. 2006. Effects of prenatal exposure to cigarette smoke on offspring tumor susceptibility and associated immune mechanisms. Toxicol Sci 89:135-144.
Abstract: Epidemiologic evidence suggests that prenatal exposure to intact (unfractionated) cigarette smoke (CS) increases the incidence of cancer in the offspring. A toxicology study was carried out to examine the effects and underlying mechanisms of prenatal exposure to mainstream cigarette smoke (MCS) on offspring resistance to tumor challenge and surveillance mechanisms critical for the recognition and destruction of tumors. Pregnant B6C3F1 mice were exposed by inhalation to MCS for 5 days/week (4 h/day from gestational day 4 to parturition). Smoke-induced effects on offspring-host resistance to transplanted tumor cells; natural killer (NK) cell and cytotoxic T-lymphocyte (CTL) activity; cytokine levels; lymphoid organ immune cell subpopulations; and histology-were examined in 5-, 10- and 20-week-old male and female offspring. At a concentration of smoke roughly equivalent to smoking < 1 pack of cigarettes/day, prenatally exposed male offspring challenged at 5 week of age with EL4 lymphoma cells demonstrated a greater than two-fold increase in tumor incidence (relative to age-/gender-matched air-exposed offspring); tumors in prenatally smoke-exposed pups also grew significantly faster. Cytotoxic T-lymphocyte activity in the smoke-exposed 5- and 10-week-old male pups was significantly less than that of the age- and gender-matched controls. No effects of prenatal CS exposure were observed on offspring NK activity, cytokine levels, lymphoid organ histology, or immune cell subpopulations. Results demonstrated that exposure of pregnant mice to a relevant dose of MCS decreased offspring resistance against transplanted tumor cells and persistently reduced CTL activity in prenatally exposed pups. This study provides biological plausibility for the epidemiologic data indicating that children of mothers who smoke during pregnancy have a greater risk of developing cancer in later life.

Ng SP, Zelikoff JT. 2007. Smoking during pregnancy: subsequent effects on offspring immune competence and disease vulnerability in later life. Reprod Toxicol 23:428-437.
Abstract: About 1 million babies are born each year after prenatal cigarette smoke (CS) exposure from maternal smoking which does not include involuntary maternal exposure to passive smoke. While past emphasis has been on immediately obvious perinatal consequences (e.g., preterm delivery, and low birthweight), smoking during pregnancy has recently emerged as a possible risk factor for later onset disease outcomes in the prenatally exposed offspring. This review brings together those epidemiologic and toxicologic studies demonstrating a link between prenatal CS exposure and subsequent disease vulnerabilities in the progeny. While disorders such as obesity, and type 2 diabetes are included in this category, this paper focuses on two immunologically-related outcomes, cancer and asthma. The review defines the current state of knowledge in this understudied area of children's health, sheds light on the seriousness of such disease vulnerabilities, and reveals gaps that need to be filled to provide a better understanding of the extent and nature of the problem.

Nikaido Y, Yoshizawa K, Danbara N, Tsujita-Kyutoku M, Yuri T, Uehara N, Tsubura A. 2004. Effects of maternal xenoestrogen exposure on development of the reproductive tract and mammary gland in female CD-1 mouse offspring. Reprod Toxicol 18:803-811.
Abstract: The objective of this study was to examine the effects of maternal exposure to xenoestrogen, at levels comparable to or greater than human exposure, on development of the reproductive tract and mammary glands in female CD-1 mouse offspring. Effects of genistein (GEN), resveratrol (RES), zearalenone (ZEA), bisphenol A (BPA) and diethylstilbestrol (DES) were examined. Beginning on gestational day 15, pregnant CD-1 mice were administered four daily subcutaneous injections with 0.5 or 10 mg/kg/day of GEN, RES, ZEA or BPA, 0.5 or 10 microg/kg/day of DES dissolved in dimethylsulfoxide (DMSO), or DMSO vehicle (n = 6). Vaginal opening was monitored, 6 animals per group were autopsied at 4, 8, 12 and 16 weeks of age and estrous cyclicity was monitored from 9 to 11 weeks of age. Maternal exposure to xenoestrogen accelerated puberty onset (vaginal opening) and increased the length of the estrous cycle; mice treated with GEN, RES, BPA or DES spent more time in diestrus, and ZEA-treated mice spent more time in estrus. Lack of corpora lutea and vaginal cornification were observed at 4 weeks of age in the high-dose GEN (33%) and RES (17%) groups, and in the high- and low-dose BPA groups (33 and 50%, respectively) and DES groups (83 and 100%, respectively). Lack of corpora lutea and vaginal cornification was observed in the high-dose ZEA group at 4, 8, 12 and 16 weeks of age (83, 100, 83 and 33%, respectively). Mammary gland differentiation was accelerated in ZEA- and BPA-treated mice with corpora lutea at 4 weeks of age. ZEA-treated mice without corpora lutea showed mammary growth arrest at 8, 12 and 16 weeks of age; their mammary glands consisted only of a dilatated duct filled with secreted

fluid. Mammary gland growth was similar with xenoestrogens other than ZEA or BPA to that of the controls at all time points. High-dose GEN and RES and high- and low-dose BPA and DES exerted transient effects on the reproductive tract and mammary glands, whereas ZEA exerted prolonged effects.

Nilsen TIL, Romundstad PR, Troisi R, Potischman N, Vatten LJ. 2005. Birth Size and Colorectal Cancer Risk: a Prospective Population Based Study. Gut 54:1728-1732.
Abstract: Objective: To study whether birth size influences colorectal cancer risk in adulthood. Design: A cohort of Norwegian men and women identified from midwives' birth records with long term cancer follow up through the Norwegian Cancer Registry. Setting: St Olav's University Hospital, Trondheim, Norway. Participants: 16 016 women and 19 681 men born between 1920 and 1958 and alive in 1960. Outcome measures: Incidence rate ratios (RRs) for colorectal cancer with 95% confidence intervals (CIs) and two sided p values for trend across categories of birth dimensions. Results: Men whose birth length was less than 51 cm had a nearly twofold higher risk of colorectal cancer (RR 1.9 (95% CI 1.0-3.7)) compared with men who were 53 cm or more, after adjustment for birth cohort, maternal age at childbearing, length of gestation, gestational hypertension or pre-eclampsia, birth order, maternal height, and indicators of maternal socioeconomic status. The association displayed a linear trend across categories of birth length (p(trend) = 0.03). Among men, similar associations were found for birth weight and head circumference, but for women there was no association between any of these birth dimensions and risk of colorectal cancer. Conclusion: The results suggest that among men, but not women, being relatively short at birth is associated with increased risk of colorectal cancer in adulthood, indicating that intrauterine growth could be important for colorectal carcinogenesis.

Nilsson A, Morgan JP, Book SA. 1985 . Investigations of 90Sr in dogs. I. Pathogenesis of radiation-induced bone tumors. Acta Radiol Oncol 24:95-111.
Abstract: Purebred beagle dogs given 90Sr and unirradiated controls were studied for over two decades. Pregnant females were fed different doses of 90Sr from day 21 post-conception until the offsprings reached an age of 540 days. In an additional experiment two dose levels were given in a single intravenous dose to dogs 540 days old. Radiographically the earliest skeleton lesions were characterised by small linear, solitary, cortical lucencies. These as well as tumors were more frequently noted in the higher exposure levels. They affected the appendicular skeleton almost as frequently as the axial skeleton. The lesions were predominantly found in the diaphysis, at the angle and near the acetabulum in the tubular bones, mandible and pelvis, respectively. The lesions within the diaphysis originated in the cortical bone. Histologically these lesions were characterised by different types of porosities. These could be empty or filled by a defect and/or immature, dysplastic fibrous repair tissue, within the frame of which malignant transformations seemed to take place as evidenced by malignant clones and micro-osteosarcomas. A comparison is made of the histologic events in dogs and mice and a tentative pathogenesis of 90Sr induced bone tumors is discussed.

Nilsson H, Jogi A, Beckman S, Harris AL, Poellinger L, Pahlman S. 2005. Hif-2 Alpha Expression in Human Fetal Paraganglia and Neuroblastoma: Relation to Sympathetic Differentiation, Glucose Deficiency, and Hypoxia. Exp Cell Res 303:447-456.
Abstract: Solid tumors are frequently necrotic and hypoxic due to poor vascularization. Tumor cells adapt to hypoxia by modulating their phenotype. Key players in this process are the hypoxia-inducible factors (HIF-1alpha to 3alpha). HIFs are also expressed during normal development; for example, HIF-2alpha is specifically expressed and appears to be involved in the development of the murine sympathetic nervous system (SNS). Here, we demonstrate that HIF-2alpha protein is selectively present in human fetal week 8.5 SNS paraganglia. Neuroblastoma is derived from SNS precursors. In a subset of neuroblastomas, a spontaneous neuronal to neuroendocrine differentiation occurs in areas adjacent to necrotic zones. As HIF-2alpha activity has been associated not only with hypoxic but also with hypoglycemic conditions, we have investigated putative effects of hypoxia, glucose depletion, and HIF-2alpha on the neuroblastoma phenotype. HIF-2alpha was detected in hypoxic and in well-oxygenized neuroblastoma cells and tissue. presumably reflecting their embryonic features. With regard to differentiation, hypoxic cells lost their neuronal/neuroendocrine features and gained marker gene expression associated with an immature. neural crest-like phenotype. Low glucose potentiated the effect of hypoxia. These findings suggest that poorly, vascularized neuroblastomas become immature and maintain a more aggressive phenotype, which possibly could involve a sustained stabilization and activation of HIF-2alpha. (C) 2004 Elsevier Inc. All rights

reserved.

Nilsson PM, Hofvendahl S, Hofvendahl E, Brandt L, Ekbom A. 2006. Smoking in pregnancy in relation to gender and adult mortality risk in offspring: the Helsingborg Birth Cohort Study. Scand J Public Health 34:660-4.
Abstract: BACKGROUND: Smoking in pregnancy is a well-documented risk factor for fetal growth impairment and poor perinatal outcomes. Less is known about the long-term effects of maternal smoking on offspring mortality. METHODS: A follow-up study in national registers on total mortality and cancer based on a birth cohort from Helsingborg, Sweden, including data on 2,010 sons and 1,982 daughters born to mothers for whom the smoking habits during pregnancy (50% smokers) have been recorded. RESULTS: A total of 92 offspring deaths were recorded (54 men, 38 women) during follow-up. Of these deaths, 43 deaths were related to trauma, 6 to circulatory disease, and 2 to endocrine disorders. In men, an elevated mortality risk was associated with increasing maternal smoking habits (p for trend 0.011), but in women with low birth weight (p for trend 0.006). A total of 47 incident offspring cancers were registered (18 in men and 29 in women). No significant relation was noted for maternal smoking habits and cancer in the offspring. CONCLUSIONS: Maternal smoking during pregnancy is associated with an increased mortality risk in early adult life for male offspring but not for female offspring. This could represent the possible consequence of an increased susceptibility in male fetuses.

Nomura T. 1983. X-ray-induced germ-line mutation leading to tumors. Its manifestation in mice given urethane post-natally. Mutat Res 121:59-65.
Abstract: Treatment of parental ICR mice with X-rays resulted in a significant increase of lung tumors in F1 offspring, which were inherited dominantly with about 40% penetrance. If germ-line mutation leads to heritable tumors, all cells composing the lungs must be mutated and have an equal likelihood of forming tumors. After treatment with carcinogenesis-promoting agents, unusually large clusters of tumor nodules developed in the lungs. When urethane was given to F1 offspring of parents that had been irradiated with 216 rad of X-rays, a large number of offspring (18.0%) developed large clusters of tumor nodules in the lung, whereas only 2.8% did so in the non-irradiated control, an indication of germ-line mutations. The incidence of the affected tumor clusters was more than twice (2.4-fold) that of affected progeny without urethane treatment postnatally, indicating enhancement of penetrance. If increased penetrance after urethane treatment (the multiplying ratio being 2.41) was taken into account in the dose-response data of the previous report, doubling doses were estimated to be about 25 and 50 rad for spermatids and spermatogonia respectively. These values are similar to those for other types of gonial mutation. Curiously, no tumors were produced by radiation in the offspring when exposure of male patterns was in utero (day 15 of gestation). The F1 offspring, which had no lung-tumor-causing mutations, were also highly resistant to post-natal treatment with urethane, developing no clusters of tumor nodules in the offspring. This suggests that, without tumor mutations, carcinogens rarely produce tumors.

Nomura T. 1984. Induction of persistent hypersensitivity to lung tumorigenesis by in utero X-radiation in mice. Environ Mutagen 6:33-40.
Abstract: A single dose (36 rad) of X rays was given to mouse embryos and neonates that were then treated with urethane at 21 days of age. Although in utero X-radiation to mice was not tumorigenic, it significantly increased lung tumor susceptibility to a postnatally-given carcinogen, urethane. X-ray induction of persistent hypersensitivity to lung tumorigenesis was apparent at all stages during days 0 to 14 of gestation (except on day 6), but was not observed at late fetal and neonatal stages.

Nomura T. 2003. Transgenerational carcinogenesis: Induction and transmission of genetic alterations and mechanisms of carcinogenesis. Mutation Research-Reviews in Mutation Research 544:425-432.
Abstract: Parental exposure, i.e. germ cell exposure to radiation and chemicals, increased the incidence of tumors and malformations in the offspring, and the germ-line alterations that cause cancer are transmissible to further generations. However, tumor incidences were 100-fold higher than those of ordinary mouse mutations and there were apparent strain differences in the types of induced tumors. In human, higher risk of leukemia is reported in the children of fathers who had been exposed to radionuclides at the nuclear reprocessing plants or to diagnostic doses of radiation. However, these findings in mice and men have not been confirmed in the children of atomic bomb survivors in Hiroshima and Nagasaki. Another important finding was that germ-line exposure was very weakly tumorigenic by itself. However, the-transmissible alterations caused persistent hypersensitivity to tumor induction in the offspring, e.g. enhanced by postnatal

treatment with tumor promoting/carcinogenic agents. The above results suggest that transmissible alterations might be imprinted in germ cells for the future development of cancer by the postnatal environment. Many gene loci concerning immunological, biochemical and physiological function might be involved, and the cumulative changes in such genes may slightly elevate or enhance tumor incidences, although mutations of tumor suppressor genes such as p53 were also detected in some offspring and genomic instability may modify tumor occurrence in transgenerational manner. In fact, Gene Chip analysis showed suppression and/or over-expression of many functional genes rather than cancer-related genes in the preconceptionally irradiated cancer prone progeny. (C) 2003 Elsevier B.V. All rights reserved.

Nomura T. 2006. Transgenerational effects of radiation and chemicals in mice and humans. J Radiat Res (Tokyo) 47 (Suppl. B):B83-B97.
Abstract: Parental exposure of mice to radiation and chemicals causes a variety of adverse effects (e.g., tumors, congenital malformations and embryonic deaths) in the progeny and the tumor-susceptibility phenotype is transmissible beyond the first post-radiation generation. The induced rates of tumors were 100-fold higher than those known for mouse specific locus mutations. There were clear strain differences in the types of naturally-occurring and induced tumors and most of the latter were malignant. Another important finding was that germ-line exposure elicited very weak tumorigenic responses, but caused persistent hypersensitivity in the offspring for the subsequent development of cancer by the postnatal environment. Activations of oncogenes, ras, mos, abl, etc. and mutations in tumor suppressor genes such as p53 were also detected in specific tumors in cancer-prone descendants. However, the majority of tumors observed in the progeny were those commonly observed in the strains that were used and oncogene activations were rarely observed in these tumors. It can be hypothesized that genetic instability modifies tumor occurrence in a transgenerational manner, but so far no links could be established between chromosomal and molecular changes and transmissible tumor risks. Our data are consistent with the hypothesis that cumulative changes in many normal but cancer-related genes affecting immunological, biochemical and physiological functions may slightly elevate the incidence of tumors or fasten the tumor development. This hypothesis is supported by our GeneChip analyses which showed suppression and/or over-expression of many such genes in the offspring of mice exposed to radiation. In humans, a higher risk of leukemia and birth defects has been reported in the children of fathers who had been exposed to radionuclides in the nuclear reprocessing plants and to diagnostic radiation. These findings have not been supported in the children of atomic bomb survivors in Hiroshima and Nagasaki, who were exposed to higher doses of atomic radiation. However, it will be important to follow the human subjects, especially for adult type cancers and chronic diseases throughout their lives to determine whether the mouse studies can predict human responses.

Nomura T, Kanzaki T. 1977. Induction of urogenital anomalies and some tumors in the progeny of mice receiving diethylstilbestrol during pregnancy. Cancer Res 37:1099-1104.
Abstract: Pregnant mice were given a single dose (10 mug/g body weight) of diethylstilbestrol (DES) on Days 7 to 19, which correspond to the first to fifth lunar months in humans, after the authors, using a 14C-labeled compound, confirmed easy placental penetration by DES. Treatment with DES on Days 15 to 19 resulted in the induction of persistent urogenital sinus (15.8 to 92.5%) and hypertrophy of the portio vaginalis (11.8 to 73.3%) in female offspring, and treatment on Days 17 and 19 resulted in the induction of undescended testes and their hypogenesis (70.4 to 73.3%) in male offspring, although treatment with DES at other stages of pregnancy and after birth did not cause these alterations. The incidence of various tumors (lung adenoma, granulosa cell tumor, etc.) increased significantly (31.0 to 37.9%) when DES was given on Days 15 and 17, which correspond to the stage sensitive to other carcinogens. However, adenosis and adenocarcinoma of the vagina were not observed in the offspring.

Nomura T, Nakajima H, Ryo H, Li LY, Fukudome Y, Adachi S, Gotoh H, Tanaka H. 2004. Transgenerational transmission of radiation- and chemically induced tumors and congenital anomalies in mice: Studies of their possible relationship to induced chromosomal and molecular changes. Cytogenetic & Genome Research 104:252-260.
Abstract: This article provides a broad overview of our earlier studies on the induction of tumors and congenital anomalies in the progeny of X-irradiated or chemically treated mice and our subsequent (published, hitherto unpublished and ongoing) investigations aimed at identifying potential relationships between genetic changes induced in germ cells and the adverse effects manifest as tumors and congenital

anomalies using cytogenetic and molecular approaches. The earlier studies document the fact that tumors and congenital anomalies can be induced by irradiation or treatment with certain chemicals such as urethane and that these phenotypes are heritable i.e., transmitted to generations beyond the first generation. These findings support the view that transmissible induced genetic changes are involved. The induced rates of congenital abnormalities and tumors are about two orders of magnitude higher than those recorded in the literature from classical mutation studies with specific locus mutations. The cytogenetic studies addressed the question of whether there were any relationships between induced translocations and induced tumors. The available data permit the inference that gross chromosomal changes may not be involved but do not exclude smaller induced genetic changes that are beyond the resolution of the techniques used in these studies. Other work on possible relationship between visible chromosomal anomalies (in bone marrow preparations) and tumors were likewise negative. However, there were indications that some induced cytogenetic changes might underlie induced congenital anomalies, i.e., trisomies, deletions and inversions were observed in induced and transmissible congenital anomalies (such as dwarfs, tail anomalies). Studies that explored possible relationships between induction of minisatellite mutations at the Pc-3 locus and tumors were negative. However, gene expression analysis of tumor (hepatoma)-susceptible offspring of progeny descended from irradiated male mice showed abnormal expression of many genes. Of these, only very few were oncogenes. This lends some support to our hypothesis that cumulative changes in gene expression of many genes, which perform normal cellular functions, may contribute to the occurrence of tumors in the offspring of irradiated or chemically treated mice.

Norman MA, Holly EA, Ahn DK, Preston-Martin S, Mueller BA, Bracci PM. 1996. Prenatal exposure to tobacco smoke and childhood brain tumors: Results from the United States West Coast childhood brain tumor study. Cancer Epidemiology, Biomarkers & Prevention 5:127-133.
Abstract: Data from a large, population-based case-control study were analyzed to investigate the relationship between prenatal exposure to tobacco smoke and childhood brain tumors (CBTs). A total of 540 CBT patients, diagnosed between 1984 and 1991, were identified from population-based tumor registries in 19 West Coast counties that included Seattle, WA (13 counties), San Francisco, CA (5 counties), and Los Angeles, CA (1 county). Random digit dial was used to select 801 control subjects from the three geographical regions to obtain a case:control ratio of 1:2 in San Francisco and Seattle and 1:1 in Los Angeles. The data first were analyzed separately by geographical site and then were combined with adjustments made for gender, age at the time of diagnosis (or reference date of control subjects), birth year of the index child, and maternal race. No association was found between the risk of CBTs and maternal or paternal smoking before pregnancy and there was no association between CBTs and maternal smoking during pregnancy [odds ratio (OR) = 0.98; 95% confidence interval (CI) = 0.72-1.3]. A slightly increased OR for CBTs was found for paternal smoking during pregnancy in the absence of maternal smoking (OR = 1.2; 95% CI = 0.90-1.5) and for maternal exposure to passive smoke from any source (OR = 1.2; 95% CI = 0.95-1.6). The results of this analysis are consistent with results from several prior epidemiological studies that showed no significant association between CBTs and maternal smoking before or during pregnancy or maternal exposure to passive smoke during pregnancy.

Norman MA, Holly EA, Preston-Martin S. 1996. Childhood brain tumors and exposure to tobacco smoke. Cancer Epidemiology, Biomarkers & Prevention 5:85-91.
Abstract: Brain tumors are the second most common cancer in children after leukemia, yet the etiology of childhood brain tumors remains unknown. Tobacco smoke contains several dozen compounds that are known to be carcinogens. Among these are N-nitroso compound precursors, principally tobacco-specific nitrosamines. Although smoking has not been identified as a significant risk factor for the development of brain tumors in adults, fetuses and infants have incompletely formed blood-brain barriers that may allow the passage of carcinogenic tobacco metabolites into the central nervous system and initiate the formation of neural tumors. In this review, we present data from case-control and cohort studies published between 1971 and 1995 that examined the relationship between parental smoking during pregnancy and childhood brain tumors (CBTs). The majority of these studies found little association between CBTs and maternal smoking before or during pregnancy or between CBTs and maternal exposure to passive smoke during pregnancy.

NTP. 2006. NTP Toxicology and Carcinogenesis Studies of Transplacental 3'-Azido-3'-Dioxythymidine (AZT) (CAS No. 30516-87-1) in Swiss (CD-1(R)) Mice (in utero Studies). Natl Toxicol Program Tech Rep Ser :1-

184.
Abstract: 3'-Azido-3'-deoxythymidine (AZT) is the most widely used and evaluated chemotherapeutic agent for the treatment of persons with acquired immune deficiency syndrome (AIDS) and persons seropositive for human immunodeficiency virus (HIV). The study in this report was conducted to obtain information on AZT transplacental carcinogenicity at doses that were lower than those used in previous NCI studies and analogous to therapeutic doses. Male and female Swiss (CD-1(R)) mice were exposed to AZT (greater than 99% pure) during all of gestation. Genetic toxicology studies were conducted in mouse peripheral blood erythrocytes. Groups of 22, 28, 34, or 46 female mice (F(0) generation) were administered AZT in 0.5% methylcellulose by gavage at doses of 50, 100, 200, or 300 mg AZT/kg body weight 7 days per week for 29 to 39 days (day of delivery). A vehicle control group of 22 female mice received methylcellulose alone. Each female group was divided into two groups with dosing started 1 week apart in order to facilitate cohabitation, mating, and delivery. Groups of six, six, seven, nine, or twelve undosed male mice were cohabited with the vehicle control and 50, 100, 200, and 300 mg/kg dosed females, respectively, on study days 9 to 13 and then discarded. Pups (F(1) generation) were culled (0, 50, and 100 mg/kg groups) to yield a maximum of five pups/sex per litter on postnatal day 4; no more than four pups/sex per litter were used in the study. On postnatal day 25, all surviving 200 and 300 mg/kg pups were placed on study. After culling and randomization to cage groups, the 0, 50, 100, 200, and 300 mg/kg groups consisted of 50, 50, 50, 37, and 32 male pups and 50, 50, 50, 40, and 42 female pups, respectively. Decreased litter size and fertility rates were observed in the 200 and 300 mg/kg F0 dams. Survival of all exposed groups of F(1) mice was similar to that of the vehicle controls. Mean body weights of 200 mg/kg males were generally less than those of the vehicle controls after week 29. Mean body weights of 300 mg/kg males were less during the first year of the study, but these mice recovered and body weights were generally similar to those of the vehicle controls at the end of the study. The incidences of alveolar/bronchiolar carcinoma and of adenoma or carcinoma (combined) in 200 and 300 mg/kg males were significantly greater than those in the vehicle controls. The incidences of histiocytic cellular infiltration of the lung in 200 and 300 mg/kg males were significantly increased. GENETIC TOXICOLOGY: The NTP conducted a number of studies of the genetic toxicity of AZT, independent of this transplacental carcinogenicity study. In these genetic toxicity studies, AZT (50, 75, 100, or 150 mg/kg) administered to pregnant Swiss (CD-1(R)) dams, beginning prior to conception and continuing throughout gestation and lactation, induced high levels of micronucleated polychromatic erythrocytes (PCEs) in pups sampled on postnatal days 1 and 4. Direct gavage treatment of these transplacentally and lactationally exposed pups, beginning on postnatal day 4, resulted in further increases in the frequencies of micronucleated PCEs on postnatal days 8 and 21. The percentage of PCEs among erythrocytes in pups was significantly elevated over normal adult levels, indicating a high rate of erythropoiesis in neonatal mice. The percentage of PCEs was decreased in all pups exposed to AZT, consistent with treatment-related bone marrow toxicity. CONCLUSIONS: Under the conditions of this study, there was clear evidence of carcinogenic activity in F(1) male mice exposed transplacentally to AZT based on increased incidences of alveolar/bronchiolar neoplasms. There was no evidence of carcinogenic activity in F(1) female mice exposed transplacentally to AZT at 50, 100, 200, or 300 mg/kg. Reproductive toxicity in the form of decreased litter size and fertility rates was observed in dams in the 200 and 300 mg AZT/kg dose groups. Synonyms: AZT; 3'-azido-2',3'-dideoxythymidine; azidodeoxythymidine; azidothymidine; 3'-azidothymidine; 3'-deoxy-3'-azidothymidine; 3'-deoxy-(8CI) (9CI); BW A509U; Compound S; ZDV; zidovudine Trade Name: Retrovir(R).

Nyari TA, Dickinson HO, Hammal DM, Parker L. 2003. Childhood solid tumours in relation to population mixing around the time of birth. Br J Cancer 88:1370-1374.
Abstract: In a retrospective cohort study of 673 787 live births in the Northern Region of England, 1975-1994, we investigated whether a higher level of population mixing around birth was a risk factor for solid tumours, by diagnostic group (Hodgkin's disease, brain and spinal tumours, neuroblastoma, other solid tumours), diagnosed during 1975-2001 under age 15 years. Logistic regression was used to relate risk to population mixing, based on (i) all movers and (ii) incomers from outside the region. Both ward and county district level analyses were performed. There was a decreased risk of brain and spinal tumours with increasing population mixing based on incomers from outside the region (OR for trend across three categories=0.79, 95% CI: 0.66-0.95, P=0.01 in the ward level analysis). Although this may be because of chance, it is consistent with a role of exposure to infection and immunological response in the aetiology of these tumours. For other tumour groups, there was no consistent evidence of an association between risk

and population mixing.

Nyari TA, Dickinson HO, Parker L. 2003. Childhood cancer in relation to infections in the community during pregnancy and around the time of birth. Int J Cancer 104:772-777.
Abstract: In a retrospective cohort study of 404,106 live births in the northern region of England, 1975-1986, we investigated whether higher levels of community infections during the mother's pregnancy and in early life were risk factors for cancer, by diagnostic group (leukaemia and non-Hodgkin's lymphoma, Hodgkin's disease, brain/spinal tumours, neuroblastoma, other tumours), diagnosed 1975-2001 under age 15 years. Logistic regression was used to relate risk to measures of community infections (measles, respiratory and other infections) in 3 prenatal and 2 postnatal quarters. There was an increased risk of Hodgkin's disease among children exposed around birth to higher levels of measles (odds ratio for trend = 2.3, 95% confidence interval 1.3-4.2, p = 0.01). For other diagnostic groups, there was no consistent evidence of an association between risk and exposure to infections. Although the significant association observed for Hodgkin's disease may be a chance finding, consequent to multiple hypothesis testing or the ecologic nature of the study, it is consistent with other recent epidemiologic results suggesting that the risk of Hodgkin's disease may be associated with exposure to infections.

O'Connell JT, Mutter GL, Cviko A, Nucci M, Quade BJ, Kozakewich HP, Neffen E, Sun D, Yang A, McKeon FD, Crum CP. 2001. Identification of a basal/reserve cell immunophenotype in benign and neoplastic endometrium: A study with the p53 homologue p63. Gynecol Oncol 80:30-36.
Abstract: BACKGROUND: Metaplastic differentiation, including squamous, mucinous, and tubal (ciliated), is common in both benign and neoplastic endometrium, and the cell of origin for this pathway is poorly understood. In this study, expression of a marker for basal and reserve cells in cervical squamous mucosa, designated p63, was investigated in a spectrum of endometrial alterations. METHODS: One hundred ninety different endometria from 132 patients were examined, including fetal (6), premenarchal (3), benign cyclic (29) and noncyclic (54), hyperplastic (14), and neoplastic (93) endometrial glandular epithelia. The latter included conventional endometrioid carcinomas with and without mucinous, ciliated, and squamous metaplasia, and uterine papillary serous carcinoma (UPSC). RESULTS: p63 expression was identified in basal/subcolumnar cells in the fetal endometrium in a distribution similar to that in basal/reserve cells of the cervix. Staining was confined to individual scattered basal and suprabasal cells in cycling endometrium. In polyps and postmenopausal endometria, focal clusters of p63-positive cells were identified in inactive glands or surface epithelium. Metaplastic (squamous or mucinous) epithelia, either alone or in conjunction with hyperplasias or carcinomas, exhibited the most intense staining, primarily in basal or subcolumnar cells. In some cases, immediately adjacent nonmetaplastic columnar epithelium also stained positive. UPSCs contained only rare scattered p63-positive cells. CONCLUSIONS: Cells with a basal or reserve cell phenotype exist in the endometrium during fetal life, are not conspicuous during the reproductive years, but may emerge during shifts in differentiation. Whether these cells signify specialized multipotential endometrial cells is not clear, but the similarity of these cells to basal/reserve cells of the cervix and their association with neoplasia merit further study.

Oda H, Zhang SM, Tsurutani N, Shimizu S, Nakatsuru Y, Aizawa S, Ishikawa T. 1997. Loss of p53 is an early event in induction of brain tumors in mice by transplacental carcinogen exposure. Cancer Res 57:646-650.
Abstract: Experimental carcinogenesis studies using p53-deficient mice have suggested that loss of function of this tumor suppressor gene is generally not an early event but is rather related to tumor progression, However, the biological functions of p53 and the accumulating evidence of alteration in human tumors imply a possible role for loss of p53 in the initial stages of tumorigenesis. Ethylnitrosourea administration to p53-heterozygous pregnant mice resulted in rapid development of primary brain tumors, which are extremely rare in mice, in 70% of the p53-null offspring. Brain tumors also developed later in 4% of heterozygous mice, but they had lost the wild-type allele. Thus, loss of normal p53 gene expression is of direct significance to early events in brain tumorigenesis, and this tumor suppressor gene may protect embryos from DNA damage in the brain induced by transplacental carcinogen exposure.

Ogris E. 1997. Exposure with J-131 during pregnancy: Significance for mother and child. Acta Med Austriaca 24:150-153.
Abstract: The embryonal stage in mammalians is characterized by a quick proliferation and differentiation of cells. The special features of this stage of development in all living beings is therefore an increased

sensitivity for the exposure with ionizing radiation. Radiation exposure during the prenatal development can therefore lead to various impairments, which can be short-termed or long-termed, showing effects even in the postnatal period. The pattern of radiation induced effects is dependent upon the radiation dose on the one hand and upon the stage of fetal development when radiation exposure occurs on the other hand. Radiation induced effects can be growth retardation, malformations, functional impairments or death as well as increased occurrence of cancer and leucemia during childhood. The main effects of a radiation exposure in the fetal period are: 1) lethal effects for the embryo, 2) malformations and changes in growth or other functional changes, 3) mental retardation, 4) induction of malignomas including leucemia. Lethal effects can be induced experimentally in animals by relatively low radiation doses of 10 cGy, administered before or immediately after the implantation of the embryo. Malformations can be induced if the exposure occurs during the period of organogenesis especially if the radiation exposure occurs during the active stage of increased cell formation and cell differentiation of a specific organ. For many types of effects of ionizing radiation especially for the death of the embryo or fetus and for macroscopic anatomical malformation a dose-effect relationship with certain treshold doses can be supposed. This treshold dose is not smaller with low LET. Radiation exposure at the end of the organogenesis and during the following fetal period can induce growth retardation and functional disturbancies, which are characterized by abnormalities in the postnatal period. Of special importance are the abnormalities of the CNS, like mental retardation particularely if the radiation exposure occurred during the intervall between the 8(th) and 15(th) week of pregnancy. During that time period cell formation for the development of the frontal brain occurs. The induction of this type of abnor malities as well as of other malformations is due to non stochastic effects. A treshold dose of 5 cGy ist discussed. The induction of malignancies and leucemia as a consequence of a radiation exposure in the prenatal period is to be seen as a deterministic (non stochastic) radiation effect. The sensitivity of the fetus for these effects ist 2 to 3 times higher than that of adults.

Ohgaki H, Hard GC, Hirota N, Maekawa A, Takahashi M, Kleihues P. 1992. Selective mutation of codons-204 and codon-213 of the p53 gene in rat-tumors induced by alkylating n-nitroso compounds. Cancer Res 52:2995-2998.

Abstract: Kidney and esophageal tumors induced by alkylating N-nitroso compounds in rats contain a high incidence (75-100%) of G --> A transition mutations in the p53 gene. These are almost selectively (89%) located in the first base of codon 204 and the second base of 213, leading to amino acid substitutions Glu --> Lys and Arg --> Gln, respectively. In contrast to human neoplasms, a considerable fraction of rat kidney and esophageal tumors carries multiple p53 mutations. All nephroblastomas induced by transplacental exposure to N-nitrosoethylurea and 56% of esophageal tumors induced by N-nitrosomethylurea showed double mutations in codons 204 and 213 of exon 6. The selective targeting of p53 codons by alkylating nitrosamines may provide a basis for molecular epidemiological studies on this class of chemical carcinogens.

Ohgaki H, Kleihues P, Hard GC. 1991. Ki-ras mutations in spontaneous and chemically-induced renal tumors of the rat. Mol Carcinog 4:455-459.

Abstract: A high frequency of point mutations at codon 12 of the Ki-ras gene has previously been reported for rat kidney mesenchymal tumors induced by methylating N-nitroso compounds. In this study, we analyzed renal tumors with divergent histogenesis, i.e., mesenchymal tumors (sarcomas), cortical epithelial tumors (carcinomas), and embryonal tumors (nephroblastomas). Renal mesenchymal tumors and carcinomas were induced in juvenile or young adult Wistar rats by a single dose of N-nitrosodimethylamine (NDMA) while nephroblastomas were induced in Nb hooded rats by a single transplacental dose of N-nitrosoethylurea (NEU). Nephroblastomas developing spontaneously in WAB/Not rats were also examined. Amplification of Ki-ras sequences from formalin-fixed, paraffin-embedded tissue by the polymerase chain reaction was followed by direct DNA sequencing. GGT --> GAT point mutations at codon 12 of the Ki-ras gene were found in 9 of 12 (75%) renal mesenchymal tumors and in 9 of 12 (75%) cortical epithelial tumors induced by NDMA. Even higher incidences were observed in nephroblastomas (8/8; 100%) induced by NEU and in spontaneous nephroblastomas (10/11; 91%). These results indicate that Ki-ras mutations are frequent events during the development of kidney tumors irrespective of their histogenesis and suggest that they may play an important role in renal carcinogenesis in rats. These data further indicate that mutational activation of Ki-ras proto-oncogenes in carcinogen-induced rat kidney tumors occurs in a tissue-specific, rather than cell-specific, manner.

Ohtaki K, Kodama Y, Nakano M, Itoh M, Awa AA, Cologne J, Nakamura N. 2004. Human fetuses do not register chromosome damage inflicted by radiation exposure in lymphoid precursor cells except for a small but significant effect at low doses. Radiat Res 161:373-379.
Abstract: Human fetuses are thought to be highly sensitive to radiation exposure because diagnostic low-dose X rays have been suggested to increase the risk of childhood leukemia. However, animal studies generally have not demonstrated a high radiosensitivity of fetuses, and the underlying causes for the discrepancy remain unidentified. We examined atomic bomb survivors exposed in utero for translocation frequencies in blood lymphocytes at 40 years of age. Contrary to our expectation of a greater radiosensitivity in fetuses than in adults, the frequency did not increase with dose except for a small increase (<1%) at doses below 0.1 Sv, which was statistically significant. We interpret the results as indicating that fetal lymphoid precursor cells comprise two subpopulations. One is small in number, sensitive to the induction of both translocations and cell killing, but rapidly diminishing above 50 mSv. The other is the major fraction but is insensitive to registering damage expressed as chromosome aberrations. Our results provide a biological basis for resolving the long-standing controversy that a substantial risk of childhood leukemia is implicated in human fetuses exposed to low-dose X rays whereas animal studies involving mainly high-dose exposures generally do not confirm it. (C) 2004 by Radiation Research Society.

Olivero OA, Anderson LM, Diwan BA, Haines DC, Harbaugh SW, Moskal TJ, Jones AB, Rice JM, Riggs CW, Logsdon D, Yuspa SH, Poirier MC. 1997 Nov 5. Transplacental effects of 3'-azido-2',3'-dideoxythymidine (AZT): tumorigenicity in mice and genotoxicity in mice and monkeys. J Natl Cancer Inst 89:1602-8.
Abstract: BACKGROUND: When given during pregnancy, the drug 3'-azido-2',3'-dideoxythymidine (AZT) substantially reduces maternal-fetal transmission of human immunodeficiency virus type 1 (HIV-1). However, AZT has been shown to be carcinogenic in adult mice after lifetime oral administration. In this study, we assessed the transplacental tumorigenic and genotoxic effects of AZT in the offspring of CD-1 mice and Erythrocebus patas monkeys given AZT orally during pregnancy. METHODS: Pregnant mice were given daily doses of either 12.5 or 25.0 mg AZT on days 12 through 18 of gestation (last 37% of gestation period). Pregnant monkeys were given a daily dose of 10.0 mg AZT 5 days a week for the last 9.5-10 weeks of gestation (final 41%-43% of gestation period). AZT incorporation into nuclear and mitochondrial DNA and the length of chromosomal end (telomere) DNA were examined in multiple tissues of newborn mice and fetal monkeys. Additional mice were followed from birth and received no further treatment until subjected to necropsy and complete pathologic examination at 1 year of age. An anti-AZT radioimmunoassay was used to monitor AZT incorporation into DNA. RESULTS: At 1 year of age, the offspring of AZT-treated mice exhibited statistically significant, dose-dependent increases in tumor incidence and tumor multiplicity in the lungs, liver, and female reproductive organs. AZT incorporation into nuclear and mitochondrial DNA was detected in multiple organs of transplacentally exposed mice and monkeys. Shorter chromosomal telomeres were detected in liver and brain tissues from most AZT-exposed newborn mice but not in tissues from fetal monkeys. CONCLUSIONS: AZT is genotoxic in fetal mice and monkeys and is a moderately strong transplacental carcinogen in mice examined at 1 year of age. Careful long-term follow-up of AZT-exposed children would seem to be appropriate.

Olsen J. 2000. Prenatal exposures and long-term health effects. Epidemiol Rev 22:76-81.

Olshan AF, Anderson L, Roman E, Fear N, Wolff M, Whyatt R, Vu V, Diwan BA, Potischman N. 2000. Workshop to identify critical windows of exposure for children's health: Cancer work group summary. Environ Health Perspect 108 Suppl 3:595-597.
Abstract: We considered whether there are discrete windows of vulnerability in the development of cancer and which time periods may be of the greatest importance. Cancer was considered broadly, including cancers in childhood as well as adult cancers that may have an in utero or childhood origin. We concluded that there was evidence from animal and epidemiologic studies for causal relationships for preconceptional, in utero, and childhood exposures and cancer occurrence in children and adults. However, the evidence is incomplete and all relevant critical windows may not have been identified. The comprehensive evaluation of the relative importance of specific time windows of exposure is limited. Improvements in the design of epidemiologic studies and additional animal studies of mechanisms are warranted.

Olshan AF, Breslow NE, Falletta JM, Grufferman S, Pendergrass T, Robison LL, Waskerwitz M, Woods WG, Vietti TJ, Hammond GD. 1993 . Risk factors for Wilms tumor. Report from the National Wilms Tumor Study.

Cancer 72:938-944.
Abstract: BACKGROUND. Previous epidemiologic studies have indicated that several factors may be associated with an increased risk of Wilms tumor including paternal occupational exposures, maternal exposure during pregnancy to cigarettes, coffee or tea, oral contraceptives, hormonal pregnancy tests, hair-coloring products, maternal hypertension, vaginal infection during pregnancy, and higher birth weight of the child. The current study examines the nonoccupational risk factors using questionnaire data from a large national collaborative clinical trial. METHODS. Parents of 200 children registered with the National Wilms Tumor Study and 233 matched controls, identified using telephone random-digit dialing, completed a self-administered questionnaire about a variety of risk factors. RESULTS. As opposed to some previous studies, no association was found for mother's smoking during pregnancy (10+ cigarettes per day; odds ratio [OR] = 0.73; 95% confidence interval [CI] = 0.40-1.34), maternal consumption of coffee or tea during pregnancy (4+ cups per day; OR = 1.31; CI = 0.57-3.01), or hypertension during pregnancy (OR = 0.96; CI = 0.45-2.06). In addition, no association was found in this study for hormone exposure during pregnancy, hair dye use, vaginal infection during pregnancy, or high birth weight. A previously unreported association with a history of household insect extermination was found (OR = 2.16; CI = 1.24-3.75). CONCLUSIONS. In general, the study failed to confirm most of the previously reported maternal risk factors for Wilms tumor. Understanding the possible role of paternal exposures may be the best objective for further research on potential risk factors for Wilms tumor.

Olshan AF, Smith J, Cook MN, Grufferman S, Pollock BH, Stram DO, Seeger RC, Look AT, Cohn SL, Castleberry RP, Bondy ML. 1999. Hormone and fertility drug use and the risk of neuroblastoma: A report from the Children's Cancer Group and the Pediatric Oncology Group. Am J Epidemiol 150:930-938.
Abstract: Previous epidemiologic studies have suggested an association between maternal sex hormone use during pregnancy, including infertility medication, and an increased risk of neuroblastoma in the offspring. The authors conducted a case-control interview study from 1992 to 1996 that included 504 children less than 19 years of age whose newly diagnosed neuroblastoma was identified by two national collaborative clinical trials groups in the United States and Canada, the Children's Cancer Group and the Pediatric Oncology Group. Controls, matched to cases on age, were identified by random digit dialing. No association was found for use of oral contraceptives before or during pregnancy (first trimester odds ratio (OR) = 1.0, 95% confidence interval (CI): 0.5, 2.1). The odds ratio was slightly elevated for history of infertility (OR = 1.4, 95% CI: 0.9, 2.1) and ever use of any infertility medication (OR = 1.2, 95% CI: 0.7, 2.2). Specifically ever use of clomiphene was associated with a 1.6-fold increased risk (95% CI: 0.8, 3.0) but not periconceptionally or during the index pregnancy. A suggestive pattern was found for gender of the offspring, with an increased risk for males but not for females after exposure to oral contraceptives or clomiphene. This study did not find consistent and large increased risks for maternal use of hormones, but the suggestion of an association for male offspring requires further consideration.

Ono T, Saito Y, Komura J, Ikehata H, Tarusawa Y, Nojima T, Goukon K, Ohba Y, Wang JQ, Fujiwara O, Sato R. 2004. Absence of mutagenic effects of 2.45 GHz radiofrequency exposure in spleen, liver, brain, and testis of lacZ-transgenic mouse exposed in utero. Tohoku J Exp Med 202:93-103.
Abstract: A possible mutagenic effect of 2.45 GHz radiofrequency exposure was examined using lacZ-transgenic Muta(TM) mice. Pregnant animals were exposed intermittently at a whole-body averaged specific absorption rate of 0.71 W/kg (10 seconds on, 50 seconds off which is 4.3 W/kg during the 10 seconds exposure). Offspring that were exposed in utero for 16 hours a day, from the embryonic age of 0 to 15 days, were examined at 10 weeks of age. To minimize thermal effects, the exposure was given in repeated bursts of 10 seconds of exposure followed by 50 seconds of no exposure. Mutation frequencies at the lacZ gene in spleen, liver, brain, and testis were similar to those observed in non-exposed mice. Quality of mutation assessed by sequencing the nucleotides of mutant DNAs revealed no appreciable difference between exposed and non-exposed samples. The data suggest that the level of radiofrequency exposure studied is not mutagenic when administered in utero in short repeated bursts.

