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Summary of the Workshop on Information Needs to Address Children's Cancer Risk

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This report was prepared by Eastern Research Group, Inc. (ERG), an EPA contractor (Contract No. 68-C-98-148, Work Assignment No. 2000-01) as a general record of discussions during the Workshop on Information Needs to Address Children's Cancer Risk. This workshop was co-sponsored by EPA's National Center for Environmental Assessment and National Institutes of Health's National Institute of Environmental Health Sciences. As requested by EPA, this report captures the main points and highlights of discussions held during plenary sessions. The report is not a complete record of all details discussed nor does it embellish, interpret, or enlarge upon matters that were incomplete or unclear. Statements represent the individual views of each workshop participant; none of the statements represent analyses by or positions of the NIEHS or the EPA.

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INTRODUCTION

On March 30–31, 2000, the U.S. Environmental Protection Agency (EPA)'s Office of Research and Development and the National Institute of Environmental Health Sciences (NIEHS) cosponsored a workshop entitled "Information Needs to Address Children's Cancer Risk." The workshop focused on a discussion of children's cancer risk assessment and related data needs to address issues that were raised during public review of The Agency's 1999 Draft Revised Guidelines for Carcinogen Risk. These issues include:

- Characterizing the ideal data set to adequately address children's cancer risk.
- Proposed approaches to using available data in the absence of the ideal data set.

The background for discussions at the Workshop is the reality that chemical-specific data are often lacking to specifically address children's cancer risk from environmental chemical exposures. Consequently, the assessment of children's risk is currently addressed by evaluations of traditional bioassays in mature animals, comparative biochemistry and physiology between adult and developing animals and humans, and public-health-protective default positions in the absence of child-specific data. The Workshop focused on four topics areas:

- **Topic 1:** Current and Proposed Approaches to Assessing Children's Cancer Risk.
- **Topic 2:** Enhanced Use of Test Data Related to Children's Cancer Risk.
- **Topic 3:** Future Directions for Toxicology Testing to Address Children's Cancer Risk.
- **Topic 4:** Epidemiological/Molecular Epidemiology Information to Address Children's Cancer Risk.

The cosponsors invited the participation of leaders in the area of human health testing, research, and assessment who represented the pediatric, toxicological, and risk assessment communities. The invited participants addressed not only the induction of childhood cancer, but also increased risks of cancer during adulthood as a consequence of childhood exposure. Observers participated in the discussions of issues specific to topic areas and contributed comments during periods of general discussion.

This report summarizes the Workshop discussions. Appendix A lists the Workshop participants, and Appendix B provides a list of observers. The meeting agenda and charge to participants can be found in Appendices C and D, respectively. Appendix E contains copies of the overheads used in the presentations. Appendix F lists the background materials provided to participants prior to the meeting.

THURSDAY, MARCH 30

WELCOME AND CHARGE TO WORKSHOP PARTICIPANTS
William Farland and Michael Firestone

William Farland, Director of EPA's National Center for Environmental Assessment, and George Lucier of NIEHS welcomed the participants and observers on behalf of the sponsoring Agencies.

Michael Firestone of EPA's Office of Children's Health Protection noted that the intent of EPA and NIEHS in sponsoring the Workshop was not to seek recommendations or reach consensus decisions. The main purpose, he said, was to obtain individual views and perspectives on children's cancer risk assessment and related data needs, and to address issues that have arisen during review of EPA's Draft Revised Guidelines for Carcinogen Risk Assessment. He said Workshop participants should focus on how discussions might have an impact on the ongoing effort to revise EPA's Cancer

Guidelines. He listed the specific issues that would be the focus of discussion during the Workshop (see "Charge to Workshop Participants" in Appendix D and "Charge to the Children's Cancer Workshop Participants" in Appendix E):

- Characterizing the content of the ideal data set to adequately address children's cancer risk, with a focus on data needed for assessing the impact of childhood (including *in utero*) exposures to carcinogens and the issues related to hazard identification and dose-response analyses.

- Addressing not only induction of childhood cancer, but also increased risks of cancer during adulthood resulting from childhood exposure.

- Considering how current bioassay testing protocols might be redesigned to better answer questions related to children's cancer risk and what additional types of data might be brought to bear on children's cancer risk assessment.

- Defining what are the elements of a "**cogent** biological rationale," as presented in the draft revised cancer guidelines, for addressing modes-of-action for children's cancer.

- Answering whether and how a "**cogent**" rationale that is sufficiently health-protective of children can be made based on the kinds of **data that are typically collected by and available** to Federal and State health science agencies at the present time.

- Defining what **additional data**, such as cancer mode-of-action and comparative pharmacokinetics and pharmacodynamics in adults and children, might be useful in developing a "**cogent**" rationale.

- Addressing whether the assessment of children's risks, as it is currently conducted by evaluations of traditional bioassays in mature animals using sensitive responders, is sufficiently public-health-protective in the absence of child-specific data.

In discussing these points, participants noted that the Workshop's purpose was not to describe idealized research protocols that might be developed to provide all data necessary to characterize children's cancer risks, and urged that discussions remain focused on the questions of how best to use available methods and data to address children's cancer risks. An observer noted that the last

issue—whether current use of traditional bioassays in mature animals is sufficiently protective in the absence of child-specific data—might imply a simple "yes" or "no" answer, and urged that the Workshop go beyond that answer. Abe Tobia asked whether the Workshop would be involved in looking at design of future studies, noting that it would require a significant effort. Lynn Goldman replied that the Workshop's charge allows discussion of new study designs, but emphasized the need to consider current issues as expressed in the draft Guidelines. George Lucier encouraged Workshop participants not to get bogged down with a great deal of detail and specificity when addressing future needs. He also asked them to remember, during the discussions, that the revised Guidelines should be able to stand the test of time and adequately capture the need for new approaches and strategies to be used in toxicology testing as it relates to childhood cancer. Abe Tobia repeated his view that the Workshop should focus on what is currently being done and potentially relevant to the current Guidelines. William Farland noted that the Workshop schedule included an opportunity to discuss possible directions for future research. He suggested that specific changes in protocol should be addressed by a separate panel or Workshop in the future.

SENSITIVITY OF CHILDREN TO ENVIRONMENTAL TOXICANTS
Lynn Goldman

Dr. Goldman noted that the Workshop faced a challenging task in addressing childhood cancer and its potential causes as well as children's exposures to carcinogens, which are two separate but important issues in terms of risk assessment. She said Workshop participants should be mindful of the fact that EPA and other government agencies represented at the Workshop make decisions each day with respect to cancer risks and that the goal of the Workshop was to make positive contributions to those decisions. She noted that the purpose of the Workshop was not to specifically evaluate EPA's Cancer Risk Assessment Guidelines or to replace other mechanisms for review of the Guidelines. Dr. Goldman presented an overview of issues related to childhood cancer:

- They have a low rate of occurrence and there is uncertainty about trends in occurrence.
- Childhood cancers are limited to a few unique types that are found in children but not adults and tend to reflect fetal derivation of cells and prenatal exposures.
- Most childhood cancers have short latency periods; many are characterized by known genetic and familial associations.
- There is a high probability of genetic/environmental interactions in children's susceptibilities to cancer.

Dr. Goldman noted that childhood cancer mortality has been decreasing but that there were increases in the rates of acute lymphocytic leukemia and brain cancers among children 1980s. Some research suggests that childhood is a time of greater susceptibility to cancer, Dr. Goldman said. The possibility that children and the developing fetus face risks not seen in adults is supported by examples such as *in utero* exposure to DES during a specific period of fetal development and the subsequent occurrence of vaginal cancer and diseases that resemble birth defects. This suggests a hormonally driven process that changes cell differentiation. Other examples of childhood-specific risks are incidences of radiation-induced cancers that have a short latency and suggest increased risk during developmental periods of rapid cell division. Exposure to tobacco during periods of rapid cell division may also explain observed relationships between age of smoking initiation and lifetime risk for lung cancer and a persistence of risk after people stop smoking. Although only a small percentage of cancers are due solely or in part to environmental exposures, these cancers may account for 5–25 percent of annual cancer deaths, and therefore represent a large public health burden. Dr. Goldman suggested that, in considering the adequacy of the rodent bioassay model, the Workshop's discussions of childhood susceptibility should focus on:

- Genetic susceptibilities, including inherited predisposition and polymorphisms that result in pharmacokinetics that affect dose.

- Reduced latency that results from rapid tissue growth during childhood.
- The persistence of effects due to mutations or alterations of cell differentiation.
- Nutritional factors.
- Hormonal factors, including the influence of exogenous hormones such as DES.

Dr. Goldman asked participants and observers to respond to these points and to add other issues that would be relevant to the Workshop's goals of considering how the EPA Guidelines can properly address children's cancer risks.

Discussion

Rochelle Tyl said the Workshop should consider the repair capacity of a young organism compared with an older more developed organism, the differences in metabolism between prenatal or perinatal animals and adult animals, and clearance. These issues may reveal reasons why the young may be more susceptible, Dr. Tyl said.

Paul Foster recommended consideration of the developmental "window" during which exposure occurs. Chris Portier said that consideration of cancers resulting from viral exposures also should be considered. Dr. Portier and Dr. Goldman both noted that the interaction of multiple factors is an important consideration but one that would be very difficult to examine in bioassays. David Wallinga suggest adding consideration of immature immune systems and the protective factors such as the the patency of the blood-brain barrier in immature animals. Lauren Zeise noted that certain exposure factors should be considered; she cited as an example the increased exposure to contaminants in drinking water of a child being fed infant formula.

