MEETING SUMMARY
PRESIDENT'S CANCER PANEL
ENVIRONMENTAL FACTORS IN CANCER

October 21, 2008
Indianapolis, Indiana

OVERVIEW

This meeting was the second in the President's Cancer Panel's (PCP, the Panel) 2008/2009 series, *Environmental Factors in Cancer*. The meeting focused on agricultural exposures as they relate to cancer risk. The agenda for the meeting was organized into two discussion panels.

PARTICIPANTS

President's Cancer Panel (PCP)

LaSalle D. Leffall, Jr., M.D., F.A.C.S., Chair

Margaret Kripke, Ph.D.

National Cancer Institute (NCI), National Institutes of Health (NIH)

Abby Sandler, Ph.D., Executive Secretary, PCP, NCI

Panelists

Michael C.R. Alavanja, Dr.P.H., Senior Investigator, Division of Cancer Epidemiology and Genetics, National Cancer Institute

Laura E. Beane Freeman, Ph.D., Research Fellow, Division of Cancer Epidemiology and Genetics, National Cancer Institute

Suzanne E. Fenton, Ph.D., Research Biologist, Reproductive Toxicology Division, U.S. Environmental Protection Agency

Joan D. Flocks, J.D., M.A., Director, Social Policy Division, Center for Governmental Responsibility, University of Florida Levin College of Law

Tyrone B. Hayes, Ph.D., Professor, Department of Integrative Biology, University of California, Berkeley

Heather Logan, Director, Cancer Control Policy and Information, Canadian Cancer Society

Marion Moses, M.D., Founder and President, Pesticide Education Center

Peggy Reynolds, Ph.D., M.P.H., Senior Research Scientist, Northern California Cancer Center

Sandra Steingraber, Ph.D., Scholar in Residence, Interdisciplinary and International Studies Program, Ithaca College

Mary H. Ward, Ph.D., Senior Investigator, Division of Cancer Epidemiology and Genetics, National Cancer Institute

OPENING REMARKS—LaSALLE D. LEFFALL, JR., M.D., F.A.C.S.

On behalf of the Panel, Dr. Leffall welcomed invited participants and the public to the meeting. He introduced Panel members, provided a brief overview of the history and purpose of the Panel, and described the aims of the current series of meetings.

PANEL I

DR. MICHAEL ALAVANJA:

ENVIRONMENTAL FACTORS IN CANCER: AGRICULTURAL EXPOSURES

Background

Dr. Michael Alavanja is a senior investigator in the Division of Cancer Epidemiology and Genetics at the National Cancer Institute and a Captain in the U.S. Public Health Service. He designed the Agricultural Health Study (AHS) and has been the Principal Investigator and Project Officer of the study since its inception in 1993. Dr. Alavanja has received 12 awards from the U.S. Public Health Service including the distinguished Meritorious Service Award for his work in the conception, development, and execution of the AHS. He has also received awards for his work on assessing lung cancer risk from second-hand smoke and domestic radon exposure. Dr. Alavanja has served on a number of expert committees for the International Agency for Research on Cancer (IARC) and the U.S. Environmental Protection Agency. He is a Fellow of the American College of Epidemiology and a member of their Board of Directors.

Key Points

- The World Bank estimates that occupational exposure to pesticides may exceed 1 billion people and other surveys have indicated that nearly every person in the United States is either directly or indirectly exposed to pesticides. This includes 50 million Americans—as estimated by the U.S. Department of Agriculture (USDA)—who drink water that is intermittently contaminated with pesticides or other agricultural chemicals.
- IARC has labeled agricultural insecticides as probable human carcinogens, but only identified two pesticides—arsenic and dioxin—as known human carcinogens. There is a vital public health need to identify the human carcinogens in the group of pesticides/insecticides that are currently on the market.
- The AHS found that 16 percent of farmers had experienced a high-exposure pesticide event, however, 95 percent of these events were not reported to public health authorities. It is estimated that 25,000 agricultural workers worldwide experience unintentional pesticide poisoning each year. Seasonal farm workers tend to be at the greatest risk for this type of exposure, as they do not always receive training in the safe use, storage, and disposal of pesticides.
- Studying pesticides and their resulting health effects has proven to be difficult. To ascertain exposures, their relation to the onset of disease, and eliminate false positives requires a large prospective cohort with frequent exposure to pesticides and other chemicals of interest. Further, comprehensive exposure assessment requires gathering field toxicity measurements, as well as medical and family history, occupational history, demographic profiles, and biologic tissue samples.
- The AHS is evaluating 82 of the world's most frequently used pesticides for exposure-response associations. The study is focusing on occupationally exposed pesticide applicators in two important agricultural states—North Carolina and Iowa. As of September 2008, 12 pesticides were observed to show an increased risk of some cancer with increasing use of the pesticide. Significant associations were observed for prostate, lung, bladder, pancreas, and colon cancer, as well as for leukemia and multiple myeloma. However, these associations were based on a limited number of cases and replication of these first-time findings are needed.

- Pesticide carcinogenicity extends beyond lymphomas, leukemias, multiple myeloma, and prostate cancer, but the lifestyle of farmers may mask some of these associations. Farmers smoke less and exercise more than the general population and consequently have lower rates of lung and colon cancer.
- Most pesticides are observed to have an exposure response linked to some human cancers, but are not genotoxic. Therefore, epigenetic events—heritable associations with gene and chromatin expression without the accompanying change in the DNA sequence—need to be explored. Current premarket regulatory testing of pesticides may need to be reevaluated due to the heavy reliance on genotoxicity testing, and postmarket surveillance of the adverse effects of pesticides needs to be enhanced.

