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Considerations of Early Life Exposure to Chemical Carcinogens

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Considerations of Early Life Exposure to Chemical Carcinogens

Introduction & Purpose

This paper identifies, evaluates, and analyzes issues relevant to the increased susceptibility of children from environmental exposures to carcinogens. These issues are important considerations to update and revise the Model Toxics Control Act (MTCA) Cleanup Regulation consistent with new scientific information and regulatory guidance.

Scientific Issues Being Considered

Ecology is considering and analyzing a number of scientific issues.

Issue 1: The U.S. Environmental Protection Agency (U.S. EPA) published new guidance (Guidelines for Carcinogen Risk Assessment) in March 2005. Ecology is considering several revisions to the MTCA rule to incorporate the updated methods for identifying and evaluating carcinogens that are contained in this guidance. Is this guidance consistent with current scientific information?

Issue 2: The U.S. EPA published new guidance (Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens) in March 2005. Ecology is considering several revisions to the MTCA rule to incorporate methods for evaluating child exposure to carcinogens contained in this document. Is this guidance consistent with current scientific information on early life state exposure to carcinogens with a mutagenic mode of action?

Issue 3: The California Environmental Protection Agency (Cal-EPA) has developed methods and policies for making early-life stage adjustments to carcinogens with other modes of action. Is this approach consistent with current scientific information on early-life stage exposure to carcinogens with other (non-mutagenic) modes of action?

Issue 4: What sources of scientific uncertainty and variability should Ecology consider when evaluating these issues and potential changes to the MTCA cleanup regulation?

Background Information

The MTCA Cleanup Regulation provides default exposure scenarios and risk-based equations to establish cleanup levels protective of human health and the environment for soils, surface waters and groundwaters, and air. WAC 173-340-702 (11) states the Department of Ecology (Ecology) will review and, as appropriate, update WAC 173-340-700 through 173-340-760 at least once every five years. As part of the five-year review of the MTCA Cleanup Regulation, Ecology plans to review and, where appropriate, revise and update MTCA consistent with new scientific information and regulatory guidance.

In March 2005, the U.S. Environmental Protection Agency addressed the potential for increased susceptibility to cancer caused by exposures to environmental chemicals during an early life-stage in "Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens."[1] This regulatory guidance is a companion document to the revised "Guidelines for Carcinogen Risk Assessment" originally published by the U.S. EPA in 1986.[2]

Environmental Regulatory Emphasis on Children

In 1993, the National Research Council (NRC) of the National Academy of Sciences published "Pesticides in the Diets of Infants and Children" noting important differences between children and adults when evaluating the risks to children from exposures to environmental pesticides. [3] In 1994, the National Research Council published the seminal "Science and Judgment in Risk Assessment" which extended the previous 1993 publication and concluded "Children are a readily identifiable subpopulation with its own physiologic characteristics (such as body weight), uptake characteristics (such as food consumption patterns) and inherent susceptibilities."[4]

The National Research Council further noted that not accounting for this increased susceptibility may significantly underestimate risks and that U.S. EPA should adopt a default assumption to better account for differences in susceptibility. The NRC reports, along with mounting scientific evidence that supports the increased vulnerability of the developing fetus and child to environmental exposures, culminated in the 1997 Presidential Executive Order 13045, "Protection of Children from Environmental Health Risks and Safety Risks" which states "each Federal agency: shall ensure that its policies, programs, activities, and standards address disproportionate risks to children that result from environmental health risks or safety risks."[5]

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[1] Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens. U.S. Environmental Protection Agency, Risk Assessment Forum, March 2005. EPA/630/R-03/003F. (Available at http://www.epa.gov/iris/children032505.pdf)

[2] Guidelines for Carcinogen Risk Assessment. U.S. Environmental Protection Agency, Risk Assessment Forum, 2005. EPA/630/P-03/001F.

[3] NRC, 1993. National Research Council,.Pesticides in the Diets of Infants and Children. National Academy Press. Washington, DC. 1993.

[4] NRC, 1994. National Research Council, Science and Judgment in Risk Assessment. National Academy Press. Washington, DC. 1994. Page 220.

[5] U.S. Executive Order 13045. (1997) Protection of Children from Environmental Health Risks and Safety Risks. The White House, Office of the Press Secretary. April 21, 1997. Available at http://yosemite.epa.gov/ochp/ochpweb.nsf/content/whatwe_executiv.htm

In response, federal, state, and international agencies have been investigating methods to improve ways to evaluate exposures and assess the risks to children from environmental contaminants.

- U.S. EPA has a formal policy that directs all its programs to consider risks to infants and children consistently and explicitly as part of any risk assessment generated during its decision-making process, including establishing standards to protect public health and the environment.[6]
- Parallel activities by the U.S. Food and Drug Administration and the International Programme for Chemical Safety of the World Health Organization establishes policies and procedures to evaluate the exposures and assess the risks for infants and children based on relevant periods of exposure in developmental life-stages and subsequent outcomes that may not be expressed until later life-stages.[7 & 8]
- Responding to the California 1999 Children's Environmental Health Protection Act, the California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, has developed and extended U.S. EPA's policies and procedures for the protection of infants and children to include the evaluation of early-life susceptibility to all carcinogens, not limited to mutagenic carcinogens.[9 & 10]

In 2008, the National Research Council agreed with the U.S. EPA 2005 Cancer guidelines that patterns of susceptibility differ among various life stages and should be given formal consideration in future risk assessments. As developed by U.S. EPA's 2005 Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens, the NRC further noted that the development of generic factors for early-life susceptibility is a "step in the right direction" to more formally consider susceptibility in early-life stages.[11]

Washington Risk Policies

The risk-based policies and procedures in the MTCA Cleanup Regulation are based on a single direct contact exposure pathway and do not explicitly account for early life exposures to

[6] Policy on Evaluating Health Risks to Children. 1995. Office of the Administrator, Washington, DC. Available at http://www.epa.gov/osa/spc/2poleval.htm.

