President's Cancer Panel
Environmental Factors in Cancer
September 16, 2008

"Occupational Carcinogens – Environmental Carcinogens: A Fine Line"

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The President's Cancer Panel has devoted four sessions over the next four months to a consideration of the role of environmental factors in cancer. These sessions individually focus on different aspects occupational and environmental exposures, each of which is important; however, it is clear that all are intimately related to one another.

Historically, relatively high exposure levels in workplace settings led to identification of human carcinogens, many of which have made their way into soil, air, water and commercial products. Regulation in one area impacts others. Failure to regulate likewise has widespread impact. Two of numerous examples in support of this observation follow.

Cadmium and cadmium compounds are naturally occurring substances. Cadmium (Cd) compounds were evaluated for carcinogenicity by IARC very early in its monograph program (IARC Monographs: Evaluation of Carcinogenic Risk, Vol 2, 74-99, 1973). Cd is relatively rare in the earth's crust and enters air, water and soil primarily through manufacturing operations (electroplating, production of refined Cd metal and other processes) as well as through the application of phosphate fertilizers. The most significant source of exposure was found at that time to be through food. Fertilized soils have been found to contain two to six times the Cd concentration as nearby unfertilized land. As early as 1961, Schroeder and Balassa (J. Chron Dis, 14:236, 1961) posited that the primary food sources of Cd in the U.S. were seafood and grain products. Cadmium is also contained in cigarette smoke, and IARC estimated that smokers accumulate 0.5 mg for each pack year of cigarette smoking via inhalation. Cadmium was determined to fall into class 2A, a probable human carcinogen.

Southern Louisiana has long had strikingly high rates of pancreatic cancer (Mason, McKay, Hoover et al. Atlas of Cancer Mortality for US Counties 1950-1969, DHEW publication NIH 75-780). Our previous research found a two-fold increased risk of pancreatic cancer in persons reporting "Cajun" (Acadian) ancestry, cigarette smoking, rural residence and high consumption of seafood, rice and pork. The risks associated with rural residence and dietary factors were more apparent in persons with Cajun ancestry. (Falk et al, Am J. Epidemiol, 128:324-336, 1988) More recently a second case-control study of pancreatic cancer in this same geographic area was undertaken to evaluate the role of cadmium in pancreatic cancer risk, as a common denominator in cigarette smoking, rice and seafood consumption and possible fertilizer exposure in rural

areas. Rice is the predominant starch of Acadian diets, similar to Asian diets, and is often consumed with pork products. Preliminary studies have confirmed high Cd concentration in Louisiana rice: 8 ng/g dry weight in a popular locally grown rice compared to rice imported from Italy tested at the same time of 2.65 ng/g. Further, after rice is harvested each fall, the previously fertilized rice fields designed to hold water for growing rice are flooded again and crawfish, a staple shellfish in the area, are farmed. Analyses from this study are on-going; however, analysis of urinary cadmium concentrations (ug/g creatinine) in cases and controls support the association of cadmium as a risk factor for pancreatic cancer with a greater than 4-fold increased risk of pancreatic cancer associated with urinary cadmium excretion.

Despite decades old research in occupational settings and supporting animal studies and the establishment of Cd as a lung carcinogen and a suspected carcinogen for prostate cancer and pancreatic cancer, not enough has been done to prevent exposure. Food is not routinely tested for cadmium, tobacco smoke continues to provide a hefty dose of Cd along with 50 or so other carcinogens, and although a permissible exposure limit (PEL) was set by OSHA over half a million workers in manufacturing continue to have some level of exposure.

