UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
RESEARCH AND DEVELOPMENT

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MUSC Children's Services
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Dear Dr. Reigart:

On May 12 you wrote Administrator Carol Browner about the concerns of the Children's Health Protection Advisory Committee as to the proposed EPA cancer risk assessment guidelines. While acknowledging the significant scientific advances regarding carcinogenesis and the need to embody these findings in the new guidelines, the Committee wanted to ensure that the risks to children were ably addressed. The Committee developed a list of questions that expressed their concerns. A special session of the Agency's Science Advisory Board in July is devoted specifically to risks in children. Part of the meeting will be devoted to a discussion of the responses to the questions that were developed by the drafters of the Cancer Risk Assessment Guidelines, a technical panel of the Risk Assessment Forum (attached).

The Committee's questions focus on three recurring themes: the evidence needed to define a mode of action and deviate from a linear dose response extrapolation, whether cancer modes of action are similar for children and adults, and elements associated with exposure assessment. Our submission starts with a short exposition on the nature of the cancer risk assessment process; it sets a context for evaluating the assessment of hazards and risks to any segment of the population. We then address the recurring issues and finally respond to each of the questions.

We look forward to the discussion of our responses to the Committee's questions at the upcoming SAB meeting.

Sincerely yours,

William P. Wood

William P. Wood, Ph.D.
Executive Director
Risk Assessment Forum

Enclosure

cc: Dr. Norine Noonan

2 July 1999

RISK ASSESSMENT FORUM TECHNICAL PANEL

QUESTIONS CONCERNING THE DRAFT EPA CANCER RISK ASSESSMENT GUIDELINES from the CHILDREN'S HEALTH PROTECTION ADVISORY COMMITTEE (12 May 1999)

BACKGROUND: CANCER RISK ASSESSMENT PRINCIPLES

Cancer risk assessment for environmental chemicals includes an evaluation of information of varying types into a determination of the likelihood an agent is a human carcinogen and, if so, what might be the shape of the chemical dose-cancer response relationship. Primary hazard information comes from studies in humans and animals. Epidemiologic studies have identified human carcinogens mainly for workplace chemicals and pharmaceuticals, but also in other cases. In most cases, identification of potential carcinogens comes from analysis of animal studies, mainly rats and mice. Typically, animals are put on test after sexual maturation, with dosing extending for 18-24 months. For most agents, the test material is administered in the food or water or is given by oral gavage at the highest dose that can be tolerated for about 2 years. Other relevant but less commonly used routes include inhalation and dermal administration. Rarely, rodent cancer testing commences in the perinatal period, either in utero or early postnatal. To understand the significance of these exposures, results are compared to a traditional bioassay where dosing commences after sexual maturation.

Other hazard information complements the cancer studies: evaluation of the handling of the chemical by the body (e.g., metabolism, excretion), analysis of data on chemicals structurally related to the compound under investigation, other toxic effects produced by the chemical, and mode of carcinogenic action information (e.g., mutagenicity, cellular toxicity). Determination of the cancer causing potential in humans is a weight of the evidence judgment employing all of the hazard information. The EPA proposed cancer risk assessment guidelines use hazard descriptors and a detailed narrative to depict the likelihood of human carcinogenicity.

Risks from exposure to chemicals that are judged to have human carcinogenic potential generally embody a default position that dose response relationships are linear. Deviation from linearity demands the demonstration of a mode of action that does not include direct mutagenicity and which supports a nonlinear dose response relationship. Determination of a mode of action requires an extensive data base which aptly describes the carcinogenic process and which is supported by scientific peer review.

Evaluation of carcinogenic hazards and risks for children include the same steps as those

used for adults. Because of the growth and differentiation that occurs from the time of conception through the first 15 years, the young may be a sensitive subpopulation concerning the development of cancer from exposure to environmental pollutants. Any such information of this type is incorporated into the weight of evidence determination, as called for in the draft assessment guidelines, to reach conclusions as to any disproportionate hazards and risks. In some cases mode of action information may impart understanding concerning responses in the young. Metabolism and exposure may be other important variables.

QUESTIONS

The Children's Health Protection Advisory Committee developed 9 questions with a number of subparts that deal with aspects of the draft cancer risk assessment guidelines. There are three recurring themes: one deals with information needed to determine a mode of carcinogenic action and to deviate from a linear default dose response relationship; another questions whether cancer modes of action differ between children and adults; and the other deals with exposure determination during the childhood period. The generic issues will be addressed first, followed by the specific questions. Some of the questions cannot be fully answered at this time, and further research is needed.