Oravec CT, Samuel MJ, D'Ambrosio SM. 1985. Metabolism of 7,12-dimethylbenz(a)anthracene and its DNA adduct formation in human fetal kidney and intestinal cells in culture. Drug Metabolism & Disposition 13:76-80.
Abstract: Epithelial cell cultures derived from human fetal intestine and kidney were analyzed for their capability to metabolize 7,12-dimethylbenz(a)anthracene (DMBA) and form DNA-DMBA adducts. Both

the intestinal and kidney cells were able to metabolize DMBA to water and organic soluble metabolites and formed DMBA-DNA adducts. Intestinal cells metabolized 39.5 +/- 25.2% of the DMBA to organic soluble products and 2.9 +/- 0.4% to water-soluble metabolites after 24-hr incubation. Kidney cells yielded 27.4 +/- 18.1 and 3.8 +/- 2.7% organic and water-soluble metabolites, respectively. Kidney cells appeared to produced larger amounts of 7,12-dihydroxymethylbenz(a)anthracene and DMBA-8,9-dihydrodiols than intestinal cell cultures, while intestinal cells produced greater amounts of phenol metabolites. The level of DNA-DMBA adducts formed in the intestinal and kidney cell cultures after 24-hr incubation were 20.4 +/- 17.1 and 36.7 +/- 25.3 mumol DMBA/mol DNA-phosphate, respectively. Major elution peaks were observed where the DMBA-1,2-epoxide-3,4-dihydrodiol-deoxyguanosine adduct eluted. These data indicate qualitatively similar, but quantitatively different, levels of DMBA metabolites and DMBA-DNA adducts produced by human fetal intestinal and kidney epithelial cells in culture.

Otaka Y, Chida T, Yamagishi Y, Kitamura S. 2002. Carcinogenicity test in B6C3F1 mice after parental and prenatal exposure to 50 Hz magnetic fields. Bioelectromagnetics 23:206-213.
Abstract: Some epidemiological studies suggest association of childhood cancer with occupational exposure of the parents to magnetic fields. To test this relationship, 50 each of C57BL/6J female and C3H/HeJ male mice were exposed for 2 and 9 weeks, respectively, to 50 Hz sham (group A), 0.5 (group 13), and 5 mT (group C) sinusoidal alternating magnetic fields. They were mated under the exposure for up to 2 weeks, and the exposure was continued until parturition. All the B6C3F1 offspring, without adjusting numbers of animals, were clinically observed without exposure to magnetic field for a nominal 78 weeks from 6-8 weeks of age after weaning and then euthanized for pathological examination according to a routine carcinogenicity test. 540 pups entered the test, and the survival rate was 96.7%. No F1 mouse died of tumoral diseases before a male in A group died of stomach cancer at 43 weeks of age. The first animal death in the exposed groups due to tumor occurred at 71 weeks of age. Eighteen animals died before necropsy at 84-86 weeks of age. No significant difference was detected in the final number of survivors and incidence of tumors between groups A and B, or A and C. Concerning reproduction total implants in group B were less than in group A and the difference was on the borderline of significance (P = .05). This difference was not reproduced in a later duplicate experiment. (C) 2002 Wiley-Liss, Inc.

Painter RC, De Rooij SR, Bossuyt PM, Osmond C, Barker DJ, Bleker OP, Roseboom TJ. 2006. A possible link between prenatal exposure to famine and breast cancer: a preliminary study. Am J Hum Biol 18:853-6.
Abstract: In a study of 475 women born around the 1944-1945 Dutch famine, women exposed to prenatal famine more often reported a history of breast cancer than nonexposed women (hazard ratio, 2.6; 95% confidence interval, 0.9-7.7). They also had alterations in reproductive risk factors. Prenatal famine may increase breast cancer incidence.

Palmer JR. 2002. Risk of breast cancer in women exposed to diethylstilbestrol *in utero*: Preliminary results (United States). Cancer Causes & Control 13:753-758.
Abstract: A synthetic estrogen, diethylstilbestrol (DES), was widely prescribed to pregnant women during the 1950s and 1960s but was later discovered to be associated with an increased risk of clear-cell carcinoma of the vagina and cervix in female offspring. DES has not been linked to other cancers in female offspring, but studies of other prenatal factors such as twin gestation and pre-eclampsia have indicated that in-utero estrogen levels may influence breast cancer risk. We evaluated the relation of in-utero DES exposure to the risk of adult breast cancer.
A cohort of 4821 exposed women and 2095 unexposed women, most of whom were first identified in the mid-1970s, were followed by mail questionnaries for an average of 19 years. Reported cancer outcomes were validated by medical record review. Breast cancer incidence in DES-exposed daughters were compared with cancer incidence in unexposed daughters with use of Poisson regression analysis, adjusting for year of birth, age at menarche, age at first birth, and number of births.
The rate ratio for incidence of invasive breast cancer in exposed versus unexposed women was 1.4 (95% confidence interval (CI) = 0.7-2.6). DES exposure was not associated wtih an increased risk of breast cancer in women under 40 years, but among women aged 40 and older the rate ratio was 2.5 (95% CI=1.0-6.3). The rate ratio for the association of DES exposure with estrogen receptor-positive tumors was 1.9 (95% CI=0.8-4.5).
While not statistically significant, the overall 40% excess risk, arising exclusively from the subset of estrogen receptor-positive cases, raises a concern calling for continued investigation.

Palmer JR, Wise LA, Hatch EE, Troisi R, Titus-Ernstoff L, Strohsnitter W, Kaufman R, Herbst AL, Noller KL, Hyer M, Hoover RN. 2006. Prenatal diethylstilbestrol exposure and risk of breast cancer. Cancer Epidemiology Biomarkers & Prevention 15:1509-1514.
Abstract: It has been hypothesized that breast cancer risk is influenced by prenatal hormone levels. Diethylstilbestrol (DES), a synthetic estrogen, was widely used by pregnant women in the 1950s and 1960s. Women who took the drug have an increased risk of breast cancer, but whether risk is also increased in the daughters who were exposed in utero is less clear. We assessed the relation of prenatal DES exposure to risk of breast cancer in a cohort of DES-exposed and unexposed women followed since the 1970s by mailed questionnaires. Eighty percent of both exposed and unexposed women completed the most recent questionnaire. Self-reports of breast cancer were confirmed by pathology reports. Cox proportional hazards regression was used to compute incidence rate ratios (IRR) for prenatal DES exposure relative to no exposure. During follow-up, 102 incident cases of invasive breast cancer occurred, with 76 among DES-exposed women (98,591 person-years) and 26 among unexposed women (35,046 person-years). The overall age-adjusted IRR was 1.40 [95% confidence interval (95% CI), 0.89-2.22]. For breast cancer occurring at ages >= 40 years, the IRR was 1.91 (95% CI, 1.09-3.33) and for cancers occurring at ages >= 50 years, it was 3.00 (95% CI, 1.01-8.98). Control for calendar year, parity, age at first birth, and other factors did not alter the results. These results, from the first prospective study on the subject, suggest that women with prenatal exposure to DES have an increased risk of breast cancer after age 40 years. The findings support the hypothesis that prenatal hormone levels influence breast cancer risk.

Pang D, Mcnally R, Birch JM. 2003. Parental smoking and childhood cancer: Results from the United Kingdom Childhood Cancer Study. Br J Cancer 88:373-381.
Abstract: There are strong a priori reasons for considering parental smoking behaviour as a risk factor for childhood cancer but case - control studies have found relative risks of mostly only just above one. To investigate this further, self-reported smoking habits in parents of 3838 children with cancer and 7629 control children included in the United Kingdom Childhood Cancer Study (UKCCS) were analysed. Separate analyses were performed for four major groups (leukaemia, lymphoma, central nervous system tumours and other solid tumours) and more detailed diagnostic subgroups by logistic regression. In the four major groups, after adjustment for parental age and deprivation there were nonsignificant trends of increasing risk with number of cigarettes smoked for paternal preconception smoking and nonsignificant trends of decreasing risk for maternal preconception smoking (all P-values for trend > 0.05). Among the diagnostic subgroups, a statistically significant increased risk of developing hepatoblastoma was found in children whose mothers smoked preconceptionally (OR = 2.68, P = 0.02) and strongest (relative to neither parent smoking) for both parents smoking (OR = 4.74, P = 0.003). This could be a chance result arising from multiple subgroup analysis. Statistically significant negative trends were found for maternal smoking during pregnancy for all diagnoses together (P < 0.001) and for most individual groups, but there was evidence of under-reporting of smoking by case mothers. In conclusion, the UKCCS does not provide significant evidence that parental smoking is a risk factor for any of the major groups of childhood cancers. (C) 2003 Cancer Research UK.

Park SK, Garcia-Closas M, Lissowska J, Sherman ME, Mcglynn KA, Peponska B, Bardin-Mikoajczak A, Zatonski W, Szeszenia-Dabrowska N, Brinton LA. 2006. Intrauterine environment and breast cancer risk in a population-based case-control study in Poland. Int J Cancer 119:2136-2141.
Abstract: High estrogen exposure in utero may increase breast cancer risk later in life. However, studies of the associations between perinatal factors presumed to affect the fetal hormonal environment and breast cancer risk are inconsistent. We used data from a population-based case-control study of 2,386 incident breast cancers and 2,502 controls in Poland to evaluate risks associated with various perinatal characteristics. After adjusting for confounders, we found a significant trend (p = 0.01) of breast cancer risk with birth weight (OR = 1.54, 95% CI 1.08-2.19 for birth weights > 4,000 g vs. < 2,500 g). Subjects with a high birth order (>= 6) were at reduced risk (OR = 0.81, 0.61-1.06) when compared with first born subjects. Birth weight was somewhat a stronger risk predictor among subjects whose cancers were diagnosed at 50 years of age or older (OR = 1.84, 1.19-2.85) than among those with cancers diagnosed at younger ages (OR = 1.14, 0.61-2.12). Subjects whose mothers smoked during their pregnancies were at slightly higher risk than those who never smoked (OR = 1.21, 0.99-1.47), but the risk was similar to mothers who only smoked at other times (OR = 1.22, 0.81-1.84). Breast cancer risk was not related to paternal smoking, maternal age, gestational age or twin status. Our results add support to the growing evidence that some perinatal

exposures may relate to breast cancer risk. Additional studies are needed to confirm associations and clarify the biologic mechanisms underlying these associations. Published 2006 Wiley-Liss, Inc.

Perantoni AO, Turusov VS, Buzard GS, Rice JM. 1994. Infrequent transforming mutations in the transmembrane domain of the neu oncogene in spontaneous rat schwannomas. Mol Carcinog 9:230-235 .
Abstract: Ethylnitrosourea (ENU) given transplacentally to rats induces schwannomas of the cranial, spinal, and peripheral nerves, with a high frequency of mutations in the neu proto-oncogene. To establish the requirement for such mutations in tumorigenesis of the Schwann cell, spontaneous schwannomas from BD-Vl rats were evaluated for transforming mutations in the transmembrane domain of the protein encoded by the neu protooncogene. While all five schwannomas induced transplacentally with ENU were shown to contain T-->A transversions in base 2012 of neu by selective oligonucleotide hybridization and dideoxy sequencing of polymerase chain reaction-amplified products from paraffin sections, only one of nine spontaneous schwannomas from untreated rats had the same mutation. Examination of tumors for mutations in codon 12 of Ki-ras revealed normal alleles. Therefore, the high frequency of mutations in neu in ENU-induced tumors may be directly attributable to the carcinogen or to the period of development at which exposure occurred, and transforming mutations of the transmembrane domain of neu are not required for tumorigenesis of the Schwann Cell. (C) 1994 Wiley-Liss, Inc.*

Perera F, Tang DL, Whyatt R, Lederman SA, Jedrychowski W. 2005. DNA damage from polycyclic aromatic hydrocarbons measured by benzo[a]pyrene-DNA adducts in mothers and newborns from Northern Manhattan, the World Trade Center area, Poland, and China. Cancer Epidemiology Biomarkers & Prevention 14:709-714.
Abstract: Polycyclic aromatic hydrocarbons (PAH), of which benzo[a]pyrene is a representative member, are combustion-related environmental pollutants and include known carcinogens. Laboratory animal studies indicate that the dose of PAHs to the fetus is on the order of a 10th that to the mother and that there is heightened susceptibility to PAH-induced carcinogenesis during the fetal and infancy periods. Carcinogen-DNA adducts, a measure of procarcinogenic genetic damage, are considered a biomarker of increased cancer risk. Here we compare the levels of benzo[a]pyrene-DNA adducts as a proxy for PAH-DNA damage measured in maternal blood and newborn cord blood obtained at delivery in four different populations of mothers (total of 867) and newborns (total of 822), representing a 30-fold range of exposure to ambient PAHs. The populations include residents in Northern Manhattan, participants in a study of the effects of the World Trade Center disaster, residents in Krakow, Poland, and residents in Tongliang, China. Mean adduct concentrations in both maternal and cord blood and the proportion of samples with detectable adducts, increased across the populations [Northern Manhattan < World Trade Center (WTC) < Krakow < Tongliang], consistent with the trend in estimated ambient exposure to PAHs ($P < 0.001$). For mothers, the means in the respective populations were Northern Manhattan (0.21 adducts per 10(8) nucleotides), WTC (0.23 adducts per 10(8) nucleotides), Krakow (0.28 aidducts per 10(8) nucleotides), Tongliang (0.31 adducts per 10 nucleotides); the corresponding means in the newborns were Northern Manhattan (0.23), WTC (0.24), Krakow (0.29), Tongliang (0.31). The percentage of mothers with detectable levels of adducts in the respective populations were Northern Manhattan (36.8%), WTC (57.5%), Krakow (72.9%), Tongliang (73.4%); the corresponding percentages among the newborns were Northern Manhattan (42.4%), WTC (60.6%), Krakow (71.1%), Tongliang (79.5%). Despite the estimated 10-fold lower PAH dose to the fetus based on laboratory animal experiments, the adduct levels in the newborns were similar to or higher than in the mothers. This study suggests that the fetus may be 10-fold more susceptible to DNA damage than the mother and that in utero exposure to polycyclic aromatic hydrocarbons may disproportionately increase carcinogenic risk. The data support preventive policies to limit PAH exposure to pregnant women and children.

Perera FP, Jedrychowski W, Rauh V, Whyatt RM. 1999. Molecular epidemiologic research on the effects of environmental pollutants on the fetus. Environ Health Perspect 107:451-460.
Abstract: Evidence shows that fetuses and infants are more affected than adults by a variety of environmental toxicants because of differential exposure, physiologic immaturity, and a longer lifetime over which disease initiated in early life can develop. in this article we review data on the effects of in utero exposure to common environmental contaminants, including polycyclic aromatic hydrocarbons (PAH), particulate matter and environmental tobacco smoke (ETS). We then summarize results from our molecular epidemiologic study to assess risks from in utero exposures to ambient air pollution and ETS. This research

study, conducted in Poland, used biomarkers to measure the internal and bioeffective dose of toxicants and individual susceptibility factors. The study included 160 mothers and 160 newborns. Ambient air pollution was significantly associated (p less than or equal to 0.05) with the amount of PAH bound to DNA (PAH-DNA adducts) in both maternal and infant cord white blood cells (WBC). Newborns with elevated PAH-DNA adducts (greater than the median) had significantly decreased birth weight (p = 0.05), birth length (p = 0.02), and head circumference (p = 0.0005) compared to the newborns with lower adducts (n = 135). Maternal and infant cotinine levels were increased by active and passive cigarette smoke exposure of the mother (p less than or equal to 0.01). An inverse correlation was seen between newborn plasma cotinine (nanograms per milliliter) and birth weight (p = 0.0001) and length (p = 0.003). Adducts were elevated in placental tissue and WBC of newborns who were heterozygous or homozygous for the cytochrome P4501A1 Mspi restriction fragment length polymorphism (RFLP) compared to newborns without the RFLP. Levels of PAH-DNA and cotinine were higher in newborns than mothers. These results document that there is significant transplacental transfer of PAH and ETS constituents from mother to fetus, that PAH-DNA adduct levels in maternal and newborn WBC were increased with environmental exposure to PAH from ambient pollution, and that the fetus is more sensitive to genetic damage than the mother. The study also provided the first molecular evidence that transplacental PAH exposure to the fetus is compromising fetal development. ii confirmed, these findings could have significant public health implications since a number of studies have found that reduction of head circumference at birth correlates with lower intelligence quotient as well as poorer cognitive functioning and school performance in childhood. Key words: air pollution, cigarette smoking, CYP1A1 Mspi RFLP, GSTM1, newborns, PAH-DNA adducts, Poland.

Perera FP, Tang DL, Tu YH, Cruz LA, Borjas M, Bernert T, Whyatt RM. 2004. Biomarkers in maternal and newborn blood indicate heightened fetal susceptibility to procarcinogenic DNA damage. Environ Health Perspect 112:1133-1136.
Abstract: Polycyclic aromatic hydrocarbons (PAHs) such as benzo[a]pyrene (BaP) are widespread air contaminants released by transportation vehicles, power generation, and other combustion sources. Experimental evidence indicates that the developing fetus is more susceptible than the adult to carcinogenic effects of PAHs, although laboratory studies in rodents suggest that the dose to fetal tissues is an order of magnitude lower than that to maternal tissues. To assess fetal versus adult susceptibility to PAHs and environmental tobacco smoke (ETS), we compared carcinogen-DNA adducts (a biomarker associated with increased cancer risk) and cotinine (a biomarker of tobacco smoke exposure) in paired blood samples collected from mothers and newborns in New York City. We enrolled 265 nonsmoker African-American and Latina mother-newborn pairs in New York City between 1997 and 2001 (estimated average ambient air BaP concentrations < 0.5 ng/m(3)). Despite the estimated 10-fold lower fetal dose, mean levels of BaP-DNA adducts as determined by high-performance liquid chromatography-fluorescence were comparable in paired New York City newborn and maternal samples (0.24 adducts per 10(8) nucleotides, 45% of newborns with detectable adducts vs. 0.22 per 10(8) nucleotides, 41% of mothers with detectable adducts). However, by the Wilcoxon signed-rank test, the levels in newborns were higher (p = 0.02). Mean cotinine was higher in newborns than in mothers (1.7 ng/mL, 47% detectable vs. 1.28 ng/mL, 44% detectable). Consistent with our prior study in a Caucasian Polish population, these results indicate increased susceptibility of the fetus to DNA damage and reduced ability to clear ETS constituents. The findings have implications for risk assessment, given the need to protect children as a sensitive subset of the population.

Peters FM, Preston-Martin S, Yu MC. 1981. Brain tumors in children and occupational exposure of parents. Science 213:235-237.
Abstract: Ninety-two cases of brain tumor in children less than 10 years old were compared with 92 matched controls for parental occupational history. Cases were more likely than controls to show maternal occupations involving chemical exposure, paternal occupations involving solvents, and employment of father in the aircraft industry. These three factors were not affected by adjustment for the potential confounding variables examined in this study.

Petkova-Bocharova T, Stoichev II, Chernozemsky IN, Castegnaro M, Pfohl-Leszkowicz A. 1998. Formation of DNA adducts in tissues of mouse progeny through transplacental contamination and/or lactation after administration of a single dose of ochratoxin A to the pregnant mother. Environmental & Molecular Mutagenesis 32:155-162.

Abstract: Ochratoxin A (OTA) is a mycotoxin which has been detected in foods of plant origin, in edible animal tissues, and in human sera, urine, and milk in many countries. OTA is nephrotoxic and carcinogenic in mice and rats and is suspected to play a key role in the etiology of Balkan endemic nephropathy and/or associated urinary tract tumors. In the present study, some early signs of genetic impairment, including the presence of DNA adducts in target tissues from the progeny of mice after administration of a single OTA dose during late pregnancy, have been investigated. By the P-32-postlabeling method, several characteristic DNA adducts with the same Ri valves were detected in kidney and liver of both the OTA-treated mice and their progeny-the Fetus and the offspring. No adduct was found in tissues From control animals. Different adducts were most important in kidney and liver DNA and some were organ-specific. High levels of DNA adducts were detected in the kidneys of male progeny, whereas in the Female progeny and the mothers they were detected almost exclusively in the liver. This result correlates well with the carcinogenicity in mice: the target organ For males is the kidney, while for females it is the liver. High levels of DNA adducts were also found in fetuses. These results provide evidence For a direct genotoxic action of OTA in the progeny through transplacental contamination, which constitutes a new serious health hazard of exposure to this toxin. (C) 1998 Wiley-Liss, Inc.

Petridou E, Trichopoulos D, Dessypris N, Flytzani V, Haidas S, Kalmanti M, Koliouskas D, Kosmidis H, Piperopoulou F, Tzortzatou F. 1996. Infant leukaemia after in utero exposure to radiation from Chernobyl. Nature 382:352-353.
Abstract: There has been no documented increase in childhood leukaemia following the Chernobyl accident. However, different forms of childhood leukaemia may not be equally susceptible to radiation carcinogenesis. Infant leukaemia is a distinct form associated with a specific genetic abnormality. Outside the former Soviet Union, contamination resulting from the Chernobyl accident has been highest in Greece and Austria and high also in the Scandinavian countries(1-4). All childhood leukaemia cases diagnosed throughout Greece since 1 January 1980 have been recorded. Here we report that infants exposed in utero to ionizing radiation from the Chernobyl accident had 2.6 limes the incidence of leukaemia compared to unexposed children (95% confidence interval, 1.4 to 5.1; P approximate to 0.003), and those born to mothers residing in regions with high radioactive fallout were at higher risk of developing infant leukaemia. No significant difference in leukaemia incidence was found among children aged 12 to 47 months. Preconceptional irradiation had no demonstrable effect on leukaemia risk at any of the studied age groups.

Pettersson A, Akre O, Richiardi L, Ekbom A, Kaijser M. 2007. Maternal smoking and the epidemic of testicular cancer--a nested case-control study. Int J Cancer 120:2044-6.
Abstract: For no apparent reason, the incidence of testicular cancer has increased to epidemic proportions in many countries. Pregnancy smoking has been suggested to be a cause. Previous analytical studies have been negative, but the inherent difficulties in retrospective assessment of this exposure have led to no definite conclusion. We have conducted a population-based case-control study on 192 cases of testicular germ-cell cancer-born in Sweden in 1973 onwards and aged >/=15 at cancer diagnosis-and 494 matched controls, where data on maternal smoking were collected during pregnancy. We found no association with testicular cancer for maternal smoking during pregnancy (OR, 0.91; 95% CI, 0.64-1.30), and there was no evidence of a dose-response effect. We conclude that the epidemic rise in testicular cancer in many populations is not due to the surge in smoking among women.

Pinorinigodly MT, Myers SR. 1996. HPLC and GC/MS determination of 4-aminobiphenyl haemoglobin adducts in fetuses exposed to the tobacco smoke carcinogen in utero. Toxicology 107:209-217.
Abstract: Maternal-fetal exchange of the potent tobacco-related human carcinogen, 4-aminobiphenyl, was studied in women nonsmokers and in women smokers as well as in the corresponding fetuses during pregnancy. Smoking status of the women in the study was assessed via questionnaire and measurement by immunoassay of serum cotinine in maternal and fetal blood samples. 4-Aminobiphenyl was extracted from both maternal and fetal blood samples using organic solvent extractions and the released amine was qualitatively and quantitatively characterized by analysis of the samples by high pressure liquid chromatography (HPLC) and gas chromatography coupled with mass spectrometry (GC/MS). Background levels (pg 4-aminobiphenyl/g haemoglobin) of 4-aminobiphenyl-haemoglobin adducts were detected in maternal nonsmokers (mean +/- S.D; 29.6 +/- 16.2 (GC/MS); 23.7 +/- 13.5 (HPLC)) and in fetal samples (14.0 +/- 6.5 (GC/MS); 10.0 +/- 4.6 (HPLC)). Elevated levels of 4-aminobiphenyl-haemoglobin adducts

were found in maternal smokers (488 +/- 174 (GC/MS); 423 +/- 154 (HPLC)) as well as in the corresponding fetal blood samples (244 +/- 91 (GC/MS); 197 +/- 77 (HPLC)). This study confirms that a potent tobacco-related carcinogen, 4-aminobiphenyl, crosses the human placenta and binds to fetal haemoglobin in significantly higher concentrations in smokers when compared to nonsmokers.

Platt KL, Dienes HP, Tommasone M, Luch A. 2004. Tumor formation in the neonatal mouse bioassay indicates that the potent carcinogen dibenzo[def,p]chrysene (dibenzo[a,l]pyrene) is activated in vivo via its trans-11, 12-dihydrodiol. Chem Biol Interact 148:27-36.
Abstract: The hexacyclic aromatic hydrocarbon dibenzo[def,p]chrysene, better known as dibenzo[a,l]pyrene (DBP) in the field of chemical carcinogenesis, is present in the environment as a combustion product of organic matter. This compound is probably the strongest chemical carcinogen ever tested. As ultimate genotoxic metabolites of DBP two electrophilically reactive species are discussed: (i) radical cations generated by one-electron oxidation, and (ii) fjord region dihydrodiol epoxides formed via the trans-11,12-dihydroxy 11,12-dihydro derivative of DBP (11,12-dihydrodiol). In order to delineate the metabolic pathway(s) involved in tumor formation by DBP, newborn Crl:CD(R)-1(ICR)BR mice were intraperitoneally treated with the parent compound, its 11,12-dihydrodiol, and the two diastereomeric fjord region dihydrodiol epoxides. Due to severe acute and chronic toxicity, the total dose of DBP and of the 11, 12-dihydrodiol was limited to 40 nmol. For the same reason the dihydrodiol epoxides could only be applied in doses up to 0.4 nmol. The tumor incidence was determined 55 +/- 1 weeks after treatment. Under these conditions, DBP and its 11, 12-dihydrodiol induced lung tumors (incidence: 86.5% versus 92.0%; yield: 2.88 versus 7.44 tumors per mouse), liver (incidence: 57.7% versus 60.0%; yield: 3.63 versus 5.28 tumors per mouse) and other organs (incidence: 36.5% versus 32.0%; yield: 0.56 versus 0.52 tumors per mouse). By contrast, only lung tumors at low incidence were detected in mice treated with solvent only (incidence: 28.8%; yield: 0.58 tumors per mouse). As with the parent hydrocarbon, mice treated with low doses of diastereomeric syn- and anti-dihydrodiol epoxides of DBP showed increased tumor incidences in liver (incidence: 19.0 and 46.7%; yield: 0.36 and 1.47 tumors per mouse, respectively), and in various other organs (incidence: 7.1 and 20.0%; yield: 0.07 and 0.20 tumors per mouse, respectively). In consideration of the 100-fold differences in the doses of compounds applied in this study, the tumor-inducing potency increases in the order DBP < 11,12-dihydrodiol < anti-dihydrodiol epoxide. This result provides strong evidence that the potent carcinogen DBP is activated in vivo in the mouse via its 11,12-dihydrodiol and not preferentially through alternative pathways. (C) 2004 Elsevier Ireland Ltd. All rights reserved.

Podvin D, Kuehn CM, Mueller BA, Williams M. 2006. Maternal and birth characteristics in relation to childhood leukaemia. Paediatr Perinat Epidemiol 20:312-22.
Abstract: Our objective was to investigate the association of childhood leukaemia with selected maternal and birth characteristics by conducting a population-based case-control study using linked cancer registry and birth certificate records for Washington State. We compared maternal and infant characteristics of 595 Washington-born residents <20 years old with leukaemia diagnosed during 1981-2003, and 5,950 control children, using stratified analysis and logistic regression. Maternal age 35+ years (odds ratio [OR] 1.5; 95% confidence interval [CI] 1.1, 2.0), infant birthweight 4,000+ g (OR 1.4; 95% CI 1.1, 1.8), neonatal jaundice (OR 1.5; 95% CI 1.1, 2.1), and Down's syndrome (OR 31.3; 95% CI 6.4, 153.4) were associated with an increased risk of leukaemia. Among women with 2+ pregnancies, having at least two prior early (<20 weeks' gestation) fetal deaths was also associated with an increased risk (OR 1.5; 95% CI 0.97, 2.1). Maternal unmarried status (OR 0.7; 95% CI 0.6, 0.9) and African American race (OR 0.5; 95% CI 0.3, 0.9) were associated with a decreased risk. These results were more marked for acute lymphocytic leukaemia (ALL) than for acute myeloid leukaemia (AML), and for leukaemia diagnosed <5 years of age. These results may provide clues to the aetiology of childhood leukaemia. Genetic epidemiological studies are needed to expand our knowledge of inherent and possibly prenatal influences on the occurrence of this disease.

Pogoda JM, Preston-Martin S. 1997 . Household pesticides and risk of pediatric brain tumors. Environ Health Perspect 105:1214-1220.
Abstract: A follow-up to a population-based case-control study of pediatric brain tumors in Los Angeles County, California, involving mothers of 224 cases and 218 controls, investigated the risk of household pesticide use from pregnancy to diagnosis. Risk was significantly elevated for prenatal exposure to flea/tick pesticides -odds ratio (OR) = 1.7; 95% confidence interval (CI), 1.1-2.6-, particularly among subjects less

than 5 years old at diagnosis (OR = 2.5; CI, 1. 2-5.5). Prenatal risk was highest for mothers who prepared, applied, or cleaned up flea/tick products themselves (OR = 2.2; CI, 1.1-4.2; for subjects <5 years of age, OR = 5.4; CI, 1.3-22.3). A significant trend of increased risk with increased exposure was observed for number of pets treated (p = 0.04). Multivariate analysis of types of flea/tick products indicated that sprays/foggers were the only products significantly related to risk (OR =10.8; CI, 1.3-89.1). Elevated risks were not observed for termite or lice treatments, pesticides for nuisance pests, or yard and garden insecticides, herbicides, fungicides, or snail killer. Certain precautions,if ignored, were associated with significant increased risk: evacuating the house after spraying or dusting for pests (OR = 1.6; CI, 1.0-2.6), delaying the harvest of food after pesticide treatment (OR = 3.6; CI, 1.0-13.7), and following instructions on pesticide labels (OR = 3. 7;CI, 1.5-9.6). These findings indicate that chemicals used in flea/tick products may increase risk of pediatric brain tumors and suggest that further research be done to pinpoint specific chemicals involved.

Pogoda JM, Preston-Martin S. 2001. Maternal cured meat consumption during pregnancy and risk of paediatric brain tumour in offspring: potentially harmful levels of intake. Public Health Nutrition 4:183-189.
Abstract: Objective: To describe the relationship between specific levels of nitrite intake from cured meat consumption during pregnancy and the relative risk of paediatric brain tumours in the offspring, Design: Exposure data were previously collected for a population-based case-control study of paediatric brain tumours; data on nitrite content were obtained by a comprehensive literature review of surveys of residual nitrite content in cured meats published in the USA and Canada. The level of nitrite intake for each mother was predicted by year of pregnancy based on survey results. Dose-response was evaluated both categorically and continuously using polynomial and quadratic spline regression. Setting: The US west coast: Los Angeles County, the San Francisco-Oakland Bay Area and the Seattle-Puget Sound area. Subjects: There were 540 cases diagnosed between 1984 and 1990 at ages varying from 0 to 19 years, and 801 controls frequency-matched by geographic area, age and birth year. Results: In general, survey results suggest a trend of decreasing nitrite levels in cured meats over time. We observed a moderate increase in brain tumour risk in the offspring of mothers with relatively low levels of nitrite consumption from cured meats during pregnancy, and a two- to three-fold risk increase in offspring of mothers who consumed 3 mg day(-1) nitrite from cured meats (about 125 g day(-1) of cured meat consumption throughout the pregnancy). Conclusions: A substantial risk of paediatric brain tumour appears to be associated with relatively high levels of maternal cured meat consumption during pregnancy. A more scientifically valid approach than a literature review to estimate nitrite intake from cured meats and data from a large group of highly exposed subjects would be useful in determining potentially harmful levels.

Poirier MC, Olivero OA, Walker DM, Walker VE. 2004. Perinatal genotoxicity and carcinogenicity of anti-retroviral nucleoside analog drugs. Toxicology & Applied Pharmacology 199:151-61.
Abstract: The current worldwide spread of the human immunodeficiency virus-1 (HIV-1) to the heterosexual population has resulted in approximately 800,000 children born yearly to HIV-1-infected mothers. In the absence of anti-retroviral intervention, about 25% of the approximately 7,000 children born yearly to HIV-1-infected women in the United States are HIV-1 infected. Administration of zidovudine (AZT) prophylaxis during pregnancy reduces the rate of infant HIV-1 infection to approximately 7%, and further reductions are achieved with the addition of lamivudine (3TC) in the clinical formulation Combivir. Whereas clinically this is a remarkable achievement, AZT and 3TC are DNA replication chain terminators known to induce various types of genotoxicity. Studies in rodents have demonstrated AZT-DNA incorporation, HPRT mutagenesis, telomere shortening, and tumorigenicity in organs of fetal mice exposed transplacentally to AZT. In monkeys, both AZT and 3TC become incorporated into the DNA from multiple fetal organs taken at birth after administration of human-equivalent protocols to pregnant dams during gestation, and telomere shortening has been found in monkey fetuses exposed to both drugs. In human infants, AZT-DNA and 3TC-DNA incorporation as well as HPRT and GPA mutagenesis have been documented in cord blood from infants exposed in utero to Combivir. In infants of mice, monkeys, and humans, levels of AZT-DNA incorporation were remarkably similar, and in newborn mice and humans, mutation frequencies were also very similar. Given the risk-benefit ratio, these highly successful drugs will continue to be used for prevention of vertical viral transmission, however evidence of genotoxicity in mouse and monkey models and in the infants themselves would suggest that exposed children should be followed well past adolescence for early detection of potential cancer hazard.

Pombo-de-Oliveira MS, Koifman S. 2006. Infant acute leukemia and maternal exposures during pregnancy. Cancer Epidemiol Biomarkers Prev 15:2336-41.
Abstract: Infant acute leukemia (IAL) has a unique profile characterized by the high incidence of translocations involving the MLL gene located at the 11q23 region. To test the potential role of intrauterine and perinatal factors linked to the risk of IAL development, a hospital-based case-control study was conducted in different cities of Brazil. A total of 202 children (ages 0-21 months) with newly diagnosed IAL was enrolled (1999-2005), and 440 age-matched controls were selected from the same hospitals wherein IAL cases were treated. A statistically significant association between maternal use of hormones during pregnancy and IAL was observed [odds ratio (OR), 8.76; 95% confidence interval (95% CI), 2.85-26.93] in a multivariable analysis. The association of certain exposures during pregnancy (hormones, dipyrone, metronidazole, and misoprostol) and MLL gene rearrangements was tested using a case-case approach. Despite the lack of statistical significance, the magnitude of the OR for maternal exposure to dipyrone (OR, 1.45; 95% CI, 0.75-2.86), metronidazole (OR, 1.72; 95% CI, 0.64-4.58), quinolones (OR, 2.25; 95% CI, 0.70-25.70), and hormones (OR, 1.88; 95% CI, 0.50-7.01) may suggest the occurrence of interactions between such maternal exposures during pregnancy and MLL rearrangements, yielding into IAL development. The strong and statistically significant association between IAL and estrogen exposure during pregnancy observed in this study deserves further investigation to investigate its role in intrauterine leukemogenesis.

Potischman N, Troisi R. 1999. In-utero and early life exposures in relation to risk of breast cancer. Cancer Causes & Controls 10:561-573.
Abstract: OBJECTIVES: In response to a hypothesis by Trichopoulos that risk of adult breast cancer is related to high estrogen exposure in utero, studies have been undertaken using proxy indicators of prenatal estrogens. The epidemiologic studies addressing these early factors will be reviewed, consistency with proposed biologic mechanisms will be addressed and recommendations for future research will be presented. METHODS: All studies identified in the literature addressing these in utero and early life factors related to adult breast cancer will be included in the review. The study results will be summarized by risk factor, followed by commentary on the findings. RESULTS: Review of epidemiologic studies suggests strong risks related to having been born of a twin pregnancy and reduced risks from a preeclamptic or eclamptic pregnancy. Birthweights greater than 4,000 grams have been associated with relative risks of 1.5-1.7 for breast cancer compared with normal birthweights (2,500-2,999 grams). Having been breastfed as an infant has been associated with a 20-35% reduction in risk of premenopausal breast cancer in four of six studies evaluating this factor. Some studies suggest an influence of older maternal age, perhaps only for firstborn offspring, but the data are not consistent. Smoking during the pregnancy does not seem to impart any risk for the daughter, severe nausea for two or three trimesters may be related to increased risk, and results are inconsistent for birth length, placental weight and gestational age. CONCLUSION: Although the results from epidemiologic studies assessing prenatal exposures are consistent with the hypothesis concerning estrogen exposure, the specific biologic mechanisms remain largely unknown. Relatively few epidemiologic studies have been published addressing these novel hypotheses; more studies with innovative research methods and analytic approaches are warranted to evaluate these exposures in the distant past.

Potischman N, Troisi R, Thadhani R, Hoover RN, Dodd K, Davis WW, Sluss PM, Hsieh CC, Ballard-Barbash R. 2005. Pregnancy hormone concentrations across ethnic groups: Implications for later cancer risk. Cancer Epidemiology Biomarkers & Prevention 14:1514-1520.
Abstract: A variety of in utero factors have been associated with risk of adult cancers, particularly birth weight, toxemia, and gestational age. These factors are thought to reflect hormonal exposures during pregnancy. We hypothesized that the prenatal hormonal milieu may explain part of the variation in cancer rates across ethnic groups, for example, the higher incidence of breast cancer in the Caucasian compared with Hispanic women and the higher incidence of prostate and lower incidence of testicular cancers among African-Americans compared with Caucasians. We measured hormones in early pregnancy blood samples from three ethnic groups in a health care plan in Boston, MA. Mean levels of androstenedione, testosterone, estrone, and prolactin were significantly lower in Caucasian women compared with Hispanic women. Although not statistically significant, estradiol levels were lower in Caucasian compared with Hispanic or African-American women. Concentrations of androstenedione, testosterone, and progesterone were notably higher in African-American compared with Caucasian or Hispanic women. These data are consistent with

hypotheses that in utero hormonal exposures may explain some of the ethnic group differences in cancer risk.

Pour PM. 1986 . Induction of exocrine pancreatic, bile duct, and thyroid gland tumors in offspring of Syrian hamsters treated with N-nitrosobis(2-oxopropyl)amine during pregnancy. Cancer Res 46:3663-3666.
Abstract: We examined the effect on the Syrian hamster fetal pancrease of N-nitrosobis(2-oxopropyl)amine (BOP), a potent pancreatic carcinogen in adult hamsters. Pregnant Syrian hamsters (F0 generation) were treated with BOP (10 mg/kg body weight) at the 8th, 10th, 12th, and 14th days of gestation (for a total dose of 40 mg/kg body weight). Treatment was well tolerated and all hamsters delivered, at term, pups (F1 generation = 24 females and 27 males) with no abnormalities in number per mother or in physical and behavioral conditions, when compared to matched F1 controls (20 females and 17 males). The experiment was terminated when hamsters in each group (F0 and F1) were 46 weeks old. Pancreatic tumors were found in 89% of the BOP-treated F0 generation and in 5 (50%) of their male litters, but none was seen in their female progeny or in any hamsters from the F1 control group. Tumors in the BOP-treated F0 generation hamsters were ductular adenomas (78%), ductular carcinomas in situ (11%), and ductal/ductular carcinomas (33%). Tumors in their litters were ductular adenomas (20%), ductular carcinomas in situ (10%), and poorly differentiated tumors (20%) that resembled human pancreatoblastomas. The incidence of common duct polyps (44%), gallbladder polyps (44%), and cholangiomas (44%) was significantly higher in the BOP-treated F0 generation than in their litters (which had incidences of 10, 0, and 40%, respectively). Pulmonary and renal neoplasms occurred only in the F0 generation, whereas ovarian and thyroid gland neoplasms were found only in the F1 generation. Results indicate a differing susceptibility of fetal and maternal tissues to BOP.

Pour PM. 1986 . Transplacental induction of gonadal tumors in rats by a nitrosamine. Cancer Res 46:4135-4138.
Abstract: Ovarian and testicular tumors were induced in the offspring (F1 generation) of MRC rats that received single or multiple doses of N-nitrosobis(2-oxopropyl)amine on the 14th, 18th, and/or 20th days of pregnancy. The ovarian tumor incidence was significantly higher (46%) in the F1 generation exposed to the carcinogen a single time at the 18th day of gestation, when compared to those exposed at the 14th (P less than 0.005) or 20th days (P less than 0.025), and was highest in those exposed to N-nitrosobis(2-oxopropyl)amine repeatedly (at the 14th through 20th days of gestation). Morphologically ovarian tumors were of a mixed stromal cell-coelomic type. Testicular tumors were of mixed Leydig cell-glandular types and occurred in a higher incidence in the F1 generation exposed to N-nitrosobis(2-oxopropyl)amine at the 14th through 20th day of gestation, compared with those exposed to the carcinogen at other times of the gestation period (P less than 0.0005). This is the first report of transplacental gonadal tumor induction by a nitrosamine.

Preston-Martin S, Gurney JG, Pogoda JM, Holly EA, Mueller BA. 1996. Brain tumor risk in children in relation to use of electric blankets and water bed heaters - Results from the United States west coast childhood brain tumor study. Am J Epidemiol 143:1116-1122.
Abstract: The possible relation between the occurrence of brain tumors in children and exposure to electric blankets or electrically heated water beds was investigated in a multicenter, population-based case-control study conducted on the West Coast of the United States, Information on maternal exposure during pregnancy or direct exposure to the subject child was collected by in-person interview from the mothers of 540 case children and 801 control children. Cases were 19 years of age or younger and were diagnosed between 1984 and 1991. Controls were recruited using a random digit dialing procedure. The risk of brain tumor occurrence from in utero exposure to either electric blankets (odds ratio (OR) = 0.9, 95% confidence interval (CI) 0.6-1.2) or heated water beds (OR = 0.9, 95% CI 0.6-1.3) was not elevated, Brain cancer risk did not vary by use in any trimester of pregnancy, and children with mothers who reported use throughout their pregnancy had no increased risk, Similar results were observed for exposure to the child, in that no association between brain cancer and use of electric blankets (OR = 1.0, 95% CI 0.6-1.7) or heated water beds (OR = 1.2, 95% CI 0.7-2.0) was observed, Risks did not vary significantly by age, sex, race, socioeconomic status, or histologic category for either in utero exposure or child's exposure. This study provides no evidence io support the hypothesis that there is a relation between brain cancer occurrence in children and 50-/60-Hz magnetic field exposure from the use of electric blankets and heated water beds.

Preston-Martin S, Pogoda JM, Mueller BA, Holly EA, Lijinsky W, Davis RL. 1996 . Maternal consumption of cured

meats and vitamins in relation to pediatric brain tumors. Cancer Epidemiology, Biomarkers & Prevention 5:599-605.
Abstract: Brain tumors are the leading cause of death from childhood cancer, yet the causes of most of these tumors remain obscure. Few chemicals are effective in causing brain tumors experimentally after systemic administration of low doses; a notable exception is one group of N-nitroso compounds, the nitrosamides (in particular the nitrosoureas). Feeding pregnant animals nitrosamide precursors (e.g., sodium nitrite and an alkylamide such as ethylurea) causes a high incidence of nervous system tumors in offspring. This population-based epidemiological study was designed to test the hypothesis that maternal consumption during pregnancy of meats cured with sodium nitrite increases the risk of brain tumors among offspring. The intake of vitamins C and E blocks endogenous formation of nitroso compounds and was expected to be protective. Mothers of 540 children under age 20 with a primary brain tumor diagnosed during 1984-1991 and 801 control children in the same 19 counties on the U.S. West Coast were interviewed. Risk increased with increasing frequency of eating processed meats [odds ratio (OR) = 2.1 for eating at least twice a day compared to not eating; 95% confidence interval (CI) = 1.3-3.2; P = 0.003). Risk also increased with increasing average daily grams of cured meats or mg of nitrite from cured meats (P for each <0.005) but not with nitrate from vegetables. Daily use of prenatal vitamins throughout the pregnancy decreased risk (OR = 0.54; CI = 0.39-0.75). Risk among mothers who consumed above the median level of nitrite from cured meat was greater if vitamins were not taken (OR = 2.4; CI = 1.4-3.6) than if they were (OR = 1.3). These effects were evident for each of three major histological types and across social classes, age groups, and geographic areas. This largest study to date of maternal diet and childhood brain tumors suggests that exposure during gestation to endogenously formed nitroso compounds may be associated with tumor occurrence. Laboratory exploration is needed to: (a) define dietary sources of exposure to alkylamides; (b) investigate the reactivity of nitrite in high concentration such as around bits of cured meats in the stomach after ingestion compared to nitrite in dilute solution; and (c) confirm that simultaneous ingestion of alkylamides and cured meats leads to the endogenous formation of nitrosamides.