[7] WHO, 2006. World Health Organization 2006. Environmental Health Criteria 237. Principles for Evaluating Health Risks in Children Associated with Exposure to Chemicals.

[8] FDA is guided by legislation (Best Pharmaceuticals for Children Act, U.S. FDA, 2002; Amendment to Section 11 of the Food and Drug Modernization Act, U.S. FDA, 1997; Pediatric Research Equity Act, U.S. 108th Congress, 2003) and guidance documents, Guidance for Industry-How to Comply with the Pediatric Research Equity Act and Guidance to Industry-Nonclinical Safety Evaluation of Pediatric Drug Products.

[9] Technical Support Document for Cancer Potency Factors: Methodologies for derivation, listing of available values, and adjustments to allow for early life stage exposures. 2008. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment.

[10] Air Toxics Hot Spots Program Risk Assessment Guidelines, Part II, Technical Support Document for Cancer Potency Factors, June 2008, Public Review Draft, California Environmental Protection Agency, Office of Environmental Health Hazard Assessment.

[11] NRC, 2008. Science and Decisions: Advancing Risk Assessment. National Research Council of the National Academies. National Academies Press Prepublication Copy, November 2008.

carcinogens with the carcinogenic response expressed later in life. Hence, the MTCA Cleanup Regulation does not reflect these recent advances in technical information and regulatory guidance.

Issues 1 & 2: Consistency with Current Scientific Information and Regulatory Guidance

Issue 1: EPA published new guidance (Guidelines for Carcinogen Risk Assessment) in March 2005. Ecology is considering several revisions to the MTCA rule to incorporate the updated methods for identifying and evaluating carcinogens that are contained in this guidance. Is this guidance consistent with current scientific information?

AND

Issue 2: EPA published new guidance (Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens) in March 2005. Ecology is considering several revisions to the MTCA rule to incorporate methods for evaluating child exposure to carcinogens contained in this document. Is this guidance consistent with current scientific information on early life state exposure to carcinogens with a mutagenic mode of action?

Life-stage Susceptibility and Cancer Risks to Children

Cancer is one of many adverse health effects that may occur in children resulting from exposures to environmental contaminants. Using different methodologies to evaluate cancer potency, the U.S. Environmental Protection Agency (U.S. EPA) and the California Environmental Protection Agency (Cal-EPA) have independently concluded that risks of cancer from exposures to carcinogens occurring from conception through puberty can be different than those cancer risks from exposures occurring in adulthood. Exposure to a carcinogen early in life may result in greater lifetime risk of cancer for several reasons:

- Cancer is a multi-stage process and the occurrence of the first stages of the carcinogenic process in childhood increases the chance that the entire carcinogenic process will be completed, and a cancer produced, within an individual's lifetime.
- Tissues undergoing rapid growth and development may be especially vulnerable to carcinogenic agents. During periods of increased cell proliferation there is rapid turnover of DNA, and more opportunity for misrepair of damage (that is, DNA breaks, crosslinks, adducts) or alterations resulting permanent changes to the DNA (that is, mutations, altered DNA methylation) that may ultimately lead to cancer.
- During early life-stages or development, a greater proportion of the body's cells are undifferentiated stem cells, and undifferentiated stem cells represent a large target population of somatic cells capable of passing along permanent changes to the DNA during future cell divisions.
- There may be greater sensitivity to hormonal (such as endocrine disrupting) carcinogens early in life since the development of many organ system is under hormonal control (such as, male and female reproductive systems, thyroid control of Central Nervous System development).

- Anatomical, physiological, and behavioral characteristics may influence or play a role in increased cancer risk from exposures during critical development periods such as differences in immunological activity, intestinal absorption, biliary and kidney excretion, blood and fat distribution, and expression of enzyme systems that activate or detoxify carcinogens.

Early-Life Stage Cancer Potency Adjustments

Identification of Childhood Life-Stage Age Groups

Working independently, U.S. EPA and Cal-EPA have assessed and developed age groupings to help evaluate childhood exposures to environmental contaminants. Both agencies apply age-related factors to adjust the cancer potencies to consider early life susceptibility for infants and children. Although the age groupings between the agencies vary slightly the adjustment factors are the same. For the U.S. EPA, the age adjustment factors are termed: Age Dependent Adjustment Factors (ADAFs)[12]; for Cal-EPA the age adjustment factors are termed Age Sensitivity Factors (ASFs)[13].

An expert panel workshop was held in 2000 by U.S. EPA to consider behavioral and physiological changes in children that may guide the development of a generic set of age groupings to assess cancer susceptibility from early life exposures. Participants in the workshop focused on those aspects of development relevant to exposure and potential dose, not toxicity. The workshop proceedings were published [14] and then used to develop the associated U.S. EPA guidance for applying the early life-stage age groupings. [15]

Some of the behavior-related and physiological-related characteristics that were considered in the recommended childhood age groups are provided in Appendix D. The life-stage descriptor and corresponding age grouping are given in Table 1.