A. Generic Issues

1. Mode of carcinogenic action and deviating from a linear dose response relationship

Mode of carcinogenic action is at the heart of the revised EPA cancer risk assessment guidelines. This position arose because of the significant scientific breakthroughs that have developed concerning the causes of cancer among organisms throughout the animal kingdom. Application of the draft guidelines to the determination of a mode of action is a data rich determination. A significant body of information is required to show that a specific mode underlies the process leading to cancer at a given site.

In the absence of mode of action or other key information, EPA adopts conservative default positions. Animal tumor findings are presumed to be relevant to humans, and cancer risks are assumed to conform with low dose linearity. Mode of action information may either confirm these presumptions or alter concern for human hazard and risk. For instance, epidemiologic and experimental studies in humans or human cells along with animal data may indicate that an agent poses a cancer risk to humans by a mutagenic mode of action. In exceptional cases, mode of action data may indicate that animal tumor findings may not be relevant to human hazard (e.g., male rat kidney tumors associated with accumulation of α2u-globulin accumulation). More commonly, animal hazard information will be judged to be relevant to humans but cancer dose-response relationships will be expected to show nonlinearity. In such a case where linearity does not pertain, the objective is to identify precursor events to cancer formation and to assess their significance. By so doing, regulatory actions canbe directed to preventing precursor events and,

thereby, prevening cancer development.

Linear dose response extrapolation is the EPA default position for all chemicals that lack mode of action information. The presence of such mode of action information can either confirm or reject linearity. Generally, one needs information showing that a chemical is not directly mutagenic and there is a demonstrated mode of action that does not conform to linearity, before the linear default is removed. The acceptability of risk is always a risk management decision. Given historical actions at EPA, it is recognized that areas of regulatory concern for lifetime linear risk are in the neighborhood of 10^{-4} to 10^{-6}. An analogous range of consideration will develop for nonlinear cancer risks as the Agency begins to apply the finalized risk assessment guidelines.

2. **Modes of action are different in children and adults**

Implicit in a number of the Advisory Committee questions is the issue whether cancer modes of action are different between children and adults. For certain cancers that may be the case; for cancers induced by radiation, pharmaceuticals and viruses, that may not be the case.

Causes of human cancers vary with the tumor type. Factors so far identified include such things as inherited conditions (Tomlinson, 1997), associations with congenital malformations (Bosland, 1996; Cortes, 1998) and a variety of biological, physical and chemical factors. In some cases tumors in children and adults have been compared. Children and adults not uncommonly develop the same spectrum of tumors when they have inherited gene and chromosomal mutations, like Li-Fraumeni syndrome. With ionizing radiation which operates through mutagenic means, both the young and the old develop the same tumors, with the only difference generally being that children are about 2-fold more sensitive (NRC, 1990). Studies with anticancer drugs (cytotoxic and immunosuppressive) demonstrate again a similar spectrum of tumors (Hale et al., 1999; Kushner et al., 1998; Larson et al., 1996; Nyandoto et al., 1998). Various viral infections like Epstein Barr and hepatitis B lead to lymphoma and liver cancer, respectively, in both age groups (Lindahl et al., 1974; Mahoney, 1999).

EPA review of about 40 rodent carcinogenicity studies with a perinatal chemical exposure component led to three conclusions: perinatal exposure alone does not always result in carcinogenicity; perinatal exposure alone or adult exposure alone produces similar tumor types; and combined perinatal and adult exposures often produces higher tumor incidences than either perinatal only or adult only dosing (U.S. EPA, 1996). There are several consequences that can be inferred from this somewhat limited but consistent data base. It would seem that the developing organism is sensitive to the carcinogenic potentialities of some but certainly not all chemical agents. When cancer is induced following perinatal exposure, the sites are like those seen after extra utero exposure alone, with few exceptions. These exceptions will be addressed separately. Likewise, cancer incidence may be greater following combined exposure than with perinatal alone or extra utero alone exposures. The nature of this difference needs further study. On the one hand, the young may be innately more sensitive to carcinogenic effects; on the other hand, the increased incidence may reflect a greater total dose or a greater time of dosing or possibly a

combination of factors.