Preston-Martin S, Yu MC, Benton B, Henderson BE. 1982. N-Nitroso compounds and childhood brain tumors: A case-control study. Cancer Res 42:5240-5245.
Abstract: We questioned mothers of 209 young brain tumor patients and mothers of 209 controls about experiences of possible etiological relevance which they had during pregnancy or which their children had while growing up. Long-suspected brain tumor risk factors such as head trauma and X-rays appeared to be factors for relatively few cases. Increased risk was associated with maternal contact with nitrosamine-containing substances such as burning incense (odds ratio, 3.3; p = 0.005), sidestream cigarette smoke (odds ratio, 1.5; p = 0.03), and face makeup (odds ratio, 1.6; p = 0.02); with maternal use of diuretics (odds ratio, 2.0; p = 0.03) and antihistamines (odds ratio, 3.4; p = 0.002); and with the level of maternal consumption of cured meats (p = 0.008). These drugs contain nitrosatable amines and amides, and the cured meats contain nitrites, chemicals which are precursors of N-nitroso compounds. We propose a hypothesis that brain tumors in these young people are related to in utero exposure to N-nitroso compounds and their precursors, the most potent nervous system carcinogens known in experimental animals.

Preston RJ. 2004. Children as a sensitive subpopulation for the risk assessment process. Toxicology & Applied Pharmacology 199:132-41.
Abstract: For cancer risk assessment purposes, it is necessary to consider how to incorporate sensitive subpopulations into the process to ensure that they are appropriately protected. Children represent one such potentially sensitive subpopulation that is of quite considerable magnitude. The data needs include sensitivity to the induction of childhood cancers compared to adult cancers and relative sensitivity of early-life exposures for the formation of tumors in adults. These needs as far as human data are concerned are best met for ionizing radiations, for which it has been shown in the atomic bomb survivors that early-life exposures are more effective at inducing cancers later in life. The risk assessment approach for ionizing radiations, however, is based on tumor data itself for total population exposures so that there is no requirement to consider specifically the impact of early-life exposures. In the case of environmental chemicals, the majority of the tumor data used for risk assessments are from rodent bioassays. There is a paucity of data that allow for a comparison of the response to early-life exposures compared to that for adult-only exposures. This presents a fairly difficult challenge to the identification of a general sensitivity factor or a chemical-specific sensitivity factor for early-life exposures. The U.S. Environmental Protection Agency (EPA) has not, until recently, incorporated a general adjustment for early-life exposure to

carcinogens into its risk assessment guidelines. The Agency has relied on the fact that, in the absence of specific data to the contrary, the linear extrapolation for rodent tumor data provided appropriate protection. When specific data are available, then an adjustment can be calculated. In its most recent draft guidelines, however, a general adjustment has been proposed for mutagenic chemicals. A 10-fold risk adjustment is recommended for the first 2 years of life, a 3-fold adjustment for years 3-15, and no adjustment for exposures after age 15. For chemicals that do not have a mutagenic mode of action, no adjustment is recommended because the data for deriving such an adjustment are simply not available. Clearly, this is an interim position that is dependent on more pertinent data being collected. A significant component of this is to conduct cancer bioassays that include early-life exposures.

Previtali SC, Quattrini A, Pardini CL, Nemni R, Feltri ML, Boncinelli E, Canal N, Wrabetz L. 1999. Laminin receptor alpha 6 beta 4 integrin is highly expressed in ENU-induced glioma in rat. Glia 26:55-63.
Abstract: Laminins and their receptors influence neoplastic growth and invasiveness. We recently reported the abnormal expression of a laminin receptor, alpha 6 beta 4 integrin, in human astrocytomas. To further investigate the role of alpha 6 beta 4 in gliomas, we produced an experimental model of glioma in rat by transplacental ethylnitrosourea (ENU) administration. This animal model allowed us to study the timing of alpha 6 beta 4 expression during tumor development and the topography of expression in the tumor and the surrounding tissue. Immunohistochemistry, in situ hybridization, and immunoprecipitation studies demonstrated that alpha 6 beta 4 heterodimer forms in experimental gliomas, and confirmed that alpha 6 beta 4 is expressed diffusely in neoplastic cells and reactive astrocytes, but not in normal glia surrounding the tumors. Interestingly, alpha 6 beta 4 was expressed from the early phases of tumor development, and more highly expressed by cells in the proliferative centers of the tumors. Both neoplastic cells and reactive astrocytes also expressed the glial growth factor (neuregulin) receptors, Erb-B2 and Erb-B3. Finally, alpha 6 beta 4 expression was reduced in a subset of tumor blood vessels. Thus, this study suggests a potential role for alpha 6 beta 4 in the pathogenesis of gliomas. Furthermore, this is the first description of altered integrin expression in experimental gliomas; transplacental ENU-induced gliomas in rat will provide a useful model to study the role of altered adhesion in the pathogenesis of human gliomas. GLIA 26:55-63, 1999. (C) 1999 Wiley-Liss, Inc.

Prins GS, Birch L, Tang WY, Ho SM. 2006. Developmental estrogen exposures predispose to prostate carcinogenesis with aging. Reprod Toxicol 23:374-382.
Abstract: Prostate morphogenesis occurs in utero in humans and during the perinatal period in rodents. While largely driven by androgens, there is compelling evidence for a permanent influence of estrogens on prostatic development. If estrogenic exposures are abnormally high during the critical developmental period, permanent alterations in prostate morphology and function are observed, a process referred to as developmental estrogenization. Using the neonatal rodent as an animal model, it has been shown that early exposure to high doses of estradiol results in an increased incidence of prostatic lesions with aging which include hyperplasia, inflammatory cell infiltration and prostatic intraepithelial neoplasia or PIN, believed to be the precursor lesion for prostatic adenocarcinoma. The present review summarizes research performed in our laboratory to characterize developmental estrogenization and identify the molecular pathways involved in mediating this response. Furthermore, recent studies performed with low-dose estradiol exposures during development as well as exposures to environmentally relevant doses of the endocrine disruptor bisphenol A show increased susceptibility to PIN lesions with aging following additional adult exposure to estradiol. Gene methylation analysis revealed a potential epigenetic basis for the estrogen imprinting of the prostate gland. Taken together, our results suggest that a full range of estrogenic exposures during the postnatal critical period - from environmentally relevant bisphenol A exposure to low-dose and pharmacologic estradiol exposures - results in an increased incidence and susceptibility to neoplastic transformation of the prostate gland in the aging male which may provide a fetal basis for this adult disease.

Rajpert-De Meyts E. 2006. Developmental model for the pathogenesis of testicular carcinoma in situ: genetic and environmental aspects. Hum Reprod Update 12:303-323.
Abstract: Carcinoma in situ testis (CIS), also known as intratubular germ cell neoplasia (ITGCN), is a pre-invasive precursor of testicular germ cell tumours, the commonest cancer type of male adolescents and young adults. In this review, evidence supporting the hypothesis of developmental origin of testicular germ cell cancer is summarized, and the current concepts regarding aetiology and pathogenesis of this disease are

critically discussed. Comparative studies of cell surface proteins (e.g. PLAP and KIT), some of the germ cell-specific markers (e.g. MAGEA4, VASA, TSPY and NY-ESO-1), supported by studies of regulatory elements of the cell cycle (e.g. p53, CHK2 and p19-INK4d) demonstrated a close similarity of CIS to primordial germ cells and gonocytes, consistent with the pre-meiotic origin of CIS. Recent gene expression profiling studies showed that CIS cells closely resemble embryonic stem cells (ESCs). The abundance of factors associated with pluripotency (NANOG and OCT-3/4) and undifferentiated state (AP-2 gamma) may explain the remarkable pluripotency of germ cell neoplasms, which are capable of differentiating to various somatic tissue components of teratomas. Impaired gonadal development resulting in the arrest of gonocyte differentiation and retention of its embryonic features, associated with an increasing genomic instability, is the most probable model for the pathogenesis of CIS. Genomic amplification of certain chromosomal regions, e.g. 12p, may facilitate survival of CIS and further invasive progression. Genetic studies, have so far not identified gene polymorphisms predisposing to the most common non-familial testicular cancer, but this research has only recently begun. Association of CIS with other disorders, such as congenital genital malformations and some forms of impaired spermatogenesis, all rising in incidence in a synchronous manner, led to the hypothesis that CIS might be a manifestation of testicular dysgenesis syndrome (TDS). The aetiology of TDS including testicular cancer remains to be elucidated, but epidemiological trends suggest a primary role for environmental factors, probably combined with genetic susceptibility.

Rajpert-De Meyts E, Skakkebaek NE. 1993. The possible role of sex hormones in the development of testicular cancer. Eur Urol 23: 54-9; discussion 60-1.
Abstract: The peak incidence of testicular cancer in young men suggests that gestational development and events during early infancy and puberty are important in the pathogenesis of the disease. There are two potentially significant events: the transformation of fetal germ cells into carcinoma-in-situ cells (CIS) and later conversion of CIS cells into fully invasive cancer. Several hypotheses suggest an endocrinological background to testicular neoplasia. Based on epidemiological and experimental evidence, the possible role of oestrogens, androgens and gonadotrophins is discussed in this review. The role of Sertoli cells and the importance of interplay between endocrine and paracrine factors is also stressed.

Ramesh A, Inyang F, Knuckles ME. 2004. Modulation of adult rat benzo(a)pyrene (BaP) metabolism and DNA adduct formation by neonatal diethylstilbestrol (DES) exposure. Experimental & Toxicologic Pathology 56:129-138.
Abstract: This study seeks to elucidate the role of diethylstilbestrol (DES), a synthetic estrogen on benzo(a)pyrene (BaP) metabolism in the male rat reproductive tissues. Offspring of timed-pregnant Sprague-Dawley rats were neonatally treated on days 2, 4, and 6 post-partum with 1.45 micromol/kg of DES. Ten weeks after birth, the adult rats were challenged with radiolabeled benzo(a)pyrene (3H BaP) (10 micromol/kg) and the rats were sacrificed 2 h after BaP exposure. Prostrate, testis, lung, liver, urine and feces samples were collected and extracted using a mixture of H2O, MeOH and CHCl3. The extracts were analyzed by reverse phase HPLC. The concentrations of BaP organic metabolites in DES rats were lower compared to controls (vehicle-treated rats). On the other hand, concentrations of aqueous metabolites were significantly increased in DES treated animals. The toxication to detoxication ratios were significantly decreased in DES rats compared to controls. This trend is also reflected in the decreased concentrations of BaP-DNA adducts in DES rats. Collectively these results suggest that DES is capable of modulating the metabolic pathway of BaP towards detoxification thereby preventing the manifestation of toxicity.

Ramos JG, Varayoud J, Sonnenschein C, Soto AM, Muńoz de Toro M, Luque EH. 2001. Prenatal exposure to low doses of bisphenol A alters the periductal stroma and glandular cell function in the rat ventral prostate. Biol Reprod 65:1271-1277.
Abstract: Environmental estrogens (xenoestrogens) are chemicals that bind to estrogen receptor, mimic estrogenic actions, and may have adverse effects on both human and wildlife health. Bisphenol A (BPA), a monomer used in the manufacture of epoxy resins and polycarbonate has estrogenic activity. In male rodents prenatal exposure to BPA resulted in modifications at the genital tract level. Our objective was to examine the effects of in utero exposure to low, environmentally relevant levels, of the xenoestrogen BPA on proliferation and differentiation of epithelial and stromal cells on the prepubertal rat ventral prostate. To characterize the periductal stromal cells phenotype the expression of vimentin and smooth muscle alpha-actin was evaluated. Androgen receptor (AR) and prostatic acid phosphatase (PAP) expression were also evaluated in epithelial and stromal compartments. Prenatal exposure to BPA increases the

fibroblastic:smooth muscle cells ratio and decreases the number of AR-positive cells of periductal stroma of the ventral prostate. In contrast, no differences in AR expression were observed in epithelial cells between control and BPA-treated groups. No changes in proliferation patterns were observed in epithelial and stromal compartments; however, the expression of PAP was diminished in prostate ductal secretory cells of rats in utero exposed to BPA. Our results suggest that prenatal exposure to BPA altered the differentiation pattern of periductal stromal cells of the ventral prostate. These findings are significant in light of the data on human prostate cancers where alterations in the stroma compartment may enhance the invasive and/or malignant potential of the nascent tumor.

Rehm S, Devor DE, Henneman JR, Ward JM. 1991 . Origin of spontaneous and transplacentally induced mouse lung tumors from alveolar type II cells. Exp Lung Res 17:181-195.
Abstract: Mouse lung tumors were induced transplacentally in offspring by treating C3H/HeNCrMTV- and Swiss Webster [Tac:(SW)fBR] mice during different periods of gestation with a single i.p. injection of N-nitrosoethylurea (ENU) at 0.5 mmol or 0.74 mmol/kg. Quantitative and qualitative evaluation of the lung tumors in the offspring at ages ranging from 1 week to 52 weeks was carried out by light microscopic study of hematoxylin and eosin-stained (H&E) serial and step sections. By nitroblue tetrazolium enzyme histochemistry, 3-hydroxybutyrate dehydrogenase (seen predominantly in Clara cells) was localized in frozen tissue sections. By avidin-biotin peroxidase complex immunohistochemistry, various specific cellular and nuclear markers were investigated on paraffin sections (antisera against surfactant apoprotein, Clara cell antigen, lysozyme, and 5-bromo-2' deoxyuridine). Normal lung and lung tumors were also studied by electron microscopy. A histological method was developed to assess all lesions present in the entire lung. It was shown that solid and papillary tumor types arose individually and that mixed solid/papillary forms represented a progression of the benign solid adenoma to the malignant papillary carcinoma. Immunocytochemical localization of DNA synthesis with 5-bromo-2' deoxyuridine gave the highest labeling indices at early stages of tumor growth. As the size of the papillary tumors increased, fewer nuclei were labeled/mm2 of tumor section. Lack of both specific Clara cell antigen and 3-hydroxybutyrate dehydrogenase and the absence of typical nonosmiophilic Clara cell granules indicated a cell of origin other than Clara cells. Evidence for alveolar type II cell origin of both solid and papillary neoplasms in spontaneous and induced tumors was found in the expression of surfactant apoprotein, the presence of mature lamellar bodies (solid tumors) or small lamellar bodies, and immature stages of lamellar bodies (papillary tumors). Lysozyme was present in mature alveolar type II cells and solid tumors but absent in fetal lung and papillary neoplasms. Tumors induced on gestation day 14 or day 16 had all developed by 2 weeks of age and generally did not increase in multiplicity with age, whereas those induced on day 18 showed a protracted development with regard to frequency, growth (size), and progression. The multiplicity of mouse lung tumors induced at different stages of fetal development paralleled the number of alveolar type II precursor cells (i.e., followed a bell-shaped pattern peaking on day 16 of gestation).

Rehm S, Ward JM, Anderson LM, Riggs CW, Rice JM. 1991. Transplacental induction of mouse lung tumors: stage of fetal organogenesis in relation to frequency, morphology, size, and neoplastic progression of N-nitrosoethylurea-induced tumors. Toxicol Pathol 19:35-46.
Abstract: Pregnant C3H/HeNCr MTV- mice were given a single intraperitoneal injection of 0.5 mmol N-nitrosoethylurea/kg on days 14, 16, or 18 of gestation. Six of the male offspring were sacrificed for study at the ages of 2, 4, 8, 16, 32, and 52 weeks. Grossly visible lung tumors were counted and all lungs were sectioned completely, saving every tenth section for histologic evaluation. All N-nitrosoethylurea-induced mouse lung tumors have previously been shown to originate from alveolar type II cells. Lung tumors were diagnosed as solid, papillary, or mixed solid/papillary types, and at the largest area of each tumor, the perimeter was measured and compared with the number of sections per tumor. The fraction of tumors detected grossly depended on size and, on average, only 51% of neoplasms present were detected macroscopically. A significant correlation was seen between the mean number of histological sections and perimeter length per tumor, in particular for small and medium sized papillary neoplasms. The growth of solid tumors was limited to a maximum size, after which they progressed towards papillary types. The numbers of transplacentally induced mouse lung tumors were distributed in direct proportion to the weight of the individual lung lobes, unrelated to day of treatment of type or tumor. Tumor biology depended on the day of treatment reflecting numbers of degree of differentiation of fetal alveolar type II cells, i.e., the target cell: most tumors developed in offspring treated on day 16, tumor size was greater and progression from solid to papillary neoplasms faster at earlier treatments, increase in tumor multiplicity postnatally was only

seen in mice treated late in gestation, and mice treated on day 14 or day 16 showed a consistent ratio of solid to papillary tumors.

Rehm S, Ward JM, ten Have-Opbroek AA, Anderson LM, Singh G, Katyal SL, Rice JM. 1988 . Mouse papillary lung tumors transplacentally induced by N-nitrosoethylurea: Evidence for alveolar type II cell origin by comparative light microscopic, ultrastructural, and immunohistochemical studies. Cancer Res 48:148-160.
Abstract: A histogenetic study was designed to evaluate controversial findings on the cell of origin of tubular/papillary lung tumors in mice, i.e., bronchiolar Clara cell versus alveolar type II cell. N-Nitrosoethylurea (0.5 mmol or 0.74 mmol/kg) was given to pregnant C3H (C3H/HeNCr MTV-) and Swiss Webster [Tac:(SW)fBR] mice as a single i.p. injection on Day 14, 15, 16, or 18 of gestation. The offspring were studied at various ages ranging from 7 days to 52 wk. Serial sections of the whole lung (100 to 200 sections per mouse) showed that solid/alveolar and papillary tumors arose from the pulmonary acinus, invading the bronchioles only as the tumors grew. Furthermore, a mixture of solid and papillary patterns within a single module did not represent a merging of two tumors but a progression from the solid to the papillary form. By use of two rabbit antisera against mouse lung surfactant apoproteins found in normal alveolar type II cells, it was shown by the avidin-biotin peroxidase complex procedure, by the peroxidase-antiperoxidase technique, and by indirect immunofluorescence that both solid and papillary tumors contained these proteins that are specific markers for alveolar type II cells. With a rabbit anti-rat Clara cell antiserum, none of the tumors studied was immunoreactive while normal Clara cells were reactive. The nitroblue tetrazolium formazan stain for dehydrogenase enzymes, found particularly in Clara cells, did not reveal these enzymes in any lung tumors from either strain. Ultrastructurally, no typical features of the mature Clara cell were detected in papillary or other pulmonary neoplasms. However, all tumors showed characteristic alveolar type II cell structures such as various stages of lamellar body formation, although these features were less well differentiated in the papillary tumors. Argentaffin dense bodies, representing lysosomes and immature forms of lamellar bodies, were commonly observed in papillary tumors. Some features of the papillary tumors such as cell shape, high glycogen content, and primary cilia were equivalent to those seen in pulmonary epithelial precursor cells during fetal development. With age, the papillary tumors became invasive, accumulated neutral lipids, and developed bizarre cleaved nuclei and lamellated nuclear pseudoinclusions. In conclusion, the papillary lung tumors of the mouse, at least those induced transplacentally by N-nitrosoethylurea, constitute less well-differentiated or poorly differentiated alveolar type II cell adenomas or carcinomas with fetal morphological and biochemical properties.

Reuter VE. 2005. Origins and molecular biology of testicular germ cell tumors. Mod Pathol 18:S51-S60.
Abstract: Testicular germ cell tumors can be divided into three groups (infantile/prepubertal, adolescent/young adult and spermatocytic seminoma), each with its own constellation of clinical histology, molecular and clinical features. They originate from germ cells at different stages of development. The most common testicular cancers arise in postpubertal men and are characterized genetically by having one or more copies of an isochromosome of the short arm of chromosome 12 [i(12p)] or other forms of 12p amplification and by aneuploidy. The consistent gain of genetic material from chromosome 12 seen in these tumors suggests that it has a crucial role in their development. Intratubular germ cell neoplasia, unclassified type (IGCNU) is the precursor to these invasive tumors. Several factors have been associated with their pathogenesis, including cryptorchidism, elevated estrogens in utero and gonadal dysgenesis. Tumors arising in prepubertal gonads are either teratomas or yolk sac tumors, tend to be diploid and are not associated with i(12p) or with IGCNU. Spermatocytic seminoma (SS) arises in older patients. These benign tumors may be either diploid or aneuploid and have losses of chromosome 9 rather than i(12p). Intratubular SS is commonly encountered but IGCNU is not. The pathogenesis of prepubertal GCT and SS is poorly understood.

Reynolds P, Urayama KY, Von Behren J, Feusner J. 2004. Birth characteristics and hepatoblastoma risk in young children. Cancer 100:1070-1076.
Abstract: BACKGROUND. Although hepatoblastoma is a very rare childhood cancer, its incidence appears to be rising, especially among children with very low birth weight. With the exception of documented correlations with certain congenital anomalies, the etiology of hepatoblastoma remains largely unknown. METHODS. Using California's population-based cancer registry, the authors identified 113 children ages birth-4 years with hepatoblastoma who were diagnosed between 1988 and 1997. Ninety-nine of those 113 children (88%) were matched to a California birth certificate, and randomly selected controls from the

same birth certificate files were matched to cases (4:1) according to the month and year of birth and gender. Odds ratios (OR) and 95% confidence intervals (95% Cl) were estimated using conditional logistic regression analyses. RESULTS. A strikingly elevated risk of hepatoblastoma was found in children who were born with very low birth weight (< 1500 g; OR, 50.57; 95% Cl, 6.59-387.97). A plot of the distribution by birth weight showed interesting peaks at birth weights < 1000 g and 3000-3499 g among cases. Children who weighed < 1000 g showed a statistically significant, linear trend toward being diagnosed at an older age (P = 0.036), which seemed to be explained in part by gestational age. CONCLUSIONS. The results confirmed previously reported findings of an increased hepatoblastoma risk among children with very low birth weight and suggested that the etiology may differ between children with very low birth weight and children with normal birth weight. (C) 2004 American Cancer Society.

Reynolds P, Von Behren J, Gunier RB, Goldberg DE, Harnly M, Hertz A. 2005. Agricultural pesticide use and childhood cancer in California. Epidemiology 16:93-100.
Abstract: Background: Household pesticide use has been associated with higher risk for several childhood malignancies, but few studies have evaluated risks associated with residential proximity to agricultural pesticide use. We conducted a population-based case-control study of early childhood cancer (age 0-4 years) among California children born between 1990 and 1997 and mother's residential proximity to agricultural applications of pesticides at the time of the child's birth. Methods: Included in the study were 2189 case children and 4335 controls matched for birth date and sex. We estimated the in utero exposure potential from specific chemicals and chemical groups used in the 9 months before birth within a half mile of the maternal residence.. We computed odds ratios (ORs) using conditional logistic regression. Results: No striking patterns emerged. There were modestly elevated ORs for leukemias associated with probable and possible carcinogen use, and with nearby agricultural applications of organochlorines and organophosphates during pregnancy. Two commonly used pesticides were associated with higher leukemia risk when comparing the highest and lowest categories: metam sodium (OR = 2.05; 95% confidence interval = 1.01-4.17) and dicofol (1.83; 1.05-3.22). Conclusions: The few elevated risk associations in this study are consistent with chance, given the large number of comparisons, but they may deserve more careful consideration. Future studies that integrate specific temporal and spatial exposure potential for targeted pesticides will be important in further evaluating risks associated with childhood cancer.

Rhind SM, Rae MT, Brooks AN. 2003. Environmental influences on the fetus and neonate--Tming, mechanisms of action and effects on subsequent adult function. Domest Anim Endocrinol 25:3-11.
Abstract: Environmental influences on fetal and neonatal development can affect neural, reproductive, immune and cardiovascular function in adult humans and animals. The effects can be exerted at many different stages of development from before conception to after birth. Effects may even be exerted during a preceding generation. Some known and some possible mechanisms are reviewed. Systems likely to be affected include the brain, hypothalamus, pituitary and adrenal glands and the gonads. The effects may be exerted through altered gene expression at any stage of development or through changes in organ structure or physiology.

Rice D, Barone S Jr. 2000. Critical periods of vulnerability for the developing nervous system: Evidence from humans and animal models. Environ Health Perspect 108 Suppl 3:511-533.
Abstract: Vulnerable periods during the development of the nervous system are sensitive to environmental insults because they are dependent on the temporal and regional emergence of critical developmental processes (i.e., proliferation, migration, differentiation, synaptogenesis, myelination, and apoptosis). Evidence from numerous sources demonstrates that neural development extends from the embryonic period through adolescence. In general, the sequence of events is comparable among species, although the time scales are considerably different. Developmental exposure of animals or humans to numerous agents (e.g., X-ray irradiation, methylazoxymethanol, ethanol, lead, methyl mercury, or chlorpyrifos) demonstrates that interference with one or more of these developmental processes can lead to developmental neurotoxicity. Different behavioral domains (e.g., sensory, motor, and various cognitive functions) are subserved by different brain areas. Although there are important differences between the rodent and human brain, analogous structures can be identified. Moreover, the ontogeny of specific behaviors can be used to draw inferences regarding the maturation of specific brain structures or neural circuits in rodents and primates, including humans. Furthermore, various clinical disorders in humans (e.g., schizophrenia, dyslexia, epilepsy, and autism) may also be the result of interference with normal ontogeny of developmental

processes in the nervous system. Of critical concern is the possibility that developmental exposure to neurotoxicants may result in an acceleration of age-related decline in function. This concern is compounded by the fact that developmental neurotoxicity that results in small effects can have a profound societal impact when amortized across the entire population and across the life span of humans.

Rice JM, Rehm S, Donovan PJ, Perantoni AO. 1989. Comparative transplacental carcinogenesis by directly acting and metabolism-dependent alkylating agents in rodents and nonhuman primates. IARC Sci Publ :17-34.
Abstract: Transplacental carcinogenesis by N-ethyl-N-nitrosourea (ENU) was studied in patas (Erythrocebus patas) and rhesus (Macaca mulatta) monkeys. Repeated intravenous injections throughout pregnancy caused gestational choriocarcinoma in female patas monkeys and a variety of non-trophoblastic neoplasms in their offspring. Latent periods for transplacentally induced tumours varied from less than one month to more than ten years. One case of congenital neoplasm was observed. Certain kinds of neoplasms were observed only in transplacentally exposed offspring, and not in monkeys given the same carcinogen during juvenile or adult life. These included a variety of embryonal tumours, especially nephroblastoma, and tumours of the brain, mostly gliomas. Schwannomas of the peripheral nervous system were not observed in patas monkeys given ENU. One embryonal tumour yielded DNA that transformed NIH 3T3 cells in a transfection assay. Similar protocols performed in rhesus monkeys also yielded a variety of tumours in the offspring, including brain tumours; but in this species the most common embryonal tumour was pulmonary blastoma, and no choriocarcinoma was seen in adult females given ENU during pregnancy. Administration of N-nitrosodiethylamine to patas monkeys during pregnancy at first appeared to have had no effect on the offspring, but administration of phenobarbital beginning at four years of age resulted in the rapid appearance of multiple hepatocellular tumours. With regard to potential human risk from prenatal exposure to carcinogens, three conclusions deserve special emphasis: (1) the extreme susceptibility of the fetal primate central nervous system to certain chemical carcinogens, which confirms and reinforces what was previously known from studies in rodents; (2) the prolonged latency of transplacentally initiated epithelial tumours and the importance of subsequent postnatal exposure to promoting agents; and (3) the concurrent risk of transplacental chemical carcinogenesis in offspring and gestational choriocarcinoma in the mother, suggesting that gestational choriocarcinoma with its short latent period may serve as an epidemiologically exploitable marker for human populations in which transplacental carcinogenesis is likely.

Richiardi L, Pettersson A, Akre O. 2007. Genetic and environmental risk factors for testicular cancer. International Journal of Androl .
Abstract: Germ-cell testicular cancer has a well-characterized descriptive epidemiology, whereas the aetiology remains largely unknown. It is believed that exposures acting prenatally are instrumental to germ-cell cancer development, although no specific exposure has been identified. Several epidemiological studies have investigated a number of indicators of prenatal exposures, such as birth order, gestational duration, birth weight, maternal age and nausea during pregnancy, but results are inconsistent. This paper briefly reviews the current support for genetic and environmental factors in testicular cancer aetiology. In particular, we have summarized the evidence suggesting a strong role of inherited susceptibility, which is probably carried by the effect of several unknown moderate-risk genes. We have illustrated inconsistencies in the previous studies on prenatal factors by estimating the heterogeneity and pooled odds ratios among twelve studies investigating the association between low birth weight and testicular cancer. We have discussed the possibility that puberty is another time window during which environmental factors may increase the risk of testicular cancer. Finally, we have reviewed the results from studies on cryptorchidism and impaired fertility in relation to risk for testicular cancer. In conclusion, we propose that future aetiological studies on testicular cancer should take postnatal exposures acting during puberty into account and, whenever possible, investigate both main effects and interactions among prenatal factors, genetic factors and postnatal factors.

Robboy SJ, Szyfelbein WM, Goellner JR, Kaufman RH, Taft PD, Richard RM, Gaffey TA, Prat J, Virata R, Hatab PA, McGorray SP, Noller KL, Townsend D, Labarthe D, Barnes AB. 1981 . Dysplasia and cytologic findings in 4,589 young women enrolled in diethylstilbestrol-adenosis (DESAD) project. American Journal of Obstetrics & Gynecology 140:579-586.
Abstract: This report presents the cytologic findings and the rates of dysplasia for 4,589 young women enrolled in the National Cooperative Diethylstilbestrol-Adenosis (DESAD) Project. Mucinous columnar

cells and/or metaplastic squamous cells with or without mucinous droplets were encountered in 22% of vaginal scrape smears from all diethylstilbestrol (DES)-exposed participants identified by review of prenatal records and in 43% of women in whom vaginal epithelial changes (VEC) were observed by colposcopy or by iodine staining. The frequency of cellular findings in the vaginal scrape smears was closely related to the timing of the administration of the DES to the mother. With increasing age of the daughters, the overall frequencies of both the mucinous and metaplastic cells decreased; relative to each other, an increasing proportion was metaplastic squamous cells. These data suggest that, as the women grow older, vaginal adenosis regresses by the process of squamous metaplasia. Endometrial type cells were found in 2% of vaginal scrape smears. Their cyclical occurrence during the menstrual cycle and lack of correlation with the presence of VEC indicated an origin from the uterine corpus rather than the tuboendometrial type of adenosis. Squamous cell dysplasia of the vagina and cervix was detected by biopsy or scrape smear specimens in 1.8% of DES-exposed women in the record review group. The rate of unexposed women was twice as high. In general, the rates of dysplasia were higher in the cervix than vagina, and the more severe degrees of dysplasia were encountered only in those women who were referred to the DESAD Project or who themselves requested entry. Four patients who were referred or who themselves requested entry were found to have clear cell adenocarcinoma of the vagina. The vaginal smear provided the first clue to the presence of an abnormality in three of them.

Robison LL, Buckley JD, Daigle AE, Wells R, Benjamin D, Arthur DC, Hammond GD. 1989 . Maternal drug use and risk of childhood nonlymphoblastic leukemia among offspring. An epidemiologic investigation implicating marijuana (a report from the Childrens Cancer Study Group). Cancer 63:1904-1911.
Abstract: The Childrens Cancer Study Group conducted a case-control study designed to assess in utero and postnatal exposures in children with acute nonlymphoblastic leukemia (ANLL). Analyses were performed for reported maternal use of medications and drugs in the year preceding and during the index pregnancy of the 204 case-control pairs. An 11-fold risk (P = 0.003) was found for maternal use of mind-altering drugs just prior to or during the index pregnancy. Compared with ANLL cases not exposed to marijuana, exposed cases were significantly younger at diagnosis of ANLL (P less than 0.01) and were more often of the myelomonocytic and monocytic subtypes (P less than 0.01). Use of antinausea medication for more than 11 weeks was also associated with a significantly elevated relative risk of 2.81 and a dose-response relationship was noted (P = 0.05 for trend). These results suggest that maternal drug use of marijuana may have an etiologic role in childhood ANLL and may be specific for morphologically defined subgroups.

Rodriguez JW, Kirlin WG, Wirsiy YG, Matheravidathu S, Hodge TW, Urso P. 1999. Maternal exposure to benzo[a]pyrene alters development of T lymphocytes in offspring. Immunopharmacology & Immunotoxicology 21:379-396.
Abstract: Childhood cancer has been increasing significantly over the past two decades in the United States, suggesting that environmental exposures may be playing a causative role. One such cause may be maternal smoking during pregnancy. Suspected carcinogens in cigarette smoke and environmental pollution include N-nitrosamines and polycyclic aromatic hydrocarbons, which may be several micrograms per exposure. Previously, we have shown that mouse progeny of mothers exposed to benzo[a]pyrene (B[a]P) during midpregnancy had abnormalities in their humoral and cell-mediated immune response. Immunodeficiency was detectable during gestation, at one week after birth and persisted for 18 months. Tumor incidences in progeny were eight to 10-fold higher than in controls. The present study compared frequencies of CD4+, CD8+, V gamma 2+, and V beta 8+ T cells in progeny following in utero exposure to B[a]P. The significant reduction in newborn CP4+CD8+, CD4+CD8+V beta 8+ thymocytes and CD4+ splenocytes from 1-week-old progeny, suggests that B[a]P induces abnormal changes in developing T cells. These early alterations may lead to postnatal T cell supression, thus providing a more suitable environment for the growth of tumors later in life. These:results suggest that developmental immunosuppression mediated by B[a]P may play a critical role in the relationship between maternal exposures and childhood carcinogenesis.

Rodriguez JW, Kohan MJ, King LC, Kirlin WG. 2002. Detection of DNA adducts in developing CD4(+)CD8(+) thymocytes and splenocytes following in utero exposure to benzo[a]pyrene. Immunopharmacology & Immunotoxicology 24:365-381.
Abstract: Environmental carcinogen exposure may play an important role in the incidence of cancer in

children. In addition to environmental pollutants, maternal smoking during pregnancy may be a contributing factor. Major carcinogenic components of cigarette smoke and other combustion by-products in the environment include polycyclic aromatic hydrocarbons (PAH). Mouse offspring exposed during midpregnancy to the PAH, benzo[a]pyrene (B[a]P), show significant deficiencies in their immune functions, observed in late gestation which persist for at least 18 months. Tumor incidences in these progeny are 8 to 10-fold higher than in controls. We have demonstrated a significant reduction in thymocytes (CD4(+) CD8(+), CD4(+) CD8(+) Vbeta8(+), CD4(+) CD8(+) Vgamma2(+)) from newborn and splenocytes (CD4(+) CD8(-))from 1-week-old mouse progeny exposed to B[a]P in utero. To investigate possible causes of the observed T cell reduction, we analyzed the thymocytes and splenocytes from progeny and maternal tissues for the presence of B[a]P-DNA adducts. Adducts were detected in maternal, placental and offspring lymphoid tissues at day 19 of gestation.. at birth and 1-wk after birth. The presence of B[a]P-DNA adducts in immature T cells may, in part, explain the previously observed T cell immunosuppression and tumor susceptibility in mice exposed to B[a]P in utero. The effects of DNA lesions on progeny T cells may include interference with normal T-cell development. These results provide a possible explanation for the relationship between maternal smoking during pregnancy and childhood carcinogenesis.

Rogalla P, Drechsler K, Frey G, Hennig Y, Helmke B, Bonk U, Bullerdiek J. 1996 . HMGI-C expression patterns in human tissues. Implications for the genesis of frequent mesenchymal tumors. Am J Pathol 149:775-779.
Abstract: Cytogenetically visible aberrations of chromosomal region 12q14-15 in a variety of frequent benign human tumors reflect rearrangements of the HMGI-C gene. The mechanisms by which the HMGI-C gene contributes to tumorigenesis are mostly unknown, although frequently aberrant transcripts containing exons 1 to 3 of HMGI-C and ectopic sequences from other genes due to breaks within the third intron of HMGI-C are detectable. This is the first report analyzing human tissue samples mainly of mesenchymal origin by a highly sensitive polymerase-chain-reaction-based approach detecting HMGI-C expression. We found HMGI-C expression in embryonic tissue but no expression in any of several adult tissues tested except for two myometrial tissues. These data suggest that HMGI-C is mainly expressed in human tissues during embryonal and fetal development. Thus, its particular role for tumor development may be due to the expression of at least exons 1 to 3 rather than to the formation of fusion transcripts.

Roman E, Watson A, Beral V, Buckle S, Bull D, Baker K, Ryder H, Barton C. 1993 . Case-control study of leukaemia and non-Hodgkin's lymphoma among children aged 0-4 years living in west Berkshire and north Hampshire health districts. BMJ 306:615-621.
Abstract: OBJECTIVE--To investigate the relation between parental employment in the nuclear industry and childhood leukaemia and non-Hodgkin's lymphoma. DESIGN--Case-control study. SETTING-West Berkshire and Basingstoke and North Hampshire District Health Authorities. SUBJECTS--54 children aged 0-4 years who had leukaemia or non-Hodgkin's lymphoma diagnosed during 1972-89, who were born in the study area and were resident there when cancer was diagnosed. Six controls were selected for each case: four from hospital delivery registers and two from livebirth registers maintained by the NHS central register. Controls were matched for sex, date of birth (within six months), and area of residence at birth and time of diagnosis. MAIN OUTCOME MEASURES--Parents' employment by the nuclear industry and exposure to ionising radiation at work. RESULTS--Five (9%) of the 54 cases and 14 (4%) of the 324 controls had fathers or mothers, or both, who had been employed by the nuclear industry (relative risk 2.2, 95% confidence interval 0.6 to 6.9). Nuclear industry employees who work in areas where exposure to radiation is possible are given film badges to monitor their exposure to external penetrating ionising radiation. Three fathers of cases and two fathers of controls (and no mothers of either) had been monitored in this way before their child was conceived (relative risk 9.0, 95% confidence interval 1.0 to 107.8). No father (of a case or control) had accumulated a recorded dose of more than 5 mSv before his child was conceived, and no father had been monitored at any time in the four years before his child was conceived. A dose-response relation was not evident among fathers who had been monitored. CONCLUSIONS--These results suggest that the children of fathers who had been monitored for exposure to external penetrating ionising radiation in the nuclear industry may be at increased risk of developing leukaemia before their fifth birthday. The finding is based on small numbers and could be due to chance. If the relationship is real the mechanisms are far from clear, except that the effect is unlikely to be due to external radiation; the possibility that it could be due to internal contamination by radioactive substances or some other exposure at work should be pursued. The above average rates of leukaemia in the study area cannot be accounted for

by these findings.

Ross JA, Xie Y, Davies SM, Shu XO, Pendergrass TW, Robison LL. 2003. Prescription medication use during pregnancy and risk of infant leukemia (United States). Cancer Causes & Control 14:447-451.
Abstract: Objective: We explored whether maternal medication use during pregnancy may be an important etiologic area for investigation in studies of infant leukemia. Methods: In this case-control study, associations were explored between specific medications as recorded in the medical records of 243 mothers of infants who were diagnosed with leukemia at <18 months of age and 393 mothers of infants without leukemia identified through random digit dialing. Cases included 157 acute lymphoblastic (ALL), 77 acute myeloid (AML), and nine other leukemias. A total of 27 different drugs that were prescribed for at least six women were analyzed. Results: Overall, non-statistically significant negative associations (Odds ratios, OR < 0.5) were observed with amoxicillin, nystatin, clomiphene, levothyroxine, cefaclor, and trimethobenzamide HCL. When cases were restricted to either myeloid or lymphoblastic leukemia, cotrimoxazole was prescribed for five ALL case mothers and no matched controls; no association with cotrimoxazole was observed with AML. Conclusions: Given the number of comparisons, chance cannot be ruled out for any of the associations found here. However, a strength of this study is the lack of recall bias. The disparate data observed between AML and ALL in some instances may indicate areas of interest; they will be explored further in a case-control study of infant leukemia that is currently underway.

Rothman KJ, MacMahon B, Lin TM, Lowe CR, Mirra AP, Ravnihar B, Salber EJ, Trichopoulos D, Yuasa S. 1980. Maternal age and birth rank of women with breast cancer. J Natl Cancer Inst 65:719-722.
Abstract: Data from a large international case-control study of breast cancer suggested that women born to young mothers had a 25% lower risk of breast cancer. The association was not secondary to a tendency for these women themselves to have had children at early ages. The data provided no indication of a meaningful association between breast cancer risk and birth rank. Confounding was controlled by stratification according to a summary confounder score.

Rothschild TC, Boylan ES, Calhoon RE, Vonderhaar BK. 1987 . Transplacental effects of diethylstilbestrol on mammary development and tumorigenesis in female ACI rats. Cancer Res 47:4508-4516 .
Abstract: Female ACI rats were exposed to diethylstilbestrol (DES) transplacentally and followed to 10 months of age to assess the effect of the drug on mammary development and tumorigenesis. Pregnant rats were given injections of vehicle (sesame oil) or DES (total dose, 0.8 micrograms = low DES or 8.0 micrograms = high DES) on days 15 and 18 of gestation. Pellets containing 2.5 mg DES + 17.5 mg cholesterol (DES pellet) or 20 mg cholesterol (chol pellet) were implanted s.c. into 12-week-old female offspring, creating 6 experimental groups: vehicle exposure + chol pellet (1) or + DES pellet (2); low DES exposure + chol pellet (3) or + DES pellet (4); high DES exposure + chol pellet (5) or + DES pellet (6). At sacrifice, representative mammary tissue and all palpable mammary tumors were removed for histopathological analysis. Each of the 6 experimental groups contained a minimum of 32 rats from at least 14 litters. In computation of data, the unit of analysis was the litter. Groups which had received any DES (prenatally or postnatally) were found to have elongated nipples and enlarged pituitaries. The mammary gland whole mounts from all rats in groups 4 and 6 displayed extensive lobuloalveolar proliferation comparable to that seen in DES pellet controls (group 2). Mammary glands of approximately 75% of rats in groups 3 and 5 were categorized as showing the lowest grade of differentiation while this undifferentiated condition was seen in only 36% of group I controls. No palpable mammary tumors were found in rats exposed to vehicle in utero (group 1). But in group 5, a total of 6 tumors in 5 animals derived from 4 different litters were obtained, a difference shown to be statistically significant. Group 3 had 1 rat with 8 tumors. Among rats bearing the DES pellet, tumor latency was shortened significantly in both groups exposed to DES in utero. By 22 weeks after pellet implantation, 100% of the DES-exposed litters (groups 4 and 6) contained at least 1 tumor-bearing rat compared to about 50% of the tumor-bearing litters in group 2. Tumor multiplicity at sacrifice was increased significantly in the group exposed prenatally to the higher dose of DES. Histologically, the overwhelming majority of palpable mammary tumors from all tumor-bearing treatment groups were classified as adenocarcinomas. Prenatal exposure to DES did not alter the ratio of malignant to benign lesions observed, nor did it affect the degree of differentiation noted in the adenocarcinomas.(ABSTRACT TRUNCATED AT 400 WORDS)

Rubin BS, Murray MK, Damassa DA, King JC, Soto AM. 2001. Perinatal exposure to low doses of bisphenol A

affects body weight, patterns of estrous cyclicity, and plasma LH levels. Environ Health Perspect 109:675-680.
Abstract: The nonsteroidal estrogenic compound bisphenol A (BPA) is a monomer used in the manufacture of polycarbonate plastics and resins. BPA may be ingested by humans as it reportedly leaches from the lining of tin cans into foods, from dental sealants into saliva, and from polycarbonate bottles into their contents. Because BPA is weakly estrogenic--approximately 10,000-fold less potent than 17ß-estradiol--current environmental exposure levels have been considered orders of magnitude below the dose required for adverse effects on health. Herein we demonstrate measurable effects on the offspring of Sprague-Dawley female rats that were exposed, via their drinking water, to approximately 0.1 mg BPA/kg body weight (bw)/day (low dose) or 1.2 mg BPA/kg bw/day (high dose) from day 6 of pregnancy through the period of lactation. Offspring exposed to BPA exhibited an increase in body weight that was apparent soon after birth and continued into adulthood. In addition, female offspring exposed perinatally to the high dose of BPA exhibited altered patterns of estrous cyclicity and decreased levels of plasma luteinizing hormone (LH) in adulthood. Administration of neither the doses of BPA that caused effects during perinatal exposure nor a 10-fold higher dose was able to evoke a uterotropic response in ovariectomized postpubertal females. These data indicate an increased sensitivity to BPA during the perinatal period and suggest the need for careful evaluation of the current levels of exposure to this compound.

Rustia M, Schenken J. 1976 . Transplacental effects of ethylnitrosourea precursors ethylurea and sodium nitrite in hamsters. Zeitschrift Fur Krebsforschung Und Klinische Onkologie. Cancer Research & Clinical Oncology 85:201-207.
Abstract: Four simultaneous dosages of the ethylnitrosourea precursors, ethylurea and sodium nitrite, were administered intragastrically to pregnant hamsters at 100 mg/kg and 50 mg/kg respectively, from the 12-15th days of pregnancy. The treatment induced multiple neurogenic tumors of the peripheral nervous system in the offspring. Female progeny developed a greater incidence and multiplicity of peripheral nervous system tumors with significantly shorter latencies than males, thus establishing evidence that the tumors were age and sex dependent. The tumors presented varied morphological patterns and upon transplantation, grew regularly, exhibiting their malignant nature. The possible influence of estrogenic hormones on the development and growth of peripheral nervous system tumors and comparative aspects of the relationship between prenatal and postnatal carcinogenesis with regard to the ensuing tumor spectra as a consequence of exposure to the same chemical agent, are discussed.