Frederica Perera said that racial, ethnic, or cultural variability may play a role in susceptibility but cannot be modeled using rodent bioassays. Joseph DeGeorge observed that possible genetic predispositions and racial or ethnic variabilities may play as large a role in adults as in children, and might therefore be beyond the scope of the Workshop. Dr. Perera and Dr. Goldman responded that genetic predisposition may play an important role in cell growth and differentiation and therefore might be particularly important during periods in life when there is rapid cell growth. George Lucier said there would be a mushrooming of information about the relationship between genetic predispositions and diseases that are easily detectable, such as childhood cancers. How to use that information in childhood cancer risk assessments is going to be very difficult, he said. Dr. DeGeorge repeated his observation that genetic predispositions and racial or cultural factors do not represent defining factors between the effects of fetal or children's exposures and adult exposures, and are a bigger issue than the Workshop's focus on childhood cancer risks. Mark Miller noted that there are genes that may be associated carcinogenicity or susceptibility in childhood but are not associated with adult cancers. Chris Portier said that genetic predisposition is an important area to explore for differences between adults and children. For example, genes that "turn on" during a particular stage of development may point out windows of opportunity. Polymorphisms in those genes coupled with exposure at a certain time could have a serious effect. Because these genes tend to be selected out of the population, it is very difficult to gather information without specifically looking for it, Dr. Portier said.

Michael Thun said that an underlying theme in the discussion seemed to be the question of the conditions under which a study in rodents can give the wrong answer to questions about childhood cancer. For example, he noted, a study in animals may not show a problem but under a special circumstance such as nutritional deficiency or the presence or absence of a polymorphism there may be a problem. The number of possible permutations of conditions that would need to be studied is huge, and it will be a long time until there is a bioassay that will tell whether there is a problem in all subjects.

EPA now factors in a protective margin—the upper 95 bound—to cope with this problem, but from the point of view of a biologist, Dr. Thun said, all bioassays provide incomplete information.

Lauren Zeise suggested that another issue to consider is timing. Exposure early in life has more time to interact with other exposures to cause cancer, but timing is not now addressed in Guideline default procedures, she said.

Leslie Robison noted that children's cancers tend to be very specific types of cancers, and said that extrapolating from data acquired in animal models may not have anything to do with the induction of the unique spectrum of cancers that occur in children.

Abe Tobia said that 90-day animal assays may not reveal problems but do not allow for a pathological continuum that leads to some childhood cancers and, from that perspective, short term studies may yield false negative data. A very important issue, he said, is the need to conduct a long-term definitive study that detects these cancers and can be used to determine whether that relates back to childhood. Rochelle Tyl said that the key problem with 90-day studies and chronic studies is that exposure starts in animals that have gone through puberty and are essentially adults. This misses the most vulnerable stages of development for some cancers, and even 2-year or 3-year bioassays that begin exposure at 6 to 8 weeks will not detect cancers resulting from *in utero* or lactational exposure.

CHILDREN'S ENVIRONMENTAL HEALTH
Lynn Goldman

It is crucial to recognize that children are not little adults and are exposed in ways that have no parallel in adult life. For example, breast-feeding is an exposure route only for infants. Moreover, a child's metabolism may be more or less capable than an adult's of breaking down, inactivating, or

activating toxic substances. The rapid growth and development of organ systems that takes place during childhood increases the vulnerability of children, who also have more years of future life in which diseases with long latency periods might develop.

Children's exposure to dioxin is more than two orders of magnitude greater during their first years of life, when they are breast fed, than later in life, Dr. Goldman pointed out. Intake rates for water, food, and air, per kilogram of body weight, are greater for children than for adults, and some routes of exposure are different in children. Because infants, toddlers, and preschool-age children spend much of their time on the floor or on the ground and use their hands and mouths to explore these environments, they are exposed in different ways to different contaminants than are adults. In addition, children's diets frequently focus on certain foods that are relatively uncommon in adult diets, she noted.

Discussion

George Lucier asked what types of information are now available that indicate the relative magnitude of children's body burdens of toxics compared with those of adults. Dr. Goldman replied that there is very little available. William Farland said that the EPA was initiating studies of very small populations as a first step in measuring national human exposures, and is participating in planning stages of a longitudinal birth cohort study that will provide more detailed information on exposure and body burden. Chris Portier said that measurement of body burdens would provide more relevant information than measurement of exposure and intake. Dr. Goldman said that there are very few animal studies that provide information relating body burden in mothers to body burden in the fetus. Joseph DeGeorge noted that intake rates as well as metabolic elimination rates change rapidly throughout childhood. Dr. Goldman noted that animal studies may not be able to accurately model these changes in humans. Dr. DeGeorge said that the Food and Drug Administration had conducted surveys of literature to obtain

information on organ development and profiles of metabolism as it changes through childhood. The data are difficult to find and, he added, it is very difficult to develop a parallel between adult animals and adult humans, and even more difficult to find juvenile animal models that represent juvenile humans. Dr. Farland suggested that pharmacokinetic modeling may offer a better understanding of dose in both humans and animals. Refining these studies, he said, will improve the ability to understand the effects of target doses on target tissues. This would eliminate the sometimes misleading reliance on measuring exposure and intake levels.

Frederica Perera noted that the multiple or repeated exposures lead to complex interactions that are not well understood, and that these interactions may have different effects in children than in adults. David Wallinga said that, unlike adults, children have a fairly predictable set of exposures through types of food or specific medications, but these predictable mixtures have not been considered in risk assessment. Lauren Zeise suggested that studying body burdens of compounds that act by similar mechanisms may be more valuable than concentrating on the body burden of a single compound, particularly when determining whether the observed dose-response should be considered in a linear or nonlinear way.

Joseph DeGeorge noted that existing data acquired through neonatal rodent assays demonstrates that juvenile animals are more susceptible than adults to carcinogens. There is no need to develop new tests to detect differential sensitivity. What is needed, he said, is an understanding of why there is greater sensitivity and how it applies to humans. George Lucier noted that for a few effects, such as breast cancer, information exists to show that animal data can be applied to human risk. Using lessons from these few models that have been well explained would help develop other mechanistic animal models that can be applied to humans. Dr. DeGeorge noted that more than 90 chemicals have been tested in juvenile animals, and a neonatal mouse assay, which can identify tumor effects within a

year, is now being studied as an alternative to the two-year adult bioassay. Dr. Portier noted that much of the published data is from studies that rely on one or two doses and does not tell very much about the curvature of the dose-response. This is important, he said, because there may be chemicals that cause adult cancer through a very nonlinear mechanism but have a linear mechanism in infants. Dr. Goldman observed that it is important to fully explore the issue of susceptibility versus exposure, because differences in susceptibility would result in different dose-response curves in children and adults with the same exposures.

Dr. Portier noted that the same mechanism of action can have different effects at different ages or stages of development. For example, he said, a carcinogen may be activated by metabolism but is then mediated by an organism's repair capacity. If that capacity is low in the child and high in the adult, there might be linearity in the child and nonlinearity in the adult, even though the same mechanism is involved.

Chris Wilkinson said the Workshop should recognize that the EPA's current draft represents a good set of cancer risk assessment guidelines that should not be further delayed by extensive discussion of specific children's cancer issues. These issues are very important, he said, but should not become a barrier to finalizing the Guidelines. He suggested that the Workshop's goal should be to identify four or five major factors that could be incorporated into the Guidelines and move forward. Dr. Farland noted that the Workshop has been charged specifically to address childhood sensitivity and to assure that the guidance put forward is public-health-protective. Abraham Tobia said the Workshop should focus on identifying a few topics that can be fully explored. He said the Guidelines represent a solid framework and should be implemented, and that fuller discussion of other issues will come later. It is important that the regulated community understand what kind of information it is expected to generate.

David Goldsmith said that susceptibility must be looked at as a result of interactive effects. He also noted that it is necessary to understand the role of changes in immunologic competence as a child matures. Sam Kacew said that the role of lactation and breast feeding, which had been mentioned as means of exposure, should also be considered in terms of development of the immune system. He suggested that the Workshop also consider other nutritional factors, both protective and harmful. Paul Foster said that fetal dosimetry and lactational transfers are critical measures that should be developed to provide first-hand practical information on how much of a chemical crosses the placenta and how much is transferred in milk.

Jeanette Wiltse said that information about mode of action from a 2-year bioassay or from a 2-generation study is not relevant when exposure begins *in utero*. She suggested that Guidelines should encourage studies on mode of action in the very young animal, which is not part of the standard protocol. Dr. Tobia said that the regulated community wants to provide information that will be used in the risk assessment process. Sometimes that information is outside the required data but may help make a case for a different way of modeling a carcinogen. But, he added, unless the information is used in decision-making there is no benefit to doing the work necessary to gather it. Dr. Farland said that relevant information may be available in data that are routinely collected for endpoints other than children's cancer. Dr. Portier said that it is important to determine what kind of information is necessary to understand the mode-of-action issue in children, and that type of information cannot be derived from current data on adult animals. Philip Landrigan said that it is simply not possible to extrapolate from the adult experience to predict what is going on in the neonate or the infant. He urged that the Workshop focus on the role of the Guidelines as a means to protect human health. He said that this goal is best achieved by assessing the risks in children, who are the most vulnerable segment of the population.

FRIDAY, MARCH 31

EXPOSURE OF CHILDREN TO ENVIRONMENTAL TOXICANTS
Philip Landrigan

Workshop chair Philip Landrigan opened the Workshop's second session by observing that the explicit goal of the Guidelines should be prevention of disease, not detailed understanding of mechanisms of action. Risk assessment should be considered in a public health context, he said, and he noted that two centuries of medical advances had dramatically reduced the incidence and mortality of infectious diseases in the U.S. During the past 50 years the number of synthetic chemicals entering the environment has increased enormously, and few of these chemicals have been subjected to toxicity testing. To discuss detailed mechanisms of action for a few chemicals while basic toxicity data are lacking for many chemicals is putting the cart before the horse, he said.