In experimental animal studies focusing on perinatal exposure only, positive responses are noted only for strong mutagenic compounds that are positive in multiple species in traditional chronic bioassays on adults (Flammang et al., 1997). It would seem that if significant advances in detecting in utero and early extra utero environmental carcinogenic influences in rodents are to be made, they must await development of new understanding and technologies. Certain rodent transgenic systems may be rewarding.

Most often differences between carcinogenic effects in the young and adults can be traced to differences in the body's handling of chemical agents (metabolism and toxicokinetics). The fetus, infant and child may have metabolic capabilities that are qualitatively or quantitatively at variance with those in adults. The young may lack the capability to handle an exogenous chemical, which can have variable effects. If the parent compound is the toxic moiety, children may have enhanced susceptibility compared to adults, whereas they may have less hazard potential when it is a metabolite which has toxic properties (Snodgrass, 1992). Quantitatively, metabolism in the young is often faster than in adults which can also lead to corresponding changes in dose and, thus, cancer risk (Renwick, 1998).

Information on unique carcinogenic effects following in utero (or early postnatal) exposure is very unusual indeed. In humans, pharmacological use of diethylstilbestrol (DES) during pregnancy for threatened abortion resulted in increased incidence of clear cell adenocarcinoma of the vagina but not of other cancers in the daughters exposed in utero. It is thought that DES induces malformations during development that put vaginal cells at risk for cancer. For instance, risks for vaginal adenosis and dysplasia are high, while cancer only develops in about 1.5 in 1000 exposed persons (Hatch et al., 1998; Robboy et al., 1984; Vessey, 1989). Mice treated neonatally with tamoxifen develop uterine carcinoma, while animals dosed as adults are free of cancer; humans develop uterine carcinomas from tamoxifen (Newbold et al., 1997; Wogan, 1997). In rats, chronic exposure with saccharin that commences in utero or early extra utero results in development of bladder cancer, while initiation of exposure at postweaning does not (Cohen and Ellwein, 1991); the reason for this difference is not fully understood.

Although there are similarities between childhood and adult tumors, significant differences exist. Tumors of childhood generally show more embryonic cell tumors, while adults have more carcinomas. Some tumors are quite unique to the young like, tumors of the sympathetic nervous system or adrenal medulla (neuroblastoma), kidney (Wilm's tumor), eye (retinoblastoma) or bone (Ewings' sarcoma). Such findings suggest that the carcinogenic process inhibits normal cell differentiation or enhances dedifferentiation to an embryonal cell type. Unlike many adult cancers, rarely has it been possible to identify environmental causes of childhood cancer, attributable to some degree to the rarity of most childhood cancers. Many of the childhood cancers occur as manifestation of hereditary syndromes; inherited factors are less prominent among adult cancers. Finally, there is often a very restricted number of gene and chromosomal mutations of cellular control factors in childhood cancers, whereas there are many different

changes in adult cancers (Grufferman, 1998; Israel, 1995). Animal models for most of the tumors in childhood do not exist. More work is needed to discern the modes of action of these rare tumors and to understand the potential role of environmental influences.

3. Childhood exposure estimation

Exposure assessments are, ideally, developed for each population at risk. This is especially important when exposures differ qualitatively or quantitatively among groups. Considerations for the development of exposure assessments are presented in EPA's Guidelines for Exposure Assessment and its Exposure Factors Handbook (U.S. EPA, 1992, 1997). As the cancer guidelines mainly deal with hazard and dose-response assessment, the detailed guidance for conducting exposure assessment is embodied in the above documents, independent of the cancer guidelines.

The treatment of mode of action in the new cancer guidelines is revealing several areas where exposure assessment practices will need to change. One area is in the identification of subpopulations that are more sensitive to a particular identified mode of action. Because these subpopulations face higher risks from each unit of exposure, it will become more important to accurately assess how much exposure a sensitive subpopulation receives. Another area is the need to better characterize background exposures to different subpopulations. Because the new cancer guidelines will allow for nonlinear dose-response assessments, the risk from an incremental unit of exposure will be different depending on where on the dose-response curve a subpopulation's background exposure falls. With a nonlinear dose-response curve, a small incremental exposure in a subpopulation with no background exposure will carry little or no risk (because it falls on the part of the dose-response curve that is flat), while another subpopulation with high background exposure can have a large risk from the same incremental exposure (because it falls on the part of the dose-response curve that is steep).