Safe S. 2005. Clinical Correlates of Environmental Endocrine Disruptors. Trends in Endocrinology and Metabolism 16:139-144.
Abstract: Endocrine disrupting chemicals (EDCs), such as environmental estrogens, are hypothesized to be associated with a global decrease in sperm counts, other male reproductive tract problems and increasing rates of female breast cancer. Results of human population studies do not support the association between certain organochlorine EDCs and female breast cancer. Moreover, there is minimal evidence linking EDCs or exposure to other environmental chemicals with male reproductive tract problems. With the exception of the increasing incidence of testicular cancer, it is also questionable whether male reproductive tract problems are increasing, decreasing or unchanged. However, several studies report large differences in sperm count and quality and other endocrine-related problems within countries and regions, but the environmental, dietary and/or lifestyle factors responsible remain unknown.

Samuelsen SO, Bakketeig LS, Tretli S, Johannesen TB, Magnus P. 2006. Head Circumference at Birth and Risk of Brain Cancer in Childhood: a Population-Based Study. Lancet Oncology 7:39-42.
Abstract: Background Studies have found only a weak or no association between birthweight and brain cancer in childhood. However, previous studies have not assessed the association between head circumference at birth and brain cancer. We aimed to assess the risk of brain cancer in childhood according to head circumference at birth. Methods We investigated the association between incidence of brain cancer in childhood and factors recorded at birth such as head circumference, birthweight, and gestational age based on the Norwegian medical birth registry from 1978-98, linked to the Norwegian cancer registry from 1978-2002. Findings We analysed 1 010 366 individuals with 12 378 172 person-years of follow-up, from which 453 individuals aged 0-15 years were diagnosed with brain cancer. The relative risk of brain cancer was 1 . 27 (95% CI 1 .16-1 . 38) per 1-cm increase in head circumference after adjustment for birthweight, gestational age, and sex. Interpretation Head circumference is positively associated with incidence of brain

cancer in childhood, suggesting that brain pathology originates during fetal life.

Sanderson M, Williams MA, Malone KE, Stanford JL, Emanuel I, White E, Daling JR. 1996. Perinatal factors and risk of breast cancer. Epidemiology 7:34-37.
Abstract: A high level of endogenous estrogen in utero has been hypothesized to be a possible risk factor for breast cancer. We used information from two population-based case-control studies to investigate the relation between perinatal factors and risk of invasive breast cancer among women age 21-45 years (746 cases, 960 controls) and women age 50-64 years (401 cases, 439 controls). Breast cancer cases were ascertained through a population-based cancer registry, and controls were selected by random digit dialing. After adjustment for age, menopausal status, and maternal smoking, the birthweight-breast cancer association in women age 21-45 years followed a J-shaped curve, with women whose birthweight was less than 2,500 gm [odds ratio (OR) = 1.3; 95% confidence interval (CI) = 0.9-2.0] and 4,000 gm or more (OR = 1.7; 95% CI = 1.1-2.5) at increased risk. Women age 50-64 years who were 4,000 gm or more at birth appeared to be at slightly reduced risk of breast cancer (OR = 0.6; 95% CI = 0.3-1.1). With the exception of maternal smoking, there was little effect of other perinatal factors on breast cancer risk in either group. These results support the hypothesized association between intrauterine estrogen exposure and subsequent risk of breast cancer.

Sandson TA, Wen PY, LeMay M. 1992 . Reversed cerebral asymmetry in women with breast cancer. Lancet 339:523-524.
Abstract: Altered intrauterine hormonal environment might predispose to both atypical cerebral asymmetry and breast cancer. We therefore investigated computed tomographic scans of 79 right-handed, white patients with breast cancer and 97 controls to assess the pattern of cerebral asymmetry. Women with breast cancer had a reversed pattern of cerebral asymmetry significantly more often than did controls (p less than 0.0001 for both frontal and occipital width. Our findings suggest that an intrauterine or early life factor, probably hormonal, could predispose to breast cancer in adulthood.

Sarasua S, Savitz DA. 1994. Cured and broiled meat consumption in relation to childhood cancer: Denver, Colorado (United States). Cancer Causes & Control 5:141-148.
Abstract: The association between cured and broiled meat consumption by the mother during pregnancy and by the child was examined in relation to childhood cancer. Five meat groups (ham, bacon, or sausage; hot dogs; hamburgers; bologna, pastrami, corned beef, salami, or lunch meat; charcoal broiled foods) were assessed. Exposures among 234 cancer cases (including 56 acute lymphocytic leukemia [ALL], 45 brain tumor) and 206 controls selected by random-digit dialing in the Denver, Colorado (United States) standard metropolitan statistical area were compared, with adjustment for confounders. Maternal hot-dog consumption of one or more times per week was associated with childhood brain tumors (odds ratio [OR] = 2.3, 95 percent confidence interval [CI] = 1.0-5.4). Among children, eating hamburgers one or more times per week was associated with risk of ALL (OR = 2.0, CI = 0.9-4.6) and eating hot dogs one or more times per week was associated with brain tumors (OR = 2.1, CI = 0.7-6.1). Among children, the combination of no vitamins and eating meats was associated more strongly with both ALL and brain cancer than either no vitamins or meat consumption alone, producing ORs of two to seven. The results linking hot dogs and brain tumors (replicating an earlier study) and the apparent synergism between no vitamins and meat consumption suggest a possible adverse effect of dietary nitrites and nitrosamines.

Sasaki S. 1991 . Influence of the age of mice at exposure to radiation on life-shortening and carcinogenesis. Journal of Radiation Research (Tokyo) 32 Suppl 2:73-85.
Abstract: Female B6C3F1 mice were irradiated on day 17 prenatal age, or day 0, 7, 35, 105, 240 or 365 postnatal age with 0.95, 1.9, 2.85, 3.8 or 5.7 Gy of gamma-rays from 137Cs. They were allowed to live out their entire life spans under specific pathogen free conditions. All the mice were given autopsies at death and were examined histologically for neoplastic and non-neoplastic diseases. The mice in the early postnatal period were most sensitive to the life-shortening effect of radiation. The shortening effect of irradiation given during the late fetal period was almost the same as that given during the young adult period. Incidences of lung, liver, pituitary, ovarian and bone tumors and malignant lymphoma of the lymphocytic type increased after irradiation of mice in the late fetal period. Mice in the early postnatal period are more susceptible to the induction of liver and ovarian tumors and malignant lymphoma of the lymphocytic type than are fetal mice. Myeloid leukemia and Harderian gland tumor did not develop in

excess when mice were irradiated in fetal or in neonatal period; whereas, these neoplasms were induced by irradiation during the adult period.

Sasaki S, Kasuga T, Sato F, Kawashima N. 1978 . Late effects of fetal mice x-irradiated at middle or late intrauterine stage. Gann 69:167-177.
Abstract: Mice of F1 hybrids of (C57BL/6xWHT) strains were exposed in utero to 200 R of X-rays at 12 or 16 approximately 18 days post coitum. Mice of both sexes were allowed to live through their life span, and the induction of tumors, growth retardation, and induction of degenerative diseases were examined. A significant enhancement of lung, pituitary gland, and ovary tumorigenesis was observed in mice irradiated at the late intrauterine stage. Also, incidence of liver and skin tumors was increased slightly in this group, whereas thymic lymphomas were not induced. Persistent growth retardation, several congenital malformation, and amyloid degeneration were found in mice irradiated at the middle intrauterine stage. However, no increases incidence of tumors was seen in this group. Moreover, incidnece of lymphoreticular tissue tumors, lung tumors, and leiomyosarcomas of uterus was significantly decreased by irradiation at the middle intrauterine stage from the unirradiated control and the late intrauterine irradiated group.

Saunders R. 2005. Static Magnetic Fields: Animal Studies. Progress in Biophysics & Molecular Biology 87:225-239.
Abstract: Various experimental studies carried out over the last 30-40 years have examined the effects of the chronic or acute exposure of laboratory animals to static magnetic fields. Many of the earlier studies have been adequately reviewed elsewhere; few adverse effects were identified. This review focuses on studies carried out more recently, mostly those using vertebrates, particularly mammals. Four main areas of investigation have been covered, viz., nervous system and behavioural studies, cardiovascular system responses, reproduction and development, and genotoxicity and cancer. Work on the role of the natural geomagnetic field in animal orientation and migration has been omitted. Generally, the acute responses found during exposure to static fields above about 4 T are consistent with those found in volunteer studies, namely the induction of flow potentials around the heart and the development of aversive/avoidance behaviour resulting from body movement in such fields. No consistently demonstrable effects of exposure to fields of similar to1 T and above have been seen on other behavioural or cardiovascular endpoints. In addition, no adverse effects of such fields on reproduction and development or on the growth and development of tumours have been firmly established. Overall. however. far too few animal studies have been carried out to reach any firm conclusions. (C) 2004 Elsevier Ltd. All rights reserved.

Savitz DA, Chen JH. 1990. Parental occupation and childhood cancer: review of epidemiologic studies. Environ Health Perspect 88: 325-337.
Abstract: Parental occupational exposures might affect childhood cancer in the offspring through genetic changes in the ovum or sperm or through transplacental carcinogenesis. The 24 published epidemiologic studies of this association have all used case-control designs, with controls generally selected from birth certificates or from general population sampling. Occupational exposures were inferred from job titles on birth certificates or through interviews. A large number of occupation-cancer associations have been reported, many of which were not addressed or not confirmed in other studies. Several associations have been found with consistency: paternal exposures in hydrocarbon-associated occupations, the petroleum and chemical industries, and especially paint exposures have been associated with brain cancer; paint exposures have also been linked to leukemias. Maternal exposures have received much less attention, but studies have yielded strongly suggestive results linking a variety of occupational exposures to leukemia and brain cancer. The primary limitations in this literature are the inaccuracy inherent in assigning exposure based on job title alone and imprecision due to limited study size. Although no etiologic associations have been firmly established by these studies, the public health concerns and suggestive data warrant continued research.

Schiffer D, Giordana MT, Vigliani MC, Cavalla P. 1991. Relationship between glial reaction to a stab wound and tumor-development after receiving transplacental ethylnitrosourea in the rat. Acta Neuropathol (Berl) 83:30-38.
Abstract: Fisher 344 rats born from mothers treated with ethylnitrosourea (ENU) 50 mg/kg intravenously were injured at the 1st and 2nd month of extrauterine life by a transcranial stab. The wound affected cerebral cortex, white matter and basal ganglia. The animals were killed 15 and 45 days and 5 months after

injury and cell reaction was studied histologically and immunohistochemically. Bromodeoxyuridine (BrdUrd) was administered 1 h before sacrifice and the labeled cells were evaluated. In ENU-treated rats injured at 1 month of age only minor differences were found in comparison with injured controls. In ENU rats injured at 2 months of age and killed 15 days later, a higher number of BrdUrd-labeled cells was found in comparison with controls; 45 days after injury the cell reaction acquired the aspect of a microtumor, however, no microtumor unrelated with the needle track was present. In ENU rats killed 5 months after the injury, there was no difference between injured and not injured ENU-treated rats, as far as the aspect and the number of tumors were concerned. The tumor phenotype was, thus, anticipated by the cell response to trauma in ENU rats. The interpretation is that the additional cell division, in response to trauma, anticipate not only the phenotypic, but also the cell kinetics changes, as indicated by BrdUrd labeling.

Schlegel J, Piontek G, Kuhne C, Bartels HJ, Kraus A , Kappler R, Mennel HD. 1999. Molecular genetic characterisation of intracerebrally transplanted brain tumours. Experimental & Toxicologic Pathology 51:41-45.
Abstract: The aim of the present study was the characterisation of genetic alterations in two different experimental gliomas, induced in rats from the inbred strain BDIX by transplacental ethylnitrosourea with subsequent serial transplantation. The genes investigated have been shown previously to be altered during human glial tumour progression and include the gene for the epidermal growth factor receptor (EGFR), the genes for the cell cycle regulators cyclin dependent kinase 4 (CDK4), cyclinD1 (cycD1), the p16 gene (MTS1/INK4) and the retinoblastoma gene (RB). Using a semi-quantitative PCR-based screening method no gross alterations could be detected in these genes, demonstrating that nitrosourea-induced glial rumours of rats do not harbour those genetic changes which typically arise in human malignant gliomas. Thus, the use of this tumour model for gene therapy trials is questionable.

Schmahl W, Geber E, Lehmacher W. 1985 . Diaplacental carcinogenic effects of 5-azacytidine in NMRI-mice. Cancer Lett 27:81-90.
Abstract: 5-Azacytidine was applied to NMRI-mice (1-2 mg/kg) either on gestation day 12, 14, or 16. In the first case it mainly induced leukemias, while in the latter experiments leukemias, lung adenomas and soft tissue sarcomas represent the main effects. The experiments performed on gestation day 14 led to tumor rates below the spontaneously occurring tumor frequencies in NMRI-mice. There is a clear-cut inverse dose-response relationship in leukemia induction, as the higher dose principally shows a lower degree of effectiveness. This, as well as a reduction of tumor frequency below control levels after application of this drug on day 14, can be explained by an "overkill" effect. The cytotoxic and embryolethal efficacy of the agent thus surpasses the transformation effects at the cellular genome. While a negative correlation between the general embryotoxicity of azacytidine and the simultaneous tumor inducibility is to be observed, there is no correlation at the target organ level between the embryotoxic and the carcinogenic effects.

Schmahl W, Kriegel H. 1980. Ovary tumors in NMRI mice subjected to fractionated X-irradiation during fetal development. Journal of Cancer Research & Clinical Oncology 98:65-74.
Abstract: Fractionated X-irradiation of pregnant mice was performed either during late organogenesis (gestational days 11-13), during the early fetal period (g.d. 14-16), or during both periods (g.d. 11-16). The offspring were observed for 39 months. A significant increase of ovary tumor frequency was observed with 3 X 1.2 Gy, applied either in late organogenesis or in the early fetal period. Lower X-irradiation doses were ineffective in these periods with respect to ovary tumor development. A sharp increase in ovary tumor frequency resulted after irradiation with 6 X 0.8 Gy or 6 X 1.2 Gy. The highest incidence of ovary cysts was observed after 3 X 1.0 Gy or 3 X 1.2 Gy on g.d. 11-13, while the frequency of these cysts was lowest in the animals irradiated six times, which, however, showed a high ovary tumor frequency. Autoradiography of the fetal ovaries either 1 or 6 days after irradiation at the late organogenesis stage revealed a persistent depression of this organ's proliferation rate throughout pregnancy. This may be consistent with the low tumor inducibility after X-irradiation in this period.

Schoenig GP, Goldenthal EI, Geil RG, Frith CH, Richter WR, Carlborg FW. 1985. Evaluation of the dose response and in utero exposure to saccharin in the rat. Food Chem Toxicol 23:475-490.
Abstract: A two-generation bioassay on sodium saccharin (NaS), involving 2500 second-generation male rats, was designed to determine the dose response for urinary bladder tumours in male rats and to evaluate

other changes possibly related to the occurrence of the tumours. Six treatment groups (125-700 rats/group) were fed dietary levels of NaS ranging from 1.0 to 7.5%. To evaluate the role of in utero exposure, two additional groups were exposed to NaS either only during gestation via dams fed diet containing 5.0% NaS or for a single generation beginning at birth. In the latter group, the nursing dams were placed on an NaS diet immediately after giving birth and their offspring were weaned onto diets containing 5.0% NaS. A third additional group, included to evaluate the specificity of NaS and the role of excess sodium in the occurrence of urinary bladder tumours, was fed diet containing sodium hippurate (NaH) for two generations--5.0% NaH to the first generation and to the second until 8 wk old, and subsequently 3.0% because of unexpected toxicity. A clear dose response for urinary bladder tumours was observed in the second-generation NaS-treated male rats. The steep slope of the dose-response curve indicated a rapid decline in tumour incidence with decreasing dose. The 1.0% dietary level (fed to 700 rats) was considered to be a no-effect level for bladder tumours. The only other treatment-related pathological changes were an increase in urinary bladder weight in rats fed greater than or equal to 3.0% and an increase in mineralization of the kidneys with greater than or equal to 1.0%. Several physiological effects were seen in the NaS-treated groups showing an increase in bladder tumours (i.e. those fed greater than or equal to 3.0%). Some changes, e.g. depressed growth and increased water consumption, were indicative of a general disturbance of these rats, but analysis of body-weight, food-consumption, compound-consumption and water-consumption data revealed no correlations within any dose group between these quantitative data and the occurrence of bladder tumours. Other changes indicative of the compromised situations of the rats fed high dietary levels of NaS were anaemia in weanling rats fed 5.0 or 7.5% and a reduction in litter size at dietary levels greater than or equal to 3.0%. Changes in urine volume and urine osmolality were highly correlated with the occurrence of the urinary bladder tumours.(ABSTRACT TRUNCATED AT 400 WORDS)

Schuz J, Kaletsch U, Kaatsch P, Meinert R, Michaelis J. 2001. Risk factors for pediatric tumors of the central nervous system: Results from a German population-based case-control study. Medical & Pediatric Oncology 36:274-282.
Abstract: Background, From 1993 to 1997 we conducted two population-based case-control studies on childhood cancer and a variety of potential risk factors in Germany. One case group involved children under the age of 15 years having a tumor of the central nervous system (CNS). Procedure, For both studies, one conducted in the northwestern area of Germany, the other covering the whole of West Germany, incident cases were identified from the nationwide German Childhood Cancer Registry, and controls were randomly selected from complete population registration flies. Results. In total 466 pediatric CNS tumor cases and 2,458 controls were available for analyses. We observed only few positive associations, namely, between CNS tumors and low birth weight [<2,500 g; odds ratio (OR), 1.73; 95% confidence interval (CI), 1.06-2.84], between ependymoma and maternal smoking during pregnancy (>10 cigarettes per day: OR, 4.71;95%, CI, 1.69-13.1), and between astrocytoma and exposure to wood preservatives (OR, 1.91; 95%, CI, 1.22-3.01). CNS tumors were not associated with high birth weight, duration of breast feeding, maternal age at time of delivery, duration of gestation, previous fetal losses, paternal smoking during pregnancy, maternal alcohol consumption, the chilli's exposure to pesticides, maternal diagnostic X-ray examinations during pregnancy, X-ray examinations of the child, or exposure to residential magnetic fields. Conclusions. Despite the large study population, we found only few factors that were associated with CNS tumors or one of the morphological subgroups. Therefore, our results suggest that aspects of the prenatal and neonatal period play only a minor role in the etiology of pediatric CNS tumors. Med. Pediatr. Oncol. 36:274-282, 2001. (C) 2001 Wiley-Liss. Inc.

Segal DH, Germano IM, Bederson JB. 1997. Effects of basic fibroblast growth factor on in vivo cerebral tumorigenesis in rats. Neurosurgery 40:1027-1033.
Abstract: OBJECTIVE: In vitro evidence suggests that basic fibroblast growth factor (bFGF) promotes tumor cell proliferation and angiogenesis. In this study, we evaluated the early and delayed effects of recombinant human bFGF on the early and late phases of in vivo, in situ tumorigenesis in rats. METHODS: Brain tumors were induced by transplacentally exposing fetal rats to N-nitrosoethylurea on Day 17 of pregnancy. On postnatal (PN) Day 60 or 90, N-nitrosoethylurea-exposed rats underwent stereotactic intraventricular implantation of Gelfoam saturated with bFGF (60 mu g) or vehicle; the rats were killed 4 days (early group) or 30 days (delayed group) later. The early and delayed effects of bFGF on the early phase of tumorigenesis (PN Day 60) were evaluated in 14 and 10 rats, respectively; early and delayed

effects on the late phase of tumorigenesis (PN Day 90) were evaluated in 12 rats each. RESULTS: Histological examination 30 days after implantation showed a significantly higher tumor rate in rats that had been treated with bFGF on PN Day 90, compared with vehicle-treated control rats ($P < 0.05$); furthermore, in the bFGF-treated animals there was significantly greater intratumoral and periventricular glial fibrillary acidic protein expression, as determined immunohistochemically. Increased vascularity in the tumor ipsilateral to the implant was found in 2 of 14 rats that had been treated with bFGF on PN Day 60. CONCLUSION: These findings support in vitro evidence that bFGF and its receptor complex are implicated in the genesis and progression of N-nitrosoethylurea-induced brain tumors in this animal model.

Shankar S, Davies S, Giller R, Krailo M, Davis M, Gardner K, Cai H, Robison L, Shu XO. 2006. In utero exposure to female hormones and germ cell tumors in children. Cancer 106:1169-1177.
Abstract: BACKGROUND. Maternal exposure to exogenous female hormones during pregnancy has been implicated as a risk factor for malignant germ cell tumors (GCTs) in the offspring in some epidemiologic studies of testicular and ovarian carcinoma in adults. METHODS. From 1996 to 2002, 278 children younger than 15 years of age with malignant GCTs and 423 healthy controls, frequency-matched for geographic location, age, and sex were enrolled in a case-control study to investigate whether in utero exposure to female hormones is associated with the risk of malignant GCT in children. Cases were recruited from 84 institutions in the U.S. and controls were enrolled through random digit dialing. Information was obtained through telephone interview with the biological mothers of the subjects and through blinded review of the mothers' medical records. RESULTS. Neither self-reported (odds ratio [OR] = 1.15; 95% confidence interval [CI], 0.63, 2.12) nor medical chart based (OR = 1.14; 95% CI, 0.75, 1.73) maternal exposure to exogenous female hormones was related to malignant GCT risk. Pregnancy-related conditions that may have altered serum levels of circulating female hormones were also unrelated to the risk of GCT in the offspring. CONCLUSION. This study failed to provide strong evidence to support the hypothesis that maternal exposure to exogenous female hormones during pregnancy increases the risk of GCT in the offspring.

Sharpe CR, Franco EL, Decamargo B, Lopes LF, Barreto JH, Johnsson RR, Mauad MA. 1995. Parental exposures to pesticides and risk of Wilms tumor in Brazil. Am J Epidemiol 141:210-217.
Abstract: Wilms' tumor is one of the most common abdominal childhood malignancies, Wilms' tumor rates in Brazil are among the highest in the world. This prompted the Brazilian Wilms' Tumor Study Group to conduct a hospital-based, multicenter, case-control investigation of environmental risk factors for the disease, Between April 1987 and January 1989, the authors collected information on relevant occupational exposures by interviewing the parents of 109 Wilms' tumor cases admitted to hospitals in Sao Paulo, Salvador, Belo Horizonte, and Jau, Also interviewed were the parents of 218 age- and sex-matched control children who had been admitted for treatment of nonneoplastic diseases to the same or nearby hospitals, Odds ratios (ORs) adjusted for income and education were calculated by conditional logistic regression. Consistently elevated risks were seen for farm work involving frequent use of pesticides by both the father (OR = 3.24, 95% confidence interval (CI) 1.2-9.0) and the mother (OR = 128.6, 95% CI 6.4-2,569), These risk elevations were restricted to cases diagnosed after 2 years of age (ORs > 4), for paternal exposure, and after 4 years of age (OR = 14.8, 95% CI 2.2-98.8), for maternal exposure. Risk elevations were also more pronounced among boys (paternal exposure OR = 8.56, 95% CI 2.1-35.1; maternal exposure OR = 4.60, 95% CI 0.8-26.4) than among girls (paternal exposure OR = 1.31, 95% CI 0.4-4.1; maternal exposure OR = 2.03, 95% CI 0.5-8.9).

Sharpe RM. 2003. The 'oestrogen hypothesis'- where do we stand now? Int J Androl 26:2-15.
Abstract: The original 'oestrogen hypothesis' postulated that the apparent increase in human male reproductive developmental disorders (testis cancer, cryptorchidism, hypospadias, low sperm counts) might have occurred because of increased oestrogen exposure of the human foetus/neonate; five potential routes of exposure were considered. This review revisits this hypothesis in the light of the data to have emerged since 1993. It addresses whether there is a secular increasing trend in the listed disorders and highlights the limitations of available data and how these are being addressed. It considers whether new data has emerged to support the suggestion that increased oestrogen exposure could cause these abnormalities and reviews new data on potential routes via which such increased exposure could have occurred. Secular trends: The disorders listed above are now considered to represent a syndrome of disorders (testicular dysgenesis syndrome, TDS) with a common origin in foetal life. Testicular cancer has increased in incidence in

Caucasian men worldwide and lifetime risk is 0.3-0.8%. Secular trends in cryptorchidism are unclear but it is by far the commonest (2-4% at birth) congenital abnormality in either sex. Secular trends for hypospadias are not robust, although most studies suggest a progressive increase; registry data probably under-estimates incidence, but based on this data hypospadias is the second most common (0.3-0.7% at birth) congenital malformation. Retrospective analyses of sperm count data show a global downward trend but this is inconclusive - prospective studies using standardized methodology show significant differences between countries and very low sperm counts in the youngest cohort of men. For all disorders, other then testis cancer, standardized prospective studies are the best way forward and are in progress across Europe. Oestrogen effects: Evidence that foetal exposure to oestrogens can induce the above disorders has strengthened. New pathways via which such changes could be induced have been identified, including suppression of testosterone production by the foetal testis, suppression of androgen receptor expression and suppression of insulin-like factor-3 (InsL3) production by foetal Leydig cells. Other evidence suggests that the balance between androgen and oestrogen action may be important in induction of reproductive tract abnormalities. Oestrogen exposure: Although many new environmental oestrogens have been identified, their uniformly weak oestrogenicity excludes the possibility that they could induce the above disorders. However, emerging data implicates various environmental chemicals in being able to alter endogenous levels of androgens (certain phthalates) and oestrogens (polychlorinated biphenyls, polyhalogenated hydrocarbons), and the former have been shown to induce a similar collection of disorders to TDS. Other mechanisms via which increased fetal exposure to pregnancy oestrogens might occur (increasing trend in obesity, dietary changes) are also discussed.

Sharpe RM. 2006. Pathways of endocrine disruption during male sexual differentiation and masculinisation. Best Practice & Research Clinical Endocrinology & Metabolism 20:91-110.
Abstract: After testis formation, further development of a male phenotype (masculinisation) is driven by three hormones from the foetal testis: anti-Mullerian hormone, insulin-like factor 3, and testosterone. These hormones divert the development of reproductive and other organs from female to male and also play a role in testis development. The hormone dependence of masculinisation renders this process inherently susceptible to disruption by factors that interfere with hormone production, bioavailability, metabolism, or action. This susceptibility is illustrated by the high prevalence of congenital masculinisation disorders (cryptorchidism, hypospadias) and disorders in young adult men (low sperm counts, testis cancer), which may also stem from maldevelopment (dysgenesis) of the foetal testis. Testicular dysgenesis occurring in humans, or which is induced in animal models by foetal exposure to certain phthalates, is associated with impaired hormone production by the foetal testis. There is currently no definitive evidence that exposure of humans to environmental chemicals can induce testicular dysgenesis and/or impair masculinisation, though pathways via which this could potentially occur are established.

Shaw AK, Infante-Rivard C, Morrison HI. 2004. Use of medication during pregnancy and risk of childhood leukemia (Canada). Cancer Causes & Control 15:931-937.
Abstract: Objective: To examine risk of childhood acute lymphoblastic leukemia (ALL) associated with maternal use of medications during pregnancy; in particular medications known or suspected to be teratogenic. Methods: Seven hundred and eighty nine children (<15 years old) diagnosed with ALL in the province of Quebec between 1980 and 2000 were recruited for study. A similar number of population based controls matched to cases (1:1) by sex and age were chosen from family allowance or health insurance files. Information was gathered via telephone interview with the subjects' parents. Data were analyzed using conditional logistic regression. Results: Risk of childhood ALL was significantly increased in the offspring of mothers who reported using any medication (adjusted odds ratio (ORadj)=1.3, 95% CI 1.0-1.6) or any teratogenic medication (ORadj=1.4, 95% CI 1.1-1.9) during pregnancy. Among specific medication categories, only central nervous system depressants were associated with a significantly increased risk, although elevated odd ratios were found for anti-epileptics, immunosuppressants, oral contraceptives, and illicit drugs. Risk associated with use of teratogenic medications was higher with increased dose and in children diagnosed before two years of age. Conclusion: A modest increase in risk of ALL was found among children of mothers who used medication during pregnancy.

Shen J, Liu J, Xie YX, Diwan BA, Waalkes MP. 2007. Fetal onset of aberrant gene expression relevant to pulmonary carcinogenesis in lung adenocarcinoma development induced by in utero arsenic exposure. Toxicol Sci 95:313-320.

Abstract: Arsenic is a human pulmonary carcinogen. Our work indicates that in utero arsenic exposure in mice can induce or initiate lung cancer in female offspring. To define early molecular changes, pregnant C3H mice were given 85 ppm arsenic in drinking water from days 8 to 18 of gestation and expression of selected genes in the fetal lung or in lung tumors developing in adults was examined. Transplacental arsenic exposure increased estrogen receptor-alpha (ER-alpha) transcript and protein levels in the female fetal lung. An overexpression of various estrogen-regulated genes also occurred, including trefoil factor-3, anterior gradient-2, and the steroid metabolism genes 17-beta-hydroxysteroid dehydrogenase type 5 and aromatase. The insulin growth factor system, which can be influenced by ER and has been implicated in the pulmonary oncogenic process, was activated in fetal lung after gestational arsenic exposure. In utero arsenic exposure also induced overexpression of (x-fetoprotein, epidermal growth factor receptor, L-myc, and metallothionein-1 in fetal lung, all of which are associated with lung cancer. Lung adenoma and adenocarcinoma from adult female mice exposed to arsenic in utero showed widespread, intense nuclear ER-alpha expression. In contrast, normal adult lung and diethylnitrosamine-induced lung adenocarcinoma showed little evidence of ER-a. expression. Thus, transplacental arsenic exposure at a carcinogenic dose produced aberrant estrogen-linked pulmonary gene expression. ER-a activation was specifically associated with arsenic-induced lung adenocarcinoma and adenoma but not with nitrosamine-induced lung tumors. These data provide evidence that arsenic-induced aberrant ER signaling could disrupt early life stage genetic programing in the lung leading eventually to lung tumor formation much later in adulthood.

Shibata A, Minn AY. 2000. Perinatal sex hormones and risk of breast and prostate cancers in adulthood. Epidemiologic Review 22:239-248.

Shu XO, Gao YT, Brinton LA, Linet MS, Tu JT, Zheng W, Fraumeni JF Jr. 1988. A population-based case-control study of childhood leukemia in Shanghai. Cancer 62:635-644.
Abstract: A population-based case-control interview study of 309 childhood leukemia cases and 618 healthy population control children was conducted in urban Shanghai, China. Like some studies in other countries, excess risks for both acute lymphocytic leukemia (ALL) and acute nonlymphocytic leukemia (ANLL) were associated with intrauterine and paternal preconception diagnostic x-ray exposure, and with maternal employment in the chemical and agricultural industries during pregnancy. ANLL was linked to maternal occupational exposure to benzene during pregnancy, whereas both ALL and ANLL were significantly associated with maternal exposure to gasoline and the patient's prior use of chloramphenicol. New findings, previously unsuspected, included an association of ANLL with younger maternal age at menarche (odds ratio [OR] = 4.3; 95% confidence interval (CI) = 1.3-13.9); a protective effect for long-term (greater than 1 year) use of cod liver oil containing vitamins A and D for both ALL (OR = 0.4; 95% CI = 0.2-0.9) and ANLL (OR = 0.3; 95% CI = 0.1-1.0); and excess risks of ANLL among children whose mothers were employed in metal refining and processing (OR = 4.6; 95% CI = 1.3-17.2) and of ALL associated with maternal occupational exposure to pesticides (OR = 3.5; 95% CI = 1.1-11.2). No relationships were found with late maternal age, certain congenital disorders, or familial occurrence, which have been related to childhood leukemia in other studies. In contrast with other reports, an excess of leukemia, primarily ANLL, occurred among second or later-born rather than firstborn children.

Shu XO, Jin F, Linet MS, Zheng W, Clemens J, Mills J, Gao YT. 1994. Diagnostic-x-ray and ultrasound exposure and risk of childhood-cancer. Br J Cancer 70:531-536.
Abstract: In a population-based case-control study of 642 childhood cancer cases and the same number of matched controls in Shanghai, China, we evaluated the relationship between diagnostic X-ray (preconception, pre- and post-natal) and antenatal ultrasound exposure and the subsequent risk of developing three major types of childhood cancer (acute leukaemia, lymphoma and brain tumours) and all childhood neoplasms combined. Consistent with previous studies, prenatal X-ray exposure was found to be associated with an 80% increased risk of childhood cancers, although the estimation was based on 4% and 2% exposed cases and controls and was only marginally statistically significant (P = 0.08). Post-natal X-ray exposure was also linked with a small elevation in the risk of all cancers and the major categories of malignancies in children. Little evidence, however, was found to relate parental preconception X-ray exposure with the subsequent cancer risk in offspring, regardless of the exposure window and the anatomical site of X-ray exposures. This study adds further to the growing literature indicating that antenatal ultrasound exposure is probably not associated with an increased risk of childhood cancer.

Shu XO, Nesbit ME, Buckley JD, Krailo MD, Robinson LL. 1995. An exploratory analysis of risk factors for childhood malignant germ-cell tumors: Report from the Childrens Cancer Group (Canada, United States). Cancer Causes & Control 6:187-198.
Abstract: A study of 105 patients with childhood malignant germ-cell tumors (MGCT) and 639 community controls was conducted utilizing a large epidemiologic database collected by the Childrens Cancer Group from 25 member institutions in the United States and Canada. This study was designed to explore the risk factors of this malignancy whose etiology remains poorly understood. A structured, self-administered questionnaire was used to collect exposure information, and data were analyzed using an unconditional logistic regression model with adjustment for relevant confounders. Consistent with the findings from studies of adult MGCT, gestational age was associated inversely with risk of MGCT, with a 70 to 75 percent reduction in risk for children born at term compared with those born pre-term. Parental, particularly maternal, self-reported exposure to chemicals or solvents (odds ratio [OR] = 4.6, 95 percent confidence interval [CI] = 1.9-11.3) and OR = 2.2, CI = 1.1-4.7 for maternal and paternal exposure, respectively) and plastic or resin fumes (OR = 12.0, CI = 1.9-75.0 [maternal] and OR = 2.5, CI = 1.0-6.5 [paternal]) were associated with elevated risk of MGCT. New findings, not reported previously, include a positive relationship of MGCT risk with birthweight and prolonged breastfeeding, an inverse association between MGCT risk and number of cigarettes smoked by the mother during pregnancy, and a 3.1-fold increased risk (CI = 1.5-6.6) associated with maternal urinary infections during index pregnancy. Although these findings need confirmation from future studies, they suggest a potential influence of in utero exposure to maternal endogenous hormones, parental environmental exposures, and maternal diseases during pregnancy in the development of childhood MGCT.

Shu XO, Perentesis JP, Wen W, Buckley JD, Boyle E , Ross JA, Robison LL. 2004. Parental exposure to medications and hydrocarbons and *ras* mutations in children with acute lymphoblastic leukemia: A report from the Children's Oncology Group. Cancer Epidemiology Biomarkers & Prevention 13:1230-1235.
Abstract: Ras proto-oncogene mutations have been implicated in the pathogenesis of many malignancies, including leukemia. While both human and animal studies have linked several chemical carcinogens to specific ras mutations, little data exist regarding the association of ras mutations with parental exposures and risk of childhood leukemia. Using data from a large case-control study of childhood acute lymphoblastic leukemia (ALL; age <15 years) conducted by the Children's Cancer Group, we used a case-case comparison approach to examine whether reported parental exposure to hydrocarbons at work or use of specific medications are related to ras gene mutations in the leukemia cells of children with ALL. DNA was extracted from archived bone marrow slides or cryopreserved marrow samples for 837 ALL cases. We examined mutations in K-ras and N-ras genes at codons 12, 13, and 61 by PCR and allele-specific oligonucleotide hybridization and confirmed them by DNA sequencing. We interviewed mothers and, if available, fathers by telephone to collect exposure information. Odds ratios (ORs) and 95% confidence intervals (CIs) were derived from logistic regression to examine the association of parental exposures with ras mutations. A total of 127 (15.2%) cases had ras mutations (K-ras 4.7% and N-ras 10.68%). Both maternal (OR 3.2, 95% CI 1.7-6.1) and paternal (OR 2.0, 95% CI 1.1-3.7) reported use of mind-altering drugs were associated with N-ras mutations. Paternal use of amphetamines or diet pills was associated with N-ras mutations (OR 4.1, 95% CI 1.1-15.0); no association was observed with maternal use. Maternal exposure to solvents (OR 3.1, 95% CI 1.0-9.7) and plastic materials (OR 6.9, 95% CI 1.2-39.7) during pregnancy and plastic materials after pregnancy (OR 8.3, 95% CI 1.4-48.8) were related to K-ras mutation. Maternal ever exposure to oil and coal products before case diagnosis (OR 2.3, 95% CI 1.1-4.8) and during the postnatal period (OR 2.2, 95% CI 1.0-5.5) and paternal exposure to plastic materials before index pregnancy (OR 2.4, 95% CI 1.1-5.1) and other hydrocarbons during the postnatal period (OR 1.8, 95% CI 1.0-1.3) were associated with N-ras mutations. This study suggests that parental exposure to specific chemicals may be associated with distinct ras mutations in children who develop ALL.

Shu XO, Potter JD, Linet MS, Severson RK, Han DH , Kersey JH, Neglia JP, Trigg ME, Robison LL. 2002. Diagnostic X-rays and ultrasound exposure and risk of childhood acute lymphoblastic leukemia by immunophenotype. Cancer Epidemiology Biomarkers & Prevention 11:177-185.
Abstract: The objective of this study was to evaluate the association between in utero diagnostic X-rays and childhood acute lymphoblastic leukemia (ALL) and the less well-studied relationship of this malignancy to preconception and postnatal diagnostic X-rays or fetal ultrasound exposures. The Children's Cancer Group conducted a case-control study including interviews with parents of 1842 ALL cases diagnosed under the

age of 15 years and 1986 individually matched controls. Associations of self-reported parental preconception, in utero, and postnatal X-ray exposure with risk of childhood ALL were examined using odds ratios (ORs) and corresponding 95% confidence intervals (CIS) obtained from logistic regression models among the overall group of ALL cases as well as immunophenotypic and age-specific subgroups. Overall, in utero pelvimetric diagnostic X-rays were not associated with the risk of pediatric ALL (OR, 1.2; 95% Cl, 0.8-1.7). Childhood ALL, all types combined (OR, 1.1; 95% CI, 0.9-1.2) and specific types were also not linked with postnatal diagnostic X-ray exposures. Neither maternal (OR, 0.9; 95% CI, 0.8-1.2) nor paternal (OR, 1.1; 95% CI, 0.8-1.4) lower abdominal preconception diagnostic X-rays were associated with risk of childhood ALL. Among the multiple comparisons for age-, sex-, and subtype-specific subgroups, we observed an elevated risk of total ALL among children ages 11-14 at diagnosis (OR, 2.4; 95% CI, 1.1-5.0) in relation to in utero pelvimetric diagnostic X-ray exposures and a small increase in pre-B ALL for all ages combined (OR, 1.7; 95% CI, 1.1-2.7) in relation to postnatal diagnostic Xrays. In utero diagnostic ultrasound tests were not linked with risk of childhood ALL. We found little consistent evidence that in utero diagnostic ultrasound tests or X-rays were linked with an increased risk of childhood ALL. Small increases in total or pre-B ALL risks for children in selected age groups to very low ionizing radiation exposures from postnatal or preconception diagnostic X-ray exposures may represent chance findings or biases. Future studies of diagnostic X-rays and childhood leukemia in the United States will require extensive additional efforts and resources to quantify risk because of declining in utero exposures in the general population (thus necessitating large numbers of subjects, particularly cases) and the difficulty in validating reported exposures.

Shu XO, Ross JA, Pendergrass TW, Reaman GH, Lampkin B, Robison LL. 1996 . Parental alcohol consumption, cigarette smoking, and risk of infant leukemia: A Childrens Cancer Group study. J Natl Cancer Inst 88: 24-31.

Abstract: BACKGROUND: Whether parental drinking and smoking during pregnancy are associated with an increased risk of cancer in offspring is controversial. There are some indications that maternal alcohol consumption is associated with an elevated risk of acute myeloid leukemia (AML) appearing in very young children. Evidence for an association between maternal smoking during pregnancy and risk of leukemia in offspring has been inconsistent. PURPOSE: Using data from a Children's Cancer Group case-control study, we evaluated relationships between infant leukemia risk and parental alcohol consumption and/or cigarette smoking during pregnancy or during the month prior to it. METHODS: Three hundred two leukemia cases (203 acute lymphoid leukemias [ALLs], 88 AMLs, and 11 other leukemia types) diagnosed in children at 18 months of age or younger and 558 individually matched, regional (i.e., same telephone area code and exchange number) controls were included in the analysis. Information concerning parental alcohol consumption and smoking behavior during the index pregnancy and during the month prior to it was collected by telephone interviews with the mothers of all case and control subjects and the fathers of 250 case and 361 control subjects. Odds ratios (ORs) were used to measure the risk of infant leukemia associated with parental smoking and drinking; tests for trend were used to assess dose-response relationships. The data were analyzed further after stratifying the leukemia cases according to histologic and morphologic types. Reported P values are from two-sided tests of statistical significance. RESULTS: Maternal drinking during pregnancy (compared with not drinking) was associated with ORs of 1.43 (95%) confidence interval [CI] = 1.00-2.04) for ALL and 2.64 (95% CI = 1.36-5.06) for AML. A dose-response relationship was observed for total maternal alcohol consumption during pregnancy and risk of AML ($P < .01$). Alcohol-related risk appeared to be most pronounced for children who developed AML with a morphology of M1 (myeloblastic with minimal maturation) or M2 (myeloblastic with maturation (OR = 7.62; 95% CI = 2.03-28.64). Paternal alcohol consumption did not confer an increased risk of infant leukemia. Maternal smoking during pregnancy (compared with not smoking) was negatively associated with infant leukemia risk (OR = 0.66 and 95% CI = 0.46-0.94 for total leukemia; OR = 0.45 and 95% CI = 0.21-0.96 for AML), whereas paternal smoking 1 month prior to pregnancy (compared with not smoking during the same period) was related to an elevated risk of ALL (OR = 1.56; 95% CI = 1.03-2.36). CONCLUSIONS: Maternal alcohol consumption during pregnancy increases the risk of infant leukemia, especially AML. Maternal smoking, however, does not elevate risk for either AML or ALL. IMPLICATIONS: The data suggest that in utero exposure to alcohol may contribute to leukemogenesis involving myeloid cells.

Shukla Y, Arora A. 2001. Transplacental carcinogenic potential of the carbamate fungicide mancozeb. J Environ

Pathol Toxicol Oncol 20:127-131.
Abstract: We evaluated the effects of mancozeb (Dithane M4-5), a protective carbamate fungicide, on transplacental carcinogenesis in Swiss albino mice. Mancozeb, a polymeric complex of ethylene bis (dithiocarbamate) manganese with zinc salt, is reported to possess carcinogenic and cocarcinogenic activity in various tumor models. In the present study, pregnant Swiss albino mice were administered mancozeb intraperitoneally on the 14th day of gestation. The first filial generation (F1 progeny) was promoted with a well-known tumor promoter 12-o-tetradecanoyl phorbol-13-acetate (TPA). The results revealed a significantly high tumor incidence (72%) in the F1 progeny of the animals initiated with mancozeb or a well known carcinogen 7,12-dimethyl benzanthracene (DMBA) and promoted with TPA in comparison to animals that were either from mothers given only the vehicle (DMSO) and promoted with TPA in F1 progeny or not promoted with TPA in F1 progeny. No significantly higher tumor incidence was observed in any other experimental groups. These results suggest that mancozeb or its metabolites are capable of crossing the placental barrier and can exert DNA damage and tumor initiating consequences in the fetal cells that, after promotion with TPA, get converted into neoplastic cells.

Sithanandam G, Ramakrishna G, Diwan BA, Anderson LM. 1998. Selective mutation of K-ras by N-ethylnitrosourea shifts from codon 12 to codon 61 during fetal mouse lung maturation. Oncogene 17:493-502.
Abstract: Fetal mouse lung before gestation day 17 shows unique sensitivity to causation of rapidly growing tumors by N-ethylnitrosourea (ENU). Since mouse lung tumors present a mutated K-ras oncogene, we hypothesized that this special susceptibility might reflect an unusual vulnerability of the K-ras gene. Of the lung tumors caused by ENU exposure of BALB/c mice on gestation day 14, 8/25 had a codon 12 mutation in K-ras, vs 4/25 in codon 61, Of 15 tumors after day 16 exposure, three had codon 12 and four codon 61 changes. Tumors from day 18 exposure had only codon 61 mutations (11/16), all A:T to G:C changes (CGA), By contrast, codon 12 (GGT) changes included G:C to T:A, to A:T,and to C:G, These results show significant ($P<0.01$) shift in the sensitivity of particular K-ras codons to ENU mutation, during fetal mouse lung maturation. In a test of a possible relationship to expression of K-ras, K-ras p21 was measured in lungs of fetal mice, and found to increase markedly on day 18 in comparison to days 14 and 16, Both alkylation of DIVA and base damage due to reactive oxygen species are postulated as mechanisms for mutation by ENU, whose efficacies vary with state of fetal lung maturation and K-rns expression.