Patterns of disease in children are changing in ways that are not well understood, Dr. Landrigan said, noting that asthma, childhood cancers, congenital urinary tract defects, and testicular cancer in young men have increased steadily since the early 1970s. Ten years ago the National Academy of Sciences (NAS) Committee on Pesticides and Children was charged to answer three questions that are directly relevant to the Workshop's purpose, Dr. Landrigan said. The questions are:

- Are children more heavily exposed than adults?
- Are children more susceptible to toxicity than adults?
- Do current laws and decisions protect children?

Childhood exposure to carcinogens is vastly different and greater by orders of magnitude than adult exposure. Moreover, Dr. Landrigan noted, children live and play on the floor and often put their

hands in their mouths, and their exposures come from a wider variety of environmental sources than do adults'. Children are also more vulnerable to environmental toxicants, as indicated by such examples as children's increased risk of cancer following exposure to nitrosamines and vinyl chloride, decreased ability to detoxify organophosphates, increased susceptibility to lead and alcohol (fetal alcohol syndrome), and the relationship of DES and adenocarcinoma of the vagina. Such data led the NAS Committee to note that "children are not little adults" and to conclude that:

- Children's exposures to pesticides are greater pound-for-pound than those of adults.
- Children are less well able than adults to detoxify most pesticides.
- Children's developing organ systems are highly vulnerable to pesticides.
- Children have more years of future life in which to develop chronic disease triggered by early exposure.

Dr. Landrigan emphasized that the last point is important to the Workshop's discussion because, although childhood cancers are relatively rare, exposures during childhood increase the risk of adult cancer. Dr. Landrigan cited the NAS committee conclusion that "compared to late-in-life exposures, exposures to pesticides in early life can lead to effects that are expressed only after long latency periods have elapsed. Such effects include cancer, neurodevelopmental impairment and immune dysfunction." The NAS committee concluded that traditional risk assessment does not reflect the complexity of children's exposures to carcinogens, is limited to study of too few chemicals, and largely is based on exposures of adult animals.

Commenting on earlier Workshop discussion suggesting that consideration of children's cancer risks might add a complicating layer of complexity to risk assessment, Dr. Landrigan said that children's risk should be the core of the risk assessment Guidelines. Risk assessment in a public health context has

as its goal the protection of the most vulnerable, Dr. Landrigan said, and therefore must be based on risks to children. Dr. Landrigan noted that the NAS committee made general and specific recommendations that were incorporated into the 1996 Food Quality Protection Act and led to EPA's 1996 declaration that children's health is a specific focus of the Agency's environmental health plan.

Dr. Landrigan referred to a recent journal article (Faustman, et al.) in which the authors discuss consideration of children's susceptibility in an overall framework for human risk assessment and say "An important public health challenge has been the need to protect children's health. To accomplish this goal, the scientific community needs scientifically based child-specific risk assessment methods." That comment, Dr. Landrigan said, should set the stage for the Workshop discussions. Dr. Landrigan said that defaults and safety factors have become a major component of pesticide regulation, and are applied when it is determined through research that infants and children are more vulnerable than adults to a compound or, more commonly, when there no child-specific data are available. He said defaults are not sufficiently emphasized in the Carcinogen Risk Assessment Guidelines and suggested that there be explicit mention of defaults in the Guidelines. In closing, Dr. Landrigan said that despite the work already done to draft the Guidelines, they should be fundamentally rewritten as a concise document that clearly states goals and objectives, cites previous work, describes methods, and concludes with a discussion and references. Other work done to date would be included as an appendix, he proposed.

TOPIC 1: CURRENT AND PROPOSED APPROACHES TO ASSESSING CHILDREN'S CANCER RISK
William Farland

Dr. Farland said the EPA is a public health agency with its principal focus on disease prevention. To this end, he said, the Agency's draft Guidelines have been developed to protect the most vulnerable populations and most sensitive individuals. This includes an explicit consideration of

children and their unique vulnerabilities, Dr. Farland noted. He reviewed the development of Cancer Risk Assessment Guidelines and noted that they serve not only to guide risk management but to identify research needs and to advance the science of risk assessment, particularly as it might be applied to children and other vulnerable populations. As a result, he said, cancer risk assessment is an iterative process and the Guidelines are the product of continuous dialogue and reevaluation driven by new data and models. He noted that the Guidelines are the result of interagency colloquia, peer consultation and review, three reviews by EPA's Science Advisory Board, multiple interagency reviews, and public comment. He said the Agency Risk Assessment Guidelines are:

- Statements of Agency policy regarding principles, general approaches, preferences, and default assumptions that will be applied in Agency risk assessment.
- Not a cookbook.
- Not a regulation.

The first Agency carcinogen Guidelines were issued in 1976, and new Guidelines based on the "state of the science" were issued in 1986. The 1986 Guidelines were flexible, Dr. Farland said, but provided little guidance on when or how to depart from default assumptions and therefore did not provide much incentive to collect better data. Moreover, they did not include specific consideration of children. These shortcomings led the Agency to initiate the revision of the Guidelines. The new directions for risk assessment guidelines:

- Emphasize full **characterization**.
- Expand the role of **mode of action** information and, therefore, **biomarkers**.
- Use **all information** to design dose-response approach.

- Incorporate a **two-step** dose-response assessment.

The two-step dose-response assessment first considers information within the range of observation and then explicitly considers moving from these observations into the range of inference to make, in some cases, decisions that are not testable. The Draft Carcinogen Risk Assessment Guidelines reflect a mode-of-action analysis based on physical, chemical, and biological information rather than a detailed mechanism-of-action analysis that may delay action because there would never be complete information. Risk assessment has evolved from hazard identification that relies on traditional toxicologic testing to hazard characterization through evaluation of mechanisms and biologically based models ranging from new strains of rodents to mathematical models, Dr. Farland said. Mode-of-action considerations involve asking:

- How does the chemical produce its effect?
- Are there mechanistic data that support this hypothesis?
- Have other mechanistic hypotheses been considered and rejected?

Mode-of-action data is used in dose-response assessment to:

- Construct a biologically-based or case-specific model.
- Link the dose-response curve for precursor effect to dose-response curve for tumor effect.
- Use dose-response for other effects in lieu of that for tumor effect if it is judged to be a better measure of potential risk.
- Inform assessment of possible dose-response in range of extrapolation.

In the range of extrapolation, Dr. Farland said, the dose-response assessment is:

Linear if:

- DNA-reactive or other evidence supports linearity.
- Not DNA-reactive but there are insufficient data to characterize a non-linear mode of action.

Non-linear if:

- not DNA reactive or otherwise linear, and sufficient data exist to characterize a non-linear mode of action.

Both if:

- There is differing activity at different sites.
- Linear and non-linear approaches are needed to explain complex activity.

Non-linear includes a margin of exposure approach that is new to the Guidelines, Dr. Farland said. This is an evaluation of how close the available human or animal data are to the exposure of interest. It allows for a judgment as to whether or not the increment of exposure is large enough to give regulators confidence that they are being public-health-protective.

The linear approach is public-health-conservative because, by using an upper bound on risk, it allows the Agency to project several orders of magnitude from observed data without making adjustments to account for human variability, Dr. Farland said. This is in agreement with the National Research Council's suggestion that pharmacokinetic models or scaling adjustments be applied to account for species differences in toxicokinetics, differences in exposure rate, or the magnitude of exposure in a population being considered. Low-dose extrapolation is conducted at the point of departure—the lower 95 percent confidence limit on the lowest dose associated with tumor response—determined under standard conditions on test rodents considered to be stressed, not average. The straight-line extrapolation achieves risk estimates similar to those derived by the

procedures described in the 1986 guidelines, and overestimates risk at low doses. The linear approach assures that risk to the population is not underestimated and thereby protects public health, Dr. Farland said.

Generalized models are not able to account for differences in risk due to human variability, Dr. Farland noted. Therefore a margin of exposure analysis is used when a nonlinear default is supported. If no agent-specific data suggest a differential response in children, the human variability factor is applied with adjustment to account for dose in children, but with no other additional factors to protect children, he said. The proposed Guidelines' approach to children's risk incorporates:

- Potential differences in exposure, dose, and response between children and adults.
- A case-by-case approach based on weight of evidence.
- Default science policy positions and procedures to be used in the absence of data.

The Guidelines call for separate evaluation when data suggest increased sensitivity to exposures that occur early in life and include an illustration of how these data can be applied to calculate both adult and childhood-specific unit risk estimates. In addition, Dr. Farland said, this approach provides a lifetime risk estimate that considers, both independently and additatively, increased childhood risk as well as effects in adults due to early-in-life exposure. Because slope factors and unit risk for lifetime exposure are based on adult data, the Guidelines adjust adult unit risk to account for differences in dose between adults and children, Dr. Farland said. These adjustments involve:

- Default procedures for adult-to-child risk adjustments based on differences in dose:
    - Oral dose factor—no adjustment is proposed.

- Inhalation unit risk (gases)—adjustment based on body weight and breathing rate.
- Drinking water unit risk—adjustment based on body weight and drinking water rate.

- Determining guidance for inhaled particles and dermal exposure.
- Asking whether these default procedures are appropriate and incorporating new data.

In considering dose-response in children, if a postulated mode-of-action is supported for adults but not for children, a linear low-dose default will be applied as a default for the general population, including children. This approach accounts for the possibility of increased risk to children while possibly overestimating adult risk, thereby providing public-health-protective estimates based on possible effects in the most sensitive population, Dr. Farland said. When there is no available information on mode of action in children, or when there is no cogent biological rationale that supports the assumption that mode of action in children is the same as in adults, the postulated mode of action is not considered applicable to children.