With respect to children as a sensitive subpopulation, there are many physiological and exposure differences between children and adults (Snodgrass, 1992; NRC, 1993). Many of these will be described in a supplemental Exposure Factors Handbook for Children that EPA is developing. In addition, an exposure assessment methodology change that is being brought about by consideration of children involves the calculation of average daily doses. Typically, EPA's exposure guidelines call for calculating a lifetime average daily dose when estimating exposure to carcinogens. As consideration is given to children and other special populations that are defined by stage in life, it is clear that averaging doses over a full lifetime is not appropriate in all situations. Instead, consideration is being given to averaging doses only over the critical period of exposure. The draft cancer guidelines contain a case study to illustrate this concept.

B. Specific Advisory Committee Questions

NOTE: original Advisory Committee questions have been paraphrased, grouped and reordered. The original Advisory Committee question number is in parentheses.

HAZARD AND DOSE RESPONSE CONSIDERATIONS

1. **When scientific data suggest a mode of action, what data should be required, if any, to establish its relevance to humans? (6)**

Cancer findings in humans and animals are presumed to be relevant to humans unless there is evidence to the contrary. To establish a mode of action, it is imperative that there is sufficient information to link key tumor precursor events produced by a chemical with the development of cancer. Characteristics of these linkages include such things as timing of the formation of effects, dose at which they occur, progression from one effect to the next and potential reversibility upon cessation of dosing. Judgments about a cancer mode of action must hold up under rigorous scientific peer review (see generic issues 1).

The Agency proposes to assess mode of action information in great detail (see guideline section 2.5). After summarizing all information bearing on cancer site causation, EPA will use a framework to evaluate whether a specific mode of action has been demonstrated. In those cases where a mode has been demonstrated, EPA will ensure that an appropriate judgment has been made. Positions reached will have to be consistent with a body of information accepted by the scientific community (e.g., mutagenicity); will have been described in an Agency science policy document, like those done for male rat kidney and for thyroid tumors; or they will have to pass scrutiny in a scientific peer review setting (e.g., EPA Science Advisory Board, FIFRA Scientific Advisory Panel).

2. **Are modes of action for chemicals different for children than for adults? (2)**

Radiation, pharmaceuticals and viruses have produced cancer in children and adults at the same sites; and in animals, chemicals produce the same spectrum of tumors following perinatal and adult chronic exposure. In these cases, it is reasonable to conclude that modes of action are similar. In one case, with the pharmaceutical DES, a unique tumor was found after in utero exposure that is not noted in adults receiving the drug. Environmental chemicals under EPA purview are not known to produce cancer responses that differ between children and adults. Childhood cancers often involve embryonal cell type (e.g., Wilms tumor). Their etiology is largely unknown, and further basic research is needed (see generic issues 1 and 2).

3. **What constitutes sufficient mode of action data to depart from a linear default dose response that is adequate for children and for adults? What policy should be implemented in the absence of mode of action data to assure protection of children? What policy should be followed if there are sufficient data to establish a mode of action in an adult, but not for a fetus or child? (1)**

When sufficient information is developed in mature animals to show a mode of action that

leads to a nonlinear dose response relationship for a specific tumor type (see generic issue 1), an evaluation will be made of whether it is qualitatively applicable to children. Ideally we would have chemical-specific data pertinent to the question with respect to the agent under assessment. In the absence of such data, a cogent biological rationale needs to be developed regarding whether the mode of action is applicable to children. This evaluation would cover the scientific information at large, including such considerations as age-related similarities and differences in the occurrence of the specific tumors in the population, in chemicals structurally related to the chemical under review, in metabolism and excretion of the agent, and in occurrence of pertinent biochemical, physiological and toxicological processes, including key events associated with the mode of action of the chemical. Examples are given in the draft caner guidelines: case studies for chemicals T and Z in Appendix D. Based on the similarities of tumors following exposure to radiation, pharmaceuticals and viruses (see generic issues 1 and 2), from a qualitative standpoint, it may be anticipated that the same kind of tumors may develop following childhood or adult exposure to environmental chemicals. When there are specific data or a scientific argument can be developed to illustrate the comparability between responses in children and adults, risks will be estimated by a nonlinear technique. However, when there are no agent-specific data or biological rationale supporting the comparability between responses in children and adults, a linear dose response relationship will be used for children. It should also be noted that from a quantitative perspective, age differences in toxicokinetics and exposure may lead to greater or lesser occurrence of key events. Such differences may need separate evaluation and result in separate risk estimates for the young or for that portion of a lifetime. The strength of the case for the mode of action and its relevance to children will be evaluated in the peer review of the risk assessment.