Table 1: Developmental Life-stages & Age Groups

Life-stage Descriptor	Age Group
Preconception	Reproductive age adult
Prenatal	Conception to birth
Infant	Birth to < 1 month
	1 to < 3 months
	3 to < 6 months
	6 to < 12 months
Child	1 to < 2 years
	2 to < 3 years

[12] Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens. U.S. Environmental Protection Agency, Risk Assessment Forum, March 2005. EPA/630/R-03/003F.

[13] Air Toxics Hot Spots Program Risk Assessment Guidelines, Part II, Technical Support Document for Cancer Potency Factors, June 2008, Public Review Draft, California Environmental Protection Agency, Office of Environmental Health Hazard Assessment.

[14] U.S. EPA, 2000. Summary Report of the Technical Workshop on Issues Associated with Considering Developmental Changes in Behavior and Anatomy When Assessing Exposure to Children. U.S. Environmental Protection Agency. December 2000. EPA/630/R-00/005.

[15] U.S. EPA, 2005. Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants. U.S. Environmental Protection Agency, Risk Assessment Forum. November 2005. EPA/630/P-03/003F.

	3 to < 6 years
	6 to < 11 years
Adolescent	11 to < 16 years
	16 to < 18 years
	18 to < 21 years
Adapted from EPA's Framework for Assessing Health Risks of Environmental Exposures to Children, September 2006	

Derivation of Age Adjustment Factors

Brief descriptions are provided of the methodologies used by U.S. EPA and Cal-EPA to derive life-stage-specific cancer potency factor adjustments. Major differences in the methodologies and the conclusions for the application of the adjustment factors will be noted. Additional methodological and technical details are provided by their respective guidance documents:

1) U.S. EPA, 2005. Supplemental Guidance for Assessing Susceptibility From Early Life Exposure to Carcinogens, Risk Assessment forum. March 2005. EPA/630/R-03/003F.
2) Cal-EPA, 2008. Technical Support Document for Cancer Potency Factors: Methodologies for Derivation, Listing of Available Values, and Adjustments to Allow for Early Life Stage Exposures. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment. June 2008.

U.S. Environmental Protection Agency Methodology

The U.S. EPA Supplemental Guidance focused on studies that define the potential duration and degree of increased susceptibility from early-life exposures. Barton et. al., 2005, published the description of procedures and analysis of the studies to identify chemicals causing cancer after perinatal exposure.[16]

Selection criteria were established for studies to be included in U.S. EPA's analysis to quantitatively evaluate the effect of life-stage at exposure on a carcinogenic response in experimental animal studies. Study design characteristics included experiments in which animals were exposed either as juveniles or as adults (with either a single or multiple dose in each period), and experiments in which exposure began either in the juvenile or in the adult period, but once started, continued through life.

Comparisons were made with the estimated ratio of the cancer potency from early-life exposure to the estimated cancer potency from adult exposure. Cancer potencies were estimated using a one-hit model (Weibull time to tumor model) which provides cumulative incidence for tumor onset.

U.S. EPA reviewed several hundred studies reporting information on 67 chemicals or complex mixtures which are carcinogenic via perinatal exposure. Eighteen chemicals were identified which had animal study designs involving early-life and adult exposures in the same experiment.

[16] Barton et. al., 2005. Hugh A Barton, V. James Cogliano, Lynn Flowers, Larry Calcovic, R. Woodrow Setzer, and Tracey J. Woodruff. Assessing Susceptibility from Early-Life Exposure to Carcinogens. Environmental Health Perspectives, Volume 113, Number 9, September 2005, pages 1125-1133.

Of those 18 chemicals, there were overlapping subsets of 11 chemicals involving repeated exposures during early postnatal and adult life-stages and eight chemicals using acute exposures at different ages.

Table 2. Chemicals having animal cancer study data available with early-life and adult exposures in the same experiment[17]

Chemical	Study Type
Amitrole	Repeat dosing
Benzidine	Repeat dosing
Benzo[a]pyrene (BaP)	Acute exposure
Dibenzanthracene (DBA)	Acute exposure
Dichlorodiphenyltrichloroethane (DDT)	Lifetime exposure, repeat dosing
Dieldrin	Lifetime exposure, repeat dosing
Diethylnitrosamine (DEN)	Acute exposure, lifetime exposure
Dimethylbenz[a]anthracene (DMBA)	Acute exposure
Dimethylnitrosamine (DMN)	Acute exposure
Diphenylhydantoin, 5,5-(DPH)	Lifetime exposure, repeat dosing
Ethylnitrosourea (ENU)	Acute exposure
Ethylene thiourea (ETU)	Lifetime exposure, repeat dosing
3-Methylcholanthrene (3-MC)	Repeat dosing
Methylnitrosourea (NMU)	Acute exposure
Polybrominated biphenyls (PBBs)	Lifetime exposure, repeat dosing
Safrole	Lifetime exposure, repeat dosing
Urethane	Acute exposure, lifetime exposure
Vinyl chloride (VC)	Repeat dosing

Differences in susceptibility between early-life and adult exposure was calculated as the estimated ratio of cancer potency at specific sites from early life exposure over the cancer potency from adult exposure for each of the studies.