DR. PEGGY REYNOLDS:

AGRICULTURAL EXPOSURES AND CHILDHOOD CANCER

Background

Dr. Peggy Reynolds is a Senior Research Scientist at the Northern California Cancer Center and Consulting Professor, Stanford University, Department of Health Research and Policy. She has conducted a number of cancer epidemiology studies, with a particular focus on environmental risk factors, including several geographic information system-based studies of patterns of cancer incidence in areas of high agricultural pesticide use in California. She has served as a co-investigator since their inception in 1995 for two large ongoing research efforts: a population-based case-control study of childhood leukemia, the Northern California Childhood Leukemia Study; and a prospective cohort study of cancer in women, the California Teachers Study.

Key Points

- The most common cancer in children is leukemia, which constitutes roughly a third of all childhood cancers. Little is known about the causes of cancer in children, but a number of environmental agents, including pesticides, are under investigation for their suspected link.
- Reviews of childhood cancer studies provide compelling evidence that pesticide exposure potentially predisposes children to a number of cancers. These studies are almost entirely case-control studies looking at home and garden pesticide use and exposures related to parental occupation (e.g., toxic chemical residues on clothing). However, information on residential proximity to agricultural exposures is lacking. The studies are also limited by small numbers of cases, nonspecific pesticide information, and potential case-response bias. These limitations illustrate the need for better risk assessment of agricultural exposures in children.
- Ambient exposure—dispersion of applied pesticides into unintended areas—also needs to be addressed. Pesticide drift can produce exposure in surrounding areas and varies depending on the agents of use and weather conditions at the time of application. Attempts to assess these health risks in California have involved Geographic Information System (GIS) technology, which is a way of incorporating information on environmental exposures with the incidence of disease on a community and state level.
- California has a unique data resource—since 1991, a pesticide use reporting system has required full-use reporting of all pesticide applications in the state. This system provides a wealth of information, including location, active ingredient(s), number of pounds applied, number of acres, date applied, type of crop, and application method. All of this information is recorded at the geographic detail of approximately one square mile and provides sufficient power to detect moderate increases in cancer rates. Researchers are able to quantify pesticide

levels by census block groups in the state. The reporting system is limited by its inability to capture the timing of exposure, homogeneity or heterogeneity of disease, and population subgroups.

- Of the annual average of nearly 160 million pounds of pesticides applied in the state of California, over 12 million pounds are probable carcinogens and nearly 10 million additional pounds are possible carcinogens. Socioeconomic status and ethnicity are strong predictors of potential exposure to these pesticides—Hispanic children and those of low socioeconomic status have a much higher probability of living in neighborhoods with high pesticide use. As the exact risk of exposure remains unknown, a precautionary approach to the use of these chemicals needs to be maintained.
- A large case-control study is being conducted in a 35-county area of Northern and Central California, which involves extensive interviews with parents, household surveys, and environmental sampling. The study looks at GIS-generated estimates of exposure in conjunction with self-reported exposure risk, use in households, parents' occupations, and an analysis of chemicals found in home dust samples. However, difficulties include measuring risk factors, disease latency, time windows of exposure, and degree of statistical uncertainty. Transdisciplinary efforts from epidemiologists, clinicians, geneticists, toxicologists, statisticians, geographers, health educators, and advocates are necessary to overcome these barriers.

DR. LAURA BEANE FREEMAN:

EVALUATION OF AGRICULTURAL EXPOSURES: THE AGRICULTURAL HEALTH STUDY AND THE AGRICULTURAL COHORT CONSORTIUM

Background

Dr. Laura Beane Freeman is a research fellow in the Occupational and Environmental Epidemiology Branch in the NCI Division of Cancer Epidemiology and Genetics. She received her Ph.D. in epidemiology in 2003, at which time she joined NCI as a postdoctoral fellow in the Cancer Prevention Fellowship Program. Dr. Beane Freeman is interested in occupational and environmental causes of cancer and has conducted investigations among pesticide applicators exposed to various chemicals to try to understand potential associations with cancer. In 2007, she was named co-Principal Investigator of the Agricultural Health Study.

Key Points

- The AHS is a cohort of 57,310 licensed pesticide applicators (and over 30,000 of their spouses) in North Carolina and Iowa. The initial enrollment questionnaire (given 1993 to 1997), recorded information on the *ever use* of 50 individual pesticides, including herbicides, insecticides, fungicides, and fumigants. The pesticide exposures were then ranked using an intensity-rating algorithm that accounts for factors such as application method, mixing status, whether or not someone mixed the pesticides themselves, whether or not they repaired their own equipment, and the use of protective clothing.
- Farmers are typically healthier than the general population, with higher rates of physical activity and lower rates of tobacco and alcohol use. As a result, they have lower incidence rates of lung, bladder, and colon cancer. However, farmers have a large number of unique exposures including higher levels of pesticides, viruses and endotoxins from animals; engine exhaust; biologically active dust; and other zoonotic microbes. This may explain the higher incidence rates of leukemia, multiple myeloma, non-Hodgkin's lymphoma, and lip, stomach, brain, and prostate cancers among farmers.

- Data from the AHS show that 70 percent of farmers in North Carolina have held a job off of the farm; 40 percent of those held that job for more than 20 years. Solely relying on the term "farmer" does not capture the broad spectrum of exposures these workers encounter.
- Two types of analyses are used within the AHS to examine the links between use of specific pesticides and cancer—a nested case-control analysis and a cohort analysis. The nested case-control analysis compares people with a specific cancer and those without and looks for differences in chemical exposures. The cohort analysis compares people who use a certain chemical and those who do not and looks for differences in cancer risks. Such complementary analyses provide the ability to statistically control for use of other pesticides and exposures.
- There have been over 6,000 cases of incident cancer diagnosed within the AHS cohort. Cancer incidence among farmers is approximately 15 percent lower in comparison to the general population. However, spouses of pesticide applicators have elevated risks of prostate cancer, ovarian cancer, and melanoma. The AHS does not provide conclusive evidence that any pesticide causes a specific cancer—it is the first evaluation of cancer risk in humans for many of the chemicals being studied.
- Currently, the AHS is in the process of updating exposure information. Participants were administered a telephone interview five years after the initial enrollment questionnaire was given; that information is being incorporated into the analyses. The study is also linking to cancer registries, resulting in accrual of additional cases into the cohort. Using available biologic materials, the interaction between specific genetic polymorphisms and exposure to specific pesticides will also be studied.
- A consortium of agricultural cohorts was created that includes over 1 million study participants from around the world. This type of collaboration presents the opportunity to facilitate agricultural research and study rare outcomes and exposures.