4. **What examples of unique childhood cancers or cancers in adult life following childhood exposure have been considered in developing the guidelines? (9a)**

Pertinent literature on childhood cancer and related cancer in experimental systems have been considered as background in developing the new risk assessment guidelines. A case study is included in the guidelines which illustrates the extrapolation of cancer risk in a case where combined in utero/extra utero exposure to a chemical led to more cancer than did extra utero exposure alone. An example of a unique childhood cancer was not included since (a) at the present time there is only 1 known example of a chemical producing such a cancer, (b) there are few examples in the experimental literature of such tumors, and (c) none of the examples are environmental chemicals (see generic issue 2).

EXPOSURE ESTIMATION

5. **What factors should be reviewed to determine the latent risks from exposures at different developmental stages (preconception, in utero, childhood, adolescence)? (3)**

Determination of risks associated with exposures at different times during a lifetime depends upon when the cancer is found during life and what is the mode of action accounting for

tumor development. When chemical potency varies with age, risks from exposure are determined separately for each age, then summed across age groups (an example of this is given as a case study in the cancer guideline).

If a tumor develops in young animals following chemical exposure, exposure and risk estimates need to be determined for those exposures occurring prior to tumor development. If it is known that tumors manifest during adulthood is due to exposure to the young or if chemical potency differs for various life stages, then exposure and risk should be computed for relevant stages; overall risk is the summation of risks at different stages (see generic issue 3).

6. **How do the guidelines account for the timing of exposure, especially acute exposures at sensitive developmental stages? (4)**

For chemicals without mode of action information or for those that have a direct mutagenic mode of action, the Agency uses a low dose linear default for dose response estimation. Under this scenario, the average daily lifetime exposure estimate is employed. This is a conservative estimate in that it assumes that all exposures over a lifetime may contribute to the carcinogenic process. As discussed in the draft guidelines, the import of the timing of exposure depends upon the mode of action (see generic issues 1-3 and each of the specific questions above). Where the mode of action indicates that dose rates are important in the carcinogenic process, short-term, less than lifetime exposure estimates may be more appropriate than the lifetime average daily exposure. For those agents with a nonlinear cancer dose response relationship, exposure is usually needed at some critical concentration to produce key events, and it needs to be sustained for a period of time. Cessation of exposure, especially when it occurs early in the process, may result in reversal of effects and the failure of tumor development.

7. **How should exposure assessments for special populations be addressed? Should examples be given? (7)**

The EPA exposure assessment guidelines (US EPA, 1992) require that separate analysis be conducted for definable subpopulations that are believed to be highly exposused or susceptible (see generic issue 3 and specific question 4).

RESEARCH NEEDS

8. **Are new models for acute or combined acute/chronic exposure needed? (9b)**

The interaction between chemical concentration and time of exposure in influencing the development of toxicity needs development. Current default risk assessment procedures typically define "dose" as an averaged exposure with an emphasis on "chronic effects" observed from epidemiological studies or derived from chronic animal bioassays to characterize potential lifetime risks. The development of quantitative risk assessment models has followed the premise that toxicity levels should be linearly related to the product of dose level times duration, or "C x T" (concentration

x time). Contemporary toxicology, as reflected in the revised cancer guidelines, is placing increasing emphasis on how mode of action information can help to inform the use of default procedures. It is recognized that toxicity can depend not only on the magnitude but also on the duration, frequency, and timing of exposure. Both pharmacokinetics (absorption, distribution, metabolism, and elimination) as well as pharmacodynamics (e.g., repair and proliferation rates) involve concentration and time-dependent processes.

While it is relatively straightforward to describe age-dependent exposure patterns, it is a much more complex situation to incorporate this variability into cancer risk assessments. To do so will require the development of efficient designs for studying dose-rate and age-related effects as well as the development of models that are capable of handling the entire exposure-dose-response continuum. At present these techniques have been little explored and are not yet ready for general use (ILSI, 1992).