Results were grouped into four categories depending on the ability of the chemical to express a mutagenic response:

Category 1: mutagenic chemicals administered by a chronic dosing regimen to adults and repeated dosing in the early post natal period (benzideine, diethylnitrosamine, 3-methylcholanthrene, safrole, urethane, and vinyl chlodide)

Category 2: chemicals without positive mutagenicity data administered by a chronic dosing regimen to adults and repeated dosing in the early postnatal period (amitrole,

[17] IBID, adapted from Table 1, page 1126.

dichlorodiphenyltrichoroethane (DDT), dieldrin, ethylene thiourea, diphenylhydantoin, polybrominated biphenyls)

Category 3: mutagenic chemicals administered by an acute dosing refimen (benzo[a]pyrene, dibenzanthracene, diethylnitorosamine, dimehtylbenzanthracene, dimethyl-ntyrosamine, ethylnitrosourea, methylnitrosourea, and urethane)

Category 4: chemicals with or without positive mutagenicity data with chronic adult dosing and repeated early postnatal dosing.

A quantitative cancer potency factor age adjustment was derived from repeated dosing studies with mutagenic chemicals using exposures during early postnatal and adult life-stages. Studies addressing only prenatal exposure were not used in the analysis while studies with repeated early postnatal exposures were included although these studies involved earlier maternal and/or prenatal exposure.

Conclusions Made by U.S. EPA

The U.S. EPA analysis concluded that cancer risks are higher from early life exposure than from exposure doses and durations later in life with the following age-dependent adjustment factors (ADAFs) for the following life stages:

- ADAF of 10 used for exposures of 0-2 years of age, approximates the weighted geometric mean cancer potency ratio from juvenile versus adult exposure in the repeated dosing studies;
- ADAF of 3 used for 2 to <16, data not available to calculate a specific ADAF so U.S. EPA selected half the logarithmic scale difference between the 10 fold adjustment for the first two years of life and no adjustment (1-fold) for adult exposure;
- ADAF of 1 for reflects the end of puberty and the final body height.

U.S. EPA recommends the following ADAF for carcinogens acting by a mutagenic mode of action to account for increased carcinogenic potency during early life stages (Table 2).

Table 3: Default Exposure Parameters For Early-Life Exposure[18]

Parameter	Age Groupings			
	< 2 Years	**2 to < 6 Years**	**6 to < 16 Years**	**Adult**
ADAF*	10	3	3	1
ED	2	4	10	14
BW (kg)	16	16	70	70
SIR (mg/day)	200	200	100	100
DWIR (L/day)	1	1	2	2
AF (mg/cm^2-event)	0.2	0.2	0.07	0.07
SA (cm^2)	2800	2800	5700	5700

*Age Dependent Adjustment Factor (ADAF)for carcinogens acting by a mutagenic mode of action to

[18] U.S. EPA, 2005. Supplemental Guidance for Assessing Susceptibility From Early Life Exposure to Carcinogens, Risk Assessment forum. March 2005. EPA/630/R-03/003F.

account for increased carcinogenic potency during early life stages; e.g., for ages up to 2 years the ADAF is 10 indicating a ten-fold increase in carcinogenic potency during this life stage.

California Environmental Protection Agency (Cal-EPA) Methodology

In a manner similar to that used by the U.S. Environmental Protection Agency, Cal-EPA identified age-related cancer susceptibility data from animal cancer bioassays where life-stage exposures could be distinguished.

Based on selection criteria to be included in the compilation of studies with early life exposures, two types of animal bioassay studies were included in their evaluations.

- The first types of studies evaluated by Cal-EPA are multi-life-stage exposure studies which have at least two groups of animals exposed during different life-stages of their development. These studies had one dose group exposed to a chemical only during the prenatal life-stage (from conception to birth), the postnatal life-stage (from birth to weaning), or the juvenile life-stage (from weaning to sexual maturity).
- The second type of studies evaluated by Cal-EPA included chemical specific studies where dose groups were exposed only during a particular single identified as being either prenatal, postnatal, juvenile, or adult exposure studies.

The Cal-EPA evaluation included data from studies on 23 unique carcinogens were analyzed, 20 of which are considered to act via nongenotoxic modes of action (see Table 4). Of these 20 carcinogens that act via a nongenotoxic mode of action, 15 require metabolic activation to the ultimate carcinogenic species. Fourteen carcinogens were included in the prenatal multi-life-stage exposure studies. Eighteen carcinogens were included in the postnatal multi-life-stage exposure studies. Five carcinogens were included in the juvenile multi-life-stage exposure studies.

Table 4: Carcinogens for Which Studies With Multi-Life-stage Exposures Are Available
Genotoxic carcinogens requiring metabolic activation
Benzidine
Benzo[a]pyrene
Dibutylnitrosamine
Diethylnitrosamine (DEN)
7,12—Dimethylbenz[a]anthracene (DMBA)
Dimethylnitrosamine (DMN)
Di-n-propylnitrosamine (DPN)
1-Ethyl-nitrosobiuret
2-Hydroxypropylnitrosamine
3-Hydroxyxanthine
3-Methylcholanthrene (3-MC)
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)
Safrole
Urethane
Vinyl Chloride
Genotoxic carcinogens not requiring metabolic activation

Butylnitrosourea
1,2-dimethylhydrazine
Ethylnitrosourea (ENU)
Methylnitrosourea (MNU)
β-Propiolactone
Nongenotoxic carcinogens
41,1-Bis(p-chlorophenol)-2,2,2-trichloroethane (DDT)
Diethylstilbestrol (DES)
2,3,7,8-Tetrachlorodibenzodioxin (TCDD)
Adapted from Table 1, page 38, California Environmental Protection Agency, Air Toxics Hot Spots Program, Risk Assessment Guidelines, Part II Technical Support document for Cancer Potency Factors, June 2008