DR. SUZANNE FENTON:

THE MAMMARY GLAND: A TISSUE SENSITIVE TO ENVIRONMENTAL EXPOSURES

Background

Dr. Suzanne Fenton has been a Research Biologist at the U.S. Environmental Protection Agency's (EPA) Reproductive Toxicology Division since October of 1998. Her current research involves identification of the effects of environmental components on early development, pubertal timing, lactational function, and tumor susceptibility of the mammary gland. Her research efforts have three times been awarded a Level III EPA Scientific and Technical Achievement Award, she has received an SOT Reproductive and Developmental Toxicology Specialty Section "Best Paper" in *Toxicological Sciences* award, and her work on the long-term effects of developmental exposure to perfluorinated alkyl acid was highlighted in the May 2007 issue of *Environmental Health Perspectives*. Dr. Fenton serves on the Working Group for the National Institute of Environmental Health Sciences (NIEHS) Breast Cancer and the Environment Research Centers, on the Developmental and Reproductive Toxicology Executive Committee for ILSI HESI, and as a consultant to the California Breast Cancer Research Program Special Research Initiatives.

Key Points

- About 25 to 30 percent of the 1 in 8 women that are annually diagnosed with breast cancer have familial cancer—i.e., one or more cases of cancer in their family. The other 70 to 75 percent have sporadic (non-hereditary) cancers, where lifestyle and environmental exposures

modify risk. Dichloro-diphenyl-trichloroethane (DDT) is one such environmental exposure, increasing the risk of breast cancer by sixfold if exposure occurs before the age of 14.

- Endocrine-disrupting chemicals (EDCs) are of considerable research interest due to their effect on the mammary gland and breast. EDCs can interfere with the synthesis, secretion, transport, binding action, or elimination of natural hormones in the body that are responsible for maintenance of homeostasis, reproduction, development, and behavior.
- Rodents are used to study the effects of EDCs on the mammary gland. Common structures of the rodent mammary gland also found in humans are the mammary epithelium bud and the terminal end buds (TEBs). TEBs are present just before, during, and right after puberty in both female rodents and humans, and the length of time that they are present in the breast can affect the risk of carcinogenesis because of secondary exposures to carcinogens, including UV light and x-rays.
- Dioxin was one of the first chemicals shown to have an effect on the mammary gland. Initial studies demonstrated that early-life exposure to dioxin increases the multiplicity of mammary tumors in rats given a chemical carcinogen during a critical time window. Rodents exposed on gestation day 15—the time at which the mammary bud is forming—showed the most severe and persistent effects. These effects included altered maternal behavior and decreased milk production. Offspring of the exposed rodents also exhibited effects, such as increased mortality rate and altered mammary gland development.
- Atrazine, a chlorotriazine herbicide, is another compound shown to affect the mammary gland in a manner similar to dioxin. Atrazine is a short-lived compound and documented endocrine disruptor, interfering with pituitary hormone secretion and the luteinizing hormone surge. Its short half-life in adult rats and the reported effects from chlorotriazine metabolites prompted current atrazine exposure research.
- Atrazine and other similar parent compounds are quickly metabolized in the environment and in the body. A study of rat offspring developmentally exposed to the atrazine metabolite mixture (AMM) showed that it causes mammary gland abnormalities at 10- to 1,000-fold lower doses than the parent compound.
- Developing offspring are exposed to atrazine and its metabolites via amniotic fluid and milk, although the exposures (measured by levels of metabolites) via these two routes do not appear to be the same. Short exposure times are sufficient to cause persistent effects in the mammary gland (3 days) and also the prostate (5 days). Mechanisms for these effects could include potential changes in receptor populations following atrazine exposure that lead to heightened sensitivity to the estradiol levels present in the body. Another possible mechanism is altered local growth factor gene expression.
- Dr. Fenton's laboratory has identified five diverse endocrine disruptors that cause persistent delays in mammary gland development, alter lactational development, and lead to a number of other adverse effects. Delayed development leads to longer windows of sensitivity, i.e., TEBs that are more susceptible to toxic exposures are present for longer periods of time. Girls in the U.S. are beginning breast development earlier (as young as 6 to 8 years old) resulting in an extended window of sensitivity to environmental exposures and heightened risk of breast cancer later in life.

DR. MARY WARD:

TOO MUCH OF A GOOD THING? NITRATE FROM FERTILIZERS AND CANCER

Background

Dr. Mary Ward is a senior investigator in the Occupational and Environmental Epidemiology Branch in the NCI Division of Cancer Epidemiology and Genetics. Her research focuses on two areas: (1) the evaluation of cancer risks associated with environmental exposure to pesticides and other chemicals; and (2) the role N-nitroso compounds and their precursors play in cancer development, particularly exposure to nitrate from drinking water and diet. Dr. Ward has incorporated state-of-the-art exposure assessment into her studies by developing interdisciplinary collaborations with environmental scientists, environmental engineers, hydrogeologists, geographers, and biostatisticians. She served as a reviewer for the Environmental Protection Agency's drinking water research program and on the Institute of Medicine Committee on the evaluation of a GIS-based model for estimating exposure to Agent Orange.

