# Executive Summary to The Endocrine Society's 2nd Scientific Statement on EDCs

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# DISCLOSURE – Andrea Gore

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# Definition of an EDC

Endocrinology, September 2012, 153(9):4097–4110

**Endocrine-Disrupting Chemicals and Public Health Protection: A Statement of Principles from The Endocrine Society**

R. Thomas Zoeller, T. R. Brown, L. L. Doan, A. C. Gore, N. E. Skakkebaek, A. M. Soto, T. J. Woodruff, and F. S. Vom Saal

"An endocrine disruptor is an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action."



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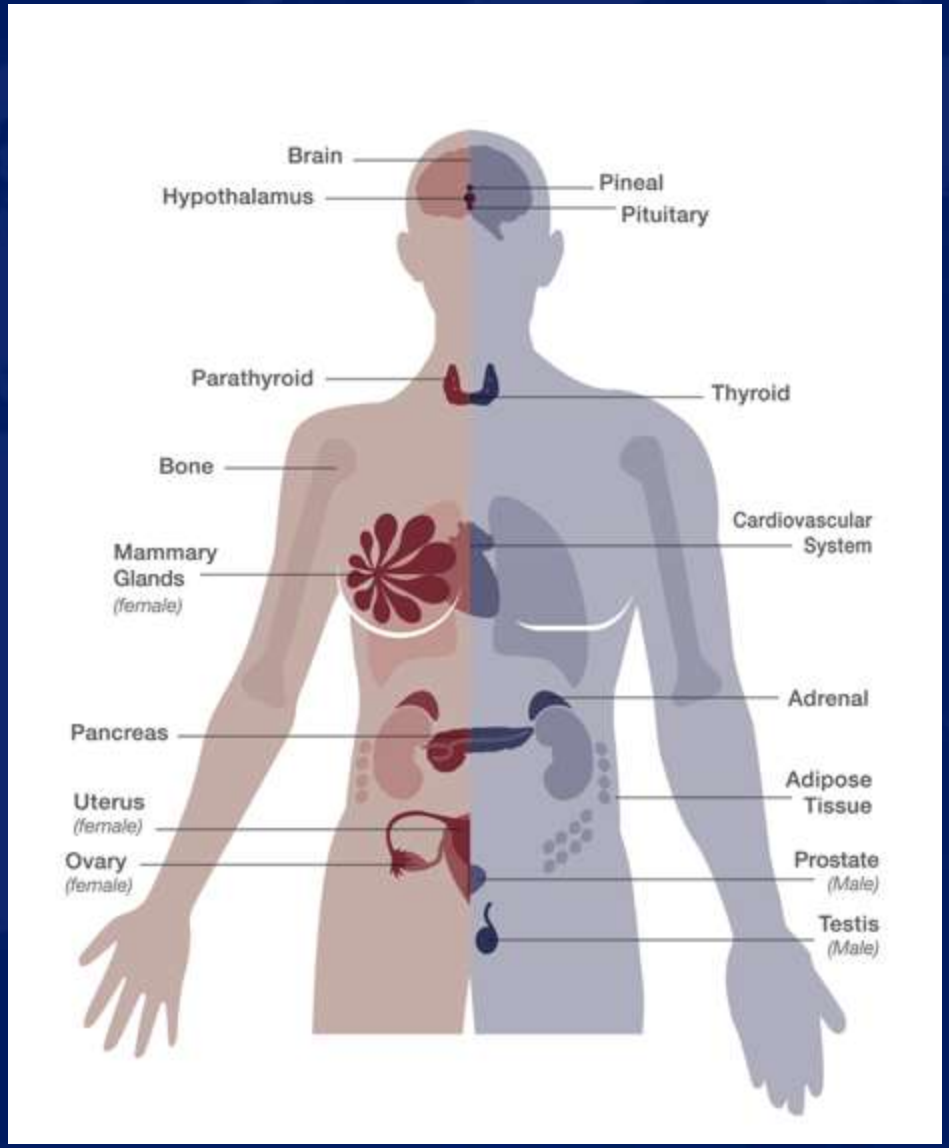
# Topics covered in EDC-2

- Obesity, diabetes, and cardiovascular disease
- Female reproductive health
- Male reproductive health
- Hormone sensitive cancers in females
- Prostate gland
- Thyroid gland
- Neurodevelopment and neuroendocrine systems



# Key Principles

- Endocrine systems are the body's interface with the environment, and are targets of environmental EDCs.
- Developmental vulnerability and latent disease.
- Dose-response characteristics, low doses, mixtures.
- Lifelong exposures.
- Molecular mechanisms are better-understood.
- The nature of an effect depends upon when, and how, it is assessed.
- Human studies, epidemiological associations of exposure and chronic disease.