Using the linearized multistage model, Cal-EPA derived a cancer potency for each of the selected studies. Cal-EPA derived the cancer potencies by a statistical distribution to account for uncertainties in the analysis. Cal-EPA used the full distribution of the cancer slope factors to derive measures of early-life susceptibility to carcinogens. Since carcinogens commonly cause more than one type of cancer or cause tumors at different sites depending on the life-stage at exposure, Cal-EPA slopes from treatment related tumors observed at multiple sites were statistically combined by summing across the potency distributions to derive an overall multisite cancer potency estimate. Hence, all treatment related tumors observed in a given life-stage were taken into account in estimating cancer potency from a particular experiment.

The sensitivity of the different life-stages was quantitatively estimated by Cal-EPA from the ratio of cancer potency derived from an early life-stage exposure experiment(s) compared to that derived from an experiment(s) conducted from adult animals. The potency distributions for individual life-stage exposures were used to derive the ratios. The life-stage potency (LP) ratios characterize the susceptibility of early life-stages to exposure to carcinogens by comparing potencies for individuals followed for similar periods of time and similarly exposed, but where the exposure occurs during different life-stages.

Cal-EPA multi-window exposure studies conducted in animals examined early-life susceptibility to carcinogen exposure during three early-life stage windows: prenatal (conception to birth), postnatal (birth to weaning), and juvenile (weaning to sexual maturity), and included data from animal studies on 32 unique carcinogens. The Cal-EPA analysis quantitatively evaluated the degree to which early life-stages, as compared to adults, are susceptible to carcinogen exposures, by driving measures of early-life susceptibility called age sensitivity factors (ASFs). A postnatal age sensitivity factor (ASF) distribution that primarily lies above the reference value of 1.0 indicates that postnatal exposures to a carcinogen result in a stronger tumor response relative to adult exposures. A total of 55 datasets on 18 carcinogens, including two carcinogens with a non-genotoxic mechanism of action were included in the analysis. For two-thirds of the studies plotted, representing 37 postnatal datasets for 15 carcinogens, the ASF distributions are significantly greater than one, unity. For 16 postnatal studies (29% of the total) representing nine carcinogens, cluster around unity. In ten of these 16 postnatal studies, the majority of the ASF distribution lies above 1.0. For two postnatal studies, or only 4% of the plotted studies, representing two carcinogens, have ASF's less than unity. The increased susceptibility of the postnatal exposure window is particularly pronounced once adjustments are made to account for the longer period of time for cancer to manifest when exposure occurs early in life. Regardless

of the adjustments for the longer time for cancer to manifest, the data indicate an inherently greater susceptibility of the postnatal period compared to the adult. The age susceptibility is further reinforced because many of the postnatal ASFs may underestimate the true susceptibility of the postnatal period, relative to adults, because many of the studies compared animals exposed during the postnatal age window to animals exposed during the juvenile age window rather than the adult.

Figures 1 and 2 below illustrate a significant proportion of the animal studies evaluated have Age Sensitivity Factors (ASFs) above unity, the reference value of 1. The location of the ASF (life-stage potency (LP) ratio distribution) in relation to the reference value of 1.0 provides an indication of the relative importance of early life exposure relative to adult exposure.[19] The majority of the distribution lies above an ASF of 1.0, indicating substantial susceptibility early in life for developing cancer later in life. The ASFs, based on Life-Stage Potency ratios, characterize the inherent susceptibility of the young compared to older animals to the carcinogen.

[19] The life-stage potency (LP) ratio is the ratio of cancer potency derived from an early-life stage exposure experiment to that derived from an experiment conducted in adult animals calculated for each multi-life-stage exposure study.