Skakkebaek NE, Berthelsen JG, Giwercman A, Muller J. 1987. Carcinoma-in-situ of the testis: Possible origin from gonocytes and precursor of all types of germ cell tumours except spermatocytoma. Int J Androl 10: 19-28.
Abstract: Based on evidence from morphological and histochemical studies and from clinical experience, the following hypotheses are proposed: carcinoma-in-situ (CIS) germ cells are malignant gonocytes; these CIS gonocytes have some capacity to regress into more primitive, totipotent embryonic cells which can give rise to all types of nonseminomatous germ cell tumours; the tumour germ cells of classical seminomas are malignant gonocytes derived from CIS gonocytes which have lost their ability to regress into totipotent embryonic cells; the ability of CIS gonocytes to regress into totipotent embryonic cells decreases with age, whereas the capacity to form classical seminoma cells is preserved; the transformation of CIS gonocytes into invasive tumours is dependent on factors such as gonadotrophins and/or testicular steroids; the pathogenesis of classical and spermatocytic seminoma are unrelated. As a consequence of these hypotheses an alternative nomenclature for carcinoma-in-situ, seminoma and dysgerminoma is suggested.

Slikker W, Mei N, Chen T. 2004. N-ethyl-N-nitrosourea (ENU) increased brain mutations in prenatal and neonatal mice but not in the adults. Toxicol Sci 81:112-120.
Abstract: The incidence of childhood cancer is increasing. One of the most common cancers for children under 15 years of age, gliomas for example, has been reported to have increased in incidence over the last 20 years by approximately 40%. The rising trend of childhood cancer in brain may be associated with environmental exposure to genotoxins and susceptibility to mutation in early development. To investigate age-dependent mutagenic sensitivity of brain tissue to genotoxins, the Big Blue mouse model was utilized in this study. Groups of five male mice were treated with a single dose of 120 mg/kg ENU transplacentally at three days before birth (prenatal), eight days (neonate) or eighteen weeks (adult) after birth. The animals were sacrificed six weeks after the treatment. The mutant frequencies and types of mutations in the brain cII gene from ENU-treated and concurrent control mice were determined. A significant increase in mutant frequencies over control was found in the prenatal and neonatal groups whereas there was no significant

difference between the adult group and its control. Molecular analysis of the mutants also indicated that the mutational spectra from the ENU-treated mice were age-dependent. The percentage of A:T-->T:A transversion, the typical type of mutation induced by ENU, was inversely related to the treatment age, whereas G:C-->A:T transition was the main type of mutation in the adult group, the same as the control. These results demonstrate a differential mutagenic effect of ENU on the mouse brain depending on the stages of development and suggest an enhanced susceptibility of brain cancer hazard for perinatal exposure to genotoxicants.

Sonnenschein C, Soto AM. 2005. Are times a' changin' in carcinogenesis? Endocrinology 146: 11-12.

Sotnichenko AI, Severin SE, Posypanova GA, Feldman NB, Grigor'ev MI, Severin ES, Petrov RV. 1999. Water-soluble 2,3,7,8-tetrachlorodibenzo-p-dioxin complex with human alpha-fetoprotein: Properties, toxicity in vivo and antitumor activity in vitro. FEBS Lett 450:49-51.
Abstract: The conditions for the formation of a non-covalent complex between 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and the human transport fetal protein, alpha-fetoprotein (AFP), have been studied. TCDD has been shown to form a stable complex with AFP in a 2:1 (TCDD:AFP) ratio. The apparent solubility of TCDD in mater increases 10(5)-fold after complex formation. The toxicity of the TCDD:AFP complex injected into mice by the intravenous route is comparable with that of free TCDD administered in oil solution per os, The complex manifests very much higher toxicity (200-1400 times) against human tumor cells (CEM, MCF-7, HepG2) in vitro and surpasses TCDD in selectivity. AFP may facilitate TCDD transport in embryonic tissues and enhance its embryotoxic and teratogenic effects. (C) 1999 Federation of European Biochemical Societies.

Soto AM, Sonnenschein C. 2004. The somatic mutation theory of cancer: growing problems with the paradigm? Bioessays 26:1097-1107.
Abstract: The somatic mutation theory has been the prevailing paradigm in cancer research for the last 50 years. Its premises are: (1) cancer is derived from a single somatic cell that has accumulated multiple DNA mutations, (2) the default state of cell proliferation in metazoa is quiescence, and (3) cancer is a disease of cell proliferation caused by mutations in genes that control proliferation and the cell cycle. From this compelling simplicity, an increasingly complicated picture has emerged as more than 100 oncogenes and 30 tumor suppressor genes have been identified. To accommodate this complexity, additional ad hoc explanations have been postulated. After a critical review of the data gathered from this perspective, an alternative research program has been proposed. It is based on the tissue organization field theory, the premises of which are that carcinogenesis represents a problem of tissue organization, comparable to organogenesis, and that proliferation is the default state of all cells. The merits of these competing theories are evaluated herein.

Spector LG, Davies SM, Robison LL, Hilden JM, Roesler M, Ross JA. 2007. Birth characteristics, maternal reproductive history, and the risk of infant leukemia: A report from the Children's Oncology Group. Cancer Epidemiology Biomarkers & Prevention 16:128-134.
Abstract: Leukemias with MLL gene rearrangements predominate in infants (< 1 year of age), but not in older children, and may have a distinct etiology. High birth weight, higher birth order, and prior fetal loss have, with varying consistency, been associated with infant leukemia, but no studies have reported results with respect to MLL status. Here, we report for the first time such an analysis. During 1999 to 2003, mothers of 240 incident cases (113 MLL+, 80 MLL-, and 47 indeterminate) and 255 random digit dialed controls completed a telephone interview. Odds ratios and 95% confidence intervals for quartile of birth weight, birth order, gestational age, maternal age at delivery, prior fetal loss, pre-pregnancy body mass index, and weight gain during pregnancy were obtained using unconditional logistic regression; P for linear trend was obtained by modeling continuous variables. There was a borderline significant linear trend of increasing birth weight with MLL+ (P = 0.06), but not MLL- (P = 0.93), infant leukemia. Increasing birth order showed a significant inverse linear trend, independent of birth weight, with MLL+ (P = 0.01), but not MLL- (P = 0.18), infant leukemia. Other variables of interest were not notably associated with infant leukemia regardless of MLL status. This investigation further supports the contention that molecularly defined subtypes of infant leukemia have separate etiologies.

Spector LG, Xie Y, Robison LL, Heerema NA, Hilden JM, Lange B, Felix CA, Davies SM, Slavin J, Potter JD,

Blair CK, Reaman GH, Ross JA. 2005. Maternal diet and infant leukemia: The DNA topoisomerase II inhibitor hypothesis: A report from the Children's Oncology Group. Cancer Epidemiology Biomarkers & Prevention 14:651-655.
Abstract: Background: The MLL 11q23 translocation arises in utero and is present in 75% of infant leukemias. That MLL+ acute myeloid leukemia (AML) can arise following chemotherapy with DNA topoisomerase 11 (DNAt2) inhibitors suggests that these substances, which also occur naturally in foods, may contribute toward infant leukemia. We hypothesized that maternal consumption of dietary DNAt2 inhibitors during pregnancy would increase the risk of infant leukemia, particularly AML(MLL+). Methods: This Children's Oncology Group case-control study consisted of 240 incident cases of infant acute leukemia [AML and acute lymphoblastic leukemia (ALL)] diagnosed during 1996 to 2002 and 255 random digit dialed controls. Maternal diet during pregnancy was determined through a food frequency questionnaire. An index of specific foods identified a priori to contain DNAt2 inhibitors as well as vegetables and fruits were created and analyzed using unconditional logistic regression. Results: There was little evidence of an association between the specific DNAt2 index and leukemia overall and by subtype. An exception was AML(MLL+); odds ratios (95% confidence intervals) comparing the second to fourth quartiles to the first were 1.9 (0.5-7.0), 2.1 (0.6-7.7), and 3.2 (0.9-11.9), respectively (P for trend = 0.10). For the vegetable and fruit index, there were significant or near-significant inverse linear trends for all leukemias combined, ALL(MLL+), and AML(MLL-). Conclusion: Overall, maternal consumption of fresh vegetables and fruits during pregnancy was associated with a decreased risk of infant leukemia, particularly MLL+. However, for AML(MLL+) cases, maternal consumption of specific DNAt2 inhibitors seemed to increase risk. Although based on small numbers, these data provide some support for distinct etiologic pathways in infant leukemia.

Spitz MR, Johnson CC. 1985. Neuroblastoma and paternal occupation. A case-control analysis. Am J Epidemiol 121:924-929.
Abstract: The peak incidence of neuroblastoma during early infancy suggests that prezygotic or prenatal exposures to carcinogens could be implicated. Several recent epidemiologic studies have suggested an association between parental exposure to petrochemicals and ionizing radiation and the development of cancer in the offspring. This paper is a population-based case-control analysis of the birth certificate data of 157 children who died in Texas from neuroblastoma in 1964-1978 and 314 controls randomly selected from all live births in Texas. Children of fathers employed in occupations with electromagnetic field exposure were at significantly increased risk (odds ratio = 2.13). The odds ratio was 11.75 for children of fathers who reported themselves to be electronics workers (6 cases, 1 control).

Starr JR, Hsu L, Schwartz SM. 2005. Performance of the Log-Linear Approach to Case-Parent Triad Data for Assessing Maternal Genetic Associations With Offspring Disease: Type I Error, Power, and Bias. Am J Epidemiol 161:196-204.
Abstract: Maternal genetic variation may serve as a biomarker in studies aimed at clarifying fetal determinants of infant or adult disease. The log-linear approach to case-parent triad data (LCPT) can be used to investigate maternal genetic polymorphisms in relation to offspring disease risk, but LCPT operating characteristics have been reported for only a limited range of situations. The authors performed a simulation study to investigate the performance of the LCPT for assessing maternal associations with offspring disease risk over a wide range of scenarios with varying sample sizes (n), high-risk allele frequencies (f), and modes of inheritance, all of which greatly affect the expected number of triads in informative categories. For most f values less than 0.5, the LCPT approach with 200 triads allowed for approximately 80% power to detect valid, unbiased maternal relative risks of 2 when inheritance was log-additive or dominant. When inheritance was recessive, this was true for most f 's greater than 0.35. Outside of this range, however, power and bias depended greatly on the mode of inheritance, f, and n. On the basis of these findings, epidemiologists may consider the LCPT a useful approach for assessing maternal relative risks unless one expects a very rare or fairly common maternal allele to increase offspring disease risk.

Stavola BL, Hardy R, Kuh D, Silva IS, Wadsworth M, Swerdlow AJ. 2000. Birthweight, childhood growth and risk of breast cancer in a British cohort. Br J Cancer 83:964-968.
Abstract: We have examined the relationship between birthweight and risk of breast cancer, taking into account growth in childhood, using data on a total of 2221 women born in 1946 and followed up to 1997. Thirty-seven breast cancers occurred during follow-up. There was evidence of greater risk of breast cancer

with greater birthweight (rate ratio = 1.76 (95% CI: 0.92, 3.35) for birthweight >/= 3.5 kg vs birthweight < 3.5 kg), which was more marked at pre-menopausal ages (RR = 2.31, 95% CI: 0.93, 5.74). The relation with birthweight was not substantially confounded by any of the measured adult risk factors. A significant interaction was observed between the effects of birthweight and height at age 7 years. Relative to those born lighter than 3.5 kg, women who were heavy at birth (>/= 3.5 kg) and short or average at 7 years (< 1.22 m) had a 21% increase in breast cancer rates (RR = 1.21; 95% CI = 0.49-2.99), while women who were heavy at birth (>/= 3.5 kg) but tall at 7 years (>/= 1.22 m) had a four-fold increase (RR = 4.01; 95% CI = 1.82-8.83). These results suggest that the effect of birthweight on breast cancer risk may be modulated by childhood growth.

Steffen C, Auclerc MF, Auvrignon A, Baruchel A, Kebaili K, Lambilliotte A, Leverger G, Sommelet D, Vilmer E, Hemon D, Clavel J. 2004. Acute childhood leukaemia and environmental exposure to potential sources of benzene and other hydrocarbons; A case-control study. Occupational & Environmental Medicine 61:773-778.

Abstract: Aim: To analyse the association between potential environmental exposure to hydrocarbons and the risk of acute childhood leukaemia. Methods: A hospital based multicentre case control study, stratified on centre, age, and sex, with 280 leukaemia cases and 285 controls was carried out. Data were collected by a standardised interview of the mothers. Results: No clear association was seen between maternal occupational exposure to hydrocarbons during pregnancy and leukaemia, or between residential traffic density and leukaemia. There was an association between dwellings neighbouring a petrol station or a repair garage during childhood and the risk of childhood leukaemia (OR 4.0, 95% CI 1.5 to 10.3), with a duration trend. The association, which appeared particularly strong for acute non-lymphocytic leukaemia (OR 7.7, 95% CI 1.7 to 34.3), was not altered by adjustment for potential confounding factors. Conclusions: Results showed an association between acute childhood leukaemia and dwellings neighbouring auto repair garages and petrol stations, which are benzene emitting sources. These findings could be due to chance, although the strength of the association and the duration trend are arguments for a causal association.

Steiner M, Burkart W, Grosche B, Kaletsch U, Michaelis J. 1998. Trends in infant leukaemia in West Germany in relation to in utero exposure due to the Chernobyl accident. Radiation & Environmental Biophysics 37:87-93.

Abstract: A temporary increase in the incidence of infant leukaemia in Greece was reported by Petridou et al., which was attributed to in utero exposure to ionising radiation resulting from the Chernobyl accident. We performed a similar analysis based on the data of the German Childhood Cancer Registry in order to check whether the observation could be confirmed by means of independent data. Applying the same definitions as Petridou et al., we also observed an increased incidence of infant leukaemia in a cohort of children born after the Chernobyl accident. More detailed analyses, regarding areas with different contamination levels and dose rate gradients over time after the accident, showed, however, no clear trend with regard to exposure. It would therefore appear less likely that the observed effect was caused by exposure to ionising radiation due to the Chernobyl accident.

Stevens RG, Hilakivi-Clarke L. 2001. Alcohol exposure in utero and breast cancer risk later in life. Alcohol & Alcoholism 36:276-277.

Storgaard L, Bonde JP, Olsen J. 2006. Male reproductive disorders in humans and prenatal indicators of estrogen exposure. A review of published epidemiological studies. Reprod Toxicol 21:4-15.

Abstract: Male reproductive disorders in humans and prenatal indicators of estrogen exposure. A review of published epidemiological studies. Reports of an increase in male reproductive disorders in several countries led to the hypothesis that estrogens during fetal life may cause reduced sperm counts, cryptorchidism, hypospadias and testicular cancer. So far the hypothesis is based on animal studies and reports from the wild life. We systematically searched the epidemiological literature for evidence linking indicators of prenatal serum levels of maternal estrogens with sperm density, hypospadias, cryptorchidism and testicular cancer in humans. Indicators of fetal estrogen exposure included direct measurements, recorded intake of hormones (diethylstilbestrol (DES), oral contraceptives (OCs) and estrogens), pregnancy conditions with known deviant estrogen level as for instance twin pregnancies and some environmental exposures. Among 425 papers we reviewed 81 publications with appropriate information. With the possible exception of testicular cancer there is no strong epidemiological evidence to indicate that prenatal exposure

to estrogen are linked to disturbed development of the male reproductive organs.

Stover PJ, Garza C. 2006. Nutrition and developmental biology - Implications for public health. Nutr Rev 64:S60-S71.
Abstract: Recent advances in understanding genome-nutrient and nutrient-network interactions, and the modifying effects of genetic variation on their function, have strengthened interests in acute and long-lasting diet/nutrition influences on health. Relationships between early and mid-gestational and perinatal conditions (including those related to maternal nutrition) and outcomes, and later-onset chronic diseases have received particular attention. Controlled animal experiments support views that responses with long-lasting effects to nutritional milieus are enabled by epigenetic and other metabolic adjustments during critical windows. Thus, underlying mechanisms are beginning to be understood. For example, chromatin remodeling during development can alter gene expression levels, fix or determine future set points critical to intra- and inter-organ communication networks, alter morphogenesis, initiate remodeling events, etc., all with lifelong consequences. These also may affect DNA mutation rates and thereby influence adult cancer and other risks. There is increasing evidence that nutrient-based strategies will be of value to the prevention or delay of onset of chronic diseases and that these strategies may require initiation during embryonic or fetal stages of development to achieve maximal benefit.

Strohsnitter WC, Noller KL, Hoover RN, Robboy SJ, Palmer JR, Titus-Ernstoff L, Kaufman RH, Adam E, Herbst AL, Hatch EE. 2001. Cancer risk in men exposed in utero to diethylstilbestrol. J Natl Cancer Inst 93:545-551.
Abstract: BACKGROUND: An association between prenatal diethylstilbestrol (DES) exposure and cancer in men, especially testicular cancer, has been suspected, but findings from case-control studies have been inconsistent. This study was conducted to investigate the association between prenatal DES exposure and cancer risk in men via prospective follow-up. METHODS: A total of 3613 men whose prenatal DES exposure status was known were followed from 1978 through 1994. The overall and site-specific cancer incidence rates among the DES-exposed men were compared with those of the unexposed men in the study and with population-based rates. The relative rate (RR) was used to assess the strength of the association between prenatal DES exposure and cancer development. All statistical tests were two-sided. RESULTS: Overall cancer rates among DES-exposed men were similar to those among unexposed men (RR = 1.07; 95% confidence interval [CI] = 0.58 to 1.96) and to national rates (RR = 0.99; 95% CI = 0.65 to 1.44). Testicular cancer may be elevated among DES-exposed men, since the RRs for testicular cancer were 3.05 (95% CI = 0.65 to 22.0) times those of unexposed men in the study and 2.04 (95% CI = 0.82 to 4.20) times those of males in the population-based rates. The higher rate of testicular cancer in the DES-exposed men is, however, also compatible with a chance observation. CONCLUSIONS: To date, men exposed to DES in utero do not appear to have an increased risk of most cancers. It remains uncertain, however, whether prenatal DES exposure is associated with testicular cancer.

Sukumar S, Barbacid M. 1990. Specific patterns of oncogene activation in transplacentally induced tumors. Proc Natl Acad Sci U S A 87:718-722.
Abstract: Transplacental exposure of rats to a single dose of the direct acting carcinogen methylnitrosourea (MNU) results in the induction of a variety of neoplasias of neuroectodermal, epithelial, and mesenchymal origin. Molecular analysis of the oncogenes present in these tumors revealed a striking degree of tissue specificity. neu oncogenes were found to be reproducibly activated in tumors derived from the peripheral nervous system (PNS), but not in those arising from the central nervous system (CNS). No ras oncogenes were found in either PNS- or CNS-derived tumors. However, Ha-ras oncogenes were detected in each of three mammary carcinomas and Ki-ras oncogenes were present in each of five kidney mesenchymal tumors. These results illustrate that phenotypic expression of activated oncogenes in vivo is not a random process and suggest that normal developmental programs may play an important role in modulating the activation of specific oncogenes by chemical carcinogens. PCR analysis revealed that each of the ras oncogenes detected in these transplacentally induced tumors became activated by the same G----A transition in the second base of codon 12. Since G----A transitions are the preferred mutations induced by MNU, it is likely that these ras oncogenes may have been directly targeted by MNU during embryonic development.

Suzumiya J, Takeshita M, Kimura N, Kikuchi M, Uchida T, Hisano S, Eura Y, Kozuru M, Nomura Y, Tomita K.

1994 . Expression of adult and fetal natural killer cell markers in sinonasal lymphomas. Blood 83:2255-2260.
Abstract: The majority of sinonasal non-Hodgkin's lymphomas (NHLs) are thought to originate from T-cell lineage. However, they often express natural killer (NK)-cell markers so that their origin still remains obscure. In this study, cell type of sinonasal NHLs were characterized by immunohistochemical and Southern blot analyses. We examined nine patients with sinonasal NHL. Six patients with tonsillar or pharyngeal non-B-cell lymphomas served as a control group. Immunohistochemical study showed that all nine cases of sinonasal NHL were CD56+CD2+, whereas controls were CD56-CD2+. According to the rearrangement of T-cell receptors (TCRs) and expression of CD3 markers, the sinonasal NHL cases were classified into three groups: TCR-CD56(Leu-19)+CD3(Leu4)- NHL (three patients), TCR-CD56+CD3+ NHL (five patients), and TCR+CD56+CD3+ NHL (one patient). In contrast, control patients' NHLs were TCR+CD56-CD3+. These results imply that eight cases of TCR-CD56+ sinonasal NHL are of NK-cell lineage. Among these eight cases, TCR-CD56+CD3+ cases (five of eight patients) were rather similar to the phenotype of fetal NK cells. From these results, the majority of sinonasal NHLs seem to originate from varying maturation stages of NK-cell lineage.

Swan SH. 2000. Intrauterine exposure to diethylstilbestrol: Long-term effects in humans. APMIS 108:793-804.
Abstract: DES is the most carefully scrutinized EDC and its history provides valuable insights into the current evaluation of less well-studied EDCs. This review summarizes the health effects of prenatal exposure to diethylstilbestrol (DES) and emphasizes the role of DES as the first endocrine disrupting chemical (EDC). Vaginal clear cell adenocarcinoma (CCAC), the most severe consequence of prenatal exposure to DES, affected only 0.1% of exposed females, while the far more prevalent teratogenic and reproductive effects of DES were only discovered when DES daughter were screened for CCAC. Initial studies, conducted before most DES daughters had tried to conceive, examined vaginal cancer and vaginal, cervical and uterine abnormalities. Subsequently, several controlled studies demonstrated the increased risk of adverse reproductive outcomes in DES daughters. While most DES daughters can eventually experience a live birth, this is less likely in women with genital tract abnormalities, in whom there is a two-thirds chance that each pregnancy will be unsuccessful. In DES sons, who have been far less studied, results suggest male reproductive toxicity, but are less consistent. The importance of dose and gestational age at initial exposure are discussed, and the implications of DES findings for the evaluation of risks from current EDCs emphasized.

Swerdlow AJ, De Stavola BL, Swanwick MA, Maconochie NE. 1997. Risks of breast and testicular cancers in young adult twins in England and Wales: Evidence on prenatal and genetic aetiology. Lancet 350:1723-1728.
Abstract: BACKGROUND: Aetiology of breast and testicular cancers may have prenatal factors, possibly exposure of the fetus to high concentrations of maternal oestrogen. Dizygotic twinning probably involves high hormone concentrations, and therefore, dizygotic twins might be at raised risk of these cancers. The aetiologies of breast and testicular cancers have genetic components, for breast cancer, especially at younger ages. Twins of these probands may, therefore, be at high risk. We investigated risk in twins of patients with breast cancer at young ages or with testicular cancer. METHODS: We identified twins with breast cancer incident at ages younger than 45 years and with incident testicular cancer in England and Wales during 1971-89 by cross-matching national cancer-registration and births records. We determined zygosity by questionnaires to the patients. The twins of probands were followed up for cancer incidence and death. We analysed risks of breast and testicular cancer in dizygotic twins compared with monozygotic twins, and in monozygotic and dizygotic twins of probands. FINDINGS: We identified 500 twins with breast cancer and 194 with testicular cancer. We found a non-significantly raised risk of breast cancer in dizygotic compared with monozygotic twins younger than 30 years (odds ratio 2.3 [95% CI 0.9-5.9]) but not older. The overall risk of testicular cancer was significantly higher in dizygotic twins than in monozygotic twins (1.5 [1.1-2.2]) consequent on a risk for seminomas was high (3.2 [1.6-6.5]; $p = 0.001$). Risk of breast cancer was significantly raised in female twins of probands (standardised incidence ratio 7.7 [4.9-12.2], $p < 0.001$). The relative risk of breast cancer was 34.7 (9.5-126.5) in monozygotic twins of women in whom breast cancer had occurred before age 35 years. The cumulative risk of breast cancer for these twins by age 40 years was 29% (13-56). The relative risk of testicular cancer was 37.5 (12.3-115.6) in twins of men with testicular cancer. The cumulative risk by age 40 years in monozygotic twins of men with testicular cancer was 14% (4-46). INTERPRETATION: The higher risks of these cancers in dizygotic than

in monozygotic twins support a prenatal aetiology, and are compatible with aetiology related to raised maternal concentrations of free, unbound oestrogens. The results for twins of probands have implications for genetic aetiology; appropriate clinical action for monozygotic twins needs consideration.

Swerdlow AJ, Huttly SR, Smith PG. 1987 . Prenatal and familial associations of testicular cancer. Br J Cancer 55:571-577.
Abstract: In a case-control study of testis cancer 259 cases with testicular cancer, 238 controls treated at radiotherapy centres and 251 non-radiotherapy hospital in-patient controls were interviewed about some possible prenatal and familial risk factors for the tumour. For firstborn men, the risk of testis cancer increased significantly according to maternal age at the subject's birth, and this effect was most marked for seminoma. The association with maternal age was not apparent for cases other than firstborn. The risk of testis cancer was also significantly raised for men from small sibships and of early birth order. These results accord with the theory that raised maternal levels of available oestrogen during the early part of pregnancy are aetiological for testicular cancer in the son, although other explanations are possible; there is evidence that seminoma risk may particularly be affected.

Swerdlow AJ, Stiller CA, Wilson LMK. 1982. Prenatal factors in the aetiology of testicular cancer: an epidemiological study of childhood testicular cancer deaths in Great Britain, 1953-73. Journal of Epidemiology & Community Health 36:96-101.
Abstract: A case-control study is reported based on 87 deaths from testicular cancer that occurred in children in Great Britain 1953-73. Factors that significantly increased relative risk were tuberculosis of the mother during the index pregnancy and maternal epilepsy; factors that increased risk but not significantly were hyperemesis in the index pregnancy, a maternal history of stillbirths, and hernia and genitourinary defects in the child. Cryptorchidism was not studied. The available evidence suggests that prenatal determinants of testicular cancer in adults are also determinants of testicular cancer in childhood. The incidence and mortality from this disease are not increasing among children in Britain and other countries, whereas there is an increasing trend in young adults in several developed countries. Probably, therefore, the secular increase in the rates of young adult testicular cancer is due to factors that affect adults but not children, the hence are likely to be postnatal.

Syddall HE, Sayer AA, Simmonds SJ, Osmond C, Cox V, Dennison EM, Barker DJP, Cooper C. 2005. Birth Weight, Infant Weight Gain, and Cause-Specific Mortality - the Hertfordshire Cohort Study. Am J Epidemiol 161:1074-1080.
Abstract: Low birth weight, a marker of adverse intrauterine circumstances, is known to be associated with a range of disease outcomes in later life, including coronary heart disease, hypertension, type 2 diabetes, and osteoporosis. However, it may also decrease the risk of other common conditions, most notably neoplastic disease. The authors describe the associations between birth weight, infant weight gain, and a range of mortality outcomes in the Hertfordshire Cohort. This study included 37,615 men and women born in Hertfordshire, United Kingdom, in 1911-1939; 7,916 had died by the end of 1999. For men, lower birth weight was associated with increased risk of mortality from circulatory disease (hazard ratio per standard deviation decrease in birth weight = 1.08, 95% confidence interval: 1.04, 1.11) and from accidental falls but with decreased risk of mortality from cancer (hazard ratio per standard deviation decrease in birth weight = 0.94, 95% confidence interval: 0.90, 0.98). For women, lower birth weight was associated with a significantly ($p < 0.05$) increased risk of mortality from circulatory and musculoskeletal disease, pneumonia, injury, and diabetes. Overall, a one-standard-deviation increase in birth weight reduced all-cause mortality risk by age 75 years by 0.86% for both men and women.

Takahashi M, Barrett JC, Tsutsui T. 2002. Transformation by inorganic arsenic compounds of normal Syrian hamster embryo cells into a neoplastic state in which they become anchorage-independent and cause tumors in newborn hamsters. Int J Cancer 99:629-634.
Abstract: Arsenic is a known human carcinogen, but little evidence exists for its carcinogenicity in animals. In order to investigate the ability of inorganic arsenics to transform normal cells into a neoplastic state, mass cultures of normal, diploid Syrian hamster embryo (SHE) cells exposed to various concentrations of sodium arsenite or sodium arsenate for 48 hr were continually passaged and tested for neoplastic transformation, as determined by anchorage-independent growth in semisolid agar and tumorigenicity in newborn hamsters. Twenty-one of 22 (96%) untreated, control cultures senesced by 20 passages. While I

culture escaped senescence, it did not acquire the ability to either grow in semisolid agar or form tumors in animals. Ten of 14 (71%) cultures exposed to sodium arsenite or sodium arsenate escaped senescence. Nine of the 10 (90%) arsenic-treated immortal cultures acquired the anchorage-independent phenotype. Five of 5 anchorage-independent cultures examined were tumorigenic. Two of 3 morphologically transformed colonies induced by sodium arsenate also acquired the ability to grow in semisolid agar when isolated. Amplification of the c-myc or c-Ha-ras oncogene was detected in 3 of 5 and 4 of 5 tumorigenic cell lines, respectively. Both c-myc and c-Ha-ras were amplified even in a preneoplastic, anchorage-dependent cell line, but neither was amplified in 6 of 9 anchorage-independent cell lines. Overexpression of c-myc and c-Ha-ras mRNA was observed in most of the neoplastically transformed cell lines but not in the preneoplastic cell line. Experiments using the methylation-sensitive restriction endonuclease isoschizomers Hpall and MspI revealed hypomethylation of c-myc and c-Ha-ras in the 5'-CCGG sequence of arsenic-exposed cell lines but not in the parental SHE cells or a spontaneously transformed cell line. Thus, inorganic arsenics induce neoplastic transformation of normal, diploid mammalian cells. Overexpression of onco-genes by DNA hypomethylation may participate in the arsenic-induced neoplastic transformation of mammalian cells. Published 2002 Wiley-Liss, Inc.(dagger).

Takano T. 2004. Fetal Cell Carcinogenesis of the Thyroid: a Hypothesis for Better Understanding of Gene Expression Profile and Genomic Alternation in Thyroid Carcinoma. Endocr J 51:509-515.
Abstract: Since the 1980s, cancer cells have been considered to be generated from well-differentiated benign cells by transformation caused by accumulating damage in their genomes. However, recent progress in gene expression analysis in thyroid malignancies has raised the possibility of another model of thyroid carcinogenesis. We propose a novel hypothesis of thyroid carcinogenesis, the fetal cell carcinogenesis hypothesis, in which cancer cells are derived From the remnants of fetal thyroid cells, instead of from normal thyroid follicular cells. This hypothesis explains well the clinical and biological features and recent molecular evidence of thyroid carcinoma. It suggests the importance of clarifying the molecular mechanism of thyroid development and the identification of fetal thyroid cells such as thyroid stein cells (TSCs), since such data will lead to a better understanding of thyroid carcinogenesis and thyroid regeneration.

Takano T, Amino N. 2005. In My View ... Fetal Cell Carcinogenesis: a New Hypothesis for Better Understanding of Thyroid Carcinoma. Thyroid 15:432-438.
Abstract: Modern advances in molecular technology have given us the chance to establish a new insight into thyroid carcinogenesis. Gene expression in thyroid malignancies usually reveals highly consistent profiles, which leads to questioning of the classic concept of multistep carcinogenesis, in which cancer cells are produced from well-differentiated benign cells by transformation caused by accumulating damage to their genome. We propose a novel hypothesis of thyroid carcinogenesis, the fetal cell carcinogenesis hypothesis, in which cancer cells are derived from the remnants of three types of fetal thyroid cells, instead of normal thyroid follicular cells. This hypothesis explains well the clinical and biologic features and recent molecular evidence of thyroid carcinoma. It suggests the importance of clarifying the molecular mechanism of thyroid development and the identification of fetal thyroid cells, especially thyroid stem cells (TSCs), because Such data will lead to better understanding of thyroid carcinogenesis and thyroid regeneration.

Tamimi Y, Dietrich K, Stone K, Grundy P. 2006 Oct 10. Paired box genes, PAX-2 and PAX-8, are not frequently mutated in Wilms tumor. Mutat Res 601:46-50.
Abstract: To determine whether PAX-2 and PAX-8 are involved in Wilms tumor (WT) pathogenesis, we sought mutations in these two genes in 99 Wilms tumors of favorable histology. We screened the entire protein coding sequences as well as the intronic regions adjacent to exons, using denaturing HPLC followed by sequencing of samples displaying abnormal chromatograms. In PAX-2, a silent polymorphism was found within exon 2 and exon 8 in 1% and 21% of cases, respectively. Three apparently silent polymorphisms were also found in PAX-8, two in exon 5 (2 of 99 cases or 2%) and one in exon 6 (22 of 99 cases or 22%), all of which were located 3' to the exons. In conclusion, no evidence for disease causing mutation was found using this technique, and so the direct involvement of either of these two genes in WT is unlikely.

Taniguchi T, Schofield AE, Scarlett JL, Morison IM, Sullivan MJ, Reeve AE. 1995 . Altered specificity of IGF2 promoter imprinting during fetal development and onset of Wilms tumour. Oncogene 11:751-756.
Abstract: The specificity of IGF2 promoter imprinting was examined in embryonal tissues and Wilms

tumour. In several fetal tissues of approximately 12 weeks gestation, IGF2 was found to be monoallelically expressed from all IGF2 promoters i.e. P1, P2, P3 and P4. However, in tissues of slightly older gestation age (15-17 weeks) relaxation of imprinting at the P1 promoter was evident, although the P2-P4 promoters remained imprinted. These data indicate that early in embryogenesis a population of cells exists in which all IGF2 promoters are imprinted, but that as development proceeds the imprinting of the P1 promoter is relaxed. The pattern of IGF2 promoter imprinting was also analysed in Wilms tumour. In some tumours, the pattern of promoter imprinting was identical to that found in early fetal kidney, indicating that this tumour originates within early embryonic kidney tissue. In contrast, in tumours in which relaxation of imprinting had occurred, imprinting relaxation affected all IGF2 promoters. This aberrant pattern of promoter imprinting, which was not detected in fetal kidney, provides further evidence that pathological relaxation of IGF2 imprinting is involved in the genesis of Wilms tumour.

Tarraf C, El-Sabban M, Bassam R, Beyrouthy M, Chamoun J, Talhouk R. 2003. Functional consequence of exposure to dieldrin on mammary development and function. Food Additives & Contaminants 20:819-828.
Abstract: The effect of dieldrin (Dln) on the development of the mammary gland and on functional parameters of CID-9 mammary cells in culture was investigated. One-month-old Sprague-Dawley female rats were bred and received intraperitoneal injection with 2.5 or 15 muM Dln during the last trimester of their gestation. Mammary glands of 15-muM Dln-treated rats showed immature alveolar structures by day 18 of gestation and abundant adipose tissue. Dln-treated rats had a lower number of pups, and the weight of pups between days 14 and 31 of age compared with non-treated rats was significantly lower. Long-term exposure of CID-9 mammary cells, cultured under non-differentiation conditions, on plastic, or under differentiation permissive conditions, dripped with EHS-matrix, to 5 or 25 muM Dln was detrimental to cell growth. The short-term effect of Dln exposure (up to 9 h) on CID-9 cells, under the same culture conditions, did not affect their beta-casein mRNA levels, but induced apoptosis, down regulated gap junction intracellular communication and induced IL-6 and TNF-alpha expression.

Tchernitchin AN, Tchernitchin NN, Mena MA, Unda C, Soto J. 1999. Imprinting: Perinatal exposures cause the development of diseases during the adult age. Acta Biol Hung 50:425-440.
Abstract: Since the early reports linking the development of clear cell cervicovaginal adenocarcinoma in young women with diethylstilbestrol treatment of their mothers during pregnancy, it became clear that perinatal exposure to several substances may induce irreversible alterations, that can be detected later in life. Current evidence suggests that these substances induce, by the mechanism of imprinting, alterations of the differentiation of several cell-types, resulting in the development of disease during the adult age. The most known delayed effects to prenatal exposure to agents displaying hormone action, pollutants, food additives and natural food components, substances of abuse and stress by the mechanism of imprinting are described. Among them, estrogens, androgens, progestins, lead, benzopyrenes, ozone, dioxins, DDT, DDE, methoxychlor, chlordecone, parathion, malathion, polychlorobiphenyls, pyrethroids, paraquat, food additives, normal food constituents, tetrahydrocannabinol, cocaine and opiates. It is concluded that perinatal exposure to several agents causes irreversible changes that determine health conditions during adulthood. Several diseases developing during adulthood probably were determined during early stages of life, under the effect of exposure or preferential mother's diet during pregnancy. Regulations to avoid these early exposures may contribute to an important improvement of health conditions of humankind.

Teuffel O, Betts DR, Dettling M, Schaub R, Schafer BW, Niggli FK. 2004 Oct. Prenatal origin of separate evolution of leukemia in identical twins. Leukemia 18:1624-9.
Abstract: Several studies involving identical twins with concordant leukemia and retrospective scrutiny of archived neonatal blood spots have shown that the TEL-AML1 fusion gene in childhood acute lymphoblastic leukemia (ALL) frequently arises before birth. A prenatal origin of childhood leukemia was further supported by the detection of clonotypic immunoglobulin gene rearrangements on neonatal blood spots of children with various other subtypes of ALL. However, no comprehensive study is available linking these clonotypic events. We describe a pair of 5-year-old monozygotic twins with concordant TEL-AML1-positive ALL. Separate leukemic clones were identified in the diagnostic samples since distinct IGH and IGK-Kde gene rearrangements could be detected. Additional differences characterizing the leukemic clones included an aberration of the second, nonrearranged TEL allele observed in one twin only. Interestingly, both the identical TEL-AML1 fusion sequence and distinct immunoglobulin gene rearrangements were identified on the neonatal blood spots indicating that separate preleukemic clones

evolved already before birth. Finally, we compared the reported twins with an additional 31 children with ALL by using the microarray technology. Gene expression profiling provided evidence that leukemia in twins harbours the same subtype-typical feature as TEL-AML1-positive leukemia in singletons suggesting that the leukemogenesis model might also be applicable generally.

Thapa PB, Whitlock JA, Brockman Worrell KG, Gideon P, Mitchel EF Jr, Roberson P, Pais R, Ray WA. 1998 . Prenatal exposure to metronidazole and risk of childhood cancer: A retrospective cohort study of children younger than 5 years. Cancer 83:1461-1468.
Abstract: BACKGROUND: To evaluate the role of in utero exposure to metronidazole (a carcinogen in some animal models) and the risk of subsequent cancer, the authors conducted a retrospective cohort study of childhood cancer. METHODS: The cohort included 328,846 children younger than 5 years born to women enrolled in Tennessee Medicaid at any time between the last menstrual period (LMP) and the date of delivery. The cohort was identified by linking files of Tennessee Medicaid mothers ages 15-44 years and children and the children's birth and death certificates for the period January 1, 1975 through December 31, 1992. Exposure data were obtained from Medicaid pharmacy records and exposure was defined as filling a metronidazole prescription that had at least a day's supply between the 30 days prior to the LMP and the date of delivery. Study cases were cohort children diagnosed with a first primary cancer before age 5 years, identified by linking the cohort with a statewide childhood cancer database for the study period. RESULTS: Cohort members contributed 1,172,696 person-years of follow-up for analysis, with children exposed (8.1%) and not exposed (91.9%) in utero to metronidazole contributing 79,716 and 1,092,980 person-years, respectively. Of 952 children younger than 5 years in the statewide cancer database, 175 met study eligibility criteria. Of these, 42 had leukemia, 30 had central nervous system (CNS) tumors, 28 had neuroblastoma, and 75 had other cancers. Using Poisson regression modeling, children exposed to metronidazole in utero had no significant increase in adjusted relative risk (RR) for all cancers (RR: 0.81; 95% confidence interval [95% CI], 0.41-1.59), leukemia (no exposed case), CNS tumors (RR: 1.23; 95% CI, 0.29-5.21), neuroblastomas (RR: 2.60; 95% CI, 0.89-7.59), and other cancers (RR: 0.57; 95% CI, 0.18-1.82). CONCLUSIONS: The authors conclude that although there was no increase in risk for all cancers associated with in utero exposure to metronidazole, the observed increased risk for neuroblastomas, although not significant, requires further evaluation.

Thomas RS, Susil B, Kola I. 1994. Activating point mutations of the neu oncogene in schwannomas induced by ethylnitrosourea exposure to day-15 and day-18 fetal rats. Int J Oncol 5:1219-1225.
Abstract: Single transplacental exposure of day 15 fetal rats to the carcinogen ethylnitrosourea (ENU) primarily induces tumours of neuroectodermal origin, whereas exposure to ENU at neonatal and adult stages results in tumours arising predominantly from secretory epithelial tissue. Expression of the neu gene is found in fetal neural tissue up until day 16 of gestation, but predominantly only in secretory epithelium after this time. The presence of an activating mutation in the neu oncogene has been associated with these ENU induced neuroectodermal tumours, and on this basis it has been proposed that only the transcriptionally active neu gene is susceptible to ENU induced mutation. In this study we compare the spectrum of tumourigenesis in rats exposed to ENU on days 15 and 18 of gestation. Neuroectodermal tumours were produced at high incidence; mostly schwannomas derived from the peripheral nervous system and some gliomas of the central nervous system. PCR analysis of DNA from these tumours reveals that schwannomas predominantly (29/37=78%) contain a mutated neu gene. This consistent T-->A transversion at codon 671 is known to convert neu into a potent oncogene. Conversely gliomas and various carcinomas do not contain such a mutation (0/13=0%). Our data reveals little difference either in tumour type or activation of the neu oncogene in rats exposed to ENU at these two stages of development. However, we do find that the c-neu gene is expressed at both days 15 and 18 in fetal rat neural tissue; albeit at lower levels by day 18.

Thompson RS, Hess DL, Binkerd PE, Hendrickx AG. 1981. The effects of prenatal diethylstilbestrol exposure on the genitalia of pubertal *Macaca mulatta*. II. Male offspring. J Reprod Med 26:309-316.
Abstract: In order evaluate the potential embryotoxic and fetotoxic effects of in utero diethylstilbestrol (DES) exposure on the developing offspring, 19 pregnant rhesus monkeys were administered 1 mg/day DES orally beginning on either day 19 (group I), 100 (group II) or 130 (group III) or gestation and termination on the day of natural birth or cesarean section. Five of ten male offspring are alive at 7 years of age. At 4 1/2 years of age, three of these five offspring exhibited one or more abnormalities of the external

genitalia, including testicular hypoplasia, preputial adhesions and undescended testes. Semen analysis following rectal electroejaculation and testicular biopsies at 5 1/2 years of age confirmed two cases of testicular hypoplasia. Semen evaluation, testicular biopsies and analysis of serum testosterone levels at 6 1/2 years of age indicated normal testicular morphology and function in all DES-exposed males as compared with colony controls. Our study, therefore, suggests that DES may affect maturation of the reproductive tract as indicated by a delay in the normal breakdown of preputial adhesions in addition to gross and microscopic evidence of testicular hypoplasia during the postpubertal period between 4 1/2 and 5 1/2 years of age. Further observations on breeding performance and fertility are required to evaluate the long-term effects of DES in this species.

Thorne C, Newell ML. 2007. Safety of agents used to prevent mother-to-child transmission of HIV: is there any cause for concern? Drug Saf 30:203-13.
Abstract: Antiretroviral drugs have been used routinely to reduce the risk of mother-to-child transmission of HIV infection since 1994, following the AIDS Clinical Trials Group 076 trial, which demonstrated the efficacy of zidovudine in reducing the risk of in utero and intrapartum transmission. The use of antiretroviral drugs in pregnancy varies geographically, with widespread use of highly active antiretroviral therapy (HAART) in resource-rich settings for delaying maternal HIV disease progression as well as the prevention of mother-to-child transmission; however, in low- and middle-income settings, abbreviated prophylactic regimens focus on the perinatal period, with very limited access to HAART to date. The potential risks associated with antiretroviral exposure for pregnant women, fetuses and infants depend on the duration of this exposure as well as the number and type of drugs. As the benefits of HAART regimens in reducing the risk of mother-to-child transmission and in delaying disease progression are so great, their widespread use has been accepted, despite the relative lack of safety data from human pregnancies. Animal studies have suggested an increased risk of malformations associated with exposure to specific antiretroviral drugs, although evidence to support this from human studies is limited. Trials, cohorts and surveillance studies have shown no evidence of an increased risk of congenital malformations associated with in utero exposure to zidovudine, or other commonly used antiretroviral drugs, with an estimated 2-3% prevalence of birth defects (i.e. similar to that seen in the general population). Exposure to prophylactic zidovudine for prevention of mother-to-child transmission is associated with a usually mild and reversible, but rarely severe, anaemia in infants. However, a medium-term impact on haematological parameters of antiretroviral-exposed infants has been reported, with small but persistent reductions in levels of neutrophils, platelets and lymphocytes in children up to 8 years of age; the clinical significance of this remains uncertain. To date, there is no evidence to suggest that exposure to antiretroviral drugs in utero or neonatally is associated with an increased risk of childhood cancer, but the potential for mutagenic and carcinogenic effects at older ages cannot be excluded. Nucleoside analogue-related mitochondrial toxicity is well recognised from studies in non-pregnant individuals, whilst animal studies have provided evidence of mitochondrial toxicity resulting from in utero antiretroviral exposure. Clinically evident mitochondrial disease in children with antiretroviral exposure has only been described in Europe, with an estimated 18-month incidence of 'established' mitochondrial dysfunction of 0.26% among exposed children. Regarding pregnancy-related adverse effects, increased risks of prematurity, pre-eclampsia and gestational diabetes mellitus have been reported by a variety of observational studies with varying strengths of evidence and with conflicting results. Based on current knowledge, the immense benefits of antiretroviral prophylaxis in prevention of mother-to-child transmission far outweigh the potential for adverse effects. However, these potential adverse effects require further and longer term monitoring because they are likely to be rare and to occur later in childhood.