Key Points

- Nitrate mainly comes from fertilizers applied in the agricultural environment; it is extremely beneficial for productivity. However, the input of nitrogen into the environment also goes up with increases in the human population. Because of this increased "human input," the nitrogen cycle has dramatically changed.
- Nitrogen constitutes 80 percent of the atmosphere; plants take up nitrogen through roots in the soil, and to a lesser extent from light. In the twentieth century, the Haber-Bosch process was introduced to take nitrogen out of the atmosphere and convert it to reactive nitrogen in the form of nitrate and ammonium fertilizers. As a result of the input of nitrate fertilizers into the soil, the amount of nitrate in ground water has risen.
- The EPA regulates nitrate at a maximum contaminate level (MCL) of 10 milligrams per liter (of nitrate nitrogen). This standard was set based on the acute health effect methemoglobinemia, but other chronic health effects have not been studied at this level. EPA regulates public water supplies by this standard, but private wells, which are not regulated, tend to have much higher levels. In agricultural states it is estimated that 20 to 25 percent of the population is exposed to nitrate in drinking water at about half the MCL. About 22 percent of private wells in these areas exceed the MCL.
- Nitrate ingested from drinking water, dark green leafy and root vegetables, and processed meats is absorbed in the body, then secreted through active transport into the saliva where oral bacteria reduce it to nitrite. The nitrite is swallowed and can react with amines and amides—found in proteins consumed—in the stomach to form nitroso compounds. The endogenous formation of nitroso compounds is catalyzed by heme iron—red meat increases production of the compounds. However, fruits and vegetables high in vitamin C or E inhibit the process. In 2006, IARC concluded that ingested nitrite and nitrate are probably carcinogenic to humans under conditions that result in endogenous nitrosation in the body.
- Over 300 nitroso compounds have been tested and 90 percent have been found to be carcinogenic in 39 animal species, including six primate species.
- A majority of IARC case-control studies show an association between dietary nitrite (largely from processed meats) and stomach cancer, with one or two also showing an association with esophageal cancer. A recent international review of the literature on diet and cancer found convincing evidence of increased colon cancer risk in relation to intake of both red and processed meats.

- Recent population-based case-control studies in agricultural states such as Iowa and Nebraska, where nitrate levels are elevated in public and private water supplies, have improved epidemiologic study designs. Historical databases of public monitoring data for nitrate were used in combination with food frequency questionnaires modified to estimate dietary nitrate. These studies were able to evaluate factors that increase nitrosation in humans—lower vitamin C and higher red meat intake. One study, a case-control of renal cell carcinoma in Iowa, found a twofold increased risk among those who had longer-duration exposure to nitrate in drinking water and were above the median intake of red meat.
- A multicenter, population-based case-control study in the western United States assessed the drinking water source of the mother during pregnancy and its link to childhood brain cancer. The study found that, in Washington State, the offspring of mothers who used water from private wells during pregnancy had increased risk of brain cancer.
- Another possible mechanism by which nitrate could cause cancer is through the thyroid; at higher levels nitrates inhibit iodide uptake by the thyroid. A study in the Netherlands in the 1990s showed a relationship between nitrate in drinking water and thyroid hypertrophy and hypoplasia in women.
- Future studies should take into account dietary sources of nitrate, nitrosation inhibitors and precursors, and medical conditions that increase nitrosation to accurately assess cancer risk.

DISCUSSION:

PANEL I

- IARC assembles a panel of experts covering the appropriate range of scientific expertise, including epidemiology, toxicology, and exposure assessment, to evaluate the literature on chemical toxicity based on animal data and to determine whether there is sufficient evidence for harm in humans. To date, they have identified one pesticide—arsenic—and one contaminate—dioxin—to be known human carcinogens. There was a general association between insecticides and an elevation of human cancers, but the studies were deemed insufficient at the time to determine which specific chemicals were associated with the elevated cancer risk.
- The risk of melanoma is potentially increased with pesticide use, particularly the chemical carbaryl (used primarily in insecticides). The risks of nonmelanoma skin cancers are difficult to assess, as state cancer registries generally do not collect information on these cancers.
- Birth defects or developmental abnormalities might be faster indicators of toxicity than carcinogenesis. Dr. Fenton's studies of the mammary gland provide a compelling model for identifying toxicities in a rapid manner. The prostate is also an informative model for early developmental effects. NIEHS, a collaborator with the Agricultural Health Study, is looking at adverse reproductive outcomes from the study data.
- Future toxicology studies should focus on metabolite data. A number of the metabolites of DDT have been evaluated, but the metabolite data for most other compounds are unknown—especially chlorotriazines, where several parent compounds all form the same metabolites. The way a person metabolizes various compounds will have a major effect on their susceptibility to both toxicity and carcinogenesis.
- The Agricultural Health Study is approaching its second generation of studies and until their previous results are replicated, inconsistencies based on pesticide ratings by the EPA and IARC will remain. These agencies' ratings do not take into account the possibility that the mechanism of action of pesticides is non-genotoxic.

- The number of cases occurring in cancer clusters is typically too small to launch a detailed investigation; the purpose of statewide studies is to detect patterns to help determine the causes of these clusters.
- Data concerning childhood cancer are still in their infancy, and the disparities facing Latino and socioeconomically disadvantaged children are particularly difficult to assess. However, half of the children enrolled in the Northern California Childhood Leukemia Study are Latino, which should provide a sufficient number of cases to identify the factors that predict risk in these different groups of children.
- There is an increased incidence of prostate cancer related to the combination of organophosphate exposure and a predisposed genetic history. Family history plays an important role in cancer risk and multiple efforts are under way to identify the interplay between genetic susceptibility and environmental exposures.
- The National Children's Study will follow early-life exposures and evaluate pubertal timing from the beginning of breast development through completion of puberty. Also, NIEHS is sponsoring the Breast Cancer and the Environmental Research Center, which has a human component that evaluates young girls going through puberty and studies the effects of early life exposures on breast development. These data, along with specific chemical information, will facilitate a faster evaluation of the risk factors for breast cancer.
- Stomach cancer is still important worldwide, but rates have decreased in the U.S. since the introduction of refrigeration in the twentieth century. Nitroso compounds and *Helicobacter pylori* infection at an early age are known risk factors.
- A concern of large epidemiologic studies, such as the Agricultural Health Study, is enrollment bias. At the design stage, the expectation was that 10,000 African Americans would be enrolled into the study, but actual enrollment was only 1,500. Migrant workers were left out of the study, as they cannot be captured using a state cancer registry.
- Epidemiologic studies are presently being conducted at the molecular level to understand mechanisms and modes of action of chemicals. Occupational and environmental studies are an ideal area to use these new technologies to uncover the gene-environment interactions involved in carcinogenesis. These emerging technologies can also be applied to exposure assessment and intermediate biologic endpoints.
- Agricultural policy in the U.S. has encouraged the extensive use of nitrate fertilizers, which has resulted in the contamination of water supplies and vast ecologic effects. Nitrogen fertilizers and pesticides are largely fossil fuel-derived chemicals; their use might be reduced as a result of market forces if oil prices continue to increase. Reduced use can also be encouraged through changed agricultural policies, i.e., better crop rotation and management.