Dr. Farland said the Agency hopes to publish the new Guidelines early in 2001, and will include a shorter supplementary guidance focused on assessment of children's risk.

Discussion

George Lucier asked how much flexibility the Guidelines would allow in order to accommodate factors such as differences between the ways in which children and adults are exposed or interspecies variations such as the 100-fold difference in half-life of dioxin in humans compared with rodents. The lack of information on such issues is a significant problem facing implementation of the Guidelines, he said. Dr. Farland noted that the Guidelines must calculate human equivalent dose from animal models. Individual cases such as dioxin would have to be considered separately and explicitly, he said, but the

standard human equivalent dose approach includes body weight to the three-quarters power as a scaling factor based on metabolic rate. Exposures coming from different sources are accounted for, in part, by the Guidelines' consideration of background exposure when calculating exposure relative to the dose-response curve, Dr. Farland said.

Lynn Goldman said the Guidelines should clearly describe the mode of action default for children when data exist only for adults. And, she noted, children are part of the general population, and referring to them as a "subpopulation" carries the risk of trivializing the issue of childhood risks, which effect all humans. Dr. Farland said that children's risk assessment begins by making an argument for a mode of action and then asking whether applying that mode of action will be protective of the most sensitive individuals in the population. Unless there are data to suggest that the mode of action applies to children or a cogent biological argument can be made to suggest that it applies, the Guidelines assume it does not and the linear default is made.

Facilitated Discussion

Abraham Tobia: One of the Guidelines' central points is the default assumption and the movement from linear to weight of evidence or the cogent argument. The Guidelines allow the regulated community to generate information that addresses the cogent argument and move away from the linear default. Dr. Tobia said that industry has begun to look at the cogent argument issue and to generate data by looking at the young without ignoring the older population. He said there is a need for more pharmacokinetic and toxicokinetic data that address questions of saturation and differential sensitivity between the young and old, and he urged that the Guidelines allow industry to be flexible in developing new studies based on emerging data relevant to the cogent argument. The Guidelines should not be inflexible prerequisites, he said.

Lauren Zeise: While linear defaults are conservative and protective, the current draft Guidelines miss important exposures very early in life and very late in life when the difference in risk can be as great as an order of magnitude. One major assumption implicit in the Guidelines that may lead to miscalculation of risk is the homogeneity assumption, she said. The Guidelines should incorporate a framework that allows adjustments for heterogeneities such as differences across the population, polymorphisms, and other variability within species, timing of exposure, and the impact of lifetime dose. The Guidelines' assumption about lifetime average dose ignores important information about timing of exposure, she said. Evaluation of epidemiological data may reveal an environmental role in childhood cancers that now have no known cause. With respect to the cogent biological rationale, it is critical to include data that make it possible to calculate and integrate the effect of chronic background exposure, she said. The mode-of action approach involves discussion of associations that support the hypothesis, she said. The Guidelines should incorporate incentives, supported by Federal agencies, for a broader testing of some hypotheses that are now employed in the mode-of-action approach.

Daniel Krewski: Dr. Krewski said the new Guidelines' emphasis on mode of action was a significant improvement, but noted that developing sufficient information on specific modes of action will be extremely difficult and emphasized that the Guidelines should encourage development of methods to acquire this information. Assumptions about lifetime average daily dose can lead to underestimations when early exposures are more important than later exposures because of children's differential susceptibility. He noted that there is a useful body of literature that describes tools which could be used to evaluate time-dependent exposures. He suggested that these methods could be modified to incorporate susceptibilities as a function of time. Inter-individual variations and genetic susceptibilities may account for more than 10-fold differences in risk, and are not be adequately accounted for in current animal bioassays, Dr. Krewski said, and he suggested an additional 10-fold assumption about risks to children. He urged that risk assessments be based on data related to *in utero* and perinatal

exposures to assure that the critical period of exposure is identified. Some carcinogens act through mechanisms that could invoke either linear or nonlinear models for risk assessment, Dr. Krewski said, and the Guidelines should incorporate models that allow for consideration of both the linear and nonlinear contributions, not one or the other. Dr. Krewski noted that pharmacokinetic studies can be a powerful tool to help identify specific susceptibilities in children. He also cautioned against an "across the board" confidence that an assumption of linearity offers the most conservative evaluation of risk. Dr. Krewski said the Guidelines should also develop methods to take into account the high risks that may be associated with human genetic factors alone or through their interaction with varied environmental risk factors.

Frederica Perera: Molecular epidemiology studies in humans make it possible to examine the issue of differential susceptibilities between the fetus and the young child and the variability among young populations. These studies take advantage of biomarkers that can detect molecular changes in samples of blood or other tissue. This approach allows a better understanding of specific exposures, early damage, and susceptibility. Studies involving polycyclic aromatic hydrocarbons and other aromatics such as pollution from coal burning, traffic, and environmental tobacco smoke show that the fetus is at least 10 times more vulnerable to damage than the mother. Other data from these studies show a differential susceptibility among the children that is related to polymorphisms in the study population. Another study of environmental tobacco smoke and preschool-age children also suggests that biomarkers can be used to identify differential susceptibility related to ethnicity. Dr. Perera suggested that biomarkers may provide a means to identify specific susceptibilities and to gather sufficient data to develop probabilistic models that could lead to improved defaults.

Discussion

George Lucier noted that recent studies, including some involving biomarkers, have found 100-fold variations in vulnerability between individuals. Michael Thun observed that the presentations and discussions at the Workshop have focused on two juxtaposed issues:

- On the one hand, a broad and "to the heart" issue of learning what causes, and what might prevent, cancer in children.
- On the other hand, the detailed mechanical considerations of risk assessment and regulation.

In between, Dr. Thun noted, is a broad area of childhood cancer and its relationship with infectious agents and pharmacological agents that may act more subtly than DES. This area may be beyond the province of the EPA, Dr. Thun said, and the Workshop should keep in mind that the EPA is not going to be able to eliminate childhood cancers. Dr. Landrigan observed that from 70 to 80 percent of childhood cancers have unknown causes, but that it is clear that some are the result of exposure to manmade synthetic chemicals. Human action is in part responsible for causing these cancers, Dr. Landrigan said, and human actions such as the development of risk assessment guidelines can be used to prevent them. Retha Newbold suggested that the Workshop should not focus on childhood cancers to the exclusion of cancers that appear later in life but may be the result of exposures that occurred in childhood.

Steven Galson asked Dr. Perera if sufficient data are available now to construct probabilistic modeling that can be used to develop new defaults. Dr. Perera replied that in her opinion enough data could now be gathered about the distribution of some genetic polymorphisms and nutritional factors, as well as known factors related to gender and ethnicity, to begin developing such models. Dr. Zeise added that some of these data could be integrated into a framework that helps describe individual differences and could be incorporated into risk characterization.

Chris Portier said there is no convincing argument that the linear default is conservative as a rule and that there is confusion in the Guidelines as to what the confidence bound derived from animal estimates really represents in terms of protection of population-based risk compared with variants around an estimate. He said the question of choosing a point of departure from the observable response region to the extrapolation region is also not clearly answered in the Guidelines. Dr. Portier said the concept of cogent biological rationale might be appropriate in adults but cannot now be applied as a reason for moving away from the linear default in assessing childhood cancer risks because not enough is known about mechanisms acting in childhood cancers. He also urged the Agency to look at data that help elucidate the effect of long-term versus short-term exposures and carcinogenesis in children.

Dr. Farland said the Guidelines should help provide the best possible judgment about risk to the population, and these judgments must then be applied to decision-making. It is important to prevent even an extremely small risk, he said, and the conservative nature of defaults makes them an important tool in decision-making. He also said the Guidelines are open to the inclusion of additional information and suggested that the Guidelines might incorporate language that actively encourages the use of information such as data on biomarkers, epidemiologic distributions, and ethnic factors. Dr. Portier noted that the draft Guidelines suggest that the defaults would apply when there is neither adequate data nor a cogent biological rationale. He urged that the Agency be very careful to support with data any action regarding children. He said that he did not believe sufficient information was available to make a cogent biological argument for the factors associating exposure to children's cancer.

TOPIC 2: ENHANCED USE OF TEST DATA RELATED TO CHILDREN'S CANCER RISK

Rochelle Tyl

The currently-employed 2-generation reproductive toxicity test (OPPTS 870.3800) monitors first-generation (F-1) animals exposed from the time they are gametes through gestation, lactation, breeding, delivery, and weaning of second generation (F-2) animals. F-1 and F-2 generation animals are exposed "from womb to tomb" in this assay, Dr. Tyl said. She described in detail the protocol and measured endpoints for evaluating effects on parental animals and offspring. This study has the most potential for getting better information about children's cancer risk than is now gathered. The study has the right exposure—spanning development from gamete through adulthood—but gathers the wrong data for assessing childhood cancer risks, Dr. Tyl said. She suggested that the study be extended to follow development of F-2 animals beyond weaning of their offspring. This would allow detection of long-latency cancers without the expense of carrying out separate chronic studies, she noted.

The prenatal developmental toxicity test (OPPTS 870.3700) involves exposure from conception to birth. Because animals are necropsied at birth, this study captures only developmental effects of the prenatal exposure and can not detect postnatal effects, Dr. Tyl noted. Without major change in protocol, this test has very little value for assessing children's cancer, she said.