Figure 1. Age Sensitivity Factors Cumulative Frequency Distribution Profile

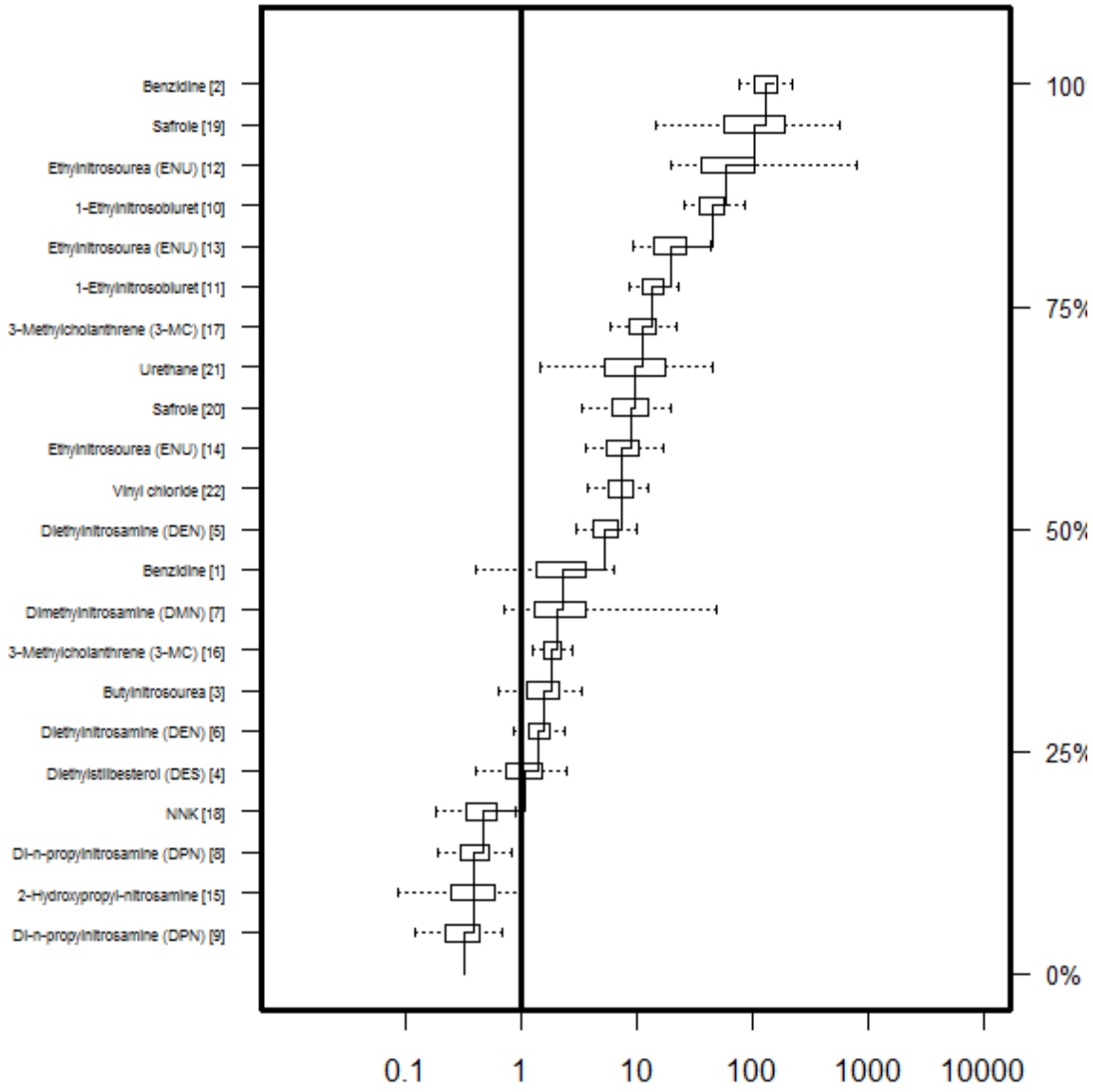
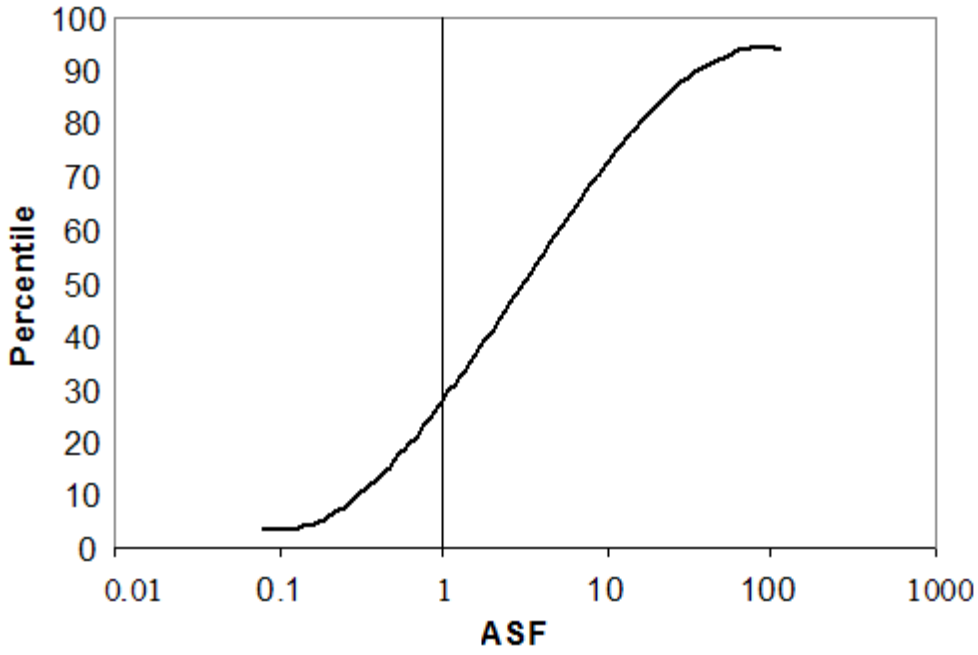


Figure 2. Prenatal ASF mixture distribution



Clinical and Epidemiological Support for Early-In-Life Susceptibility

The table below, Table 5, provides selected examples of human cases that reflect early-in-life cancer susceptibility. These selected examples of human evidence of early-in-life susceptibility to carcinogens serve to reinforce the importance of consideration of early-life exposures to carcinogens in the regulatory framework. Perhaps one of the most well known examples of early-in-life exposure and susceptibility occurred in the early 1960's when vaginal adenocarcinomas began appearing in teenagers and young women whose mothers took the synthetic estrogen diethylstilbestrol (DES) to avoid pregnancy loss. Other observations in the table below noting the susceptibility of the fetus, infants, and children to carcinogens underscore the importance of considering life stage in assessing the risks from exposures to carcinogens.