PUBLIC COMMENT

- The collaborators involved in the agriculture cohort consortium are mostly from the northern hemisphere, but the group is trying to recruit collaborators in Latin America.
- In terms of the environment, epidemiology is a very blunt tool—researchers are unable to calibrate the tools available to study environmental anomalies such as cancer clusters. The current paradigm for risk identification and prevention is not adequate to protect public health. Many successful examples of the precautionary principle can be seen in other countries; the U.S. needs to follow suit and redevelop its approach toward chemical testing and setting policy.

PANEL II

DR. TYRONE HAYES:

THE ONE-STOP SHOP: CHEMICAL CAUSES AND CURES FOR CANCER

Background

Dr. Tyrone Hayes' research focuses on the role of steroid hormones in amphibian development, with particular emphasis on metamorphosis and sex differentiation. He is well known for his work on the effects of atrazine on the feminization of amphibians. This pioneering work brought Dr. Hayes to the center of controversy between academia, industry, and regulatory agencies. As a result, he has a unique perspective into the politics of environmental science and the conduit between scientific data and policy. Dr. Hayes maintains an active and rigorous undergraduate research laboratory at the University of California, Berkeley. His work has been profiled by many news agencies, including *National Geographic*, *Discover* Magazine, and National Public Radio.

Key Points

- Color differences between male and female frogs such as the *Hyperolius puilus*—found in Kenya—are hormonally regulated, such that exposure to exogenous estrogens will induce a color change in the male that is typical of the female. Various estrogenic compounds, such as the endogenous steroid, estradiol; the synthetic steroidal estrogen, ethynyl estradiol; the potent estrogen, DES; and the estrogen mimic, DDT; all induce color changes in this frog species. These compounds, found to be estrogenic in the frog, are also known to be estrogenic in human breast cancer cells.
- Atrazine—produced by Novartis—is an herbicide that has been used by corn growers for the past 48 years in the U.S. Eighty million pounds are used annually, making it the number one pesticide contaminant of ground, surface, and drinking water. It is used in more than 80 countries, but is illegal in Europe, where Novartis is based.
- When researchers developmentally exposed the African clod frog to atrazine, it grew multiple ovaries in addition to its testes, transforming it to a hermaphrodite. Exposed North American leopard frogs were prone to growing eggs in their testes. Atrazine's proposed mechanism of action involves the induction of aromatase, which converts testosterone into estrogen and results in feminization. Data supporting this hypothesis were published in the *Proceedings of the National Academy of Sciences.* Feminization effects similar to those seen in frogs have also been recorded in fish, turtles, alligators, chickens, and quail.
- A study conducted in Columbia, Missouri in 2003 measured atrazine levels in the urine of men and found higher levels in subfertile males—men characterized by low sperm count and low semen quality—than in control males. Another study in California found that men who apply atrazine have 24,000 times the chemical in their urine than the level associated with subfertile men in Missouri. It is important to note that over 95 percent of the people who grow food in California are Mexican or Mexican-American with lower-than-average life expectancies.
- Novartis conducted a study in rats in 1994 that showed a statistically significant association between atrazine and increases in estrogen-positive/sensitive mammary tumors. A separate study in 2000 showed that atrazine reduced testosterone levels and sperm count in rats.
- In 2001, Sanderson et al. showed that a human renal carcinoma cell line produces aromatase when exposed to atrazine—the same mechanism observed in frogs, fish, turtles, rats, etc. The promoter that controls regulation of aromatase in the gonads of humans is the same in the

gonads of all vertebrates (i.e., fish, reptiles, birds, mammals). Excess aromatase and estrogen production are associated with both mammary and prostate cancer in humans.

- In 1997, a study showed that women in Kentucky whose well water was contaminated with atrazine were more likely to develop breast cancer compared to women in the area who did not drink the contaminated water.
- The *International Journal of Occupational and Environmental Medicine* published a study conducted in a Novartis Syngenta factory in St. Gabriel, Louisiana that manufactures atrazine. The community is 80 percent black. The results concluded that the increase in prostate cancer in male subjects in the community was concentrated in company employees, and more prevalent in actively working employees. Further, the prostate cancer increase was limited to men under 60 years of age.
- It is known from five independent laboratories in three different countries that atrazine works by blocking phosphodiesterase, which causes an increase in cyclic AMP (adenosine monophosphate) and in aromatase activity. The transcription factor SF1 plays an important role in this process—when SF1 is added to cell lines that do not normally contain it, there is an increase in aromatase activity. When atrazine is added, the increase is even larger.
- When breast cancer cells become damaged, they are regulated by aromatase—local aromatase expression through promoter 2 produces estrogen, which causes cancer cells to divide. Currently, the number one treatment for breast cancer is an aromatase blocker, which decreases estrogen and prevents damaged cells from spreading. Novartis, the same company that produces the aromatase-inducing atrazine, also produces aromatase blockers to treat breast cancer.