# EDCs and Human Health: Where to Start?

- Twin studies indicate that the environment plays a key role in many diseases.
- Environmental and occupational exposures (e.g. Seveso, Italy; Agent Orange; Drinking water contamination) demonstrate associations between exposure and increased cancer rates, metabolic diseases, reproductive health problems, and infertility.
- The Toxic Substances Control Act (TSCA) inventory of the U.S. EPA includes 85,000 chemicals, few of which are tested for health effects – and humans are exposed to many.



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# What did we conclude?

- There is more conclusive evidence than ever before regarding how EDCs interfere with hormones and how that affects human health.



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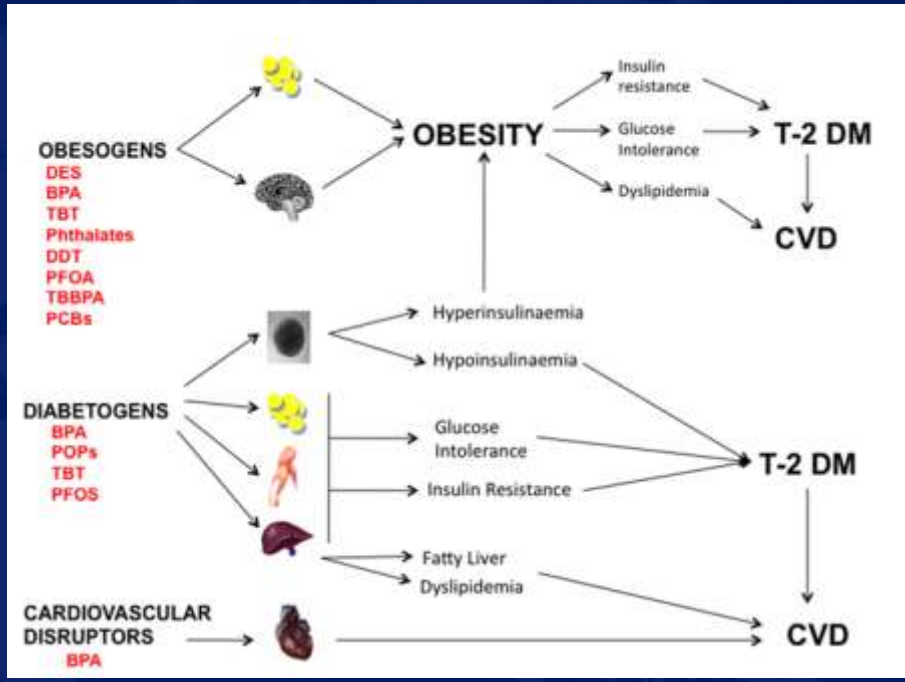
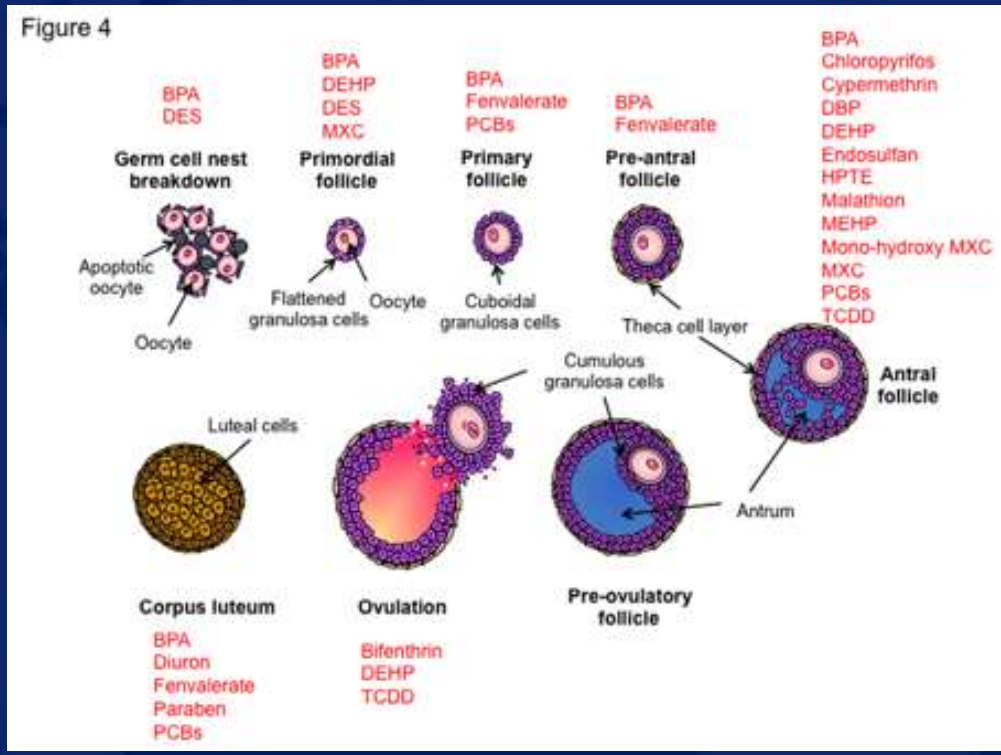
# Diabetes, Obesity, and Cardiovascular Disease