The combined chronic/carcinogenicity study (OPPTS 870.4300) involves exposure that begins at age 6-8 weeks and continues through 18 months for mice or 24 months for rats. The 90-day toxicity study (OPPTS 870.3100) involves exposure begun at 6-8 weeks and continued through 13 weeks. Immunotoxicity studies (OPPTS 870.7800) begin exposure at 6-8 weeks and continue through 28 days. These studies make it possible to detect impairment of cells involved in immune response, and may be incorporated into the combined chronic/carcinogenicity and 90-toxicity studies. Metabolism and pharmacokinetics studies (OPPTS 870.7485) begin a 7-day exposure at age 6-8 weeks and are conducted only on male animals. All of these studies begin exposure on young adult animals and can

therefore not contribute to assessing risks of exposure during development or childhood, Dr. Tyl observed.

In conclusion Dr. Tyl said that the 2-generation studies, which involve exposure beginning at implantation, hold the most promise for gathering information specific to childhood risk. Following up F-2 generation animals through a chronic study would result in a study that incorporates the appropriate exposure with long duration study. This would allow detection not only of childhood cancers but also adult cancers initiated by childhood exposure.

Facilitated Discussion

Mark Miller: A systematic review of data gathered in other animal studies may reveal timing and organ-specific information on mode of action that can be used to compare adults and children. The single-exposure carcinogenesis data base may be one area that might be fruitfully explored, Dr. Miller said. He suggested that reviewing existing research results to sort species by chemical may help identify which species are best suited as models for specific chemicals. The developing area of research into immune system effects should be integrated into testing for cancer risk in children, he said. Precancerous conditions such as myeloplastic syndrome, which progresses to acute myeloid leukemia, are frequently associated with specific genetic markers and could reveal some associations between exposures and childhood cancer, Dr. Miller suggested.

Paul Foster: Current reproductive and developmental studies involving prenatal and juvenile exposure were not designed for cancer endpoints. With some modification these tests might reveal early indicators of change related to cancer, but as they are now designed these tests reveal the most relevant exposures but the least relevant endpoints for cancer risk, Dr. Foster said. Among the current studies,

data gathered in multigenerational studies have the most potential for revealing childhood cancer risk, but the selective culling of animals in these studies must be modified to include more, and more representative, animals per generation, he said. Currently available "non-standard" data that may be collected include responses during specific developmental windows of opportunity and hormone-like activity of possible carcinogens. Dr. Foster also suggested that developmental stages of test animals compared with humans must be considered. For example, he noted, early brain development that occurs prenatally in humans takes place postnatally in rodents. Dr. Foster said that studies using transgenic rodents may increase the sensitivity of the tests for specific cancers, but he cautioned that results obtained from the study of increasingly sensitive rodents may have decreasing relevance to humans. There is a huge opportunity to use the emerging knowledge of human and animal genomics to find common mechanistic pathways for development of cancers, he said.

Dr. Foster said current prenatal developmental toxicity studies look at inappropriate endpoints and are of no practical use in studying children's cancers, but that current multigenerational studies could be modified to produce data relevant to childhood cancers. Overcoming the limitations of current studies would require modifications such as determining correct dose levels and increasing the number of animals studied from each litter, but extensive modifications run the risk of making the studies too large and complex to be conducted effectively, he said.

General Discussion

Dr. Goldman noted that the discussions of modifying current tests involve looking more and more carefully at an increasingly homogeneous population of animals, and she contrasted that with opinions voiced earlier in the Workshop suggesting that existing studies are too narrowly defined to capture the variability in exposure and susceptibility in children. One aspect that needs to be more fully

explored, she said, is the uniquely human characteristic of not breast-feeding infants. Dr. Tyl noted that even the highly inbred rodent strains used in laboratory studies do exhibit some variability, but agreed that it is small. It would not be possible, Dr. Tyl said, to design animals studies that reflect the variabilities of the human population. George Lambert agreed that the world of animal science does not reflect the conditions encountered by human children. He suggested that this disparity argues for focusing on mechanism of action in children's cancer studies. George Lucier suggested that the limited variability encountered in animal studies could be examined more thoroughly to detect early markers that might be related to variation. He also noted that a common mode of action, such as a receptor-mediated toxicant, may produce different responses depending on the timing of exposure or the organ system involved. Lucy Anderson said that studies that involve total life exposure involve influences from conception through adulthood that may be additive, synergistic, or cancel out. Identifying these effects would require different exposure patterns (preconception only, during gestation, neonatal, and adult) to assure that critical effects are detected. She also agreed with earlier comments that studies involving unculled litters studies could provide more information about variability. Joseph DeGeorge emphasized the importance of timing exposures to coincide with developmental stages, and noted that current rodent studies involve extrapolations from one developmental stage to another. Extending these extrapolations still further, from rodents to humans, must be done carefully, he noted. He suggested that more fully examining modes of action can avoid some of the uncertainties of extrapolation.

William Farland noted that the regulatory toxicology tests are a very sensitive system that is used to make judgments that rodent responses are relevant to humans for hazard identification and that what is seen at high doses is relevant to low doses. He also said that animal studies are beginning to identify biomarkers that can also be examined in human populations. He suggested that information gathered about human biomarkers might be incorporated into animal models through bioengineering. Dr. Landrigan noted that exposures in the toxicology testing mentioned by Dr. Farland began when the

animal had already reached adolescence and therefore is missing important endpoints. He suggested that more meaningful data might result from tests in which exposure began *in utero* and necropsy did not take place until the animal died naturally. Dr. Farland responded that background effects of natural aging would complicate this type of analysis, but agreed that tests in which exposure begins in adolescence miss the biological effects of early exposure. David Wallinga questioned the usefulness of standard toxicity tests using inbred animals to reflect the wide variability in humans. Moreover, he noted, the current Guidelines implicitly assume that all humans are the same because there is no mention of variabilities in susceptibility to carcinogens.

Les Robison suggested that the development of intermediate lesions might be a useful precancerous marker for some childhood cancers. He also expressed concern about the reliability of data derived from animal models to parallel the mechanisms and outcomes of human childhood cancers.

Chris Portier noted that the mode of action approach in the Guidelines likely accommodates most if not all of the concerns he had raised in earlier discussion about the strength of available information in forming a cogent biological rationale. He supported the idea of using the multigenerational study as a framework for developing a children's cancer bioassay, but observed that the selection of some animals over others for study in each litter could result in seriously overestimating or underestimating risk. The selection, he said, might be an unintended result of culling, but also might be a result of the chemical itself. He also noted that studies involving enough non-littermates to acquire meaningful data might require prohibitively large numbers of animals. George Lambert noted that studies focusing on mechanism of action would yield information relevant to risk for populations with different susceptibilities and inter-individual variations.

Chris Wilkinson noted that the discussion about problems posed by human heterogeneity and the homogeneity of animal models overlooks the broader question of whether the rodent model is adequate to assess risks in children in view of the fact that a newborn rat is essentially equivalent to a human fetus. He suggested that developing new studies might be more productive than modifying protocols of existing models because the huge numbers of animals needed for study would pose a serious problem. He asked that the Workshop concentrate less on environmental chemicals and consider ways to assess the risk of pharmaceuticals, food additives, or over-the-counter drugs, which may have substantial *in utero* impact. He said that understanding modes or mechanisms of action makes it possible to plausibly extrapolate from adult risk to children's risk.

David Goldsmith said the Workshop should be cautious in relying on developments that may or may not derive from fuller knowledge of the human genome. He also suggested that epidemiologic data can support dose-response data gathered in laboratory studies and should be integrated more fully into the risk assessment process.

John Doe said that testing homogenous animal models at maximum dose can lead to false positive associations, which is protective of public health. He also said it was important to reiterate the point that the biggest difference between adult risk and children's risk is due to exposure and not to hazard.

David Byrd said that there is a rich literature addressing the issue of the sensitivity of false positive and false negative aspects of bioassays. Unfortunately, he said, the chemicals represented in that data are not representative of the universe of environmental chemicals. He also noted that variability represented in the animal species used in current bioassays is much greater than the variability within the human population.

TOPIC 3: FUTURE DIRECTIONS FOR TOXICOLOGY TESTING TO ADDRESS CHILDREN'S CANCER RISK

Retha Newbold

Dr. Newbold focused on research into the effects of DES as an example of the cancer risk associated with prenatal exposure to estrogenic chemicals. The developing organism is extremely sensitive to estrogenic compounds, particularly during specific stages of development, and the effects of exposure may not appear until much later in life. DES was prescribed as safe and effective to reduce risk of miscarriage, but now is known to have resulted in a low incidence of vaginal cancer and a high incidence of male and female reproductive tract dysfunction on offspring. Research into the effects of DES demonstrated that a carcinogen can act across the placenta, that its activity is different from other carcinogens, and that its effects in humans can be accurately modeled in animals. Prenatal exposure of animal models results in developmental effects in both male and female mice that closely parallel the effects found in humans, thereby validating the experimental model as a means of predicting human disease. Neonatal studies, in which exposure occurs during the first week of life, demonstrate that exposure to estrogenic compounds during the period of uterine development—prenatal in humans and postnatal in mice—is associated with uterine cancer. These studies confirm the critical role of timing of exposure during developmental stages. To determine if the changes due to estrogenic exposure could be transmitted to subsequent generation, researchers bred females exposed prenatally or neonatally to control males and evaluated female F-2 offspring at maturity. Among the F-2 females, reproductive fertility was not effected, but the animals showed an increase in incidence of reproductive tract tumors. Additional research is underway to determine the mechanisms involved in these generational effects. Research advances developed through these studies of estrogenic compounds may be applied to the development of more sensitive animal models of other carcinogens.