MS. HEATHER LOGAN:

AGRICULTURAL EXPOSURE AND CANCER RISK: AN INNOVATIVE MODEL FOR PRECAUTIONARY POLICY DEVELOPMENT

Background

Heather Logan is the Senior Director, Cancer Control Policy and Information, at the Canadian Cancer Society (CCS) and the National Cancer Institute of Canada (NCIC). In this role, Ms. Logan is responsible for evaluating scientific evidence; developing health policy and position statements about emerging scientific issues, including disease prevention and health promotion; overseeing the development of print and online cancer information materials; and overseeing elements of the Society's Cancer Information Service. She graduated with a B.S. in nursing from the University of Toronto in 1991 and a master's degree in health science (health administration) in 2004, and maintains certification with the Canadian College of Health Service Executives.

Key Points

- The CCS is a national community-based organization of volunteers whose mission is the eradication of cancer and the enhancement of the quality of life of cancer patients and survivors. With the mandate to look at environmental and occupational exposures, the CCS focuses on informing Canadians so they can adopt behaviors for better health, avoid exposures to environmental and occupational carcinogens, and participate in organized screenings.
- Scientific evidence is insufficient on its own to change population behavior—a combination of evidence, key messages, and public policy are required to instill change that is successful. The media influence cancer policy, prevention, and action, but it is not well known how to leverage this influence to the advantage of public health.

- According to Canadian cancer statistics, the risk of developing cancer in both males and females has remained relatively stable for the past 10 years, indicating that the efforts of public health officials have not made a dramatic impact on cancer incidence.
- In 2001, the CCS adopted a position on cosmetic pesticides calling for a ban on cosmetic uses, which includes personal lawns, gardens, and parks. There are currently provincial bans on the sale and use of pesticides in Quebec and Ontario, and bans in 145 communities across the country. Pesticide exposures in noncosmetic situations may be higher and involve more vulnerable situations, and the CCS is committed to community engagement, public dialogue, and the engagement of experts from around the world to address these potentially hazardous situations.
- The CCS's interpretation of the precautionary principle is that when an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if scientific cause-and-effect relationships are not fully established.
- The CCS is supporting a state-of-the-science conference in November on pesticides and cancer. The objectives of the conference include: presenting the evidence on adults and occupational pesticide exposure at work, in communities, and in food and water supplies and its association with cancer risk; presenting precautionary-based policy alternatives to minimize exposures; building a knowledge exchange network for public health care professionals, advocates, and decision makers; and identifying gaps in current research.
- Science studies exposures substance by substance and does not take into account the multitude of exposures experienced daily and over a lifetime. Potential risks associated with extremely low-level exposures may be underestimated or missed entirely. Gestational exposure and windows of vulnerability also require more focused research. The current risk paradigm needs to be transformed to include these exposures.
- Communication of health risks to the public is a challenge—there are competing demands on message clarity, community engagement, and understanding. It is difficult to disseminate complex and often controversial scientific issues in an atmosphere of strong public influence and polarized opinions.
- The CCS's continued investment in occupational and environmental exposures will entail a new toxicological approach to look at multiple routes of exposure, multiple substance exposures, and windows of vulnerability. It will also work to attain a better balance between investment in research and public policy action.

DR. MARION MOSES:

PROTECTING FARM WORKER FAMILIES FROM PESTICIDES

Background

Dr. Marion Moses is Founder and President of the Pesticide Education Center in San Francisco, California.

Key Points

- Protecting farm workers and their children from pesticides is a difficult undertaking—these workers have great pride, suffer from abundant toxic exposures, and have insufficient legal protections.
- Agriculture is the only industry where child labor is legally sanctioned. The Fair Labor Standards Act of 1938 prohibited child labor in most industries, but did not impose age limits in agriculture until 1974—and even then 14-year-olds could work unlimited hours and 16-

year-olds could perform hazardous jobs, including handling pesticides. The National Child Labor Committee estimates that there are 200,000 to 800,000 children and adolescents who work in agriculture in the U.S., and at least 100,000 minors working on farms in violation of statutes every year.

- The Federal Pesticide Act of 1978 decreed that use of a pesticide must be consistent with its label; there were 70,000 pesticides on the market at that time. Acutely toxic and some nonacutely toxic pesticides are labeled as *restricted use*. Nonacutely toxic pesticides are included in this category because they may harm crops. Restricted use pesticides may not be applied without a permit, which is regulated by individual states. Pesticide regulation is one area where a national program is needed to ensure proper certification and that usage is reported for both restricted-use and general-use pesticides.
- The chronic health effects (including cancer) from low-level exposure to pesticides that meet legal requirements and for which there is no evidence of illness or misuse are unknown. Current policy allows thousands of pesticides to stay on the market while lengthy testing or retesting for health effects is performed.
- One of the problems with regulation of pesticides is that it focuses on food residues, which does not provide protection for workers who must still manufacture, transport, use, store, and dispose of the potentially toxic chemicals. At each of those steps there is enormous opportunity for exposure to workers and their children. Once in the environment, residues that persist in air, soil, and water continue to pose a threat to the biosphere and to public health.
- There should be a comprehensive, ongoing national study of all childhood cancer cases in the United States. According to American Cancer Society data, there are about 8,000 new incident cases of cancer in children each year. Children are an ideal group in which to study pesticides and other exposures as a risk factor for cancer because they have a much shorter latency for cancer, are unlikely to be smokers or drinkers, and overall do not have confounding occupational exposures. If children and pregnant spouses of farm workers are protected, then the entire community will be protected.
- About ten years ago a group of farm organizations and unions (California Rural Legal Assistance, Farm Worker Justice Fund, Farm Labor Organizing Committee, Migrant Farm Workers Justice Project, National Council of La Raza, Pesticide Education Center, and United Farm Workers of America) devised ten commitments to protect farm workers from cancer.[1] Progress has yet to be made on meeting many of these basic commitments.