- EDCs that cause or are associated with chronic diseases include BPA, phthalates, tributyltin, POPs, pesticides.
- In animals, developmental exposures disrupt adipogenesis/energy balance → obesity.
- In animals, developmental EDCs alter insulin synthesis, release, and actions → T2D.
- In humans, epidemiological studies associate EDCs with obesity, T2D, CVD.
- Molecular mechanisms involve AhR, PPARγ, ERs, among others.



# Female Reproductive Health

- EDCs including BPA, pesticides, and POPs interfere with female reproduction.
- In animals, EDCs impair ovarian development, structure and function, leading to abnormal steroidogenesis, ovulation, oocyte quality, and fertility.
- Some EDCs adversely affect the uterus, vagina, and anterior pituitary in both animals and humans.
- Disorders in women that are associated with EDCs include PCOS, endometriosis, fibroids, preterm birth, and adverse birth outcomes.



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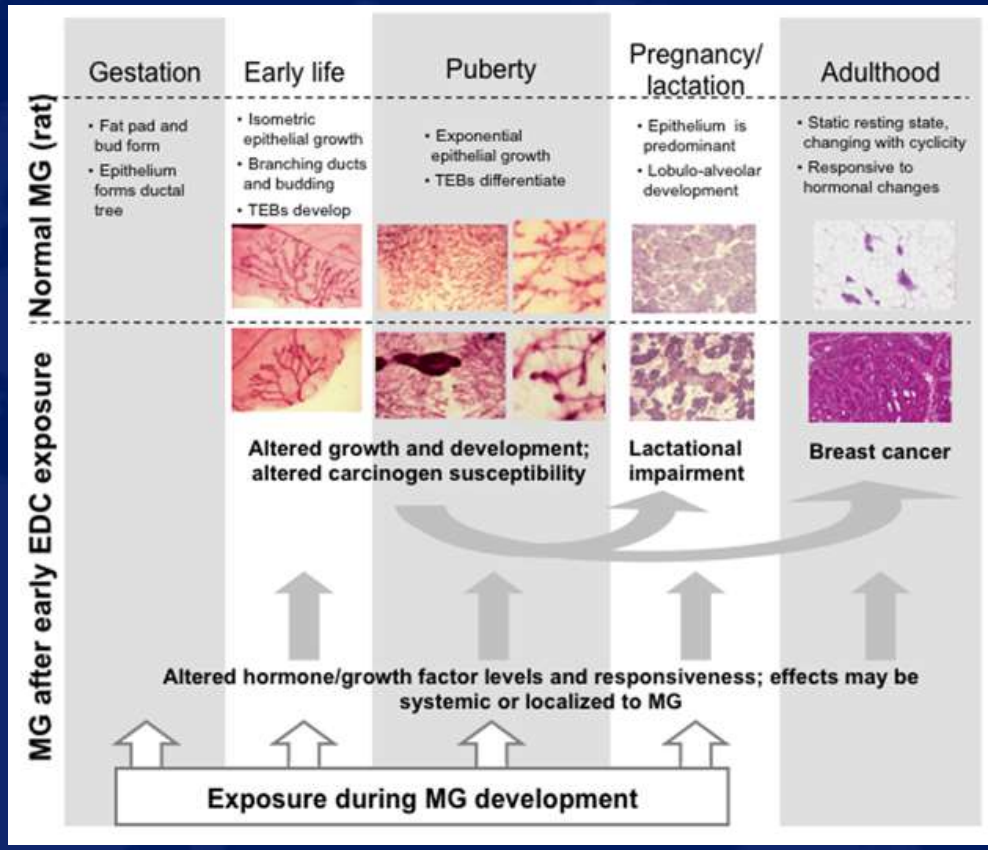
# Male Reproductive Health