The second example is that of secondhand smoke. In this case, epidemiologic research focused primarily on non-occupational exposures, beginning with exposure from spouses in the home, with occupational exposure addressed later. The 1986 Report of the Surgeon General on the Health Consequences of Involuntary Smoking concluded that involuntary smoking "can cause lung cancer in nonsmokers". Subsequent Surgeon General's Reports have reached stronger conclusions about multiple health effects. The U.S. E.P.A. conducted a detailed assessment of secondhand smoke, including long-term animal bioassays, genotoxicity and human studies (1993). This report concluded that environmental tobacco smoke is a Group A carcinogen, the classification used only when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer. In 2004 IARC found secondhand smoke to be a Group 1 carcinogen, carcinogenic to humans, after thorough hazard identification of updated data from human and animal studies over the past 20 years. In this review they also note that occupational exposure to second hand smoke is associated with an approximate 20% increased risk of lung cancer.

The first country to adopt a clean indoor air law nationwide was Ireland. Some other European countries have followed. In the United States clean indoor air laws, prohibiting indoor smoking in buildings other than residences, have come about as a result of public advocacy and have been implemented at the community and state level, but not nationwide. Many of these laws contain exemptions for certain types of businesses, in particular bars and casinos. In addition to exposing nonsmoking patrons, these exemptions place at risk employees who are often subjected to continuous exposures on 8 hour shifts from tobacco smokers at the establishments. Thus, this "environmental carcinogen" is also an occupational carcinogen without systematic regulation.

Obviously research plays the critical role in our understanding of carcinogenesis and provides the foundation for regulation. Most of the questions posed for consideration at this first session appropriately center on research and regulation. With fewer than 2% of the tens of thousands of chemicals in use today previously tested for carcinogenicity it is clear that this should be a very high priority as occupational and environmental exposures are both involuntary and preventable.

Research Needs

- Carcinogenicity and toxicity testing prior to introduction of new chemicals

- Enhanced, fast-track testing of chemicals already in use

- Research methods development at all levels (cell-based, animal and human), including evaluation of complex mixtures that characterize most exposures in occupational and general environmental settings

- Increased federal funding for relevant intramural research programs at NIH, NTP, etc and for extramural scientists

- An increased focus on occupational epidemiology, where possible within occupational cohorts with **cooperation** of industry. General population-based studies are often inefficient. In case-control studies, the proportion of cases and controls exposed to specific substances or employed in specific occupations and industries is often insufficient in terms of statistical power and exposure misclassification is likely greater because of reliance on self-reports with no external source of documentation. Population-based cohort studies compared to industry-based cohorts require larger sample sizes even with targeted geographic selection of populations in areas with occupations and industries of interest. However, prospective study designs, while more costly than case-control studies, provide stronger evidence in the absence of human experimental studies which are rarely if ever appropriate. Notable on-going prospective studies likely to yield important new findings include the Agricultural Health Study, the Sisters Study, the National Children's Study.

Address potentially high-risk subgroups:

- Research on exposures in small business in the United States which may have been overlooked in both research, regulation and monitoring

- Inclusion of migrant workers and contract workers in research, recognizing both the difficulty of identification and tracking as well as the possibility for relatively higher levels of exposure in some jobs and settings..

- Research on exposures occurring at differing points in the lifespan, *in utero* through later life.

- Increased research on occupational exposures in women

Regulation/Prevention

Regulation of those substances which have already been adequately established by research as carcinogens has been very limited. On-going monitoring of health outcomes to determine if

regulatory limits in place are in fact appropriate has likewise been extremely limited. That said, even if some or all of the research priorities suggested above are achieved, without adequate regulation or preferably prevention of additional carcinogenic or probable carcinogenic exposures, the research will be an intellectual exercise.

With those caveats, some suggestions:

Prevent rather than reduce exposures whenever possible

Test prior to the introduction of any new chemical to eliminate/minimize the need for subsequent regulation

Seek to establish a workforce and general public that are informed and knowledgeable about known and suspected carcinogenic exposures, alternatives to such exposure and trade-offs.

Although the focus of today's session is primarily on industrial and manufacturing exposures and those agencies charged with their regulation, these exposures also become "environmental". In consideration of regulatory agencies, the role of the U.S. Food and Drug Administration in preventing involuntary carcinogen exposure through our food supply needs to be addressed as well those agencies to be focused on today (OSHA, EPA, etc)