[1] The ten commitments were to: (1) prohibit the use of any pesticides known or suspected to cause cancer, birth defects, neurological damage, or that are in the highest acute toxicity category during any phase-out period; (2) prohibit all aerial application of pesticides; (3) guarantee farm workers the right to know what specific pesticides are used in their workplace through crop sheets, posting of warning signs, and training that covers health effects, protective clothing, and other safety information in a language the workers understand; (4) require and enforce a mandatory national pesticide use reporting system for all uses to include all active and inert ingredients in products; (5) require and enforce a mandatory national reporting system for all potential pesticide-related incidences and illnesses by agricultural employers and health professionals; (6) guarantee farm workers the right to bring an action to enforce their rights under the law, including employer retaliation, violation of worker protection standards, and regulation of toxic pesticides; (7) guarantee farm workers the right to organize, human representation, living wage, overtime pay, a safe workplace, and workers' compensation; (8) require and fund a continuing program with the cooperation of farm workers for biological and environmental monitoring of pesticides in farm worker families and their communities; (9) require and fund research with the cooperation and approval of farm workers to set up a program to monitor long-term effects of pesticides; and (10) change Federal and state agricultural funding to promote research in the transition from toxic pesticides to rational and sustainable pest control methods.

DR. SANDRA STEINGRABER:

WHAT WE KNOW ABOUT PESTICIDES AND BREAST CANCER

Background

Dr. Sandra Steingraber is a biologist and cancer survivor. Currently a scholar in residence at Ithaca College, she is the author of *Living Downstream: An Ecologist Looks at Cancer and the Environment*. She served on President Clinton's National Action Plan on Breast Cancer and as an advisor to the California Breast Cancer Research Program. In 2001, Dr. Steingraber was awarded the Rachel Carson Leadership Award by Chatham College. She received her Ph.D. in biological sciences at the University of Michigan.

Key Points

- Bladder cancer is considered a quintessential environmental cancer—with data going back a hundred years, there is more evidence linking toxic chemical exposures with bladder cancer risk than almost any other kind of cancer. Unfortunately, identification of carcinogens does not preclude their ongoing use.
- There are three dozen different industries that line the Illinois River Valley. In addition, farmers practice chemically intensive agriculture in this area. Drinking water wells contain traces of both farm and industrial chemicals, including those with demonstrable links to bladder cancer.
- Pesticides were first created as weapons of war. DDT was used in World War II (WWII) in response to a typhus epidemic among refugees in Italy and was later deployed to the Pacific Theater to fight a malaria epidemic among U.S. troops. At the same time, 2,4D and 2,4,5T—two phenoxy herbicides—were invented as chemical weapons of war with the intent to destroy Japanese rice crops. Nitrate, originally used for explosives, was repurposed after the war and sold as fertilizer, ensuring a continuing product market for chemical companies.
- Prior to WWII, all farming was organic—it was not dependent on chemicals to control pests. The introduction of pesticides into agriculture resulted in many unexpected pest outbreaks that had not occurred before—pesticides killed targeted pests but also killed many other insects that served as natural predators. To manage this problem, farming moved into single crop production—large-scale monocultures.
- Methods of agriculture determine what foods are available to the public. With the subsidization of corn and soy production, it can be argued that the public is exposed to more atrazine in drinking water, burdened with higher obesity rates, and imparted inexpensive red meats associated with increased risk of colon cancer. Lifestyle is an important risk factor for cancer; diet is largely determined by the price of food and what is made available to consumers in local supermarkets.
- Atrazine is an intensely soluble herbicide that poisons the plant from within. It is applied to the soil before planting and absorbed by the roots of the crop. Nitrates are applied to plants in the form of anhydrous ammonia, another water-soluble substance. These chemicals contaminate groundwater or run into streams and end up in the bodies of people living in agriculturally intense areas. Even more atrazine and nitrates are being put into the environment as farmers continue to receive increasingly high subsidies for corn.
- Any study looking at agriculture and cancer should inquire into and fund studies of communities where ethanol plants are located. There is a phenomenal amount of benzene released into the environment when ethanol is produced, and the associated health risks need to be assessed.

- Organic agriculture leaps 20 percent every year in the U.S. but needs to be fully embraced, as it comprises only 2 percent of total agriculture. Organic farming can meet the high yields of conventional farming and can also contribute to protection of our climate—organic soils sequester carbon and use much less fuel. Organic farming may also increase food security and contribute to better public health.
- Southern Illinois University's new Simmons Cooper Cancer Center is the only tertiary care cancer center in the U.S. located in a rural area and is perfectly situated to send out rapid-response teams into farming communities. Such tertiary care cancer centers can help identify patterns between pesticides in drinking water wells and particular cancers in the population.

MS. JOAN FLOCKS:

PESTICIDE POLICY AND FARM WORKER HEALTH

Background

Ms. Flocks is Director of the Social Policy Division at the Center for Governmental Responsibility, University of Florida College of Law, where she teaches Poverty Law and a seminar on Environmental Justice. She also teaches International Environmental Justice at the University of Florida/University of Costa Rica Joint Program in Environmental Law. The Center for Governmental Responsibility is Florida's senior legal and public policy research institute. Ms. Flocks' current research focuses on inequities in natural and built environments—low-income housing, pesticide exposure, and outreach to Superfund communities—and resolution of those inequities. She has worked with low-income and minority communities in Florida for twenty years, as a social and legal service provider, researcher, and project director.

Key Points

- It is often the case that policy does not reflect advances in science—its foundations are rooted in other factors such as economic interests and social and political characteristics of the parties involved.
- Farm workers are disproportionately affected by pesticides due to heightened exposures, more limited access to health care, and lower socioeconomic status. Research shows that farm workers are unaware of all of the risks involved with pesticides, especially those associated with cumulative and synergistic exposures. Risk perception and acceptance are affected by variables such as age, gender, personal sense of control, and various economic pressures. Older workers tend to be more aware of pesticide exposure than younger workers, but regulation is needed to protect all workers.
- The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), administered by the EPA, governs the registration of pesticides in agricultural workplaces. Many assume that this regulation ensures the safe application of pesticides and protection of agricultural workers. However, the reality is that the process is burdened by uncertainty, bias, and general ineffectiveness. Safety data of many pesticides vary or are unknown. And a cost benefit analysis unique to environmental protective regulations is often used, whereby matters of human health are weighed against industry's economic interests.
- Farm worker advocates often question the logic of having the EPA administer the Worker Protection Standard (WPS)—a regulatory task more suited to the Occupational Safety and Health Administration. The WPS is developed by states with the EPA retaining supervisory authority, resulting in a nationally inconsistent pattern of monitoring and enforcement practices. Enforcement is sporadic and when fines are issued, they are often negotiated downward.