Facilitated Discussion

George Lambert: Risks to children from possible carcinogens can be studied in much the same way as drugs are evaluated through pharmacokinetic and pharmacodynamic (PK/PD) models, mechanisms of action, absorption, distribution, metabolism, and effect. These studies can elucidate some of the differential susceptibilities between children and adults as well as those due to interindividual variability. PK/PD studies are well suited to identifying differences between the fetus and child or between child and adult. In humans, cells and tissues from children and adults can be used to identify biomarkers that may be predictive. Dr. Lambert noted that drugs, which are developed for use in a tightly defined population, are subjected to more stringent examination than chemicals to which the whole population made be exposed through the environment. He suggested that post-marketing surveillance of chemicals would reveal patterns of distribution, exposure, accumulated body burdens, and adverse effects.

David Wallinga: Dr. Wallinga noted that the Workshop has been struggling to deal with two different questions: what information is available and what information do we really need. He said that the information available is limited and the data are poor. For example, he noted, only a small percentage of the 80,000 registered industrial chemicals have been studied in even limited detail for toxicity or carcinogenicity. He cited the National Research Council's 1993 observation that current testing protocols do not adequately address the toxicity and metabolism of pesticides in neonate or adolescent animals. NRC also determined that infants and children are more susceptible to risk than adults to the toxic effects of chemicals, even though chemical-specific data may not be available. He noted the reasons for increased susceptibility and said that the Guidelines should incorporate strong defaults assumptions and establish high hurdles to abandoning those defaults. He said that the "cogent biological rationale" mentioned in the Guidelines is not well defined and that the default assumptions in

the Guidelines should be closely examined to assure that they are sufficiently health-protective. For example, he said, the Guidelines do not require data bearing on variability, interactions, or pharmacokinetic data in developing animals. Dr. Wallinga recommended that future testing should:

- Extend developmental toxicity tests beyond birth to account for latency.
- Assess cancer risk from pre-conceptual exposure.
- Look at effects of short-term carcinogen exposure during developmental windows.
- Require pharmacokinetics in immature animals.
- Build developmental windows of vulnerability into the testing paradigm.
- Validate and test for endocrine disruption.
- Do semiquantitative assessments of cumulative risk.

Dr. Wallinga noted in closing that child-protective changes to the Guidelines can't wait, as the Guidelines have been applied since 1996 to at least 45 pesticides and will, by the end of FY 2001, have been used to establish new or revised IRIS assessments for at least 64 other chemicals.

Joseph DeGeorge: Dr. DeGeorge said that it is important to consider the appropriateness of the juvenile animal model before it is used to make predictions for children's risk assessment. For example, he noted, if a toxicant needs activation by a metabolic process that the animal model does not contain, the risk to children will be underestimated or missed. He said that if an animal model is determined to be appropriate, the model must address exposure during the proper organ developmental stage. The timing and method of exposure must be carefully selected to assure that the effects of the chemical are isolated from confounding factors. For example, he observed, exposure through lactation also involves exposure to metabolites. Dr. DeGeorge recommended that more

biomarkers be incorporated into the Guidelines, and that new biomarkers be added when they have been validated. He said that improving dose-response assessment will be one of the most difficult challenges to the Guidelines because of the complexity of exposure in humans. For example, he noted, the effective dose of the commonly used nutritional supplement St. John's wort is reduce by 50 percent in persons taking protease inhibitors, and grapefruit juice can increase the effective exposure to other pharmaceuticals.

Discussion

Rochelle Tyl noted that much of the existing data on carcinogenicity have been based on testing at the maximum tolerated dose. This means, as a practical matter, that the test animal's metabolic capacity has been exceeded and no longer represents the effects in normal animals. This may lead to quantitative differences in the measured outcomes and lead to inaccurate conclusions about tested chemicals. John Doe said there is a practical problem associated with test methods that rely on the induction of tumors as an endpoint. This approach would involve huge experiments to assess the effect of *in utero*, early postnatal, postnatal through life, and conventional dosing protocols. This complexity could be avoided through concentration on identifying precursor events and other markers. The dilemma this poses, he noted, is that these markers will not provide information that is as definitive as tumor initiation. Penelope Fenner-Crisp noted that much of the revised and expanded testing being discussed would have to be imposed on industries, a procedure that would require regulatory authority that does not now exist. David Wallinga said that one of the purposes of defaults in risk assessment is to drive research, and they should be used to drive research that generates data specific to children's risk. George Lambert noted that the development of many FDA regulations has been driven by pharmaceuticals' risks to children, and suggested that the same concern might be brought to bear on children's risks for cancer. Angelina Duggan noted that agricultural industries are beginning to generate

epidemiologic data that can be used to evaluate family exposures to chemicals that are handled only by male farm workers. William Farland pointed out that the existing default structure accounts for human variability through the implicit assumption that humans are at least as sensitive as the most sensitive test animals.

TOPIC 4: EPIDEMIOLOGIC/MOLECULAR EPIDEMIOLOGY INFORMATION TO ADDRESS CHILDREN'S CANCER RISK

Leslie Robison

Epidemiologic research is crucial to identifying risk and working to prevent childhood cancer. These cancers are rare and unique, which makes epidemiologic study difficult. Acquiring adequate etiologic data for childhood cancer will require a national effort to create a network for research that would include:

- A national registry of children with cancer for identifying environmental and other causes of childhood cancer.
- Building upon the unique national clinical trials system for treating children with cancer.
- Identifying children at the time of diagnosis, allowing collection of tissue specimens.
- Coordination of efforts with population-based cancer registries.
- Support and facilitation of scientific studies of the highest merit by qualified investigators to study causes of cancer in children.

The effort must be national in scope because of the differences between children's cancers and those in adults and the relatively small numbers of children with any specific diagnosis. Only a national effort would be able to compile enough data about the 8,700 cases of childhood cancer diagnosed each year to make meaningful evaluations of specific cancer types. A national network would make it

possible to identify causes and to more fully understand known risks factors, Dr. Robison said, and it would also lead to advances in molecular characterization of tumors, exposure assessment methodology, and understanding genetic susceptibility. Among the improved methodologies and technologies that might be developed through a national effort are:

- GIS technologies for hypothesis generation and correlation.
- Sophisticated categorization of occupational categories relevant to specific exposures.
- Exposure assessment through the ability to detect minute quantities of substances in biological fluids and in the environment.
- Identification of biological markers of exposure and susceptibility.
- Identification of potential genetic susceptibility factors.

A national effort would overcome the limitations of previous childhood cancer causation studies and have the secondary benefit of making possible a study of patterns of care and enhancing surveillance capabilities.

The national network initiative for children's cancers could use as its foundation existing clinical trial cooperative groups such as the Children's Cancer Group and the Pediatric Oncology Group, which represent more than 200 institutions throughout North America. These existing groups, which will combine as the Children's Oncology group, have developed extensive epidemiologic data on a variety of childhood cancer, but have not yet developed substantial information on the etiologic of children's cancers. A framework for the structure and registration protocol, as well as a projected development time line have been developed. When established, the national network will make it possible to track the progression of pediatric cancer survivors and examine the effects of medical exposures to

therapeutic radiation, intermediate markers and biomarkers of effect and progression, and cancer outcome.

Facilitated Discussion

Michael Thun: The cancer control community is interested in what epidemiologic approaches will have the biggest effect in identifying the causes of childhood cancer and preventing childhood cancer. The small relative numbers of childhood cancers severely limits possibilities for epidemiologic study. For example, although there is a spike in the incidence of acute lymphoblastic leukemia between ages 2 and 4, the average number of cases is fewer than 85 per million. A cohort of 1 million children enrolled at birth and followed until age 20 would experience the following cancers:

- **Leukemia**
  Acute Lymphoblastic 596
  Acute Myeloid 154
- **Lymphoma**
  Hodgkins 240
  Non-Hodgkins 210
- **CNS – Astrocytoma** 280

Thus, even a huge cohort study would not produce numbers large enough to provide meaningful study of the incidence of the most common childhood cancers. An epidemiologic study looking at genetic polymorphisms through relation of disease to a gene would require between 2,000 and 3,000 cases to achieve enough statistical power to look at gene/environment interaction.

Dr. Thun noted that understand the causes and means of preventing childhood cancers has been a real, pervasive, and persistent concern in the public health community and among parents. It is a problem that needs to be addressed across agencies, and should not be considered separately within EPA or the National Cancer Institute, he observed. He recommended that federal agencies jointly fund a data resource that could make headway against childhood cancers, which, although rare, cause enormous grief.

Lucy Anderson: Animal models should be developed for studying factors such as susceptibility and stage specificity, which are not typically covered in current animal bioassays, Dr. Anderson said. In addition, historical literature should be investigated to gather data on stage specificity, susceptibility factors, and other issues that are meaningful to childhood studies. New studies to test putative associations, hypotheses, and the validity of biomarkers are needed. These could be well-designed modifications of current studies or new protocols involving transgenics, but they will only be carried out with government financial support, she said. The Guidelines should incorporate studies that examine the role of fathers in children's risks, an issue has been overlooked in the regulatory context even though epidemiological and animal evidence suggests an important role of paternal exposure, she said. There is reason to believe that a qualitatively novel mechanism exists to contribute to preconceptional carcinogenesis related to gene expression, she said. These tests could be designed to detect the role of paternal exposures through carcinogens in pesticides, drinking water contaminants, and tobacco smoke.

Peggy Reynolds: Evidence of an association between increased incidence of lung cancer and early initiation of smoking may suggest evidence of mechanisms of early exposure as a cause of later life cancers. A multicenter study of lung cancer in nonsmoking women, which investigated the role of environmental tobacco smoke (ETS) in cancer among nonsmokers, found no increased risk of

childhood cancers associated with childhood ETS exposures, but found that for adult cancers, women with childhood exposures had nearly twice the risk associations of women with adult ETS exposures. This finding may illustrate the issue of "shelf life" as a factor in later life development of cancers resulting from early life exposure, Dr. Reynolds noted.