- EDCs that act as anti-androgens, xenoestrogens, and dioxins, are best-characterized for impairing male reproductive health.
- Animal experiments demonstrate clearly that EDCs disrupt development of the male reproductive tract, resulting in changes collectively called testicular dysgenesis syndrome.
- In humans, the incidence of cryptorchidism and hypospadias has increased, as has testicular cancer.
- Although results vary, semen quality in men is on the decline globally, resulting in delayed time to conception.

# Hormone-sensitive Cancers in Females

- EDCs such as dioxin and BPA are associated with increased incidences of breast, endometrial, and ovarian cancer.
- There are critical periods of EDC vulnerability in breast and long-term outcomes.
- In rodents, developmental exposures to EDCs alter mammary development, susceptibility to tumors, and lactation.
- Epidemiological studies show significant associations of dioxin exposure and disrupted lactation and increased cancer risk.



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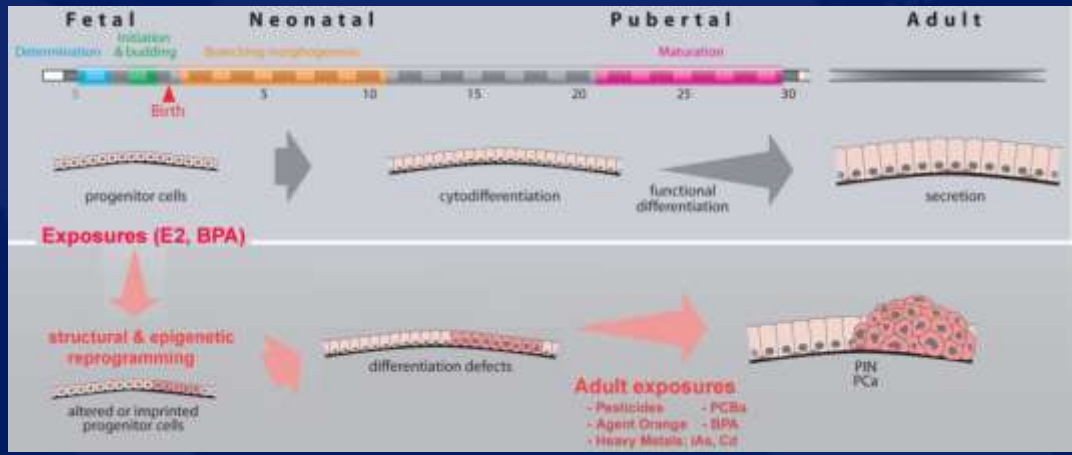
# Prostate Cancer

- EDC classes affecting Pca include pesticides, Agent Orange, PCBs, BPA, and others.
- Disruption of ERs, AR, VDR, RAR/RXRs, PRL and steroid-metabolizing enzymes, underlies altered PCa risk.
- Animal models extend evidence for increased PCa risk from developmental EDC exposures and involve mechanisms including stem cells and the epigenome.
- In humans, ↑ PCa rates & mortality in men has been linked to several of these chemicals. Some populations may be particularly vulnerable due to genetics, underscoring gene-environment interactions.
- Early life, pubertal, and adult EDC exposures are all relevant to the etiology of PCa.