- Despite regulations, there are many practical barriers that farm workers face when carrying out the WPS recommendations. Employers may not post the required information about pesticides, or post it incorrectly. Workers often do not have access to clean water and soap in the fields, nor to regular facilities for washing clothes.
- Farm workers should have the right to organize and demand adequate working conditions (i.e., put pressure on policy makers to change regulation). However, farm workers have been excluded from many of the nation's laws that protect workers' rights to organize.
- The demand for workers migrating from Mexico continues to be high and immigration reform policies create fear and anxiety among these workers, making them afraid to voice concerns about unsafe working conditions.
- Regulatory change often stems from grassroots efforts. Grassroots movements have developed new strategies of applying pressure directly on visible corporate end users of agricultural products in order to increase farm workers' wages. Farm workers have also globalized and are starting to look to other countries for alternative solutions to the environmental issues they are facing.
- Increasing farm worker knowledge about pesticide risks and safety practices is important; educational campaigns should focus on both farm workers and their families. Research has found that while farm workers may not always be concerned about their own health, they are very concerned about their families' health (particularly children's).
- Farm workers should be encouraged to inform doctors that they work on a farm and with various hazardous chemicals when seeking health care for themselves and their families.

DISCUSSION:

PANEL II

- The Canadian Cancer Society's view of the precautionary principle is that if there is a potential for harm, then steps should be taken to mitigate risk. In the case of cosmetic pesticides—i.e., pesticides used to enhance the appearance of a lawn or garden—*precaution* might result in banning them altogether. In the case of agricultural pesticides, *precaution* might mean looking at alternative crop patterns to help manage pest control. It is important to identify the criteria for invoking the precautionary principle in advance, especially when dealing with a controversial subject matter such as pesticides.
- The precautionary principle has had a long history. For example, in 1964 the Surgeon General warned the public that smoking caused lung cancer, even though there was no "proof of harm" at that time. This model of having the courage to act based on partial, but sound, evidence should be applied to environmental issues like exposure to agricultural pesticides. The indication of harm is the usual trigger for action and the weight of the evidence depends on how many people are exposed.
- A precautionary approach is particularly important in regard to epigenetics and critical windows of exposure. If precaution is not adopted early on it could take generations of humans being exposed before the real effects are uncovered.
- Before more regulation is enacted—such as for atrazine that has known health implications and is banned in other countries—the problem with enforcement of existing regulations needs to be solved. It is a huge issue that is inhibiting the protection of public health.
- With 8,000 new incident cases of cancer in children each year, they are an ideal group in which to study links between chemical exposures (such as pesticides) and cancer. When

studying children, problems that plague adult epidemiological studies can be avoided, such as a long disease latency period, recall bias, and confounding exposures.

- Atrazine might affect the progression and metastatic capability of breast cancer, but there is currently an absence of data regarding that mechanism. Studies have shown that atrazine also has effects on the pituitary gland, neurodevelopment, and immune function. However, the mechanisms of action vary and industry often uses such inconsistencies to justify keeping a product on the market.
- Patient advocates are the policy makers at the grassroots level and help drive research in many organizations. Advocates, such as those at both the American Cancer Society and the Canadian Cancer Society, play a critical role in carrying the voice of patients forward.
- The biggest challenge the CCS faces related to environmental factors in cancer is translating scientific evidence to the public. There is not much knowledge in the community about scientific design, and the more controversial an issue, the more risk that the public will lose interest before the issue has been explained.
- A national pesticide reporting program would start the process of holding people accountable for the use of toxic chemicals. This would be accomplished through an entity that enforces violations such as failure to report use, misuse, or overuse of pesticides. As exemplified in California, a full-time reporting system can be successfully paid for by a mill tax—a tax on the pesticide registrants.
- The presumption that cancer is an inherited predisposition is not evidence based. Families, especially farming families, often share their environment, and genes and the environment interact in very complex ways. The environment and lifestyle are more rational places than inherited predisposition to begin a program of cancer prevention.
- A number of community-based organizations work to ensure that farm workers are aware of what the Worker Protection Standard entails. These groups often know better than the workers themselves how they should be protected and could help contribute to the development of a more effective worker protection model.
- In every vertebrate class examined there is evidence for an endocrine mechanism consistent with the induction of estrogen. Many laboratories, including at the EPA, have shown that atrazine induces aromatase—aromatase converts androgen to estrogen in the body. If the FDA has approved Novartis and AstraZeneca to release an aromatase blocker to treat breast cancer, then the EPA should ask Novartis Syngenta to stop producing atrazine, an aromatase inducer.
- Endocrine disruptors in the environment need to be studied for their potential contribution to the rising incidence of hormone-dependent cancers. Dose responses and mechanisms of action are important aspects to consider.
- There is evidence that aromatase and local estrogen production are important in prostate cancer. Anastrazole and letrasol, two aromatase inhibitors produced by AstraZeneca and Novartis, respectively, are being tested for treatment in prostate cancer.
- In developing precautionary approaches, policy makers should be encouraged to look to jurisdictions that have enacted these approaches successfully—such as Massachusetts' Toxic Use Reduction Act and Europe's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) legislation.
- Additional populations, crops, and states need to be studied to accurately assess the health implications of those most at risk to exposure to pesticides. The Agricultural Health Study is primarily looking at whites, but 75 percent of the agricultural workforce is Latino. Farmers in