EPA's Risk Assessment Forum is examining how dose-duration relationships can be incorporated into the risk assessment process for less-than-lifetime exposures. As part of this effort, the Agency sponsored a workshop in August 1998. The workshop involved scientists with expertise in toxicology, biostatistics, risk assessment and epidemiology from both within and outside the Agency. This workshop was an extension of efforts within EPA, as well as collaborative work carried out with researchers from the Harvard School of Public Health. Workshop participants discussed the need for more studies that test the C x T hypothesis, recognizing that such studies are costly and will require the development of efficient testing schemes. Likewise, participants recommended that more emphasis be placed on mechanistic studies in order to enhance our understanding of the interaction between exposure duration, concentration, and response. The workshop generated several recommendations that are intended to encourage the generation of such data. The Risk Assessment Forum will continue with this effort and the publication of the revised cancer guidelines is seen as one way of encouraging progress in this area.

9. What research should EPA sponsor to improve its ability to evaluate the susceptibility of high-risk populations, including children? (8)

Basic and applied research is needed to help understand the nature of children that may in some cases be more susceptible to environmentally induced cancer than adults. Further research is needed in several key areas that would improve our understanding on cancer risk for children and other high-risk populations. The areas of focus on children's risk include:

a. Understanding the role of the environment in childhood cancers,
b. Identification of the role of gene-environment interactions in specific childhood cancers, and
c. Development of experimental models to better predict and characterize cancer risk for children

The research should be a joint effort among several scientific organizations at the state, national, and international levels.

A number of research activities have been proposed by various groups to address these issues

(President's, 1998; ILSI, 1996). Examples of these research initiatives include the following:

a. Establish a National Network for Research on Cancer in Children, which would build from existing NCI registries to include a central registry of cases of cancer occurring among children in the United States, and information on environmental exposures and dietary intake. Registries would serve as national resources and a platform to support research in environmental causes of cancer in children.

b. Establish a National Childhood Cancer Registry Tissue Bank, which would provide tissues specimens to researcher s to identify causes of childhood cancers.

c. Conduct prospective longitudinal studies of children exposed to known or suspected carcinogens including exposures *in utero*.

d. Study cancer susceptibility in children and the interaction between genetic alterations and environmental exposures in cancer etiology. Improve understanding of critical time periods for exposure either for certain childhood cancers and/or for certain classes of environmental carcinogens

e. Elucidate biomarkers of carcinogenic effects in children as compared to adults.

f. Study age-dependent changes in key metabolic enzyme systems of importance in activation and deactivation of carcinogens.

g. Develop appropriate dose metrics for infants and children for given routes and pathways of exposure. Improve understanding of age-related effects on uptake, absorption, and distribution, elimination of carcinogens.

h. Develop predictive toxicological models for children's cancer.

10. How do the proposed guidelines take into account the sequencing of sensitizing and subsequent potentiating events in the manifestation of cancers both in childhood and in later adolescent or adult life (e.g., how might an exposure to a medical intervention such as radiation, chemotherapy, vaccine or virus affect an individual's sensitivity to later environmental or developmental stress factors, such as onset of puberty or exposure to a chemical agent? (5)

Clinical, basic and applied research are needed to delineate the mechanisms and risk factors that underlie the development of human cancer. Only with greater understanding can the myriad of influences in a person's life be evaluated as to their potential impact on cancer development. Present operational depictions of cancer formation may aid in the development of this understanding. Such research goes beyond the purview of the EPA research program.

Risk assessment guidelines only provide a framework for the use of data in reaching conclusions about cancer hazards and risks. The Agency believes that in the future it will be through mechanistic studies on individual chemicals coupled with advances in the understanding of the etiology of cancer, along with the conduct of well designed epidemiological studies that test a series of interaction hypothesis, that will allow the guidelines to be applied to this question.

As mode of action information develops, attention needs to be given to the types and staging of chemical exposure that influence cancer development. Admittedly over-simplified, concepts have

often been used to describe operationally the carcinogenic process include initiation, promotion and progression. Mutations are associated with initiation, while cell proliferation characterizes promotion. Progression often includes further mutations and effects on growth processes. Some agents act primarily as initiators, others as promoters. Some agents are complete carcinogens, being able to affect all three carcinogenic steps. Experimental rodent studies indicate that complete carcinogenic responses can be produced in the early time periods. Likewise, initiation can occur in utero or early postnatal life and then be promoted by factors later in life (Goerttler and Lohrke, 1977). To the extent such information is available as to the staging of carcinogenic events, it should be incorporated into risk assessments.

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