Chris Portier: Establishing a cancer registry would be useful in understanding the etiology of childhood cancer and, even if it is not environmentally related, will help us to understand better the environmental issues associated with childhood cancer. Developing and following large enough cohort studies of biomarkers will be very difficult. The difficulties are more pronounced for cancers that occur in adults as the result of *in utero*, postnatal, or childhood exposures.

General Discussion

Daniel Krewski commented on the value of nationwide registries to examine childhood cancers, and discussed the types of information and biological specimens that are acquired in Canada's cancer registry. Adult cancer registries might serve as models for childhood cancer registries, which would not only be valuable in current studies but also represent an incalculable resource for future research. Leslie Robison noted that the highest single age-specific rate for childhood cancer is in the first year of life.

Some pediatric cancers have genetic origins, Dr. Robison said, but most are initiated *in utero*. He added that the evidence for a paternal role in children's cancer is driven by data on occupation, although some animal models show an association between preconceptional radiation exposure and cancer in offspring. Dr. Robison said a national birth cohort study would not be likely to make a meaningful contribution to the study of children's cancers but could reveal patterns of association

between childhood exposure and adult cancers. Moreover, he said, a birth cohort would be invaluable as a means of tracking exposures.

William Farland and Philip Landrigan described the efforts of an interagency task force, chaired by the Secretary of HHS, the Surgeon General, and the Administrator of the EPA, to initiate a nationwide birth cohort that would register at least 100,000 ethnically and racially diverse children as early as possible in pregnancy. Statistical information and biological samples would be obtained from the parents as well as the child, who would be followed with standardized examination protocols to age 18. Many details remain to be worked out, Dr. Landrigan said, but the effort has begun and has enormous promise as a means of increasing understanding of the etiology of childhood diseases other than cancer. Dr. Robison noted that although the birth cohort could not directly address childhood cancer as an outcome it would provide data on exposure assessment that could have incalculable value to the ability to do cancer related research in the future. Chris Portier said that a cancer registry would have more value to childhood cancers than a birth cohort. Philip Landrigan repeated his earlier comment that it is inarguable that children are more heavily exposed to carcinogens than are adults, that developing organ systems are more vulnerable than fully formed systems, and that children have more years of future life in which to develop cancers than do adults.

Joel Bender observed that the Workshop and similar discussions may not have been able to reduce uncertainty about the Guidelines but have been successful in articulating a national agenda to fill data gaps. A question that needs to be answered, he said, is whether the scientific community is comfortable with the Guidelines until those gaps are filled. Lynn Goldman expressed confidence that discussions would result in modifications to the Guidelines that appropriately respond to concerns about pediatric cancer. David Goldsmith asked that serious consideration be given, when establishing a birth cohort, to the disproportionate burden of severe environmental and health problems borne by minority

communities. He suggested that minority children be oversampled as a method of assuring that their risks be fully incorporated into the overall consideration of public health.

WORKSHOP SUMMARY
George Lucier

Dr. Lucier repeated the basic charge that the Workshop should serve as an opportunity to help assure that the Guidelines for Cancer Risk Assessment accommodate as much information as possible to adequately identify and assess risks to children. He noted the major themes that emerged from the Workshop presentations and discussions:

- Children should not be considered a special population; rather, childhood should be considered a stage of development characterized by increased sensitivity to chemical exposure.

- Evaluating margins of exposure requires better information on external exposures from environmental sources such as air, food, and drinking water. Data on internal exposures, as measured in blood or urine levels, is often not available for childhood exposures. Pharmacokinetic and pharmacodynamic models can help elucidate childhood exposures. All of this information should be considered with respect to exposure during critical "windows" of organ development and cell differentiation.

- Important sensitivity factors include developmental stage and genetic predisposition. Much information that will emerge from refined test protocols, human genomics studies, and other resources will bear on these issues, and organizing this new information into a coherent picture of childhood cancer will be a challenging task. Other important sensitivity issues relate to nutrition, "shelf life" (i.e., when exposure occurs during childhood, there is a long latency period available for cancers to develop), and interactions between multiple environmental, physiological, and genetic factors.

- Mode of action (MOA) assessments should evaluate conditions in which different modes lead to different risks (children compared with adults, for example) as well as when the same mode leads to different risks. Genotoxic and nongenotoxic are oversimplified distinctions when considering mode of action in the context of deciding whether to use linear or nonlinear

assumptions about risk. Background exposures must be taken into account when considering MOA, as multiple factors with the same mode of action could result in a cumulative risk.

- Dose-response studies are difficult but important, and should take into account background exposures, variability, dose selection and timing, and the applicability of surrogate markers and early indicators.

- Uncertainty factors include the realization that using defaults to account for variability is more difficult than using them to account for species differences. The 10-fold safety factors now used to account for species differences are public-health-protective, but may not accurately reflect interindividual differences or differential genetic susceptibility; therefore additional safety margins may be needed. Additional factors may be needed to adequately assess children's exposure, and linear assumptions may not always be the most conservative.

- Guidelines should not be overly prescriptive and should be able to stand the test of time. Guidelines that include highly detailed descriptions of their application may prove to be too inflexible to allow new approaches and new models to be used as they become available.

- Regarding a cogent biological rationale that justifies an assumption other than the guideline default: for children, the bar should be high enough to be public-health-protective, and the models used will require rigorous peer review.

Discussion

Rochelle Tyl asked what could be expected as a result of the Workshop. Dr. Lucier replied that the Workshop's purpose was to identify what information needs to be captured by the Guidelines in order to more fully understand children's risks. This information, he said, would be used to revise the current draft Guidelines. William Farland noted that the Workshop discussion provided valuable insight into the need for data collection and generated ideas about revisions to epidemiologic studies and laboratory testing protocols that may be incorporated into testing Guidelines to assure that they fully address risks unique to children. He also noted that the discussions of improved testing protocols would be valuable in improving other Agency guidelines. David Wallinga urged that the Guidelines incorporate

an explicit mention of principles particular to dose-response or mode of action, such as a statement that, in the absence of data to the contrary, mode of action for children is presumed to be different than for adults. A similar principle could be framed for children's exposures, Dr. Wallinga said. Dr. Lucier suggested that it would be necessary to develop credible models in order to obtain sufficient data to fill the gaps in current understanding of both susceptibility and exposure.

Dr. Lambert noted that, for many children's cancers, susceptibility may be far more significant than exposure. Michael Firestone urged that the effort to improve testing methodologies be continued beyond the revision to the Guidelines and that the issues of windows of susceptibility and differential exposure be built into the Guideline discussions of cogent biological rationale. Rochelle Tyl suggested that the Guidelines incorporate a specific definition of cogent biological rationale. Each researchers has their own perception of what the term means, she said, but the Guidelines would benefit from a definition that articulated details such as types of studies and timing of exposures that would satisfy the requirements of producing a cogent rationale. Lynn Goldman responded that the Guidelines should be less specific, not more detailed. Spelling out specifically how the Guidelines are to be applied today will make it more difficult to apply them more effectively in the future, she said. Abraham Tobia replied that the Guidelines do need some detailed and specific guidance to the research community, perhaps as appendices or illustrative examples. Such examples, he said, would provide insight into the thinking that underlies the Guidelines and therefore provide valuable direction to researchers, particularly in regulated industry. Dr. Farland noted that the Workshop discussions had generated a much clearer perception of what information is needed to clarify issues such as cogent biological rationale, and suggested that the Guidelines might benefit from inclusion of a case study or other example that more clearly articulates the concept of cogent biological rationale.

John Doe noted that new testing regimes need to be developed in response to the need for specific types of new information, and said that these new testing protocols should replace older study designs rather than being presented as add-ons to an already-burdened testing structure. Dr. Tobia said that any new studies must be rigorously tested and validated before they are incorporated into the Guidelines. He noted that the add-ons to multigenerational studies discussed earlier in the Workshop could easily lead to a protocol that requires far higher numbers of animals and round-the-clock attention by technicians and would make testing too complex and prohibitively expensive. Dr. Goldman and Retha Newbold both cautioned that animal welfare issues could become an important consideration if testing protocols become more complex, and suggested that the Agency pursue development of studies that reduce the need for animal models.

Dr. Landrigan urged that children's risk should be an integral part of the overall cancer risk Guidelines, not an afterthought. Dr. Farland said that he expected the final Guidelines to include an explicit mention of children's risks. He noted that the purpose of the Guidelines was protection of public health and that protection of children as among the most vulnerable is an integral component of that goal. This point will be clearly made in the Guidelines, he said.

Dr. Landrigan and Dr. Goldman thanked the Workshop participants and observers for their efforts and contributions. Dr. Farland expressed EPA's gratitude to the Workshop chair and cosponsor and closed the Workshop by saying that all the participants could leave knowing that they had contributed to progress.