Table 5: Examples of Early-Life Cancer Susceptibility in Humans		
Agent	**Susceptible Group**	**Biological Response**
Diethylstilbestrol (DES)[20]	Fetus	*In utero* exposure arising from administration of DES during pregnancy resulted in an increased risk of adenocarcinoma of the vagina and cervix in the daughters, but not in mothers taking the drug.
X-Irradiation treatment for Hodgkins Lymphoma[21]	Girls with developing breast tissue (10-16 years old)	10-16 year old girls considerably much more likely to develop breast cancer than those under age 10 similarly treated. 35% increased risk of cancer by age 40.
Radioactive iodine fallout from 1986 Chernobyl accident[22]	Fetus/Children	An increased risk of thyroid carcinoma was observed in children from Ukraine and Belarus exposed to radioactive iodine fallout. The greatest risk of thyroid carcinoma was observed in children aged five and under at the time of the accident.
Immunosuppresive drug treatment associated with organ allograft[23]	Children ages 18 years or less	Children are more prone to develop post-transplant lymphomas and lymphoproliferative disorders than adults (53% Vs 15%).
Adapted from Cal-EPA, 2009. Appendix J: In Utero and Early life Susceptibility to Carcinogens: the Derivation of Age-at-Exposure Sensitivity Measures. May 2009. Table 2, page 11		

Conclusions Made by Cal-EPA

To account for the effect of years available to manifest a tumor following the exposure to a carcinogen, Cal-EPA multiplied the life-stage potency ratio by a time-of-dosing factor to derive an age sensitivity factor. Cal-EPA derived age-specific sensitivity factors, similar in concept to U.S. EPA's age dependent adjustment factors, for each experiment by first calculating the life-stage potency ratio (addresses the susceptibility of early life-stages relative to adult of the

[20] Herbst AL, Ulfelder H, Poskanzer DC (1971) Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. N Engl J Med 284 (15): 878-81; Preston-Martin S (1989). Epidemiological studies of perinatal carcinogenesis. IARC Sci Publ. 96: 289-314, International Agency for Research on Cancer, Lyon France.

[21] Bhatia S, Robison LL, Oberlin O, Greenberg M, Bunin G, Fossati-Bellani F, et. al., (1996) Breast cancer and other second neoplasm after childhood Hodgkins disease. N Eng J Med 334 (12): 745-51.

[22] Moysich KB, Menezes RJ, Michalek AM (2002). Chernobyl-related ionizing radiation exposure and cancer risk: an epidemiological review. Lancet Oncol 3(5): 269-79.

[23] Penn I (2000). Post-transplant malignancy: the role of immunosuppression. Drug 23 (2): 101-13.

carcinogen) and then accounting for the effect of years available to exhibit a carcinogenic response following exposure.

In the absence of chemical specific information, Cal-EPA selected default age-sensitivity factors (age adjustment factors) to weight exposures that occur early in life for prenatal, postnatal, and juvenile exposures. The Cal-EPA default age-sensitivity factors and corresponding age ranges are:

- Default age-sensitivity factor of 10 for ages birth to 2 years
- Default age-sensitivity factor of 3 for ages 2 through 15 years
- Default age-sensitivity factor of 1 for ages greater than 15

Other State Agencies Recognizing Children's Environmental Health

Besides **Oregon** and **California**, other state environmental agencies have adopted policies and procedures to account for these differences in exposures and cancer potencies including:

- The **Michigan** Department of Environmental Quality, Toxics Steering Group agreed that the April 2005 U.S. EPA Supplemental Guidance for Early Life Exposure to Carcinogens should be used to better account for children's differential risks.[24]
- Proposed revisions to **Connecticut's** remediation standards are designed to account for increased exposure and susceptibility of children to carcinogens.[25]
- The **Texas** Commission on Environmental Quality and Department of Health recognizes that fetuses, infants, and children may be uniquely susceptible to the effects of toxic chemicals and that these vulnerabilities demand special regulatory attention. Hence, for selected chemicals Texas evaluates children's susceptibility from early-life exposures to carcinogens.[26]
- Similar to the Department of Ecology, the **Massachusetts** Department of Environmental Protection is currently evaluating the incorporation of U.S. EPA's 2005 Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens into their regulatory policies and procedures for developing risk-based cleanup standards.[27]
- The Children's Health Subcommittee of the Toxics Steering Group, **Michigan** Department of Environmental Quality, agreed that the April 2005 U.S. EPA Supplemental Guidance for

[24] Michigan Department of Environmental Qulaity, Interoffice Communication. From Gary Butterfield, Chairperson, Toxics Steering Group, Air Quality Division, To Steven E. Chester, Director, February 10, 2006. http://www.michigan.gov/documents/TSG_Jan06_minutes_150133_7.pdf

[25] Proposed Revision. Connecticut's Remediation Standard Regulations-Volatilization Criteria. March 2003 http://www.ct.gov/dep/lib/dep/site_clean_up/remediation_regulations/RvVolCri.pdf

[26] Quantitative Risk Characterization, Nueces Bay, Nueces County, TX, January 29, 2003 Prepared by the Texas Department of Health; and The Texas Commission on Environmental Quality, Development Support Document Proposed September 2008 for Vinyl Chloride.