Thorup J, Cortes D, Petersen BL. 2006. The incidence of bilateral cryptorchidism is increased and the fertility potential is reduced in sons born to mothers who have smoked during pregnancy. Journal of Urol 176:734-7.
Abstract: PURPOSE: Recent studies have demonstrated a high prevalence of cryptorchidism, decreasing semen quality and increasing incidence of testicular cancer. These changes seem to be interrelated, and may be symptoms of a common underlying entity with foundations in fetal life. We investigated the influence of maternal smoking on fertility status in offspring cryptorchidism. MATERIALS AND METHODS: We prospectively studied consecutive patients presenting to the pediatric surgery department between 1996 and 2005. A total of 157 boys 1 to 5.9 years old underwent surgery for cryptorchidism with simultaneous testicular biopsy, and exhibited well preserved testicular parenchyma. Only white patients with Danish-

speaking mothers who had reported pregnancy history including smoking habits during pregnancy and history of the offspring were included. The patients had cryptorchidism only and none received hormonal treatment before surgery. The number of spermatogonia and gonocytes per tubule cross-section was assessed and compared to normal values from autopsy material. RESULTS: The group of boys with cryptorchidism whose mothers had smoked heavily during pregnancy (ie more than 10 cigarettes daily throughout the pregnancy) had a significantly increased risk of bilateral cryptorchidism (52%, or 11 of 21 patients), and a decreased number of spermatogonia and gonocytes per tubule cross-section, which was absolute (0.097 [0 to 0.75]) and age related (14% [0% to 198%] of normal for age) compared to boys whose mothers did not smoke (20%, or 22 of 112 patients, 0.140 [0 to 2.14] and 37% [0% to 563%] of normal for age, $p < 0.01$, $p < 0.05$ and $p < 0.05$, respectively). CONCLUSIONS: A close relationship between maternal smoking during pregnancy and adverse trends in offspring reproductive health in relation to cryptorchidism was observed.

Timms BG, Howdeshell KL, Barton L, Bradley S, Richter CA, vom Saal FS. 2005. Estrogenic chemicals in plastic and oral contraceptives disrupt development of the fetal mouse prostate and urethra. Proceedings of the National Academy of Sciences USA 102:7014-7019 and cover illustration.
Abstract: Exposure of human fetuses to manmade estrogenic chemicals can occur through several sources. For example, fetal exposure to ethinylestradiol occurs because each year approximately 3% of women taking oral contraceptives become pregnant. Exposure to the estrogenic chemical bisphenol A occurs through food and beverages because of significant leaching from polycarbonate plastic products and the lining of cans. We fed pregnant CD-1 mice ethinylestradiol (0.1 μg/kg/day) and bisphenol A (10 μg/kg/day), which are doses below the range of exposure by pregnant women. In male mouse fetuses both ethinylestradiol and bisphenol A produced an increase in the number and size of dorsolateral prostate ducts and an overall increase in prostate duct volume. Histochemical staining of sections with proliferating cell nuclear antigen and mouse keratin 5 antibodies indicated that this was due to a marked increase in proliferation of basal epithelial cells located in the primary ducts. In addition, the urethra was malformed in the colliculus region and significantly constricted where it enters the bladder, which could contribute to urine flow disorders. These effects were identical to those caused by a similar 0.1 μg/kg/day dose of the estrogenic drug, diethylstilbestrol (DES), a known human developmental teratogen and carcinogen. In contrast, a 2000-fold higher DES dose completely inhibited dorsolateral prostate duct formation, revealing opposite effects of high and low doses of estrogen. Acceleration in the rate of proliferation of prostate epithelium during fetal life by small amounts of estrogenic chemicals could permanently disrupt cellular control systems and predispose the prostate to disease in adulthood.

[Cover caption:]
Computer-assisted reconstruction of an estrogenized fetal mouse urogenital system. In utero exposure of male mouse fetuses to bisphenol A, the estrogenic monomer used to make polycarbonate, causes an increase in the number and volume of developing prostate ducts and malformations of the urethra. This occurs at exposure levels below those detected in human fetuses. Dorsal-caudal view (center and top) and a series of views rotated at 30° increments.through 360°. Structures illustrated: seminal vesicles (purple); coagulating gland (dark blue); dorsal (green), lateral (yellow) and ventral (light blue) prostate ducts as they emerge from the urethra (red).

Ting AH, Mcgarvey KM, Baylin SB. 2006. The cancer epigenome - components and functional correlates. Genes & Development 20:3215-3231.
Abstract: It is increasingly apparent that cancer development not only depends on genetic alterations but on an abnormal cellular memory, or epigenetic changes, which convey heritable gene expression patterns critical for neoplastic initiation and progression. These aberrant epigenetic mechanisms are manifest in both global changes in chromatin packaging and in localized gene promoter changes that influence the transcription of genes important to the cancer process. An exciting emerging theme is that an understanding of stem cell chromatin control of gene expression, including relationships between histone modifications and DNA methylation, may hold a key to understanding the origins of cancer epigenetic changes. This possibility, coupled with the reversible nature of epigenetics, has enormous significance for the prevention and control of cancer.

Titus-Ernstoff L, Egan KM, Newcomb PA, Ding J, Trentham-Dietz A, Greenberg ER, Baron JA, Trichopoulos D,

Willett WC. 2002. Early life factors in relation to breast cancer risk in postmenopausal women. Cancer Epidemiology, Biomarkers & Prevention 11:207-210.
Abstract: We evaluated the role of early life factors in a large, population-based, case-control study of breast cancer risk in postmenopausal women. Case women in Massachusetts, New Hampshire, and Wisconsin were ascertained through state cancer registries; control women were randomly selected from drivers license lists (50-65 years of age) or Medicare beneficiary lists (65-79 years of age). Information concerning factors of interest was obtained through structured telephone interviews. Overall, 83% of eligible cases and 78% of eligible controls participated, and data from more than 2900 women were available for this analysis. We observed a weak J-shaped relationship between birth weight and breast cancer risk; the increased risk was not statistically significant for either the lowest or the highest birth weight. Parental smoking during the pregnancy was not associated with risk of breast cancer in the adult daughter. Breast cancer risk increased significantly with father's education (P = 0.01). Risk also increased with greater age of the mother at the time of the subject's birth (P = 0.04). The subject's birth rank was inversely associated with risk (P = 0.03), as was the number of older sisters (P = 0.03), but the number of older brothers, number of younger siblings, sibship gender ratio, and total sibship size were unrelated to risk. Overall, our results are consistent with previous studies and suggest that these early life factors have a modest influence on breast cancer risk in postmenopausal women.

Titus-Ernstoff L, Hatch EE, Hoover RN, Palmer J, Greenberg ER, Ricker W, Kaufman R, Noller K , Herbst AL, Colton T, Hartge P. 2001. Long-term cancer risk in women given diethylstilbestrol (DES) during pregnancy. Br J Cancer 84:126-133.
Abstract: From 1940 through the 1960s, diethylstilbestrol (DES), a synthetic oestrogen, was given to pregnant women to prevent pregnancy complications and losses. Subsequent studies showed increased risks of reproductive tract abnormalities, particularly vaginal adenocarcinoma, in exposed daughters. An increased risk of breast cancer in the DES-exposed mothers was also found in some studies. In this report, we present further follow-up and a combined analysis of two cohorts of women who were exposed to DES during pregnancy. The purpose of our study was to evaluate maternal DES exposure in relation to risk of cancer, particularly tumours with a hormonal aetiology. DES exposure status was determined by a review of medical records of the Mothers Study cohort or clinical trial records of the Dieckmann Study. Poisson regression analyses were used to estimate relative risks (RR) and 95% confidence intervals (CI) for the relationship between DES and cancer occurrence. The study results demonstrated a modest association between DES exposure and breast cancer risk, RR = 1.27 (95% CI = 1.07-1.52). The increased risk was not exacerbated by a family history of breast cancer, or by use of oral contraceptives or hormone replacement therapy. We found no evidence that DES was associated with risk of ovarian, endometrial or other cancer.

Toft G, Hagmar L, Giwercman A, Bonde JP. 2004. Epidemiological evidence on reproductive effects of persistent organochlorines in humans. Reprod Toxicol 19:5-26.
Abstract: Organochlorines are widespread pollutants in humans. Concern about adverse reproductive effects of these compounds arises from accidental exposure of humans and experimental studies. Recently, this issue has been addressed by a number of studies of exposed populations and hospital-based case-referent studies. These studies indicate that high concentrations of persistent organochlorines may adversely affect semen quality and cause testicular cancer in males, induce menstrual cycle abnormalities and spontaneous abortions in females, and cause prolonged waiting time pregnancy, reduced birth weight, skewed sex ratio, and altered age of sexual development. However, most effects have been demonstrated at exposure levels above the present day exposure level in European and North American populations. Due to inherent methodological problems in several of the available studies, additional research is needed to fully elucidate the possible adverse effects of organochlorines on human reproductive health. (C) 2004 Elsevier Inc. All rights reserved.

Toft G, Hagmar L, Giwercman A, Bonde JP. 2004. Epidemiological evidence on reproductive effects of persistent organochlorines in humans [review]. Reprod Toxicol 19:5-26.
Abstract: Organochlorines are widespread pollutants in humans. Concern about adverse reproductive effects of these compounds arises from accidental exposure of humans and experimental studies. Recently, this issue has been addressed by a number of studies of exposed populations and hospital-based case-referent studies. These studies indicate that high concentrations of persistent organochlorines may adversely affect semen quality and cause testicular cancer in males, induce menstrual cycle abnormalities

and spontaneous abortions in females, and cause prolonged waiting time pregnancy, reduced birth weight, skewed sex ratio, and altered age of sexual development. However, most effects have been demonstrated at exposure levels above the present day exposure level in European and North American populations. Due to inherent methodological problems in several of the available studies, additional research is needed to fully elucidate the possible adverse effects of organochlorines on human reproductive health.

Tomatis L. 1979. Prenatal exposure to chemical carcinogens and its effect on subsequent generations. Natl Cancer Inst Monogr :159-184.
Abstract: That exposure of pregnant animals to chemical carcinogens results in the occurrence of tumors in the progeny is well documented. Evidence has been accumulated on at least 38 chemicals pertaining to different chemical groups. The experimental evidence was followed by observations in humans regarding the increased risk of cancer in daughters of women who received stilbestrol during pregnancy. Additional experimental evidence is accumulating on the possibility that exposure during pregnancy results in an increased incidence of tumors for more than one generation of untreated descendants. Studies done on mice with DMBA and on rats with MNU and ENU showed that exposure to the carcinogens during pregnancy resulted in a high incidence of tumors in animals of the first generation and in an increased incidence of tumors at specific sites in untreated animals of the second and third generations.

Tomatis L. 1989. Overview of perinatal and multigeneration carcinogenesis. IARC Sci Publ :1-15.
Abstract: One of the characteristics of recent decades, which have seen a formidable expansion of cancer research, has been the co-existence of the generally agreed hypothesis that most cancers are multifactorial in origin, with the attitude of concentrating nevertheless on single carcinogenic agents and on attempting to quantify cancer risks as if they were due to single factors. It is not possible at present to quantitatively estimate the role of prenatal exposures to carcinogens/mutagens in determining or modulating the risk of cancer in humans. It is not unreasonable to assume, however, that the consequences of prenatal exposures and of prenatal events are among the factors that are often ignored. Prenatal events can contribute to the occurrence of cancer as the consequence of either: (1) the direct exposure of embryonal or fetal cells to a carcinogenic agent; (2) a prezygotic exposure of the germ cells of one or both parents to a carcinogen/mutagen before mating; (3) a genetic instability and/or a genetic rearrangement resulting from selective breeding which may favour a deregulation of cellular growth and differentiation. By offering the possibility of investigating the role played by events involving both germ and somatic cells, studies on prenatal carcinogenesis may become essential for a more accurate estimation of risks attributable to environmental agents, and may at the same time contribute to the understanding of some of the mechanisms underlying the genetic predisposition to cancer.

Tomatis L, Cabral JR, Likhachev AJ, Ponomarkov V. 1981 . Increased cancer incidence in the progeny of male rats exposed to ethylnitrosourea before mating. Int J Cancer 28:475-478.
Abstract: Results from previous experiments have indicated tha persistence of an increased cancer risk in subsequent generations following prenatal exposure to a chemical carcinogen. In the present experiment, the possible role of prezygotic events in determined cancer risk was investigated in the progeny of male rats treated with ethylnitrosourea (ENU) before mating with untreated females. Eight BDVI male rats were given a single i.p. dose of 80 mg/kg bw ENU and each rat was then caged at weeks 1, 2, 3 and 4 after treatment with three untreated females. Fertility was lower and preweaning mortality higher in the experimental group, as compared to controls, particularly at the 4th-week mating. Survival rates after weaning were similar in the progeny of treated males and controls, as was the total incidence of tumours. However, analysis of tumour incidence at the various organ sites showed an increased incidence of neurogenic tumours in the progeny of ENU-treated males, as compared to that of controls.

Tomatis L, Turusov VS, Cardis E, Cabral JP. 1990 . Tumour incidence in the progeny of male rats exposed to ethylnitrosourea before mating. Mutat Res 229:231-237.
Abstract: BDVI male rats were given a single i.p. dose of 80 mg/kg b.w. ethylnitrosourea (ENU), and each rat was then mated at weeks 1, 2, 3, 4 and 5 after treatment with 3 untreated females. A decrease in the fecundity of the treated males was observed, particularly when they were mated 5 weeks after ENU treatment. The average litter size was lower in the treated group, especially for females mated in week 4. No significant differences in pre- or post-weaning mortality were noted between control and treated groups. A slight, non-significant increase in the incidence of brain tumours was observed in the progeny of treated

males compared with the controls. The incidence of thyroid tumours was significantly higher in controls but this difference disappeared when adjustment was made for litter effect and intralitter dependence.

Toppari J, Larsen JC, Christiansen P, Giwercman A, Grandjean P, Guillette LJ Jr., Jegou B, Jensen TK, Jouannet P, Keiding N, Leffers H, McLachlan JA, Meyer O, Muller J, Rajpert-De Meyts E, Scheike T, Sharpe R, Sumpter J, Skakkebaek NE. 1996. Male reproductive health and environmental xenoestrogens. Environ Health Perspect 104 Suppl 4:741-803.
Abstract: Male reproductive health has deteriorated in many countries during the last few decades. In the 1990s, declining semen quality has been reported from Belgium, Denmark, France, and Great Britain. The incidence of testicular cancer has increased during the same time incidences of hypospadias and cryptorchidism also appear to be increasing. Similar reproductive problems occur in many wildlife species. There are marked geographic differences in the prevalence of male reproductive disorders. While the reasons for these differences are currently unknown, both clinical and laboratory research suggest that the adverse changes may be inter-related and have a common origin in fetal life or childhood. Exposure of the male fetus to supranormal levels of estrogens, such as diethlylstilbestrol, can result in the above-mentioned reproductive defects. The growing number of reports demonstrating that common environmental contaminants and natural factors possess estrogenic activity presents the working hypothesis that the adverse trends in male reproductive health may be, at least in part, associated with exposure to estrogenic or other hormonally active (e.g., antiandrogenic) environmental chemicals during fetal and childhood development. An extensive research program is needed to understand the extent of the problem, its underlying etiology, and the development of a strategy for prevention and intervention.

Toppari J, Skakkebaek NE. 1998. Sexual differentiation and environmental endocrine disrupters. Baillieres Clin Endocrinol Metab 12:143-156.
Abstract: Male sexual differentiation is dependent on normal testicular function, including secretion of testosterone from the Leydig cells, and mullerian-inhibiting substance from the Sertoli cells. External factors, such as anti-androgens and oestrogens, that disturb endocrine balance cause demasculinizing and feminizing effects in the developing male fetus. Oestrogens also causes adverse effects in female fetuses, whereas anti-androgens have little influence. A growing number of chemicals have been found to possess either weak oestrogenic, anti-androgenic or other hormonal activities, and these are often referred to as endocrine disrupters. In animals in the wild, abnormal sexual development has been associated with exposure to mixtures of endocrine disrupters. The emerging adverse trends in human reproductive health, such as increased incidences of cryptorchidism, hypospadias and testicular cancer, and the ubiquitous presence of endocrine disrupters in the environment, support the hypothesis that disturbed sexual differentiation could in some cases be caused by increased exposure to environmental endocrine disrupters.

Tornqvist S. 1998. Paternal work in the power industry: Effects on children at delivery. Journal of Occupational & Environmental Medicine 40:111-117.
Abstract: Although reports on reproductive disturbances among occupational groups of electrical workers have been discussed few studies have focused explicitly on. the children of workers employed in the power industry. Birth outcome and cancer in the offspring of fathers who were exposed to electric and magnetic fields at time of sperm production. were studied in two cohorts. In study 1, male occupation, in the power industry was identified in censuses. Study 2 is a prospective cohort study of newly employed power industry workers. Birth data were obtained by record linkage between censuses and several available health registers in Sweden. Multiple births, birth weight, sex, survival congenital malformations, and cancer have been analyzed with relation to the father's exposure to electric and magnetic fields one year before the child was born. There were six cancer cases among infants in the exposed group (2.4 expected) and six in the unexposed group (3.2 expected) in Study 1. Jointly, the 12 cancer cases found among the infants were more than expected (P = 0.02). However, this total excess may be random. No cancer cases were observed in the prospective study. For chromosomal abnormalities, such as Down's syndrome one case was observed among infants of exposed fathers and three cases among unexposed fathers in Study 1. In Study 2, no cases were observed. There was a slightly higher proportion of malformation diagnoses among infants of exposed fathers than among infants of unexposed fathers in Study 5 but this could be random (odds ratio = 1.59; 95% Confidence interval 0.43-1.48). No clear-cut effects on infants fathered by men who were exposed to electric and magnetic fields around the time of sperm production. could be seen in these two studies.

Tozuka Y, Watanabe N, Osawa M, Toriba A, Kizu R, Hayakawa K. 2004. Transfer of polycyclic aromatic hydrocarbons to fetuses and breast milk of rats exposed to diesel exhaust. Journal of Health Science 50:497-502.
Abstract: Polycyclic aromatic hydrocarbons (PAHs) were analyzed in maternal blood and fetuses from Fischer 344 rats exposed to diesel exhaust (DE) during pregnancy, and in breast milk from rats exposed to DE during pregnancy and lactation using high performance liquid chromatography with fluorescence detection. Concentrations of phenanthrene (Phe), anthracene (Ant) and benz[a]anthracene (BaA) were significantly higher in maternal blood of the DE group than those of the control group. Concentration of Phe in fetuses of the DE group was significantly higher than those of the control group. Concentrations of fluorene, Ant, fluoranthene (Flu), pyrene (Pyr), BaA and chrysene (Chr) tended to be higher in fetuses of the DE group. The levels of Ant, Flu, Pyr and Chr in breast milk from the DE Group were significantly higher than those of the control group. These results indicate that PAHs taken into mother rat by the inhalation of DE are transferred into fetuses via placenta and into breast milk. This is the first report to clarify the transportation of inhaled PAHs into fetuses and breast milk from mother rats.

Trichopoulos D. 1990 . Hypothesis: does breast cancer originate in utero? Lancet 335:939-940.
Abstract: Factors that increase the risk of cancer during adult life may also increase the risk of cancer when they act in utero (eg, ionising radiation and diethylstilboestrol in human beings and chemicals in animals). The existing empirical data seem to be compatible with the hypothesis that increased concentrations of oestrogens in pregnancy increase the probability of future occurrence of breast cancer in daughters.

Trivers KF, Mertens AC, Ross JA, Steinbuch M, Olshan AF, Robison LL. 2006. Parental marijuana use and risk of childhood acute myeloid leukaemia: a report from the Children's Cancer Group (United States and Canada). Paediatr Perinat Epidemiol 20:110-118.
Abstract: The aetiology of childhood acute myeloid leukaemia (AML) is largely unknown. Maternal marijuana use just before, or during pregnancy has been previously associated with childhood AML. This case-control investigation formally tested the hypothesis that parental marijuana use increases the risk of childhood AML in offspring. Incident cases of AML < 18 years of age, diagnosed between 1989 and 1993, and registered with the Children's Cancer Group (a paediatric clinical co-operative group), were eligible for inclusion. Control children were selected via random digit dialling and individually matched 1:1 to cases on age, race and residential location, except for rare morphological subtypes that were matched 1:2. Parental telephone interviews were conducted to determine exposure and covariate information. Conditional logistic regression was used to estimate matched odds ratios (OR) and 95% confidence intervals [CI] adjusted for household income, parental education and parental age. The analysis included 517 cases and 610 matched controls. A series of sensitivity analyses examined the potential for recall bias. Ever lifetime use of marijuana by mothers was not associated with childhood AML [OR = 0.89; 95% CI = 0.66,1.19]. Maternal marijuana use any time during the 3 months before, or during pregnancy was inversely associated with childhood AML [OR = 0.43; 95% CI = 0.23, 0.80]. Paternal use during the same time period was not associated with risk. Assuming a large degree of differential exposure misclassification was present, the corrected ORs ranged between 0.82 and 1.40. The previously reported positive association between maternal marijuana use before or during pregnancy and childhood AML was not confirmed. The decreased ORs observed in this study may be due to recall bias assuming plausibly low values of sensitivity

Troisi R, Hatch E, Titus-Ernstoff L, Palmer JR, Hyer M, Strohsnitter WC, Robboy SJ, Kaufman R, Herbst A, Adam E, Hoover R. 2006. Birth weight and breast cancer risk. Br J Cancer 94:1734-1737.
Abstract: Exploring whether the positive association between birth weight and breast cancer risk differs by other breast cancer risk factors may help inform speculation about biological mechanism. In these data, high birth weight was associated with breast cancer risk in younger and in more educated women, but was not associated overall.

Troisi R, Hatch EE, Titus-Ernstoff L, Hyer M, Palmer JR, Robboy SJ, Strohsnitter WC, Kaufman R, Herbst AL, Hoover RN. 2007. Cancer risk in women prenatally exposed to diethylstilbestrol. Int J Cancer 121:356-60.
Abstract: Prenatal diethylstilbestrol (DES) exposure is associated with excess risks of clear cell adenocarcinoma (CCA), and breast cancer in older women. Whether overall cancer risk is also elevated is unclear. Total and site-specific cancer risks were evaluated in the DES Combined Cohort Follow-up Study using age- and calendar-year specific standardized incidence rate ratios (SIR), and age-adjusted incidence

rate ratios (RR) comparing DES exposed and unexposed women. A total of 143 and 49 cancer cases occurred in 97,831 and 34,810 person-years among the exposed and unexposed, respectively. There was no overall excess risk among exposed women when compared with external rates (SIR 1.01; 95% confidence interval [CI] 0.86-1.2). The overall RR comparing exposed with unexposed women was 1.32 (95% CI 0.94-1.8). Breast cancer risk was elevated only among women over 40 years (RR 1.83; 95% CI 1.1-3.2). The CCA SIR among exposed women was nearly 40, and the estimated attack rate through age 39 was 1.6/1,000 women. CCA incidence decreased by over 80% after age 25 when compared with 20-24 years. Excluding CCA and breast cancer, the overall RR was 1.21 (95% CI 0.74-2.0). DES was not associated with excess risks of either endometrial or ovarian cancer. These data suggest that the DES associated increase in CCA incidence remains elevated through the reproductive years. There was no consistent evidence of risk excesses for cancers other than CCA, and breast cancer in older women. Given that the population is still young, continued follow-up is necessary to assess the overall carcinogenic impact of prenatal DES exposure. (c) 2007 Wiley-Liss, Inc.

Troisi R, Potischman N, Roberts J, Siiteri P, Daftary A, Sims C, Hoover RN. 2003. Associations of maternal and umbilical cord hormone concentrations with maternal, gestational and neonatal factors (United States). Cancer Causes & Control 14:347-355.
Abstract: Objective: Risks of some cancers in adults have been associated with several pregnancy factors, including greater maternal age and birth weight. For hormone-related cancers, these effects are hypothesized to be mediated through higher in utero estrogen concentrations. In addition, racial differences in pregnancy hormone levels have been suggested as being responsible for differences in testicular and prostate cancer risk by race. How ever, data on hormonal levels related to these characteristics of pregnancy are sparse, particularly those from studies of the fetal circulation. Methods: Estrogen and androgen concentrations were measured in maternal and umbilical cord sera from 86 normal, singleton pregnancies. Results: Birth size measures (weight, length and head circumference) were positively correlated with maternal estriol (r = 0.25-0.36) and with cord DHEAS concentrations (r = 0.24-0.41), but not with estrogens in cord sera. Maternal age was inversely correlated with maternal DHEAS, androstenedione and testosterone concentrations (r = -0.30, -0.25 and -0.30, respectively), but uncorrelated with estrogens in either the maternal or cord circulation. Black mothers had higher androstenedione and testosterone concentrations than white mothers, however, there were no racial differences in any of the androgens in cord sera. Cord testosterone concentrations were higher in mothers of male fetuses, while both maternal and cord concentrations of estriol were lower in these pregnancies. Conclusions: These data demonstrate associations between hormone concentrations and pregnancy factors associated with offspring's cancer risk, however, the hormones involved and their patterns of association differ by whether the maternal or fetal circulation was sampled. Hormone concentrations in the fetal circulation in this study are not consistent with the hypothesis that greater estrogen concentrations in high birth weight babies mediate the positive association with breast cancer risk observed in epidemiologic studies, or with the hypothesis that higher testosterone exposure in the in utero environment of black males explains their higher subsequent prostate cancer risk.

Turusov VS, Trukhanova LS, Parfenov YuD, Tomatis L. 1992. Occurrence of tumours in the descendants of CBA male mice prenatally treated with diethylstilbestrol. Int J Cancer 50:131-135.
Abstract: There is well documented evidence both in humans and in experimental animals that exposure to diethylstilbestrol (DES) during pregnancy results in an increased incidence of tumours in the progeny. The increased cancer risk has been reported to persist in the second generation descendants of DES-exposed pregnant mice. In the present experiment, female mice of the CBA strain were treated at day 17 of pregnancy with 1 microgram/g body weight of DES. The descendants of DES-treated mothers, described as F1DES, were mated among each other or with untreated animals. The F1DES females were found to be sterile when mated with either F1DES or untreated males. F1DES males were successfully mated with untreated females. In the female offspring so obtained, but not in the male, a statistically significant increased incidence of tumours was observed, in particular of uterine sarcomas, and also of benign ovarian tumours and of lymphomas.

Uma Devi P, Hossain M. 2000. Induction of solid tumours in the Swiss albino mouse by low-dose foetal irradiation. Int J Radiat Biol 76:95-99.
Abstract: Purpose: To study the tumourigenic effect of prenatal low-dose gamma-irradiation in the mouse.

Methods and materials: Pregnant Swiss albino mice were exposed to 0.1-1.5 Gy gamma-radiation on days 14 or 17 of gestation. The F-1 offspring were observed up to 18 months of age. All the mice were killed at 18 months and the incidence of tumours in different organs was recorded. Results: Exposure to doses from 0.1 to 1.5 Gy on days 14 or 17 of gestation produced a linear-quadratic dose-dependent increase in tumour incidence in adult F-1 mice. The main organs affected were the ovary, uterus, liver and spleen. The highest incidence was observed in the ovaries, which was significantly higher than spontaneous incidence, even at 0.25 Gy. In other organs the tumour incidence was not significant compared with controls at doses <0.5-1.0 Gy. Tumours in the ovary and uterus developed at an earlier age than in the liver and spleen. Conclusions: Exposure to gamma-radiation <1.0 Gy at the foetal period (days 14 or 17 of gestation) can cause induction of tumours in the Swiss albino mouse. The carcinogenic effect, particularly on the ovary among the female mouse, is detectable after low-dose foetal irradiation.

Urayama KY, Von Behren J, Reynolds P. 2007. Birth characteristics and risk of neuroblastoma in young children. Am J Epidemiol 165:486-95.
Abstract: The peak incidence of neuroblastoma during infancy suggests that certain prenatal or perinatal factors may be etiologically important. In this population-based study, California birth certificates were identified for 508 (86%) neuroblastoma cases diagnosed at less than 5 years of age between 1988 and 1997. For each case, two controls, matched on date of birth and gender, were randomly selected from the statewide birth registry. Results of multivariate analyses showed a reduced risk for children of Hispanic (odds ratio (OR) = 0.57, 95% confidence interval (CI): 0.43, 0.76) and "other" (OR = 0.56, 95% CI: 0.37, 0.85) race/ethnicity, compared with non-Hispanic Whites. Postterm/high birth weight delivery was associated with an increased risk of neuroblastoma compared with term/normal birth weight delivery among infants (OR = 6.99, 95% CI: 1.07, 45.55), while preterm birth appeared suggestive of a reduced risk among children 1-4 years of age. For children in this age group, the risk of neuroblastoma was elevated for cesarean delivery compared with vaginal delivery (OR = 1.72, 95% CI: 1.21, 2.47), and, for infants, the risk was reduced if the mother had had multiple previous pregnancies (OR = 0.39, 95% CI: 0.22, 0.69). These data suggest that etiologic factors associated with the prenatal and perinatal periods may be specific to age at neuroblastoma diagnosis.

Urquhart JD, Black RJ, Muirhead MJ, Sharp L, Maxwell M, Eden OB, Jones DA. 1991. Case-control study of leukemia and non-hodgkins-lymphoma in children in Caithness near the Dounreay nuclear installation. Br Med J 302:687-692.
Abstract: Objective-To examine whether the observed excess of childhood leukaemia and non-Hodgkin's lymphoma in the area around the Dounreay nuclear installation is associated with established risk factors, or with factors related to the plant, or with parental occupation in the nuclear industry. Design-Case-control study. Setting-Caithness local government district. Subjects-14 cases of leukaemia and non-Hodgkin's lymphoma occurring in children aged under 15 years diagnosed in the area between 1970 and 1986 and 55 controls matched for sex, date of birth, and area of residence within Caithness at time of birth. Main outcome measures-Antenatal abdominal x ray examination; drugs taken and viral infections during pregnancy; father's occupation; father's employment at Dounreay and radiation dose; distance of usual residence from the path of microwave beams, preconceptional exposure to non-ionising radiation in the father; and other lifestyle factors. Results-No raised relative risks were found for prenatal exposure to x rays, social class of parents, employment at Dounreay before conception or diagnosis, father's dose of ionising radiation before conception, or child's residence within 50 m of the path of microwave transmission beams. Results also proved negative for all lifestyle factors except an apparent association with use of beaches within 25 km of Dounreay. However, this result was based on small numbers, arose in the context of multiple hypothesis testing, and is certainly vulnerable to possible systematic bias. Conclusion-The raised incidence of childhood leukaemia and non-Hodgkin's lymphoma around Dounreay cannot be explained by paternal occupation at Dounreay or by paternal exposure to external ionising radiation before conception. The observation of an apparent association between the use of beaches around Dounreay and the development of childhood leukaemia and non-Hodgkin's lymphoma might be an artefact of multiple testing and influenced by recall bias.

Usuki S, Maekawa A, Kang HI, Shumiya S, Nagase S. 1992. High susceptibility of analbuminemic rats to neurogenic tumor-induction by transplacental administration of N-ethyl-N-nitrosourea. Jpn J Cancer Res 83:146-152.

Abstract: The susceptibilities of Nagase analbuminemic rats (NAR) and control Sprague-Dawley rats (SDR) to N-ethyl-N-nitrosourea (ENU) were compared. In Experiment I, the rats were given daily subcutaneous injections of 10 mg/kg of ENU for a week from 4 weeks of age. In Experiment II, mother rats were given a single subcutaneous injection of 60 mg/kg of ENU on day 17 of pregnancy and tumor development in their offspring was examined. In Experiment I, the incidence of neurogenic tumors was slightly, but not significantly, higher in NAR than in control rats. In Experiment II, the incidence of total tumors including neurogenic tumors was significantly higher in NAR (40/43, 93.0%) than in SDR (13/61, 21.3%). NAR showed particularly high susceptibility to induction of neurogenic tumors (34/43, 79.1%) and renal tumors (15/43, 34.9%). In an attempt to elucidate the underlying mechanisms of the increased susceptibility of NAR to ENU, O6-ethylguanine, a major premutagenic ethylated DNA adduct, was quantitated in fetal brain DNA of NAR and SDR after a pulse exposure to 60 mg/kg ENU. No significant difference in the initial formation or subsequent repair of O6-ethylguanine was observed in the two strains, indicating that abnormality at some later stage(s) of chemical carcinogenesis may lead to the increased susceptibility of NAR to induction of neurogenic tumors.

Valery PC, Mcwhirter W, Sleigh A, Williams G, Bain C. 2002. Farm exposures, parental occupation, and risk of Ewing's sarcoma in Australia: a national case-control study. Cancer Causes & Control 13:263-270.
Abstract: Objective: It has been suggested that parental occupation, particularly farming, increased the risk of Ewing's sarcoma in the offspring. In a national case-control study we examined the relationship between farm and other parental occupational exposures and the risk of cancer in the offspring. Methods: Cases were 106 persons with confirmed Ewing's sarcoma or peripheral primitive neuroectodermal tumor. Population-based controls (344) were selected randomly via telephone. Information was collected by interview (84% face-to-face). Results: We found an excess of case mothers who worked on farms at conception and/or pregnancy (odds ratio (OR) = 2.3, 95% confidence interval (CI) 0.5-12.0) and a slightly smaller excess of farming fathers; more case mothers usually worked as laborers, machine operators, or drivers (OR = 1.8, 95% CI 0.9-3.9). Risk doubled for those whose mothers handled pesticides and insecticides, or fathers who handled solvents and glues, and oils and greases. Further, more cases lived on farms (OR = 1.6, 95% CI 0.9-2.8). In the 0-20 years group, the risk doubled for those who ever lived on a farm (OR = 2.0, 95% CI 1.0-3.9), and more than tripled for those with farming fathers at conception and/or pregnancy (OR = 3.5, 95% CI 1.0-11.9). Conclusions: Our data support the general hypothesis of an association of Ewing's sarcoma family of tumors with farming, particularly at younger ages, who represent the bulk of cases, and are more likely to share etiologic factors.

Vallejo D, Sanz P, Picazo ML. 2001. A hematological study in mice for evaluation of leukemogenesis by extremely low frequency magnetic fields. Electro- & Magnetobiology 20:281-298.
Abstract: OF1 mice were chronically exposed to a 50-Hz sinusoidal East-West magnetic field of 15 muT (rms), in order to make a peripheral blood study for a leukemogenic evaluation of this non-ionizing radiation. Mating and pregnancy of ancestors (first generation), and birth, lactation, and development of second-generation female mice until adulthood occurred in the experimental field. A hematological study of both control and exposed 14- to 15-week-old and 50- to 52-week-old, second-generation females was realized. Individual diagnosis of specimens and statistical analysis of results revealed a high incidence of blood leukoproliferative disorders in 14- to 15-week-old exposed females (relative risk [RR] = 3.00, p = 0.0033). despite the resistance of this strain of mice to developing malignancies under normal environmental conditions before they are 26 weeks old. Especially elevated incidences of lymphocytic (RR = 6.50, p = 0.0021) and chronic (RR = 4.00, p = 0.0153) leukemias were associated with medium-term (14-15 weeks) exposure. After 50-52 weeks of exposure, the mortality of exposed mice was 30% versus 0% of control mice. From dead exposed females. 67% revealed some type of malignancy. Corresponding RR for blood leukoproliferative disorders of those exposed which survived was 2.57 (p = 0.0351). Especially important was the proportion of chronic leukemias after long-term (50-52 weeks) exposure (RR = 8.57, p = 0.0118). Moreover, a statistically nonsignificant increase of lymphoblastic-myeloblastic leukemias pointed to a relation between age of specimen and type of alteration. We suggest that the increase in blood leukemias in OF1 mice agrees with the results of numerous epidemiological studies.

van den Heuvel R, Gerber GB, Leppens H, Vander Plaetse F, Schoeters GE. 1995 . Long-term effects on tumour incidence and survival from 241Am exposure of the BALB/c mouse in utero and during adulthood. Int J Radiat Biol 68:679-686.

Abstract: BALB/c mice were given 100, 500 or 1500 Bq/g 241Am at day 14 of pregnancy. The offspring were separated from the mothers at birth and followed until death. In addition, adult females and one group of males were also studied for the effects of 241Am following treatment with 45-213 Bq/g. Adults treated with 241Am showed significantly shortened survival and increased incidence of osteosarcoma (to 40 - 50%). The data also suggest that the female mouse is more susceptible to induction of osteosarcoma than the male. There was also a significant increase in osteosarcoma, all bone tumours, all sarcomas, and all leukaemias in the offspring from the contaminated mothers, although this appeared to occur independently of dose. Calculations of the number of osteosarcomas induced per Gy varied for contamination of adult mice between 0.2 and 0.01 and for the offspring between 6 and 0.6. Thus, offspring seemed to be about 10 times more at risk if osteosarcomas induced per mouse Gy are compared. Surprisingly, offspring from mothers treated with 241Am displayed a longer survival time than controls, possibly due to fewer deterministic lung diseases appearing early in life.

van Wijngaarden E, Stewart PA, Olshan AF, Savitz DA, Bunin GR. 2003. Parental occupational exposure to pesticides and childhood brain cancer. Am J Epidemiol 157:989-997.
Abstract: The authors examined the risk of childhood brain cancer in relation to parental exposure to classes of pesticides among 154 children diagnosed with astrocytoma and 158 children diagnosed with primitive neuroectodermal tumors (PNET) in the United States and Canada between 1986 and 1989. Controls were selected by random digit dialing and were individually matched to cases by race, age, and geographic area. Each job in the fathers' work history and the usual occupation of mothers were assigned a probability, intensity, and frequency of exposure to insecticides, herbicides, and agricultural and nonagricultural fungicides. Elevated risks of astrocytoma were found for paternal exposure (ever vs. never) to all four classes of pesticides (odds ratio (OR) = 1.4-1.6). An increased risk of PNET was observed for only herbicides (OR = 1.5). For mothers, odds ratios for astrocytoma were elevated for insecticides, herbicides, and nonagricultural fungicides (OR = 1.3-1.6) but not agricultural fungicides (OR = 1.0). No indication was found of an increased risk for PNET. There was little indication for an association with cumulative and average parental exposure. Most risk estimates were around unity, and exposure-response patterns were absent. Overall, it seems unlikely that parental exposure to pesticides plays an important role in the etiology of childhood brain cancer.

Vandenberg LN, Maffini MV, Wadia PR, Sonnenschein C, Rubin BS, Soto AM. 2007. Exposure to environmentally relevant doses of the xenoestrogen bisphenol-A alters development of the fetal mouse mammary gland. Endocrinology 148:116-127.
Abstract: Humans are routinely exposed to bisphenol-A (BPA), an estrogenic compound that leaches from dental materials, food and beverage containers, and other plastic consumer products. Effects of perinatal BPA exposure on the mouse mammary gland have been observed in puberty and adulthood, long after the period of exposure has ended. The aim of this study was to examine fetal mammary gland development at embryonic day (E)18 and assess changes in the tissue organization and histoarchitecture after exposure to an environmentally relevant dose of BPA. In unexposed fetuses, the relative position of the fetus with respect to its female and male siblings in the uterus influenced growth of the ductal tree, which was more developed in females placed between two males than in females placed between two females. Exposure of dams to 250 ng BPA per kilogram body weight per day from E8 to E18 significantly increased ductal area and ductal extension in exposed fetuses and obliterated positional differences. In the stroma, BPA exposure promoted maturation of the fat pad and altered the localization of collagen. Within the epithelium, BPA exposure led to a decrease in cell size and delayed lumen formation. Because mammary gland development is dependent on reciprocal interactions between these compartments, the advanced maturation of the fat pad and changes in the extracellular matrix may be responsible for the altered growth, cell size, and lumen formation observed in the epithelium. These results suggest that alterations in mammary gland phenotypes observed at puberty and adulthood in perinatally exposed mice have their origins in fetal development.

Vatten LJ, Maehle BO, Lund Nilsen TI, Tretli S, Hsieh CC, Trichopoulos D, Stuver SO. 2002. Birth weight as a predictor of breast cancer: A case-control study in Norway. Br J Cancer 86:89-91.
Abstract: The hypothesis that birth weight is positively associated with adult risk of breast cancer implies that factors related to intrauterine growth may be important for the development of this malignancy. Using stored birth records from the two main hospitals in Trondheim and Bergen, Norway, we collected information on birth weight, birth length and placenta weight among 373 women who developed breast

cancer. From the same archives, we selected as controls 1150 women of identical age as the cases without a history of breast cancer. Information on age at first birth and parity were collected from the Central Person Registry in Norway. Based on conditional logistic regression analysis, breast cancer risk was positively associated with birth weight and with birth length (P for trend=0.02). Birth weights in the highest quartile (3730 g or more) were associated with 40% higher risk (odds ratio, 1.4, 95% confidence interval, 1.1-1.9) of breast cancer compared to birth weights in the lowest quartile (less than 3090 g). For birth length, the odds ratio for women who were 51.5 cm or more (highest quartile) was 1.3 (95% confidence interval, 1.0-1.8) compared to being less than 50 cm (lowest quartile) at birth. Adjustment for age at first birth and parity did not change these estimates. Placenta weight was not associated with breast cancer risk. This study provides strong evidence that intrauterine factors may influence future risk of breast cancer. A common feature of such factors would be their ability to stimulate foetal growth and, simultaneously, to influence intrauterine development of the mammary gland.

Vatten LJ, Nilsen TIL, Tretli S, Trichopoulos D, Romundstad PR. 2005. Size at birth and risk of breast cancer: Prospective population-based study. Int J Cancer 114:461-464.
Abstract: It has been hypothesized that birth size is positively associated with breast cancer risk in adulthood. We studied birth length, birth weight and head circumference at birth and subsequent risk for breast cancer in a cohort of 16,016 women in Norway. Birth length was positively associated with risk (p trend = 002), and women who were 53 cm or longer had a relative risk of 1.8 (CI = 1.2-2.6) compared with women who were shorter than 50 cm, after adjustment for birth year, length of gestation, birth order, maternal age, maternal marital status and socioeconomic status at childbearing. Mutual adjustment for birth weight did not influence the results, and further adjustment for maternal height and adult factors (age at first birth and parity) in a subset of the cohort did not change the results. For birth weight, women in the highest category (greater than or equal to 3,840 g) had an adjusted relative risk (RR) of 1.5 (CI = 1.0-2.2) compared to women in the lowest (< 3,040 g), but mutual adjustment for birth length attenuated this association (RR = 1.1; CI = 0.7-1.8). Head circumference at birth showed a similar association as birth weight, with attenuation after mutual adjustment for birth length. The positive association with birth length was stronger among women whose mothers were relatively tall (median or taller,p trend = 0.001) compared to women whose mothers were relatively short (below median, p trend = 0.67) at childbearing. The results provide evidence that intrauterine factors influence future breast cancer risk. The positive association related to birth length suggests that factors that stimulate intrauterine longitudinal growth are particularly important. (C) 2004 Wiley-Liss, Inc.

Verhagen W, Hubert CM, Mohtaschem E. 1993. Tumor-induction by transplacental infection with polyoma-virus of the F(1) generation of Wistar rats. Arch Virol 133:459-465.
Abstract: Intravenous polyoma virus inoculation into pregnant Wistar rats resulted in transplacental infection of the foetus, causing tumours and hydronephroses. Cyclosporin A reduced these effects significantly.

Verloop J, Rookus MA, van Leeuwen FE. 2000 . Prevalence of gynecologic cancer in women exposed to diethylstilbestrol in utero. New Engl& Journal of Medicine 342:1838-1839.

Von Tungeln LS, Xia QS, Bucci T, Heflich RH, Fu PP. 1999. Tumorigenicity and liver tumor ras-protooncogene mutations in CD-1 mice treated neonatally with 1-and 3-nitrobenzo[a]pyrene and their trans-7,8-dihydrodiol and aminobenzo[a]pyrene metabolites. Cancer Lett 137:137-143.
Abstract: The environmental pollutants 1- and 3-nitrobenzo[a]pyrene (1- and 3-NBaP) are metabolized by mammalian microsomes through ring oxidation to 1-NBaP trans-7,8-dihydrodiol and 3-NBaP trans-7,8-dihydrodiol, and by nitroreduction to 1- and 3-aminobenzo[a]pyrene. To determine if these compounds are tumorigenic, 1- and 3-NBaP, along with several of their metabolites and the parent benzo[a]pyrene (BaP) and its trans-7,8-dihydrodiol metabolite, were tested in the neonatal CD-I mouse bioassay. Male mice were administered i.p, injections at a total dose of 100 or 400 nmol per mouse on 1, 8 and 15 days after birth. While the liver tumor incidences for BaP, BaP trans-7,8-dihydrodiol, and the positive control 6-nitrochrysene (6-NC) were significantly higher than in the solvent control animals, all the other tested compounds exhibited no tumorigenicity. The frequency of Ha- and Ki-ras mutations in liver tumors of mice treated with BaP, BaP trans-7,8-dihydrodiol, and 6-NC were higher than in the few liver tumors isolated from control mice or mice treated with the NBaPs or their metabolites. Since 1- and 3-NBaP and their

metabolites are potent mutagens in the Salmonella assay and moderate mutagens in the Chinese hamster ovary (CHO) mammalian mutagenicity assay, our results indicate that the in vitro mutagenicity of these compounds does not correlate with their tumorigenicity. (C) 1999 Published by Elsevier Science Ltd. AU rights reserved.