APPENDIX A

WORKSHOP PARTICIPANTS

Workshop on Information Needs to Address Children's Cancer Risk

Holiday Inn Arlington at Ballston
Arlington, VA
March 30-31, 2000

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APPENDIX B

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Arlington, VA
March 30-31, 2000

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APPENDIX C

MEETING AGENDA

Workshop Agenda

Information Needs to Address Children's Cancer Risk

Holiday Inn Arlington at Ballston
4610 North Fairfax Drive
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Thursday, March 30, 2000 and Friday, March 31, 2000

Thursday, March 30, 2000

6:00 - 7:00 PM	Registration	Eastern Research Group, Inc.
7:00 - 7:15 PM	Welcome by Sponsors Introduction of Workshop Leads	William Farland/George Lucier
7:15 - 7:30 PM	Introductions	Participants
7:30 - 7:40 PM	Charge to Workshop Participants	Ramona Trovato, EPA
7:40 - 7:50 PM	Discussion	Participants
7:50 - 8:15 PM	***Sensitivity of Children to Environmental Toxicants***	**Lynn Goldman, John Hopkins**
8:15 - 8:30 PM	**Discussion**	**Participants**
8:30 - 8:55 PM	***Exposure of Children to Environmental Toxicants***	**Phil Landrigan, Mount Sinai**
8:55 - 9:10 PM	**Discussion**	**Participants**
9:10 - 9:20 PM	Comments from Observers	Observers
9:20 - 9:30 PM	Session Wrap-up/Logistics	George Lucier, NIEHS

Friday, March 31, 2000

8:00 - 8:30 AM	Registration	Eastern Research Group, Inc.
8:30 - 8:55 AM	**TOPIC 1: *Current and Proposed Approaches to Assessing Children's Cancer Risk***	**William Farland, EPA**
8:55 - 9:35 AM	**Facilitated Discussion**	**Abe Tobia, Aventis CropScience** **Lauren Ziese, CalEPA** **Dan Krewski, Univ. of Ottawa**
9:35 - 9:45 AM	**Comments/Questions**	**Observers**
9:45 - 10:15 AM	Coffee Break	

Friday, March 31 continued

10:15 - 10: 40 AM	**TOPIC 2: *Enhanced Use of Test Data Related to Children's Cancer Risk***	**Shelly Tyl, Research Triangle Inst.**
10:40 - 11:50 AM	**Facilitated Discussion**	**Mark Miller, CalEPA** **Paul Foster, CIIT** **Frederica Perera, Columbia Univ.**
11:50 - 12:00 Noon	**Comments/Questions**	**Observers**
12:00 - 1:00 PM	Lunch	
1:00 - 1:25 PM	**TOPIC 3: *Future Directions for Toxicology Testing to Address Children's Cancer Risk***	**Retha Newbold, NIEHS**
1:25 - 2:05 PM	**Facilitated Discussion**	**George Lambert, EOHSI** **David Wallinga, NRDC** **Joseph DeGeorge, FDA**
2:05 - 2:15 PM	**Comments/Questions**	**Observers**
2:15 - 2:45 PM	Break	
2:45 - 3:15 PM	**TOPIC 4: *Epidemiologic/Molecular Epidemiology Information to Address Children's Cancer Risk***	**Les Robison, Univ. of Minnesota** (Ellen Silbergeld, Univ. of Maryland**)**
3:15 - 3:55 PM	**Facilitated Discussion**	**Michael Thun, Amer. Cancer Soc.** **Lucy Anderson, NCI** **Chris Portier, NIEHS**
3:55 - 4:15 PM	**Comments/Questions**	**Observers**
4:15 - 5:00 PM	Workshop Summary/Next Steps	George Lucier

APPENDIX D

CHARGE TO PARTICIPANTS

¾ Charge to Workshop Participants ¿

Information Needs to Address Children's Cancer Risk

Thursday, March 30, 2000 and Friday, March 31, 2000
at the
Holiday Inn Arlington at Ballston
4610 North Fairfax Drive
Arlington, Virginia 22203

The purpose of the workshop is focused and derives from issues discussed in the EPA's 1999 Draft Revised Guidelines for Carcinogen Risk Assessment.

What is the content of the ideal data set to adequately address children's cancer risk?

The workshop participants will focus on data needed for assessing the impact of childhood (including *in utero*) exposures to carcinogens and the issues related to hazard identification and dose-response analyses. The participants will address not only induction of childhood cancer, but also increased risks of cancer during adulthood resulting from childhood exposure. As part of this discussion, the participants also will be asked to consider how current protocols might be redesigned to better answer questions related to children's cancer risk and what additional types of data might be brought to bear on children's cancer risk assessment. This would include information that is currently collected as well as data sets using new approaches.

What are the elements of a "cogent biological rationale," as presented in the draft revised cancer guidelines (July 1999 Draft), for addressing modes-of-action for children's cancer?

Participants will address whether and how such a rationale can be made, which is sufficiently health-protective of children, based on the kinds of data that are typically collected by and available to Federal and state health science agencies at the present time. These might include data on cancer mode-of-action, comparative pharmacokinetics and pharmacodynamics in adults and children, rate and pattern of exposure in adults and children, etc. The background for these discussions is the reality that chemical-specific data are often lacking to specifically address children's cancer risk from environmental chemical exposures. As a consequence, the assessment of children's risk is currently addressed by evaluations of traditional cancer bioassays in mature animals using sensitive responders, comparative biochemistry and physiology between adults and developing animals and humans, and public-health-protective default positions in the absence of child-specific data.

It is expected that workshop discussions will be valuable to the general risk assessment community, will provide input to Federal testing strategies for the future, and will inform the public dialogue around children's health issues as they are addressed in the EPA's draft revised cancer guidelines. A summary report of the perspectives and views coming out of this workshop will be published in the peer-reviewed, scientific literature.

APPENDIX E

OVERHEADS USED IN THE PRESENTATIONS

Overheads from
Welcome and Charge to Workshop Participants
(William Farland and Michael Firestone)

Overheads from
Sensitivity of Children to Environmental Toxicants
(Lynn Goldman)

Overheads from
Children's Environmental Health
(Lynn Goldman)

Overheads from
Exposure of Children to Environmental Toxicants
(Philip Landrigan)

Overheads from
Topic 1: Current and Proposed Approaches to Assessing Children's Cancer Risk
(William Farland)

Overheads from
Frederica Perera's Comments on Topic 1: Current and Proposed Approaches to Assessing Children's Cancer Risk

Overheads from
Topic 2: Enhanced Use of Test Data Related to Children's Cancer Risk
(Rochelle Tyl)

Overheads from
Topic 3: Future Directions for Toxicology
Testing to Address Children's Cancer Risk
(Retha Newbold)

Overheads from
David Wallinga's Comments on Topic 3: Future Directions for Toxicology Testing to Address Children's Cancer Risk

Overheads from
Topic 4: Epidemiologic/Molecular Epidemiology Information to Address Children's Cancer Risk
(Leslie Robison)

Overheads from
Workshop Summary
(George Lucier)

No electronic version of this section is available.

APPENDIX F

LIST OF BACKGROUND MATERIALS PROVIDED TO PARTICIPANTS PRIOR TO THE MEETING

Document entitled “Comparison of the effects of chemicals with combined perinatal and adult exposure vs. adult only exposure in carcinogenesis bioassays.”

Report of the 1996 FIFRA Scientific Advisory Panel meeting addressing “Comparison of the effects of chemicals with combined perinatal and adult exposure vs. adult only exposure in carcinogenesis bioassays.”

Document entitled “A proposed OPP policy on determining the need for *in-utero*/perinatal carcinogenicity testing on a pesticide.”

Report of the 1997 FIFRA Scientific Advisory Panel meeting addressing “A proposed OPP policy on determining the need for *in-utero*/perinatal carcinogenicity testing on a pesticide.”

Background paper on availability of toxicity testing data for assessing cancer risk.

American Academy of Pediatrics, Committee on Environmental Health. Cancer. In: Handbook of Pediatric Environmental Health. Elk Grove Village, IL: American Academy of Pediatrics.

Colt, J.S., and A. Blair. 1998. Parental occupational exposures and risk of childhood cancer. Environmental Health Perspectives 106(Supplement 3):909-925.

Legler, J.M., L.A.G. Ries, M.A. Smith, J.L. Warren, E.F. Heineman, R.S. Kaplan, and M.S. Linet. 1999. Brain and other central nervous system cancers: Recent trends in incidence and mortality. Journal of the National Cancer Institute 91(16):1,382-1,390.

Linet, M.S., L.A.G. Ries, M.A. Smith, R.E. Tarone, and S.S. Devesa. 1999. Cancer surveillance series: Recent trends in childhood cancer incidence and mortality in the United States. Journal of the National Cancer Institute 91(12):1,051-1,058.

National Research Council. 1993. Executive summary. In: Pesticides in the diets of infants and children. Washington, DC: National Academy Press. pp. 1-12.

Perera, F.P. 1997. Environment and cancer: Who are susceptible? Science 278:1,068-1,073.

Perera, F.P., R.M. Whyatt, W. Jedrychowski, R. Rauh, D. Manchester, R.M. Santella, and R. Ottman. 1998. Recent developments in molecular epidemiology: A study of the effects of environmental polycyclic aromatic hydrocarbons on birth outcomes in Poland. American Journal of Epidemiology 147(3):309-314.

Perera, F.P., W. Jedrychowski, V. Rauh, and R.M. Whyatt. 1999. Molecular epidemiologic research on the effects of environmental pollutants on the fetus. Environmental Health Perspectives 107(Supplement 3):451-460.

Ries, L.A.G., M.A. Smith, J.G. Gurney, M. Linet, T. Tamra, J.L. Young, and G.R. Bunin (eds). 1999. Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995. National Cancer Institute, SEER Program. NIH 99-4649. Bethesda, MD.

Tang, D., D. Warburton, S.R. Tannenbaum, P. Skipper, R.M. Santella, G.S. Cereijido, F.G. Crawford, and F.P. Perera. 1999. Molecular and genetic damage from environmental tobacco smoke in young children. Cancer Epidemiology, Biomarkers & Prevention 8:427-431.

U.S. Environmental Protection Agency. 1999. Guidelines for carcinogenic risk assessment (review draft). Washington, DC.

Zahm, S.H., and M.H. Ward. 1998. Pesticides and childhood cancer. Environmental Health Perspectives 106(Supplement 3):893-908.