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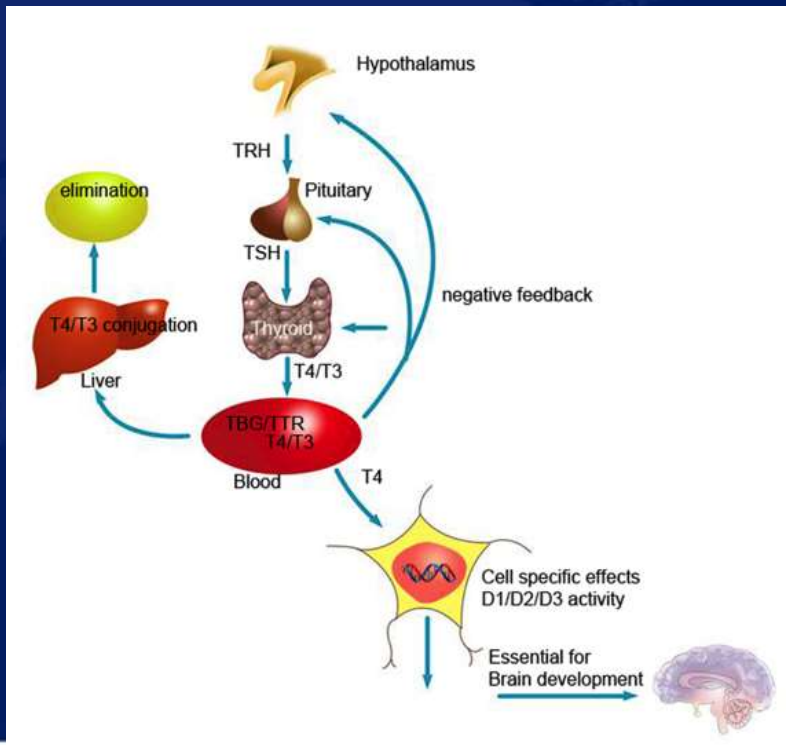
# Thyroid Gland

- Thyroid disruptors include PCBs and other POPs, phthalates, perchlorate, and BPA.
- There are many levels of regulation of the thyroid system, any of which may be EDC targets.
- Developmental exposure is extremely important due to roles of thyroid hormones in neurodevelopment.
- Mechanisms include biosynthesis, metabolism, receptor activation, and function.
- Epidemiological data show cognitive deficits in children exposed to thyroid disruptors prenatally.



# Neurodevelopment & Neuroendocrine Systems

- The brain's neuroendocrine both regulate, and are regulated by, hormones, and are highly sensitive to exposures to EDCs. These systems control reproductive, growth, stress responses, and other functions.
- Developmental exposures cause sex-specific effects on neural development and involve a variety of mechanisms.
- Animal studies show neuroendocrine and neurobehavioral effects of EDCs, with outcomes dependent upon age.
- In humans, epidemiological data support associations between higher exposures to EDCs with decreased IQ, increased neurodevelopmental problems, and other neurocognitive outcomes.



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# Recommendations for Research

- Mechanistic studies of EDC actions on hormone receptors and beyond.
- Investigate EDC effects on enzymes involved in steroidogenesis, hormone metabolism, and protein processing.
- Translate research from rodents into non-human primates, sheep, and other species.
- Evaluate EDC effects at different life stages – not just adulthood or at a single point in time.
- Consider sex and gender differences in responses to EDCs.
- Longitudinal and multi-generational analyses in animals and humans.
- Research emerging “EDCs of interest” and mixtures of low-dose EDCs.
- Team science should include basic, translational, and clinical scientists; epidemiologists; health care providers; and public health professionals.



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# Recommendations Beyond Research

- Education of the public, the media, and the government.
- Recognize that EDCs are an international problem, and develop international collaborations.
- Cultivate the next generation of EDC researchers, green chemists, physicians, and public health experts with expertise in endocrine systems.
- Funding agencies need to prioritize EDC research and prevention.
- Determine how much evidence is enough based on rigorous, peer-reviewed science – and knowing that absolute proof of harm or safety is not possible.
- Evaluation of chemicals prior to their introduction into the market is important based on evidence from replacement chemicals, latent outcomes of exposure, and transgenerational effects.



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# Mounting Evidence of Health Risks

Scientific consensus on:

- Critical and sensitive developmental periods
- Reproductive and hormone-sensitive cancers
- Thyroid effects
- Neuroendocrine and neurodevelopmental effects
- Low-dose, non-monotonic effects

Growing agreement on:

- Obesity, diabetes, cardiovascular disease
- Relationships between human (epidemiology) and experimental mechanistic (animal, cell) work



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