Waalkes MP, Diwan BA, Ward JM, Devor DE, Goyer RA. 1995. Renal tubular tumors and atypical hyperplasias in B6C3F(1) mice exposed to lead acetate during gestation and lactation occur with minimal chronic nephropathy. Cancer Res 55:5265-5271.
Abstract: Lead is a high-priority hazardous substance in humans and a renal carcinogen in adult rodents. This study assessed the carcinogenic potential and toxicity of gestational and lactational lead exposure in (C57BL/6NCr x C3H/HeN)F-1 (hereafter called E6C3F(1)) mice. Effects of a renal tumor promoter [barbital sodium (BE)] on lead-initiated lesions were also studied. Pregnant female C57BL/6NCr mice (10-15/group) previously bred with C3H/HeN males were given lead acetate (0, 500, 750 and 1000 ppm lead) ad libitum in their drinking water, starting on gestation day 12 and continuing to 4 weeks postpartum. Offspring were then weaned and divided into same-sex groups of 23-25 and observed for a maximum of 112 weeks. Other groups received lead and then continuous BE (500 ppm) ad libitum in their drinking mater from weaning onward. In control male offspring (0 lead/0 BE), renal proliferative lesions [(RPLs); defined as atypical tubular hyperplasia or tumor] occurred rarely (1 lesion-bearing mouse/23 mice examined, 4%) and did not include tumors. RPLs increased in a dose-related fashion with lead exposure (500 lead/0 BE, 4/25, 16%; 750 lead/0 BE, 6/25, 24%; 1000 lead/0 BE, 12/25, 48%) in male offspring and more often multiple. Ail lead-treated groups had renal tumors, including carcinoma, but these were most common at the highest dose (1000 lead/0 BE, 5/25). Lead-induced renal tumors arose in the absence of the extensive chronic nephropathy and lead inclusion bodies typically seen with lead carcinogenesis in rodents exposed chronically as adults. Postnatal BE exposure had no effect on RPL incidence (e.g., 1000 lead/500 BE, 8/25, 32%). Lead-treated female offspring also developed RPLs, including adenoma and carcinoma, but at a much lower rate than males. Thus, short-term lead exposure during the gestational/lactational period has carcinogenic potential in the mouse kidney.

Waalkes MP, Liu J, Ward JM, Diwan BA. 2006. Enhanced urinary bladder and liver carcinogenesis in male CD1 mice exposed to transplacental inorganic arsenic and postnatal diethylstilbestrol or tamoxifen. Toxicol Appl Pharmacol 215:295-305.
Abstract: Pregnant CD1 mice received 85 ppm arsenite in the drinking water from gestation day 8 to 18, groups (n = 35) of male offspring were subsequently injected on postpartum days 1 through 5 with diethylstilbestrol (DES; 2 microg/pup/day) or tamoxifen (TAM; 10 microg/pup/day), and tumor formation was assessed over 90 weeks. Arsenic alone increased hepatocellular carcinoma (14%), adenoma (23%) and total tumors (31%) compared to control (0, 2 and 2%, respectively). Arsenic alone also increased lung adenocarcinoma, adrenal cortical adenoma and renal cystic tubular hyperplasia compared to control. Compared to arsenic alone, arsenic plus DES increased liver tumor incidence in mice at risk 2.2-fold and increased liver tumor multiplicity (tumors/liver) 1.8-fold. The treatments alone did not impact urinary bladder carcinogenesis, but arsenic plus TAM significantly increased formation of urinary bladder transitional cell tumors (papilloma and carcinoma; 13%) compared to control (0%). Urinary bladder proliferative lesions (combined tumors and hyperplasia) were also increased by arsenic plus TAM (40%) or arsenic plus DES (43%) compared to control (0%) or the treatments alone. Urinary bladder proliferative lesions occurred in the absence of any evidence of uroepithelial cytotoxic lesions. Urinary bladder lesions and hepatocellular carcinoma induced by arsenic plus TAM and/or DES overexpressed estrogen receptor-alpha, indicating that aberrant estrogen signaling may have been a factor in the enhanced carcinogenic response. Thus, in male CD1 mice, gestational arsenic exposure alone induced liver adenoma and carcinoma, lung adenocarcinoma, adrenal adenoma and renal cystic hyperplasia. Furthermore, DES enhanced transplacental arsenic-induced hepatocarcinogenesis. In utero arsenic also initiated urinary bladder tumor formation when followed by postnatal TAM and uroepithelial proliferative lesions when followed by TAM or DES.

Waalkes MP, Liu J, Ward JM, Diwan LA. 2004. Mechanisms underlying arsenic carcinogenesis: Hypersensitivity of mice exposed to inorganic arsenic during gestation. Toxicology 198:31-38.
Abstract: Inorganic arsenic is an important human carcinogen of unknown etiology. Defining carcinogenic mechanisms is critical to assessing the human health hazard of arsenic exposure but requires appropriate

model systems. It has proven difficult to induced tumors in animals with inorganic arsenic alone. Several groups have studied the carcinogenic potential of inorganic arsenic in rodents, finding it to act as co-promoter or co-carcinogen, but not as a complete carcinogen. As gestation is a time of high sensitivity to chemical carcinogenesis, we performed two in utero exposure studies with inorganic arsenic. In the first study, pregnant mice received drinking water containing sodium arsenite at 0 (control), 42.5 and 85 ppm arsenic from gestation day 8 to 18, and the offspring were observed for up to 90 weeks. As adults, male offspring developed hepatocellular carcinoma (HCC) and adrenal tumors after in utero arsenite exposure. Although liver tumors were not induced by arsenic in female offspring, they did develop lung carcinoma, ovarian tumors, and uterine and oviduct preneoplasia. In a second study, the same doses of arsenic were used and the skin tumor promoting phorbol ester, TPA, was applied to the skin after birth in an effort to promote skin tumors potentially initiated by arsenic in utero. TPA did not promote dermal tumors after in utero arsenite exposure. Otherwise, results from the second chronic study largely duplicated the first and, irrespective of additional TPA exposure, arsenic exposure in utero induced HCC and adrenal tumors in males and ovarian tumors in females. In addition, combined arsenic and TPA induced a significant increase in hepatocellular tumors in female offspring, although arsenic alone was not effective. Thus, in utero inorganic arsenic exposure can act as a complete carcinogen in mice, with brief exposures consistently inducing tumors at several sites. In addition, it appears gestational arsenic can act as a tumor initiator in the female mouse liver, inducing liver lesions that can be promoted by TPA.

Waalkes MP, Liu J, Ward JM, Powell DA, Diwan BA. 2006. Urogenital carcinogenesis in female CD1 mice induced by in utero arsenic exposure is exacerbated by postnatal diethylstilbestrol treatment. Cancer Res 66:1337-1345.
Abstract: Transplacental inorganic arsenic carcinogenicity, together with postnatal exposure to diethylstilbestrol or tamoxifen, was studied. Pregnant CD1 mice received 85 ppm arsenic in the drinking water from gestation days 8 to 18 and were allowed to give birth. Groups (n = 35) of female offspring were injected s.c. on postpartum days 1 through 5 with diethylstilbestrol (2 mu g/pup/d) or tamoxifen (10 mu g/pup/d) and observed for 90 weeks. Arsenic alone induced some urogenital system tumors, including mostly benign tumors of the ovary and uterus, and adrenal adenoma. Diethylstilbestrol alone induced some tumors (primarily cervical) but when given after in utero arsenic, it greatly enhanced urogenital tumor incidence, multiplicity, and progression. For instance, compared with the incidence of urogenital malignancies in the control (0%), arsenic alone (9%). and diethylstilbestrol alone (21%) groups, arsenic plus diethylstilbestrol acted synergistically, inducing a 48% incidence of malignant urogenital tumors. Of the urogenital tumors induced by arsenic plus diethylstilbestrol, 80% were malignant, and 55% were multiple site. Arsenic plus diethylstilbestrol increased ovarian, uterine, and vaginal tumors, and urinary bladder proliferative lesions, including three transitional cell carcinomas. Tamoxifen alone did not increase urogenital tumors or affect arsenic-induced neoplasia but did increase arsenic-induced uroepithelial proliferative lesions. Uterine and bladder carcinoma induced by arsenic plus diethylstilbestrol greatly overexpressed estrogen receptor-alpha (ER-alpha) and pS2, an estrogen-regulated gene. In neonatal uteri, prenatal arsenic increased ER-a expression and enhanced estrogen-related gene expression induced by postnatal diethylstilbestrol. Thus, arsenic acts with estrogens to enhance production of female mouse urogenital cancers.

Waalkes MP, Ward JM, Diwan BA. 2004. Induction of tumors of the liver, lung, ovary and adrenal in adult mice after brief maternal gestational exposure to inorganic arsenic: Promotional effects of postnatal phorbol ester exposure on hepatic and pulmonary, but not dermal cancers. Carcinogenesis 25:133-141.
Abstract: Arsenic is a recognized human carcinogen and development of rodent models remains a critically important research objective. Since gestation can be a period of high sensitivity to chemical carcinogenesis, we have performed a series of transplacental carcinogenicity studies in mice with inorganic arsenic. In this study, groups of pregnant C3H mice received drinking water containing sodium arsenite (NaAsO2) at 0, 42.5 and 85 p.p.m. arsenic ad libitum from days 8 to 18 of gestation. These doses of arsenic were well tolerated. Dams delivered normally and at weaning (4 weeks) offspring were randomly put into groups (n = 25) of males or females according to maternal dose. In an attempt to promote skin cancers initiated by transplacental arsenic, duplicate groups of control or arsenic exposed offspring were topically exposed to 12-O-tetradecanoyl phorbol-13-acetate (TPA; 2 mug/0.1 ml acetone, twice/week) from 4 to 25 weeks of age. Irrespective of TPA exposure, male offspring showed arsenic-induced dose-related increases in

hepatocellular carcinoma incidence and multiplicity, as well as increases in adrenal tumor incidence and multiplicity. In female offspring, an increase in epithelial ovarian tumors occurred with arsenic exposure regardless of TPA exposure. Females also showed pre-neoplastic lesions of the reproductive tract, including hyperplasia of the uterus and oviduct, after arsenic but independent of TPA exposure. Although TPA had no effect on skin tumors, it promoted arsenic initiated liver tumors in females and lung tumors in both sexes. Thus, inorganic arsenic, as a single agent, can consistently act as a complete transplacental carcinogen in mice, inducing tumors at multiple sites, and as a tumor initiator in some tissues. Skin tumors were not initiated by arsenic in mouse fetuses possibly indicating tissue-specific mechanisms of action. This study indicates that gestation is a period of high sensitivity to arsenic carcinogenesis.

Waalkes MP, Ward JM, Liu J, Diwan BA. 2003. Transplacental carcinogenicity of inorganic arsenic in the drinking water: induction of hepatic, ovarian, pulmonary, and adrenal tumors in mice. Toxicology & Applied Pharmacology 186:7-17.
Abstract: Arsenic is a known human carcinogen, but development of rodent models of inorganic arsenic carcinogenesis has been problematic. Since gestation is often a period of high sensitivity to chemical carcinogenesis, we performed a transplacental carcinogenicity study in mice using inorganic arsenic. Groups (n = 10) of pregnant C3H mice were given drinking water containing sodium arsenite (NaAsO(2)) at 0 (control), 42.5, and 85 ppm arsenite ad libitum from day 8 to 18 of gestation. These doses were well tolerated and body weights of the dams during gestation and of the offspring subsequent to birth were not reduced. Dams were allowed to give birth, and offspring were weaned at 4 weeks and then put into separate gender-based groups (n = 25) according to maternal exposure level. The offspring received no additional arsenic treatment. The study lasted 74 weeks in males and 90 weeks in females. A complete necropsy was performed on all mice and tissues were examined by light microscopy in a blind fashion. In male offspring, there was a marked increase in hepatocellular carcinoma incidence in a dose- related fashion (control, 12%; 42.5 ppm, 38%; 85 ppm, 61%) and in liver tumor multiplicity (tumors per liver; 5.6-fold over control at 85 ppm). In males, there was also a dose-related increase in adrenal tumor incidence and multiplicity. In female offspring, dose-related increases occurred in ovarian tumor incidence (control, 8%; 42.5 ppm, 26%; 85 ppm, 38%) and lung carcinoma incidence (control, 0%; 42.5 ppm, 4%; 85 ppm, 21%). Arsenic exposure also increased the incidence of proliferative lesions of the uterus and oviduct. These results demonstrate that oral inorganic arsenic exposure, as a single agent, can induce tumor formation in rodents and establishes inorganic arsenic as a complete transplacental carcinogen in mice. The development of this rodent model of inorganic arsenic carcinogenesis has important implications in defining the mechanism of action for this common environmental carcinogen.

Wakui S, Yokoo K, Takahashi H, Muto T, Suzuki Y, Kanai Y, Hano H, Furusato M, Endou H. 2005. CYP1 and AhR expression in 7,12-dimethylbenz[a] anthracene-induced mammary carcinoma of rats prenatally exposed to 3,3,4,4 ',5-pentachlorobiphenyl. Toxicology 211:231-241.
Abstract: We previously reported the finding that prenatal exposure to a relatively low dose of 3,3',4,4',5-pentachlorobiphenyl (PCB 126) acted as an enhancing agent for 17-beta-estradiol (E2)-dependent 7,12-dimethylbenz[a]anthracene (DMBA)-induced rat mammary carcinoma, while a high dose decreased it. E2 is a known risk factor for mammary carcinoma, and CYP1A1 and 1B1 (CYP1) are the major enzymes catalyzing 2- and 4-hydroxylation of E2, respectively. We investigated the induction of CYP1 and aryl hydrocarbon receptor (AhR) in DMBA-induced mammary carcinoma using female Sprague-Dawley rats whose dams had been treated (i.g.) with 2.5 ng, 250 ng, 7.5 mu g of PCB 126/kg or the vehicle on days 13-19 post-conception. Immunohistochemical analysis revealed that the mammary carcinoma of the 250 ng group showed a significantly higher number of nuclei expressing estrogen receptor alpha (ER) and proliferating cell nuclear antigen (PCNA) compared to those of the other groups. Quantitative real-time RT-PCR analysis revealed that the 7.5 mu g group showed a significantly higher level of CYP1A1 mRNA, and that the 250 ng group showed significantly higher levels of CYP1B1 mRNA. The level of AhR mRNA was significantly higher in both the 7.5 mu g and 250 ng groups. Western blotting analysis was consistent with mRNA changes. It has been revealed that CYP1B1 catalyzes a step in the formation of 4-hydroxylated E2 metabolites, which show quite high mammary carcinogenicity. This study indicates that the enhancement of DMBA-induced mammary carcinogenicity in a relatively low PCB126 dose group might partially involve the higher expression of CYP1B1 and AhR in these carcinomas. (C) 2005 Elsevier Ireland Ltd. All rights reserved.

Wakui S, Yokoo K, Takahashi H, Muto T, Suzuki Y, Kanai Y, Hano H, Furusato M, Endou H. 2006. Prenatal 3,3',4,4',5-pentachlorobiphenyl exposure modulates induction of rat hepatic CYP 1A1, 1B1, and AhR by 7,12-dimethylbenz[a]anthracene. Toxicology & Applied Pharmacology 210:200-211.
Abstract: We previously reported the finding that prenatal exposure to a relatively low dose of PCB126 increases the rate of DMBA-induced rat mammary carcinoma, while a high dose decreased it. One of the most important factors determining the sensitivity to mammary carcinogenesis is the metabolic stage at administration of the carcinogenic agent. DMBA is a procarcinogen that recruits the host metabolism to yield its ultimate carcinogenic form, and CYP1A1 and CYP1B1 (CYP1)conduct this metabolism. We investigated the hepatic expression of CYP1 and AhR following oral administration of DMBA (100 mg/kg b.w.) (i.g.) to 50-day-old female Sprague-Dawley rats whose dams had been treated (i.g.) with 2.5 ng, 250 ng, 7.5 mu g of PCB126/kg or the vehicle on days 13 to 19 post-conception. Real-time quantitative RTPCR analysis revealed that the prenatal exposure to a relatively low dose of PCB126 (the 250 ng group) prolonged the higher expression of CYP1A1, CYP1B1, and AhR mRNA, white prenatal exposure to a high dose of PCB126 (the 7.5 mu g group) prolonged the higher expression of CYP1A1 and AhR mRNA. Western blotting and immunohistochemical analyses were consistent with mRNAs changes. Because DMBA oxidation produces a highly mutagenic metabolite and is finally catalyzed by CYP1B1, a relatively low PCB126 dose might produce the biological character to potentially increase the risk of DMBA-induced mammary carcinoma. (c) 2005 Elsevier Inc. All rights reserved.

Walker AH, Bernstein L, Warren DW, Warner NE, Zheng X, Henderson BE. 1990. The effect of in utero ethinyl oestradiol exposure on the risk of cryptorchid testis and testicular teratoma in mice. Br J Cancer 62:599-602.
Abstract: Epidemiological findings indicate that both cryptorchid testis and testicular germ cell cancer may be a result of high maternal oestrogen levels early in pregnancy. An experiment was conducted with a mouse strain (129 Sv-S1 C P) in which the males are susceptible to testicular teratomas to determine if the frequency of undescended testis and testicular teratoma in male offspring could be increased by administration of ethinyl oestradiol (EE) to pregnant mice before day 13 of gestation. This point in gestation marks the completion of the migration of germ cells to the gonadal ridge in mice and other studies with these mice have shown that the tumours are initiated in this critical time period. EE mixed with corn oil was administered by subcutaneous injection in doses of 0.02 (n = 76) and 0.2 (n = 102) mg kg-1 of body weight on gestational days 11 and 12. These mice were allowed to deliver their offspring and the males were killed at 15 days of age. Since the tumours are present from birth, this amount of time was allowed to permit the tumours to reach sufficient size for easy visual identification. Compared to controls (n = 63), who received corn oil alone, the treated mothers produced offspring who were significantly more likely to have a cryptorchid testis (P = 0.0001) and who had an increased risk, although not significant, of a testicular teratoma.

Walker BE. 1983. Uterine tumors in old female mice exposed prenatally to diethylstilbestrol. J Natl Cancer Inst 70:477-484.
Abstract: Pregnant strain CD-1 mice were treated with diethylstilbestrol (DES) or vehicle. Their female offspring were raised to old age and autopsied when terminally ill. Squamous metaplasia and adenomyosis were more common in uteri of these old mice exposed prenatally to DES than in control mice. Tumors of the uterine horns were seen in 17 of 143 DES-exposed mice and in 3 of 64 control mice. The controls had only leiomyomas, whereas 14 of the DES-exposed mice had adenocarcinomas. There were 5 cervical adenocarcinomas and 1 vaginal adenocarcinoma among treated mice but none in the control mice. Thus the effects of prenatal exposure to DES interacted with the effects of aging to produce a relatively high frequency of uterine adenocarcinoma.

Walker BE. 1984. Tumors of female offspring of mice exposed prenatally to diethylstilbestrol. J Natl Cancer Inst 73:133-140.
Abstract: Strain CD-1 female mice exposed prenatally to diethylstilbestrol (DES) (CAS: 56-53-1; alpha,alpha'-diethyl-4,4'-stilbenediol) were mated to unexposed males. Female offspring of these matings were raised to the stage of terminal illness. They were never exposed to DES and so have been referred to as "DES-lineage mice." Ten uterine adenocarcinomas and 5 ovarian cystadenocarcinomas were found in 40 DES-lineage mice. These findings were significantly different from the absence of such tumors in 24 "vehicle-lineage" mice whose mothers had received injections only of oil and alcohol. The types of tumors

that commonly occur spontaneously in the CD-1 strain appeared with comparable frequency in the 2 groups of mice. The DES-lineage mice did not show the increased frequency of adenomyosis and squamous metaplasia of the uterus, nor the reduced frequency of corpora lutea seen in mice exposed prenatally to DES.

Walker BE, Haven MI. 1997. Intensity of multigenerational carcinogenesis from diethylstilbestrol in mice. Carcinogenesis 18:791-793.
Abstract: Mice exposed prenatally to diethylstilbestrol (DES-exposed mice) can transmit a carcinogenic influence to the next generation (DES-lineage mice) when mated to control mice. The persistence of this effect was studied one generation further (DES-lineage-2 mice) by mating DES- lineage female mice to control males. The interaction of maternal dietary fat levels with DES was also tested by feeding high and low levels of dietary fat during the pregnancies that produced the final two generations. DES-lineage-2 mice, exposed to low or high fat maternal diets, had significantly more tumors than control mice with corresponding dietary fat exposure. The frequency of tumors in DES- lineage-2 mice was not significantly lower than in DES-lineage mice from a previous experiment. Thus, the multigenerational effect of DES is relatively intense in mice. If this type of carcinogenesis can occur in the human population, it poses a major threat to future generations.

Walker BE, Kurth LA. 1993 . Pituitary tumors in mice exposed prenatally to diethylstilbestrol. Cancer Res 53:1546-1549.
Abstract: Hyperprolactinemia and prolactinomas are among the abnormalities reported for women exposed prenatally to diethylstilbestrol (DES). To pursue this issue in an animal model replicating the other abnormalities of prenatal DES exposure, pituitary glands were studied in the offspring of CD-1 mice receiving an i.p. injection of 1 or 2 micrograms DES/g body weight during late pregnancy. Among 132 mice exposed prenatally to DES and then raised to terminal illness, there were 24 pituitary tumors compared to only 1 tumor among 64 controls. The tumors consisted predominantly of cells with an eccentric nucleus and cytoplasm characterized by an acidophilic core and basophilic rim. These cells were identified as lactotrophs on the basis of prolactin immunohistochemistry and by an expected variation in frequency relative to physiological states. Evaluation of ovaries from the same mice revealed a deficiency of corpora lutea and an elevated incidence of ovarian tumors. These findings are consistent with abnormal sex differentiation of the fetal hypothalamus being the cause of most adverse effects from prenatal DES exposure.

Walker DM, Malarkey DE, Seilkop SK, Ruecker FA, Funk KA, Wolfe MJ, Treanor CP, Foley JF, Hahn FF, Hardisty JF, Walker VE. 2007. Transplacental carcinogenicity of 3 '-azido-3 '-deoxythymidine in B6C3F1 mice and f344 rats. Environ Mol Mutagen 48:283-298.
Abstract: The prophylactic use of zidovudine (3'-azido-3'-deoxythymidine, AZT) during pregnancy greatly reduces transmission of HIV-1 from infected mothers to their infants; however, the affinity of host cell DNA polymerases for AZT also allows for its incorporation into host cell DNA, predisposing to cancer development. To expand upon previous transplacental carcinogenesis assays performed in CD-1 mice, the transplacental carcinogenicity of AZT was evaluated in a second mouse strain and a second rodent species. Date-mated female mice and rats were gavaged daily with 0, 80, 240, or 480 mg AZT/kg bw during the last 7 days of gestation. At 2 years postpartum, male and female B6C3Fl mouse and F344 rat offspring (n=44-46 of each sex and species/treatment group) were necropsied for gross and microscopic tissue examinations. Under the conditions of these two-year studies, there was clear evidence of carcinogenic activity based upon significant dose-related trends and increases in the incidences of hemangiosarcoma in male mice and mononuclear cell leukemia in female rats. There was some evidence of carcinogenic activity in the livers of male mice based upon a positive trend and an increased incidence of hepatic carcinoma in the high-dose AZT group. The incidence of gliomas in female rats exceeded the historical background rates for gliomas in F344 rats. P53 overexpression was detected in some AZT-treated mouse neoplasms. These and other cancer-related findings confirm and extend those of previous transplacental carcinogenicity studies of AZT in mice, support the need for long-term followup of nucleoside reverse transcriptase inhibitor (NRTI)-exposed children, and indicate the necessity for effective protective strategies against NRTI-induced side effects. Environ. Mal. Mutagen. 48:283-298, 2007. (c) 2007 Wiley-Liss, Inc.

Wan J, Winn LM. 2006. In utero-initiated cancer: the role of reactive oxygen species. Birth Defects Res C Embryo

Today 78:326-32.
Abstract: It is becoming more evident that not only can drugs and environmental chemicals interfere with normal fetal development by causing structural malformations, such as limb defects, but that xenobiotic exposure during development can also cause biochemical and functional abnormalities that may ultimately lead to cancer later on in life. Fetal toxicity may be partly mediated by the embryonic bioactivation of xenobiotics to free radical intermediates that can lead to oxidative stress and potentially lead, in some cases, to carcinogenesis. Using a number of examples, this review will focus on the role of reactive oxygen species (ROS) in the mechanisms pertaining to in utero initiated cancers.

Wanderas EH, Grotmol T, Fossa SD, Tretli S. 1998 . Maternal health and pre- and perinatal characteristics in the etiology of testicular cancer: a prospective population- and register-based study on Norwegian males born between 1967 and 1995. Cancer Causes & Control 9:475-486.
Abstract: OBJECTIVES: The aim of the present prospective study was to identify possible risk factors of testicular cancer (TC) in relation to gestation and birth. METHODS: Based on data from compulsory birth and cancer registration in Norway, odds ratios (ORs) of TC were estimated. RESULTS: Among 868068 males born between 1967 and 1995, 268 cases of germ cancer had developed by June 1996, 32 TCs before 5 years of age and 236 TCs thereafter, 48 cases being seminomas and 220 non-seminomas. There was a tendency of an inverse association between parity and TC. A previous finding from Sweden linking neonatal jaundice to risk of non-seminomas was confirmed (adjusted OR = 2.1, 95 percent confidence interval [CI] = 1.3-6.9). Significant associations were also seen for seminomas and TC diagnosed after 5 years of age. Maternal disease diagnosed before pregnancy increased the risk of TC significantly, particularly in the age group 0-4 years: Adjusted OR = 3.0, CI = 1.4-6.3. Retained placenta was significantly associated with both seminomas and non-seminomas and with TC diagnosed after 5 years of age. CONCLUSIONS: The findings of this study support the existing hypothesis that pre- and perinatal risk factors are of significance for development of TC in children and in young adults, and for seminomas and non-seminomas. The hypothesis that estrogens are involved in TC development was, among other factors, supported by the association of parity to TC. Additionally, on the basis of findings in maternal diseases and complications to pregnancy, we suggest that immune reactions during foetal life may be of significance for development of TC.

Wang SL, Chang YC, Chao HR, Li CM, Li LA, Lin LY, Papke O. 2006. Body burdens of polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls and their relations to estrogen metabolism in pregnant women. Environ Health Perspect 114:740-745.
Abstract: Polychlorinated dibenzo-p-dioxins (PCDDs, dioxins), polychlorinated dibenzofurans (PCDFs), and polychlorinated biphenyls (PCBs) are environmental endocrine disruptors that have half-lives of 7-10 years in the human body and have toxicities that probably include carcinogenesis. A high ratio of 4-hydroxyl estradiol (4-OH-E-2) to 2-hydroxyl estradiol (2-OH-E-2) has been suggested as a potential biomarker for estrogen-dependent neoplasms. In this cohort study of maternal-fetal pairs, we examined the relationship of PCDD/PCDF and PCB exposure to levels of estrogen metabolites in the sera of 50 pregnant women 25-34 years of age from central Taiwan. Maternal blood was collected during the third trimester, and the placenta was collected at delivery. We measured 17 dioxin congeners, 12 dioxin-like PCBs, and 6 indicator PCBs in placenta using gas chromatography coupled with high-resolution mass spectrometry. Estrogen metabolites in maternal serum were analyzed by liquid chromatography tandem mass spectrometry. The ratio of 4-OH-E2:2-OH-E-2 decreased with increasing exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (beta = -0.124, p = 0.004 by the general linear regression model, R = 0.4). Meanwhile, serum levels of 4-OH-E2 increased with increasing concentrations of high-chlorinated PCDFs (i.e., I,2,3,4,6,7,8-hepta-CDF: P = 0.454, p = 0.03, R = 0.30). Altered estrogen catabolism might be associated with body burdens of PCDDs/PCDFs. Our study suggests that exposure to PCDDs/PCDFs significantly affects estrogen metabolism. Therefore, PCDD/PCDF exposure must be considered when using the OH-E-2 ratio as a breast cancer marker.

Wang XJ, Bartolucci-Page E, Fenton SE, You L. 2006. Altered Mammary Gland Development in Male Rats Exposed to Genistein and Methoxychlor. Toxicol Sci 91:93-103.
Abstract: Genistein (GE) is a prevalent phytoestrogen whose presence in human and animal foods may affect biological actions of synthetic endocrine active compounds. We have previously reported that in utero and lactational exposure to high doses of GE or the endocrine active pesticide methoxychlor (MXC)

caused mammary epithelial proliferation in 21-day-old male rats. Combined exposure to GE and MXC resulted in significant feminization of the male mammary glands. The goals of the current study were to evaluate mammary responses to GE and MXC at the adult stage and investigate relevant mechanisms. Following in utero, lactational exposure (through maternal diet), and direct dietary exposure, the inguinal mammary gland of male rats (90 days of age) was found to exhibit significant morphological alterations in the groups treated with GE and/or MXC compared to the control. GE exposure (at 300 and 800 ppm concentrations) caused lobular enlargement and epithelial proliferation, whereas MXC exposure (800 ppm) led to ductal elongation and lobular enlargement. Combining the two treatments caused prominent proliferation of both ducts and alveoli; secretory material was seen in readily recognizable alveolar lumens, which are absent in untreated male mammary. We also surveyed gene expression in the mammary tissue using a cDNA microarray and evaluated relevant protein factors. The results indicated that the treatment effects are likely due to interactions between steroid hormone receptor-mediated signals and growth factor-driven cellular pathways. The distinctive responses associated with the GE+MXC combination were likely linked to enhanced actions of insulin-like growth factor 1 and related downstream pathways.

Wartenberg D. 2001. Residential EMF exposure and childhood leukemia: Meta-analysis and population attributable risk. Bioelectromagnetics Suppl 5:S86-104.
Abstract: The controversy over the possible association between magnetic field exposure and childhood leukemia has led several researchers to summarize the literature using meta-analysis. This paper reviews these previous meta-analyses and extends them by adding results from four studies published since the most recent analysis. The analyses include odds ratio calculations based on both dichotomous and continuous exposure models, heterogeneity analysis including subgroup summaries and meta-regression, "leave one out" influence analyses, and publication bias assessments. In addition, there is a review of some of the considerations of the exposure assessments used in the studies and their implications for cross-study comparisons. Finally, the results of the analyses using dichotomous and continuous exposure model are combined with national exposure data to estimate the population attributable risk of childhood leukemia among children in the US. If an association exists, as many as 175-240 cases of childhood leukemia in the US may be due to magnetic field exposure.

Webster J, Anand P, Yu B, Khan G, Dettin LE, De Assis S, Shajahan A, Hilakivi-Clarke L. 2005. Does High in Utero Hormonal Environment Increase Breast Cancer Risk by Affecting Mammary Stem/Progenitor Cell Populations? Pediatr Res 58:1010.

Wechsler W, Rice JM, Vesselinovitch SD. 1979 . Transplacental and neonatal induction of neurogenic tumors in mice: Comparison with related species and with human pediatric neoplasms. Natl Cancer Inst Monogr :219-226.
Abstract: The literature on chemical induction and natural occurrence of neurogenic tumors in mice and some unpublished data from our laboratories are reviewed. Neurogenic tumors are a minor component of the total tumorigenic response of mice to alkylating agents such as ENU and MNU. In comparison with rats, a given dose of ENU induces a much lower incidence of neurogenic tumors in mice, and the mean latency is much longer than in rats. Although most neurogenic tumors induced by ENU in mice by either transplacental or direct postnatal exposure are of glial or Schwann cell origin, as in rats, and occur most frequently in the cerebrum or cranial nerves, respectively, medulloblastomas of the cerebellum also occur in treated mice. Transplacental and neonatal exposure to ENU were much more effective in inducing neurogenic tumors than treatment later in life. Ependymomas were not seen in mice, although they are common in ENU-treated rats. Neuroblastoma of the adrenal medulla, a common human pediatric tumor, has not been induced to either species, but it does occur spontaneously in mice. The induction by ENU of medulloblastomas demonstrates that this rodent equivalent of an embryonal tumor of the human nervous system can result from exposure to exogenous chemical agents.

Weidman JR, Dolinoy DC, Murphy SK, Jirtle RL. 2007. Cancer susceptibility: epigenetic manifestation of environmental exposures. Cancer J 13:9-16 .
Abstract: Cancer is a disease that results from both genetic and epigenetic changes. Discordant phenotypes and varying incidences of complex diseases such as cancer in monozygotic twins as well as genetically identical laboratory animals have long been attributed to differences in environmental exposures. Accumulating evidence indicates, however, that disparities in gene expression resulting from variable

modifications in DNA methylation and chromatin structure in response to the environment also play a role in differential susceptibility to disease. Despite a growing consensus on the importance of epigenetics in the etiology of chronic human diseases, the genes most prone to epigenetic dysregulation are incompletely defined. Moreover, neither the environmental agents most strongly affecting the epigenome nor the critical windows of vulnerability to environmentally induced epigenetic alterations are adequately characterized. These major deficits in knowledge markedly impair our ability to understand fully the etiology of cancer and the importance of the epigenome in diagnosing and preventing this devastating disease.

Weir HK, Marrett LD, Kreiger N, Darlington GA, Sugar L. 2000. Pre-natal and peri-natal exposures and risk of testicular germ-cell cancer. Int J Cancer 87:438-443.
Abstract: The present case-control study was undertaken to investigate the association between exposure to maternal hormones and risk of testicular germ-cell cancer by histologic subgroups. Cases were males, aged 16 to 59 years, diagnosed with testicular germ-cell cancer in Ontario between 1987 and 1989. Histologic review was performed on all eligible cases for the purpose of categorizing cases as seminoma or non-seminoma (the latter classified 2 ways, with and without tumors containing seminoma). Risk factor data were collected on 502 cases, 346 case mothers, 975 age-matched controls, and 522 control mothers. Exogenous hormone exposure was associated with elevated risk (OR = 4.9, 95% CI 1.7-13.9). Several additional risk factors were associated with risk of testicular cancer: bleeding and threatened miscarriage (OR = 0.6, 95% CI 0.3-1.0), maternal cigarette smoking (12+ cigarettes/day OR = 0.6, 95% CI 0. 4-1.0). pre-term birth (OR = 1.6, 95% CI 1.0-2.5), and treatment for undescended testicle (OR = 8.0, 95% CI 3.2-20.0). First births were associated with elevated risk (OR = 1.7, 95% CI 1.0-2.8) among mothers below the age of 24 years at conception. There was little evidence that risk factors differed by histologic subgroup. We found evidence that exposure to maternal hormones, particularly estrogens, is associated with testicular germ-cell cancer risk. Not only does exposure to elevated levels (exogenous hormone use, pre-term birth, and first births among young mothers) increase risk but also exposure to relatively lower levels (heavy cigarette consumption and, perhaps, bleeding and threatened miscarriage) may decrease cancer risk.

Weiss HA, Potischman NA, Brinton LA, Brogan D, Coates RJ, Gammon MD, Malone KE, Schoenberg JB. 1997. Prenatal and perinatal risk factors for breast cancer in young women. Epidemiology 8:181-187.
Abstract: There is increasing interest in the role of early life exposures in breast carcinogenesis, especially estrogen exposure in utero. Estrogen levels during pregnancy may be higher in twin pregnancies and among older women and slightly lower among smokers. We analyzed early life risk factors in a population-based case-control study in the United States of 2,202 breast cancer cases and 2,009 controls under age 55 years. Twins were at an increased risk of breast cancer compared with singletons (relative risk = 1.62; 95% confidence interval = 1.0-2.7), particularly women with a twin brother (relative risk = 2.06), a finding consistent with the observation of high estrogen levels in dizygotic twin pregnancies. Little association was seen between maternal age at birth and breast cancer risk. We carried out further analyses for 534 cases and 497 controls under age 45 years, using data from a questionnaire completed by their mothers relating to the daughters' early life exposures. There was no evidence of an effect of smoking or diethylstilbestrol exposure during pregnancy on daughters' breast cancer risk. A reduced breast cancer risk was seen among women who had been breastfed (relative risk = 0.74; 95% confidence interval = 0.6-1.0). These findings indicate some effect of early life exposures on breast cancer risk, although the role of estrogen exposure may be less central than previously suggested.

Welshons WV, Nagel SC, Vom Saal FSV. 2006. Large effects from small exposures. III. Endocrine mechanisms mediating effects of bisphenol A at levels of human exposure. Endocrinology 147:S56-S69.
Abstract: Over 6 billion pounds per year of the estrogenic monomer bisphenol A (BPA) are used to manufacture polycarbonate plastic products, in resins lining metal cans, in dental sealants, and in blends with other types of plastic products. The ester bond linking BPA molecules in polycarbonate and resins undergoes hydrolysis, resulting in the release of free BPA into food, beverages, and the environment, and numerous monitoring studies now show almost ubiquitous human exposure to biologically active levels of this chemical. BPA exerts estrogenic effects through the classical nuclear estrogen receptors, and BPA acts as a selective estrogen receptor modulator. However, BPA also initiates rapid responses via estrogen receptors presumably associated with the plasma membrane. Similar to estradiol, BPA causes changes in some cell functions at concentrations between 1 pM and 1 nM, and the mean and median range of unconjugated BPA measured by multiple techniques in human pregnant maternal, fetal, and adult blood

and other tissues exceeds these levels. In contrast to these published findings, BPA manufacturers persist in describing BPA as a weak estrogen and insist there is little concern with human exposure levels. Our concern with human exposure to BPA derives from 1) identification of molecular mechanisms mediating effects in human and animal tissues at very low doses, 2) in vivo effects in experimental animals caused by low doses within the range of human exposure, and 3) widespread human exposure to levels of BPA that cause adverse effects in animals.

Wen WQ, Shu XO, Potter JD, Severson RK, Buckley JD, Reaman GH, Robison LL. 2002. Parental medication use and risk of childhood acute lymphoblastic leukemia. Cancer 95:1786-1794.
Abstract: BACKGROUND. Few studies have examined the risk of childhood acute lymphoblastic leukemia (ALL) associated with parental medication use. As part of a large case-control study conducted by the Children's Cancer Group, we evaluated the association between maternal and paternal medication use and the risk of ALL in offspring. METHODS. Information on selected medication use in the year before and during the index pregnancy was obtained by telephone interview. Participants included 1842 children of 14 years or younger with newly diagnosed and immunophenotypically defined ALL and 1986 individually matched controls. Data were analyzed using logistic regression models and stratified by immunophenotypes of ALL and age at diagnosis of cases. RESULTS. After adjusting for potential confounders and other medication use, we found that maternal use of vitamins (odds ratio [OR] = 0.7, 99% confidence interval [CI]: 0.5-1.0) and iron supplements (OR = 0.8, 99% CI: 0.7-1.0) only during the index pregnancy was associated with a decreased risk of ALL. Parental use of amphetamines or diet pills and mind-altering drugs before and during the index pregnancy was related to an increased risk of childhood ALL, particularly among children where both parents reported using these drugs (OR = 2.8, 99% CI: 0.5-15.6 for amphetamines or diet pills, OR = 1.8, 99% CI: 1.1-3.0 for mind-altering drugs). Stratified analyses showed that maternal use of antihistamines or allergic remedies and parental use of mind-altering drugs were strongly associated with infant ALL, whereas patterns of association between childhood ALL and parental medication use did not influence markedly the immunophenotypic subgroup of ALL. CONCLUSIONS. The findings of this study suggest that certain parental medication use immediately before and (luring the index pregnancy may influence risk of ALL in offspring. (C) 2002 American Cancer Society.

Wetherill YB, Petre CE, Monk KR, Puga A, Knudsen KE. 2002. The xenoestrogen bisphenol A induces inappropriate androgen receptor activiation and mitogenesis in prostatic adenocarcinoma cells. Molecular Cancer Therapeutics 1:515-524 .
Abstract: Treatment for prostatic adenocarcinoma is reliant on the initial androgen dependence of this tumor type. The goal of therapy is to eliminate androgen receptor activity, either through direct inhibition of the receptor or through inhibition of androgen synthesis. Although this course of therapy is initially effective, androgen-refractory tumors ultimately arise and lead to patient morbidity. Factors contributing to the transition from a state of androgen dependence to the androgen-refractory state are poorly understood, but clinical evidence in androgen-refractory tumors suggests that the androgen receptor is inappropriately activated in these cells. Thus, the mechanisms that contribute to inappropriate (androgen-independent) activation of the androgen receptor (AR) is an area of intensive research. Here we demonstrate that bisphenol A (BPA), a polycarbonate plastic monomer and established xenoestrogen, initiates androgen-independent proliferation in human prostatic adenocarcinoma (LNCaP) cells. The mitogenic capacity of BPA occurred in the nanomolar range, indicating that little BPA is required to stimulate proliferation. We show that BPA stimulated nuclear translocation of the tumor-derived receptor (AR-T877A), albeit with delayed kinetics compared with dihydrotestosterone. This translocation event was followed by specific DNA binding at androgen response elements, as shown by electrophoretic mobility shift assays. Moreover, the ability of BPA to stimulate AR-T877A activity was demonstrated by reporter assays and by analysis of an endogenous AR target gene, prostate-specific antigen. Thus, BPA is able to activate AR-T877A in the absence of androgens. Lastly, full mitogenic function of BPA is dependent on activation of the tumor-derived AR-T877A. These data implicate BPA as an inappropriate mitogen for prostatic adenocarcinoma cells and provide the impetus to study the consequence of BPA exposure on prostate cancer.

Whyatt RM, Jedrychowski W, Hemminki K, Santella RM, Tsai WY, Yang K, Perera FP. 2001. Biomarkers of polycyclic aromatic hydrocarbon-DNA damage and cigarette smoke exposures in paired maternal and newborn blood samples as a measure of differential susceptibility. Cancer Epidemiology Biomarkers &

Prevention 10:581-588.
Abstract: Human and experimental evidence indicates that the developing fetus may be more susceptible than the adult to the effects of certain carcinogens, including some polycyclic aromatic hydrocarbons (PAHs), Factors that can modulate susceptibility include proliferation rates, detoxification capabilities, and DNA repair capacity. Biomarkers can facilitate quantification of age-related susceptibility among human populations. In this study, we report on three biomarkers measured in paired blood samples collected at birth from 160 Polish mothers and newborns: 70 pairs from Krakow (a city with high air pollution including PAHs) and 90 pairs from Limanowa (an area with lower ambient pollution but greater indoor coal use). Biomarkers were: WBC aromatic-DNA adducts by P-32-postlabeling and PAH-DNA adducts by ELISA (as indicators of DNA damage from PAHs and other aromatics) and plasma cotinine (as an internal dosimeter of cigarette smoke). Correlations were assessed by Spearman's rank test, and differences in biomarker levels were assessed by the Wilcoxon signed-ranks test. A significant correlation between paired newborn/maternal samples was seen for aromatic-DNA adduct levels (r 0.3; P < 0.001) and plasma cotinine (r = 0.8; P < 0.001) but not PAH-DNA adduct levels (r = 0.14; P = 0.13). Among the total cohort, levels of the three biomarkers were higher in newborn samples compared with paired maternal samples. The difference was significant for aromatic-DNA adduct levels (16.6 +/- 12.5 versus 14.21 +/- 15.4/10(8) nucleotides; P = 0.002) and plasma cotinine (14.2 +/- 35.5 versus 8.3 +/- 24.5 ng/ml; P < 0.001) but not for PAH-DNA adduct levels (7.9 +/- 9.9 versus 5.9 +/- 8.2/ 10(8) nucleotides; P = 0.13). When analyses were restricted to the 80 mother/newborn pairs from whom the blood sample was drawn concurrently (within 1 h of each other), levels of all of the three biomarkers were significantly higher in the newborn compared with paired maternal blood samples (P < 0.05). Results suggest reduced detoxification capabilities and increased susceptibility of the fetus to DNA damage, especially in light of experimental evidence that transplacental exposures to PAHs are 10-fold lower than paired maternal exposures. The results have implications for risk assessment, which currently does not adequately account for sensitive subsets of the population.

Whyatt RM, Perera FP, Jedrychowski W, Santella RM, Garte S, Bell DA. 2000. Association between polycyclic aromatic hydrocarbon-DNA adduct levels in maternal and newborn white blood cells and glutathione S-transferase P1 and CYP1A1 polymorphisms. Cancer Epidemiology Biomarkers & Prevention 9:207-212.
Abstract: Polgcyclic aromatic hydrocarbons (PAHs) are ubiquitous environmental pollutants; a number are carcinogenic. Metabolic polymorphisms may modulate susceptibility to PAM-induced DNA damage and carcinogenesis. This study investigates the relationship between PAH-DNA adduct levels (in maternal and newborn WBCs) and two polymorphisms: (a) an MspI RFLP in the 3' noncoding region of cytochrome P4501A1 (CYP1A1); and (b) an A-->G transition in nucleotide 313 of glutathione S-transferase PI (GSTP1), resulting in an ile105val substitution, CYP1A1 catalyzes the bioactivation of PAH; the CYP1A1 MspI RFLP has been associated with cancer of the lung, GSTP1 catalyzes the detoxification of PAH; the Pa1 allele has greater catalytic efficiency toward PAH diol epoxides, The study involves 160 mothers and their newborns from Poland. Regression models controlled for maternal smoking and other confounders. No association was seen between maternal adduct levels and either polymorphism, separately or combined, However, adduct levels were higher among newborns with the CYP1A1 MspI restriction site (heterozygotes and homozygotes combined) compared with newborns lacking the restriction site (P = 0.06), Adducts were higher among GSTP1 ile/val and ile/ile newborns compared with GSTP1 val/val newborns (P = 0.08), Adduct levels were 4-fold higher among GSTP1 ile/ile newborns having the CYP1A1 restriction site compared with GSTP1 val/val newborns who lacked the CYP1A1 restriction site (P = 0.04), This study demonstrates a significant combined effect of phase I and phase II polymorphisms on DNA damage from PAHs in fetal tissues. It illustrates the importance of considering interindividual variation in assessing risks of transplacental exposure to PAHs.

Whyatt RM, Santella RM, Jedrychowski W, Garte SJ, Bell DA, Ottman R, Gladek-Yarborough A, Cosma G, Young TL, Cooper TB, Randall MC, Manchester DK, Perera FP. 1998. Relationship between ambient air pollution and DNA damage in Polish mothers and newborns. Environ Health Perspect 106:821-826.
Abstract: Industrialized regions in Poland are characterized by high ambient pollution, including polycyclic aromatic hydrocarbons (PAHs) from coal burning for industry and home healing. In experimental bioassays, certain PAHs are transplacental carcinogens and developmental toxicants. Biologic markers can facilitate evaluation of effects of environmental PAHs on the developing infant. We measured the amount of PAHs bound to DNA (PAH-DNA adducts) in maternal and umbilical white blood cells. The cohort consisted of 70 mothers and newborns from Krakow, Poland, an industrialized city with elevated air

pollution. Modulation of adduct levels by genotypes previously linked to risk of lung cancer, specifically glutathione S-transferase M1 (GSTM1) and cytochrome P4501A1 (CYP1A1) Mspi restriction fragment length polymorphism (RFLP), was also investigated. There was a dose-related increase in maternal and newborn adduct levels with ambient pollution at the women's place of residence among subjects who were not employed away from home (p less than or equal to 0.05). Maternal smoking (active and passive) significantly increased maternal (p less than or equal to 0.01) but not newborn adduct levels. Neither CYP1A1 Mspl nor GSTM1 polymorphisms was associated with maternal adducts. However, adducts were significantly higher in newborns heterozygous or homozygous for the CYP1A1 Mspl RFLP compared to newborns without the RFLP (p = 0.04). Results indicate that PAM-induced DNA damage in mothers and newborns is increased by ambient air pollution. In the fetus, this damage appears to be enhanced by the CYP1A1 Mspl polymorphism.

Wiemels JL, Cazzaniga G, Daniotti M, Eden OB, Addison GM, Masera G, Saha V, Biondi A, Greaves MF. 1999 Oct 30. Prenatal origin of acute lymphoblastic leukaemia in children. Lancet 354:1499-503.
Abstract: BACKGROUND: There is little current insight into the natural history of childhood leukaemia or the timing of relevant mutational events. TEL-AML1 gene fusion due to chromosomal translocation is frequently seen in the common form of childhood acute lymphoblastic leukaemia. We investigated whether this abnormality arises prenatally. METHODS: We identified, by reverse-transcriptase PCR screening of blood or bone marrow, TEL-AML1 fusion in 12 children, plus a pair of identical twins, aged 2-5 years from Italy and the UK, who had newly diagnosed acute lymphoblastic leukaemia. We amplified and sequenced the genomic TEL-AML1 fusion gene with a long-distance inverse PCR method. Primers were designed that could be used in short-range PCR to screen for patient-specific, leukaemia clone-specific TEL-AML1 genomic fusion sequences in neonatal blood spots from each child. FINDINGS: We initially identified TEL-AML1 fusion sequences in blood spots from the identical twins, diagnosed with concordant acute lymphoblastic leukaemia at age 4 years, who shared a single or clonotypic TEL-AML1 sequence that suggested prenatal origin in one twin. Three children were excluded because control genes could not be amplified. Of the other nine patients, six had positive blood spots. Blood spots that were classified as negative were uninformative. INTERPRETATION: Our findings showed that childhood acute lymphoblastic leukaemia is frequently initiated by a chromosome translocation event in utero. Studies in identical twins show however that such an event is insufficient for clinical leukaemia and that a postnatal promotional event is also required.

Wiemels JL, Cazzaniga G, Daniotti M, Eden OB, Addison GM, Masera G, Saha V, Biondi A, Greaves MF. 1999. Prenatal origin of acute lymphoblastic leukaemia in children. Lancet 354:1499-1503.
Abstract: BACKGROUND: There is little current insight into the natural history of childhood leukaemia or the timing of relevant mutational events. TEL-AML1 gene fusion due to chromosomal translocation is frequently seen in the common form of childhood acute lymphoblastic leukaemia. We investigated whether this abnormality arises prenatally. METHODS: We identified, by reverse-transcriptase PCR screening of blood or bone marrow, TEL-AML1 fusion in 12 children, plus a pair of identical twins, aged 2-5 years from Italy and the UK, who had newly diagnosed acute lymphoblastic leukaemia. We amplified and sequenced the genomic TEL-AML1 fusion gene with a long-distance inverse PCR method. Primers were designed that could be used in short-range PCR to screen for patient-specific, leukaemia clone-specific TEL-AML1 genomic fusion sequences in neonatal blood spots from each child. FINDINGS: We initially identified TEL-AML1 fusion sequences in blood spots from the identical twins, diagnosed with concordant acute lymphoblastic leukaemia at age 4 years, who shared a single or clonotypic TEL-AML1 sequence that suggested prenatal origin in one twin. Three children were excluded because control genes could not be amplified. Of the other nine patients, six had positive blood spots. Blood spots that were classified as negative were uninformative. INTERPRETATION: Our findings showed that childhood acute lymphoblastic leukaemia is frequently initiated by a chromosome translocation event in utero. Studies in identical twins show however that such an event is insufficient for clinical leukaemia and that a postnatal promotional event is also required.

Wiemels JL, Zhang Y, Chang J, Zheng S, Metayer C, Zhang L, Smith MT, Ma X, Selvin S, Buffler PA, Wiencke JK. 2005. RAS mutation is associated with hyperdiploidy and parental characteristics in pediatric acute lymphoblastic leukemia. Leukemia 19:415-419.
Abstract: We explored the relationship of RAS gene mutations with epidemiologic and cytogenetic factors

in a case series of children with leukemia. Diagnostic bone marrow samples from 191 incident leukemia cases from the Northern California Childhood Leukemia Study were typed for NRAS and KRAS codon 12 and 13 mutations. A total of 38 cases (20%) harbored RAS mutations. Among the 142 B-cell acute lymphoblastic leukemia (ALL) cases, RAS mutations were more common among Hispanic children (P = 0.11) or children born to mothers <30 years (P = 0.007). Those with hyperdiploidy at diagnosis (>50 chromosomes) had the highest rates of RAS mutation (P = 0.02). A multivariable model confirmed the significant associations between RAS mutation and both maternal age and hyperdiploidy. Interestingly, smoking of the father in the 3 months prior to pregnancy was reported less frequently among hyperdiploid leukemia patients than among those without hyperdiploidy (P = 0.02). The data suggest that RAS and high hyperdiploidy may be cooperative genetic events to produce the leukemia subtype; and furthermore, that maternal age and paternal preconception smoking or other factors associated with these parameters are critical in the etiology of subtypes of childhood leukemia.

Wigle DT, Arbuckle TE, Walker M, Wade MG, Liu SL, Krewski D. 2007. Environmental hazards: Evidence for effects on child health. J Toxicol Environ Health B Crit Rev 10:3-39.
Abstract: The human fetus, child, and adult may experience adverse health outcomes from parental or childhood exposures to environmental toxicants. The fetus and infant are especially vulnerable to toxicants that disrupt developmental processes during relatively narrow time windows. This review summarizes knowledge of associations between child health and development outcomes and environmental exposures, including lead, methylmercury, polychlorinated biphenyls (PCBs), dioxins and related polyhalogenated aromatic hydrocarbons (PHAHs), certain pesticides, environmental tobacco smoke (ETS), aeroallergens, ambient air toxicants (especially particulate matter [PM] and ozone), chlorination disinfection by-products (DBPs), sunlight, power-frequency magnetic fields, radiofrequency (RF) radiation, residential proximity to hazardous waste disposal sites, and solvents. The adverse health effects linked to such exposures include fetal death, birth defects, being small for gestational age (SGA), preterm birth, clinically overt cognitive, neurologic, and behavioral abnormalities, subtle neuropsychologic deficits, childhood cancer, asthma, other respiratory diseases, and acute poisoning. Some environmental toxicants, notably lead, ionizing radiation, ETS, and certain ambient air toxicants, produce adverse health effects at relatively low exposure levels during fetal or child developmental time windows. For the many associations supported by limited or inadequate epidemiologic evidence, major sources of uncertainty include the limited number of studies conducted on specific exposure-outcome relationships and methodologic limitations. The latter include (1) crude exposure indices, (2) limited range of exposure levels, (3) small sample sizes, and (4) limited knowledge and control of potential confounders. Important knowledge gaps include the role of preconceptual paternal exposures, a topic much less studied than maternal or childhood exposures. Large longitudinal studies beginning before or during early pregnancy are urgently needed to accurately measure and assess the relative importance of parental and childhood exposures and evaluate relatively subtle health outcomes such as neuropsychologic and other functional deficits. Large case-control studies are also needed to assess the role of environmental exposures and their interactions with genetic factors in relatively uncommon outcomes such as specific types of birth defects and childhood cancers. There is also an urgent need to accelerate development and use of biomarkers of exposure and genetic susceptibility in epidemiologic studies. This review supports the priority assigned by international agencies to relationships between child health and air quality (indoor and outdoor), lead, pesticides, water contaminants, and ETS. To adequately address such priorities, governments and agencies must strengthen environmental health research capacities and adopt policies to reduce parental and childhood exposures to proven and emerging environmental threats.

Wilkins JR, Mclaughlin JA, Sinks TH, Kosnik EJ. 1991. Parental occupation and intracranial neoplasms of childhood - Anecdotal evidence from a unique occupational - cancer cluster. Am J Ind Med 19:643-653.
Abstract: Near the end of the data-collection phase of a case-control interview study of environmental factors and childhood brain tumors, an unusual space-time cluster was revealed. Not only had six genetically unrelated children been diagnosed with a primary intracranial tumor in a recent 2.4 year period in a rural county in Ohio, but each child had one parent employed by the same company (two mothers, four fathers). This represents an observed/expected ratio > 70 ($p << 0.001$). All tumors were microscopically confirmed, and all case parents worked at the facility in question for at least 1 year prior to conception, during the index pregnancy, and for at least 6 months after birth. The place of parental employment was an electronics firm (Standard Industrial Classification [SIC] group number 367, electronic components and

accessories), where more than 100 chemical compounds are used by the company in a manufacturing process. Results of the cluster investigation are described, including a description of the case series. This cancer cluster is unique in that the index case series is composed of the offspring of workers, not the workers themselves.

Wilkins JR 3rd, Sinks TH Jr. 1984. Occupational exposures among fathers of children with Wilms' tumor. J Occup Med 26:427-435.
Abstract: An occupation-and-exposure linkage system was utilized to perform an epidemiologic case-control study of paternal occupation and Wilms' tumor in offspring. The first part of the study was designed to test the hypothesis that paternal lead (Pb) exposure is a risk factor for Wilms' tumor in offspring. The second part of the study was an exploratory analysis that sought to generate possible etiologic hypotheses about other paternal exposures in the workplace in relation to Wilms' tumor. Calculation of odds ratios indicated that there was no statistical difference in the frequency of occupational exposure to Pb, Pb alkyls, and Pb salts for fathers of children with Wilms' tumor and fathers of controls, a finding that contrasts sharply with the results of the one previously reported study in this area. In the exploratory phase of the study, case fathers were found more likely to have been exposed to boron, while control fathers were found more likely to have encountered insecticides, acetylene, o-chlorobenzylidene, oil orange ss, and diethylene glycol; the differences were statistically significant. Troublesome methodologic problems, including exposure misclassification, sample size, and multiple comparisons, are discussed.

Wilkins JR 3rd, Sinks TH Jr. 1984. Paternal occupation and Wilms' tumour in offspring. J Epidemiol Community Health 38:7-11.
Abstract: A case-control study was conducted to test the hypothesis that paternal occupation is a risk factor for Wilms' tumour in offspring. Occupations associated with exposure to lead (Pb) and to hydrocarbons were examined by computing odds ratios, all of which were greater than unity but not by a statistically significant margin. When painters were considered separately, children whose fathers had been so employed were six times more likely to develop Wilms' tumour than children whose fathers had other occupations. Like the results for the Pb and hydrocarbon related occupations, the estimated relative risk associated with painters did not reach statistical significance. Although these data require cautious interpretation because of the relatively small number of subjects, the results reported here are not wholly consistent with the results of the one previous study of paternal occupation and Wilms' tumour in offspring.

Winn DM, Li FP, Robison LL, Mulvihill JJ, Daigle AE, Fraumeni JF Jr. 1992 . A case-control study of the etiology of Ewing's sarcoma. Cancer Epidemiol Biomarkers Prev 1:525-532.
Abstract: An interview case-control study was undertaken to search for risk factors for Ewing's sarcoma. The 208 cases, aged 5 months to 22 years at diagnosis and all white but one, were identified from hospitals participating in the Intergroup Ewing's Sarcoma Study therapeutic trials. Two controls were sought for each case: a sibling control and an age-matched regional population control identified through random-digit dialing telephone procedures. A questionnaire was administered to the parents of cases and controls. Parents were more likely to have smoked during the pregnancy with the case than during the pregnancy with the unaffected sibling. Risks rose with the number of cigarettes the mother smoked per day during the pregnancy. Concepti exposed to less than 1 pack/day were at 3.2 times the risk, and those exposed to 1 pack or more were at 6.7 times the risk of the nonexposed. However, risks associated with smoking were lower and not statistically significant in analyses using the region-matched controls. Hernias, mostly umbilical and inguinal, were diagnosed six times more frequently among the cases compared to region-matched controls. However, hernias occurred in just 10% of cases, and the matched siblings had hernias diagnosed with the same frequency as the cases. An apparent excess of heart disorders among cases versus siblings seems likely to be an artifact of increased medical surveillance of cases.(ABSTRACT TRUNCATED AT 250 WORDS)

Wogan GN. 2007. Does perinatal antiretroviral therapy create an iatrogenic cancer risk? Environmental & Molecular Mutagenesis 48:210-214.
Abstract: Antiretroviral therapy is highly effective in reducing vertical transfer of HIV infection, sparing many thousands of children premature death from AIDS. However, accumulating evidence indicates that perinatal exposure to antiretroviral agents may place them at elevated risk of developing cancer later in life, owing to potential carcinogenic effects of the agents. An initial experimental evaluation clearly

demonstrated that AZT was a genotoxin and transplacental carcinogen of intermediate potency in CD-1 mice. This issue of Environmental and Molecular Mutagenesis contains reports of recent studies designed to confirm and extend earlier findings, and to provide further perspective that will facilitate development of strategies through which the adverse effects might be mitigated. The studies focused on various aspects of the genotoxicity and carcinogenicity of antiretroviral agents, including: mutagenesis in several in vitro experimental systems; mutations and clastogenic effects induced by transplacental administration in mice; transplacental carcinogenesis and mutations in oncogenes and tumor suppressor genes in tumors of mice; and genotoxicity and clastogenicity following perinatal exposure of HIV-infected mothers and their uninfected infants. Collectively, the results obtained provide convincing biological plausibility for the postulate that perinatal exposure to nucleoside analogs puts children at elevated risk of developing cancers later in life. They further emphasize the importance of continued surveillance of these children for increased cancer risk and indicate a need for efforts to develop less genotoxic alternative agents.

Wu RY, Yang HJ, Chiang H, Shao BJ, Bao JL. 1998. The effects of low-frequency magnetic fields on DNA unscheduled synthesis induced by methylnitro-nitrosoguanidine in vitro. Electro- & Magnetobiology 17:57-65.
Abstract: Exposure to extremely low and low frequency electromagnetic fields (ELF and LF EMF) has been reported to induce potent carcinogenic effects and adverse pregnancy outcomes. DNA damage may be an EMF target site. This study investigates both 50 Hz and 15.6 kHz magnetic fields on DNA damage/repair in the normal human amniotic FL cell. The test of unscheduled DNA synthesis (UDS) was utilized. In view of the weak effects of the magnetic fields, FL cells were simultaneously treated with methylnitro-nitrosoguanidine (MNNG), a known carcinogen. FL cells were exposed to a 50 Hz sinusoidal magnetic field at 0.3, 1.0, and 5.0 mT as well as a 16.5 kHz pulsed magnetic field at 4 and 40 mu T (p-p), respectively, for 72 h. The results showed that 50 Hz magnetic field led to nonlinear dose-dependent elevations of DNA damage (exposure to 1 mT increased DNA damage in the presence and absence of MNNG, exposure to 0.3 mT could enhance the effect of MNNG below the threshold concentration, but exposure to 5 mT exerted no influence). In addition, a 15.6 kHz field at 40 mu T (P-P) could enhance MNNG inducing DNA damage in FL cells and no effect at 4 mu T (p-p) was found, which suggests that very weak genotoxic effects of 15.6 kHz PMF may be revealed and enhanced in combination with a carcinogen. Further experiments should be conducted to observe whether so-called "intensity windows" exist in the biological effects of ELF.

Wulff M, Hogberg U, Sandstrom A. 1996. Cancer incidence for children born in a smelting community. Acta Oncol 35:179-183.
Abstract: The Ronnskar smelter in Skelleftea, Sweden, produces significant environmental pollutants, such as lead, arsenic, copper, cadmium and sulphur dioxide. The purpose of the present study was to determine whether children born to women living near the smelter during pregnancy had an increased risk of childhood cancer. The study group consisted of children born between 1961 and 1990 in the municipality of Skelleftea and parish of Holmsund. Through linkage to the Swedish Cancer Registry cancer diagnoses in the study group were obtained and compared with the expected ones based on the national incidence rates, Thirteen cases of childhood cancer were identified among children born in the vicinity of the smelter against 6.7 expected (SIR 195, 95%CI 88-300), Among distant born the observed number of cases (n=42) was similar to that expected (n=41.8).

Xu M, Nelson GB, Moore JE, Mccoy TP, Dai J, M&erville RA, Ross JA, Miller MS. 2005. Induction of Cyp1a1 and Cyp1b1and formation of DNA adducts in C57BL/6, Balb/c, and F1 mice following in utero exposure to 3-methylcholanthrene. Toxicology & Applied Pharmacology 209:28-38 .
Abstract: Fetal mice are more sensitive to chemical carcinogens than are adults. Previous studies from our laboratory demonstrated differences in the mutational spectrum induced in the Ki-ras gene from lung tumors isolated from [D2 x B6D2F1]F2 mice and Balb/c mice treated in utero with 3-methylcholanthrene (MC). We thus determined if differences in metabolism, adduct formation, or adduct repair influence strain-specific responses to transplacental MC exposure in C57BL/6 (136), Balb/c (BC), and reciprocal F1 crosses between these two strains of mice. The induction of Cyp1a1 and Cyp1b1 in fetal lung and liver tissue was determined by quantitative fluorescent real-time PCR. MC treatment caused maximal induction of Cyp1a1 and Cyp1b1 RNA 2-8 h after injection in both organs. RNA levels for both genes then declined in both fetal organs, but a small biphasic, secondary increase in Cyp1a1 was observed specifically in the

fetal lung 24-48 h after MC exposure in all four strains. Cyp1a1 induction by MC at 4 h was 2-5 times greater in fetal liver (7000- to 16,000-fold) than fetal lung (2000- to 6000-fold). Cyp1b1 induction in both fetal lung and liver was similar and much lower than that observed for Cyp1a1, with induction ratios of 8- to 18-fold in fetal lung and 10- to 20-fold in fetal liver. The overall kinetics and patterns of induction were thus very similar across the four strains of mice. The only significant strain-specific effect appeared to be the relatively poor induction of Cyp1b1 in the parental strain of 136 mice, especially in fetal lung tissue. We also measured the levels of MC adducts and their disappearance from lung tissue by the p(32) post-labeling assay on gestation days 18 and 19 and postnatal days 1, 4, 11, and 18. Few differences were seen between the different strains of mice; the parental strain of 136 mice had nominally higher levels of DNA adducts 2 (gestation day 19) and 4 (postnatal day 1) days after injection, although this was not statistically significant. These results indicate that differences in Phase I metabolism of MC and formation of MC-DNA adducts are unlikely to account for the marked differences observed in the Ki-ras mutational spectrum seen in previous studies. Further, the results suggest that other genetic factors may interact with chemical carcinogens in determining individual susceptibility to these agents during development. Published by Elsevier Inc.

Yagi T, Hibi S, Tabata Y, Kuriyama K, Teramura T, Hashida T, Shimizu Y, Takimoto T, Todo S, Sawada T, Imashuku S. 2000 . Detection of clonotypic IGH and TCR rearrangements in the neonatal blood spots of infants and children with B-cell precursor acute lymphoblastic leukemia. Blood 96:264-268.
Abstract: An attractive hypothesis is that in utero exposure of hematopoietic cells to oncogenic agents can induce molecular changes leading to overt acute lymphoblastic leukemia (ALL) in infants and perhaps older children as well. Although supported by studies of identical infant twins with concordant leukemia, and of nontwined patients with MLL gene rearrangements, this concept has not been extended to the larger population of B-lineage ALL patients who lack unique nonconstitutive mutations or abnormally rearranged genes. We therefore sought to demonstrate a prenatal origin for 7 cases of B-cell precursor ALL (either CD10(+) or CD10(-)) that had been diagnosed in infants and children 14 days to 9 years of age. Using a polymerase chain reaction-based assay, we identified the same clonotypic immunoglobulin heavy-chain complementarity determining region or T-cell receptor V(D)2-D(D)3 sequences in the neonatal blood spots (Guthrie card) and leukemic cell DNAs of 2 infants with CD10(-) ALL and 2 of the 5 older patients with CD10(+) ALL. Nucleotide sequencing showed a paucity of N or P regions and shortened D germ line and conserved J sequences, indicative of cells arising from fetal hematopoiesis. Our findings strongly suggest a prenatal origin for some cases of B-cell precursor ALL lacking specific clonotypic abnormalities.

Yamasaki H, Loktionov A, Tomatis L. 1992. Perinatal and multigenerational effect of carcinogens - Possible contribution to determination of cancer susceptibility. Environ Health Perspect 98:39-43.
Abstract: Perinatal exposure to carcinogens may contribute to the determination of susceptibility to cancer in two situations: a) exposure in utero of embryonal or fetal somatic cells to carcinogens, and b) prezygotic exposure of the germ cells of one or both parents to carcinogens. Epidemiological as well as experimental studies demonstrate that exposure to carcinogens in utero increases the occurrence of cancer postnatally. Studies with experimental animals suggest that prezygotic exposure of germ cells to carcinogens can result in an increased incidence of cancer not only in immediate but also in subsequent generations. Although several studies suggest a transgeneration effect of carcinogens in human populations, the evidence cannot yet be considered conclusive. In particular, while some hypotheses can be advanced, the mechanism(s) by which increased susceptibility or predisposition to cancer may be transmitted via the germ cells has not vet been clarified. In conjunction with exposure both in utero and prezygotically, it is important to consider postnatal exposure to possible tumor-promoting agents. Results from experimental animals suggest that oncogenes can be activated transplacentally, and human studies indicate that tumor-suppressor gene inactivation may be involved in the transgenerational effect of carcinogens.

Yeoh G, Porter I, Arcus M, Douglas A. 1989 . Transformation of cultured fetal rat liver cells by MDAB and phenobarbital. Morphological, biochemical and immunocytochemical characterization of cell lines. Carcinogenesis 10:1015-1027.
Abstract: Fetal rat liver cells derived from 19-day gestation rats were exposed in culture to the carcinogen, 3'-methyl-4-dimethyl-aminoazobenzene (MDAB) for 3 days and then maintained in medium supplemented with the tumor promoter, phenobarbital (PB). Tumors developed in immunodeficient mice inoculated with cells derived from cultures which had been maintained for more than 8 weeks. Histologically, three types

of tumors could be distinguished. One contained epithelial-like cells, which resembled what has previously been described as 'clear' epithelial cells. The second contained cells which were more basophilic, with prominent nuclei and closely resembled the hepatoma cell line Mc-A-R-777. The third group of tumors possessed cells of both varieties. Cell lines derived from these tumors were then characterized by determining their capacity to synthesize and secrete alpha-fetoprotein, albumin and transferrin by measuring the incorporation of 35S-methionine into immunoprecipitates obtained by reaction with the respective specific antibodies and the content of the respective mRNAs were determined by hybridization to cDNAs. The activity of gamma-glutamyl-transpeptidase (GGT) and the liver specific enzyme tyrosine aminotransferase (TAT), as well as the induction of TAT by dexamethasone was also evaluated. The presence of these markers in some of the cell lines strongly suggests that they are derived from parenchymal cells. In contrast, other cell lines which morphologically resemble 'clear' epithelial cells are negative, suggesting that they may be derived from non-parenchymal epithelial cells which exist in the original culture. However, some epithelial-like cell lines derived from tumors of mixed morphology appear different to those established from tumors which contained only epithelial-like cells. These express low levels of transferrin and tyrosine aminotransferase suggesting that they may be more closely related to hepatocytes than those cells which are derived from tumors which originally comprised only epithelial cells. The absence or presence of liver markers correlates with the morphology of the respective cell lines since transferrin and TAT are only present in significant levels in those lines which comprise cells with a morphology resembling hepatoma cell lines. In cell lines which show mixed morphology, immunocytochemistry reveals that significant amounts of transferrin are only present in the parenchymal-like population. Growth rate measurements show that the faster growing cell lines generally possessed lower levels of transferrin and TAT expression. It can be concluded from these studies that it is possible to transform cells derived from fetal rat liver in culture using a hepatocarcinogen.(ABSTRACT TRUNCATED AT 400 WORDS)

Yip BH, Pawitan Y, Czene K. 2006. Parental age and risk of childhood cancers: a population-based cohort study from Sweden. International Journal of Epidemiol 35:1495-503.
Abstract: BACKGROUND: Frequent germ line cells mutations were previously demonstrated to be associated with aging. This suggests a higher incidence of childhood cancer among children of older parents. A population-based cohort study of parental ages and other prenatal risk factors for five main childhood cancers was performed with the use of a linkage between several national-based registries. METHODS: In total, about 4.3 million children with their parents, born between 1961 and 2000, were included in the study. Multivariate Poisson regression was used to obtain the incidence rate ratios (IRR) and 95% confidence interval (CI). Children <5 years of age and children 5-14 years of age were analysed independently. RESULTS: There was no significant result for children 5-14 years of age. For children <5 years of age, maternal age were associated with elevated risk of retinoblastoma (oldest age group's IRR = 2.39, 95%CI = 1.17-4.85) and leukaemia (oldest age group's IRR = 1.44, 95%CI = 1.01-2.05). Paternal age was significantly associated with leukaemia (oldest age group's IRR = 1.31, 95%CI = 1.04-1.66). For central nervous system cancer, the effect of paternal age was found to be significant (oldest age group's IRR = 1.69, 95%CI = 1.21-2.35) when maternal age was included in the analysis. CONCLUSION: Our findings indicate that advanced parental age might be associated with an increased risk of early childhood cancers.

Yoshida M, Katsuda S, Tanimoto T, Asai S, Nakae D, Kurokawa Y, Taya K, Maekawa A. 2002. Induction of different types of uterine adenocarcinomas in Donryu rats due to neonatal exposure to high-dose p-t-octylphenol for different periods. Carcinogenesis 23:1745-1750.
Abstract: Inappropriate exposure to estrogens in the fetal and/or newborn period can exert irreversible influence, including carcinogenesis on the reproductive system in mammals. The present study was conducted to investigate uterine carcinogenesis in Donryu rats treated neonatally with a high-dose estrogenic compound, p-t-octylphenol (OP) for different exposure periods. Female Donryu rats were subcutaneously administered 100 mg/kg/day OP every other day for the first 5 postnatal days (PNDs 1-5) or the first 2 weeks (PNDs 1-15). They received a single injection of 20 mg/kg N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG) into a uterine horn at 11 weeks of age and were examined until 15 months of age. PNDs 1-5 OP-treated rats showed normal development of the female reproductive system, including uterine gland genesis and normal estrous cycling after vaginal opening. The treatment, however, accelerated an earlier occurrence of persistent estrus and increased the number of well differentiated uterine

adenocarcinomas as compared with controls. This indicated that PNDs 1-5 OP treatment acts as a delayed modulator of the hypothalamus-pituitary-ovarian hormonal control system and the modulation increased the serum estrogen:progesterone ratio, resulting in induction of uterine tumors. On the contrary, PNDs 1-15 OP treatment demonstrated immediate and irreversible influences on the control system, called 'androgenization', and induced abnormal uterine development manifested by prolonged persistent estrus immediately after vaginal opening and also suppression of uterine gland genesis. In addition, uterine tumor malignancy in morphological and biological property clearly increased in this group although the total number of adenocarcinomas was not increased. The present study provides evidence that neonatal exposure to a high-dose OP enhances uterine carcinogenesis in rats, and the type of uterine tumors is changed by the periods of neonatal exposure to OP, suggesting that the mechanism of uterine tumor development is dependent upon neonatal exposure periods.

Yoshimoto Y, Soda H, Schull WJ, Mabuchi K. 1995. Studies of children in-utero during atomic-bomb detonations. Advances in Chemistry Series 243:133-145.
Abstract: Although the study of mental retardation among children exposed to atomic radiation in utero has clearly shown an effect of exposure on the developing brain, the cancer risk among these individuals remains to be determined and will only be established through continued follow-up of the subjects. To this end mortality and morbidity surveys of about 1800 persons exposed in utero to the atomic bombings of Hiroshima and Nagasaki were undertaken at the Radiation Effects Research Foundation (RERF). In the years 1950-1984, when these individuals were under the age of 40, a significant excess cancer risk was observed. The relative risk at 1 Gy was about 3.8. However, in the most recent 5 years (1985-1989), there was no apparent excess of cancer, and the overall relative risk for the years 1950-1989 decreased to about two based on the 2 dozen cancer cases with DS86 dose estimates that have been seen thus far.

Yu W, Sipowicz MA, Haines DC, Birely L, Diwan BA, Riggs CW, Kasprzak KS, Anderson LM. 1999 . Preconception urethane or chromium(III) treatment of male mice: multiple neoplastic and non-neoplastic changes in offspring. Toxicology & Applied Pharmacology 158:161-176.
Abstract: Increase in neoplasia in offspring after preconception exposure of parents presents puzzling features such as high frequency of effects and lack of Mendelian inheritance. The present study examined the hypothesis that preconception carcinogenesis involves an increase in the rate of occurrence of neoplasms with a spontaneous incidence. Male NIH Swiss mice (12 per group) were exposed 2 weeks before mating (once, ip) to urethane (1.5 g/kg) or chromium(III) chloride (1 mmol/kg). Offspring (48-78/sex/group) were examined for all grossly apparent changes when moribund or at natural death, followed by histopathological diagnosis and statistical analysis. Significant exposure-related changes occurred in multiple organs. Ten to 20 percent of offspring showed changes related to paternal exposure, including at least one sired by most treated males. Pheochromocytomas occurred in both male and female offspring after both treatments, with none in controls. These neoplasms are rare in mice and suggest endocrine dysfunction as a component of preconception carcinogenesis. This was supported by increases in thyroid follicular cell and Harderian gland tumors, ovarian cysts, and uterine abnormalities. Lung tumors were increased in female offspring only. Effects seen in offspring only after paternal urethane exposure were an increase in preneoplasia/neoplasia in the glandular stomach (males) and in females, increased lymphoma but decreased incidence of histiocytic sarcoma. Increases in incidence of male reproductive gland tumors and of renal non-neoplastic lesions occurred only after chromium exposure. Thus, preconception exposure of fathers to toxicants had a significant impact on both neoplastic and non-neoplastic changes in almost all tissues in which these lesions often occur naturally during the aging process.

Yu Z, Loehr CV, Fischer KA, Louderback MA, Krueger SK, Dashwood RH, Kerkvliet NI, Pereira CB, Jennings-Gee JE, Dance ST, Miller MS , Bailey GS, Williams DE. 2006. In Utero Exposure of Mice to Dibenzo[a,L]Pyrene Produces Lymphoma in the Offspring: Role of the Aryl Hydrocarbon Receptor. Cancer Res 66:755-762.
Abstract: Lymphoma and leukemia are the most common cancers in children and young adults; in utero carcinogen exposure may contribute to the etiology of these cancers. A polycyclic aromatic hydrocarbon (PAH), dibenzo[a,l]pyrene (DBP), was given to pregnant mice (15 mg/kg body weight, gavage) on gestation day 17. Significant mortalities in offspring, beginning at 12 weeks of age, were observed due to an aggressive T-cell lymphoblastic lymphoma. Lymphocytes invaded numerous tissues. All mice surviving 10 months, exposed in utero to DBP, exhibited lung tumors; some mice also had liver tumors. To assess the

role of the aryl hydrocarbon receptor (AHR) in DBP transplacental cancer, B6129SF1/J (AHR(b-1/d), responsive) mica were crossed with strain 129S1/SvIm (AHR(d/d), non-responsive) to determine the effect of maternal and fetal AHR status on carcinogenesis. Offspring born to nonresponsive mothers had greater susceptibility to lymphoma, irrespective of offspring phenotype. However, when the mother was responsive, an AHR-responsive phenotype in offspring increased mortality by 2-fold. In DBP-induced lymphomas, no evidence was found for TP53, beta-catenin, or Ki-ras mutations but lung adenomas of mice surviving to 10 months of age had mutations in Ki-ras codons 12 and 13. Lung adenomas exhibited a 50% decrease and a 35-fold increase in expression of Rb and p19/ARF mRNA, respectively. This is the first demonstration that transplacental exposure to an environmental PAH can induce a highly aggressive lymphoma in mice and raises the possibility that PAH exposures to pregnant women could contribute to similar cancers in children and young adults.

Yun TK, Kim SH, Lee YS. 1995. Trial of a new medium-term model using benzo(a)pyrene induced lung-tumor in newborn mice. Anticancer Res 15:839-845.
Abstract: A new medium-term in vivo model was tried using pulmonary adenoma induced by benzo(a)pyrene (BP) in newborn mice. Both inbred mice such as C57BL/5J, C57BR/cdJ. A/J mice and non inbred N:GP(S) mice were used. Benzo(a)pyrene was injected in the subscapular region of newborn mice within 24 hours after birth at a dose of 0.5 mg and 1 mg per mouse, respectively. After 9 weeks lung tumor induced in N:GP(S) and A/J mice but in the other mice. The dose showing a 50% tumor incidence was found in N:GP(S) mice To be 0.5 mg of BP bur the tumor incidence was very high in A/J mice even at 40 mu g of BP, the lowest dose in this experiment. To verify) the utility of this model, ascorbic acid, carrot, beta carotene, soybean lecithin, spinach Sesamum indicum, Ganoderma lucidum, caffeine, red ginseng extract, fresh ginseng and 13-cis retinoic acid, some of which me known to have anticarcinogenic activity in various animal models, were tried with this system. Ascorbic acid, soybean lecithin, Ganoderma lucidum, caffeine and red ginseng extract showed inhibition of lung tumor incidence, while fresh ginseng, carrot, beta carotene, spinach and 13-cis retinoic acid diet not This result suggested that the 9-week medium - term model using lung tumor induced by 0.5 mg of BP was useful for the screening of cancer preventive agents.

Zack M, Adami HO, Ericson A. 1991. Maternal and perinatal risk - factors for childhood leukemia. Cancer Res 51:3696-3701.
Abstract: This report describes an exploratory Population-based study of maternal and perinatal risk factors for childhood leukemia in Sweden. The Swedish National Cancer Registry ascertained 411 cases in successive birth cohorts from 1973 through 1984 recorded in the Swedish Medical Birth Registry. Using the latter, we matched five controls without cancer to each case by sex and month and year of birth. Mothers of children with leukemia were more likely to have been exposed to nitrous oxide anesthesia during delivery than mothers of controls [odds ratio (OR) = 1.3; 95% confidence interval (CI) = 1.0, 1.6]. Children with leukemia were more likely than controls to have Down's syndrome (OR = 32.5; 95% CI = 7.3, 144.0) or cleft lip or cleft palate (OR = 5.0; 95% CI = 1.0, 24.8); to have had a diagnosis associated with difficult labor but unspecified complications (OR = 4.5; 95% CI = 1.1, 18.2) or with other conditions of the fetus or newborn (OR = 1.5; 95% CI = 1.1, 2.1), specifically, uncomplicated physiological jaundice (OR = 1.9; 95% Cl = 1.2, 2.9); or to have received supplemental oxygen (OR = 2.6; 95% CI = 1.3, 4.9). Because multiple potential risk factors were analyzed in this study, future studies need to check these findings. We did not confirm the previously reported higher risks for childhood leukemia associated with being male, having a high birth weight, or being born to a woman of advanced maternal age.

Zahm SH, Ward MH. 1998. Pesticides and childhood cancer. Environ Health Perspect 106 Suppl 3:893-908.
Abstract: Children are exposed to potentially carcinogenic pesticides from use in homes, schools, other buildings, lawns and gardens, through food and contaminated drinking water, from agricultural application drift, overspray, or off-gassing, and from carry-home exposure of parents occupationally exposed to pesticides. Parental exposure during the child's gestation or even preconception may also be important. Malignancies linked to pesticides in case reports or case-control studies include leukemia, neuroblastoma, Wilms' tumor, soft-tissue sarcoma, Ewing's sarcoma, non-Hodgkin's lymphoma, and cancers of the brain, colorectum, and testes. Although these studies have been limited by nonspecific pesticide exposure information, small numbers of exposed subjects, and the potential for case-response bias, it is noteworthy that many of the reported increased risks are of greater magnitude than those observed in studies of

pesticide-exposed adults, suggesting that children may be particularly sensitive to the carcinogenic effects of pesticides. Future research should include improved exposure assessment, evaluation of risk by age at exposure, and investigation of possible genetic-environment interactions. There is potential to prevent at least some childhood cancer by reducing or eliminating pesticide exposure.

Zemlickis D, Lishner M, Erlich R, Koren G. 1993. Teratogenicity and carcinogenicity in a twin exposed in-utero to cyclophosphamide. Teratogenesis Carcinogenesis & Mutagenesis 13:139-143.
Abstract: A 29-year-old pregnant woman diagnosed with acute lymphocytic leukemia maintained remission with daily cyclophosphamide and intermittent prednisone treatment. She delivered a male twin with multiple congenital abnormalities who was diagnosed with papillary thyroid cancer at 11 years of age and stage III neuroblastoma at 14 years of age. The female twin was unaffected and has exhibited normal development to date. First trimester exposure to cylcophosphamide has been associated with major malformations. Metabolites of cyclophosphamide have been demonstrated to be teratogens and carcinogens in animals. Differences in placental or fetal hepatic cytochrome P-450 may account for the variability in response between the twins. In addition, disparity between the twins may be the result of differences in metabolite inactivating enzymes present either in fetal liver or placenta. The risk of second malignancies caused by alkylating agents such as cyclophosphamide has been well documented in adults and children but to the best of our knowledge this is the first description of transplacental second cancer.

Zeng XX, Zhang H, Hardy RR, Wasserman R. 1998 . The fetal origin of B-precursor leukemia in the E-mu-ret mouse. Blood 92:3529-3536.
Abstract: Before the clinical onset of B-precursor lymphoblastic leukemia, E-mu-ret mice have an expansion of late pro-B cells (CD45R+CD43(+)CD24(+)BP-1(+)) within the bone marrow. To characterize the early effects of the transgene product on lymphopoiesis, we initially sequenced the Ig heavy chain (IgH) rearrangements within the late pro-B cells in 24-day-old E-mu-ret and transgene negative mice. In both mouse populations, the IgH rearrangements were polyclonal, predominately nonproductive, and exhibited similar V, D, and J gene usage. However, the frequency of N regions, a marker of postnatal lymphopoiesis, was notably different. At the VD junction, N regions were found in 25 of 25 (100. 0%) rearrangements from transgene-negative mice compared with 12 of 36 (33.3%) rearrangements from Emicro-ret mice. At the DJ junction, N regions were found in 21 of 25 (84.0%) rearrangements from transgene negative mice compared with 4 of 36 (11.1%) rearrangements from E-mu-ret mice. Subsequently, we sequenced the clonal IgH rearrangements from 9 leukemias that developed in 10-to 38-week-old mice and found that 7 leukemias had a least 1 rearrangement that lacked N regions at the DJ junction. In addition, V replacement events were observed in the 1 leukemia studied in detail. Terminal deoxynucleotidyl transferase, the enzyme responsible for N region addition, was expressed at markedly lower levels in late pro-B cells from 7- to 10-day-old E-mu-ret mice compared with transgene-negative mice. Examination of fetal lymphopoiesis in E-mu-ret mice identified a relative increase in early (CD45R+CD43(+)CD24(+)BP-1(-)) and late pro-B cells and a decrease in more differentiated CD43(-) B-lineage cells. Fetal early pro-B cells from Emicro-ret mice proliferated threefold to fivefold greater but differentiated to a lesser extent than those from transgene negative mice when cultured in vitro with interleukin-7. These data suggest that the B precursor leukemias in adult E-mu-ret mice arise from the progeny of pro-B cells generated in utero.

Zhu M, Breslin MB, Lan MS. 2002 . Expression of a novel zinc-finger cDNA, IA-1, is associated with rat AR42J cells differentiation into insulin-positive cells. Pancreas 24:139-145.
Abstract: INTRODUCTION: IA-1, an insulinoma-associated cDNA-1, encodes a zinc-finger DNA-binding protein originally isolated from a human insulinoma subtraction library. AIM: To demonstrate the restriction of IA-1 gene expression in human fetal pancreata of different gestational stages and to determine whether the expression of IA-1 gene is associated with rat AR42J cell differentiation into insulin-positive cells. METHODOLOGY: To examine whether the IA-1 gene is associated with pancreatic endocrine cell differentiation, we used a rat pancreatic amphicrine cell line, AR42J, to investigate whether the expression of the IA-1 gene coincides with AR42J cells converting into either endocrine or exocrine lineage. We also examined a set of islet transcription factors that regulate key differentiation steps involved in activating the genes that confer the specialized functions of terminally differentiated pancreatic islet cells. RESULTS: When the AR42J cells were converted into insulin-positive cells induced by GLP-1, insulinoma conditioned-medium, or both, we observed a significant elevated expression of mRNA for IA-1 and islet-specific transcription factors such as Pdx-1, NeuroD/beta2, and Nkx6.1. In contrast, dramatically decreased

expression of mRNA for IA-1 and islet-specific transcription factors was displayed when AR42J cells were converted into the acinar-like phenotype by dexamethasone. CONCLUSIONS: IA-1 gene was shown to be developmentally regulated in fetal pancreatic cells, and its expression pattern is consistent with parallel changes in islet-specific transcription factors during the endocrine differentiation of AR42J cells.

Zhu P, Liu J. 2001. [Characteristics of malignant clone from acute lymphocytic leukemia]. Zhonghua Yi Xue Za Zhi 81:1057-1061.

Abstract: OBJECTIVE: To identify the characteristics of malignant clones in leukemia. METHODS: VH region of B lymphocytes from children with ALL, patients with MM, and tissues from fetuses obtained by induced labor at different gestational stages was amplified using RT-PCR method with one primer located in VH1, VH2, VH3, VH4, VH5, or VH6 and another primer at the join region. The PCR products were then separated on sequencing gel and their VH gene fingerprints were obtained. The fingerprints from tissues of fetal liver, spleen, thymus and bone marrow, and bone marrow B cell from 15 cases of ALL and one case of MM were compared, and VH repertoire information were deduced from those fingerprints. RESULTS: The VH6 family was the dominant family in fetal liver and the VH3 family occurred predominantly in fetal spleen and bone marrow. Monoclonal proliferation of B lymphocytes was found in 9 of the 15 patients with ALL. Of these 9 cases, proliferation of VH1 was found in 3 cases, proliferation of VH6 was found in 3 cases, and proliferation of both VH3 and VH4 in 2 cases. The VH families other than leukemic clone(s) in these patients were in normal distribution or suppression status. Oligoclonality was found in one ALL case with malignant growth of VH1, VH3 and VH6. Polyclonality with nearly normal spectrum of VH1-VH6 was detected in 6 of the 15 cases. DNA sequencing of a VH3 clone from an ALL case demonstrated a similarity to the sequence of embryonic clone from a fetus of gestational age of 13 weeks. The VH sequence of one adult MM case, with hypermutation of somatic cell, was remarkably different from that of the germline. CONCLUSION: Rearrangement of VH1, VH3, VH4 and VH6 can be frequently found in ALL. It is unlikely that leukemia in childhood originates from stimulation of foreign antigens.