[27] E-Mail correspondence between Craig R. McCormack (Ecology) and Information, BWSC (DEP), October 22, 2009

Early-Life Exposure to Carcinogens be used to develop environmental screening levels, standards, risk estimates and cleanup values.[28]

According to the National Conference of State Legislators (a bipartisan organization that serves the legislators and staffs of the nation's 50 states, its commonwealths, and territories) between 1998 and 2008, there were 771 bills in 49 different states that considered children's environmental health. In 2009, there were 124 bills pending in 10 different states and 32 bills enacted in 18 different states related to children's environmental health.[29]

Selected Technical Issues Vetted by U.S. EPA and Cal-EPA

Prior to the publication of their respective guidance documents, both the U.S. EPA and Cal-EPA have responded to comments from the public or science advisory panels during their respective vetting processes.[30] The response to public comments by Cal-EPA has been reproduced and bound for the MTCA Science Advisory Panel meeting (November 23, 2009).[31] The text box below provides some common technical themes that emerged from the comments and responses made by the U.S EPA and Cal-EPA.

Selected Common Technical Themes/Concerns For Early – Life Stage Evaluations Addressed by U.S. EPA and Cal-EPA

- The best available scientific information needs to be used in chemical risk assessments.
- Current cancer risk assessment methodology is protective of both adults and children.
- Is there sufficient science to support the conclusion that early-life exposures to carcinogens result in increased susceptibility to a carcinogenic response later in life?
- Should the application of early-life exposure age-dependent adjustment factors to carcinogens be limited to those carcinogens that act through a mutagenic mode of action or applied to carcinogens with other modes of action?
- Do early-life exposures to carcinogens results in increased susceptibility to carcinogens that act through a mutagenic mode of action?
- Consideration of sufficiency of information to support early-life stage age adjustments factors based on age groupings to represent critical periods of human growth and development.

[28] Michigan Department of Environmental Quality, Interoffice Communication To Steven E. Chester, Director, From Gary Butterfield, Chairperson, Toxics Steering Group, Subject: Toxic Steering Group (TSG) Meeting Minutes. February 10 2008.

[29] The National Conference of State Legislators, Environmental Health Legislation Database Archive and Environmental Health Legislation Database. http://www.ncsl.org/Home/tabid/118/Default.aspx

[30] Review of EPA's Draft Supplemental Guidance for Assessing Cancer Suscepotibility From Early-Life Exposure to Carcinogens. A Report By The Supplemental Guidance For Assessing Cancer susceptibility Review Panel Of the EPA Science Advisory Board. EPA-SAB-04-003. March 2004. [http://yosemite.epa.gov/sab/SABPRODUCT.NSF/658FD14F8F94C7E385256F0A006C94E0/$File/sab04003.pdf]

[31] Cal-EPA Response to Public comments With A Focus on Early-Life Exposure and Susceptibility.[http://oehha.ca.gov/air/toxic_contaminants/pdf_zip/Responses101008.pdf]

Both the U.S. EPA and Cal-EPA addressed a large range of issues and concerns using an extensive body of information. There is only one substantial point of difference between the Cal-EPA's recommended policies and procedures and those of the U.S. EPA to evaluate and assess cancer susceptibility from early-life exposure to carcinogens. The substantial point of difference is the intent to apply the age dependent adjustment factors for all carcinogens, the Cal-EPA approach, as opposed to only those carcinogens with a hypothesized mutagenic mode of action per the U.S. EPA approach. Based on informed science, the U.S. EPA Science Advisory Board is in agreement with the Cal-EPA approach for the need to incorporate early life sensitivity to carcinogen exposure when estimating lifetime cancer risks.

Ecology Proposal

The Department of Ecology believes that there is sufficient information to indicate differences in patterns of exposure and cancer potencies based on differences in behavior, physiology, and anatomy between infants, children and adults.

Issue 3: Restricting Age Adjustments to Certain Carcinogens or All Carcinogens

Issue 3: The California Environmental Protection Agency (Cal-EPA) has developed methods and policies for making early-life stage adjustments to carcinogens with other modes of action. Is this approach consistent with current scientific information on early-life stage exposure to carcinogens with other (non-mutagenic) modes of action?

Application of Age Adjustment (Age Sensitivity) Factors

U.S. EPA and Cal-EPA apply age adjustment differently. The U.S. EPA applies the age adjustment factors only to those carcinogens with a mutagenic mode of action. Cal-EPA, however, does not make this distinction.

U.S. EPA

The application of age adjustment factors to mutagenic carcinogens was a policy decision made by U.S. EPA because the data for non-mutagenic carcinogens were considered to be too limited and the modes of action too diverse.

As noted in the January 16, 2001, correspondence to Carol M. Browner from Morton Lippmann, regarding the U.S. EPA Science Advisory Board's "Review of the U. S. EPA's Draft Revised Cancer Risk Assessment Guidelines Pertaining to Children"

> *"… the Subcommittee did not reach consensus on the descriptor of "Known to be Carcinogenic to Humans."* [32]

The members did not agree on whether to restrict use of this category to scenarios in which there was conclusive epidemiological data for causality. Most members favored this position. However, some members recommended that, even with less sufficient epidemiological data, an agent with strong animal evidence plus evidence (in exposed humans) that the chemical is causing measurable changes that are on the causal pathway to cancer in humans, should be considered to be carcinogenic to humans." [33]

Ecology consulted with U.S. EPA Region 10 to confirm that the decision to constrain the application of age adjustment factors to mutagenic carcinogens is a policy decision and not based

[32] U.S. EPA Correspondence From Dr. Morton Lippmann (Acting Chair, Science Advisory Board Executive Committee) to Carol M. Browner, SAB Report-Review of Revised Sctions of the Proposed Guideline cor Carcinogen Risk Assessment, EPA-SAB EC -99-015, July 29 1999 and SAB Report-Review of EPA's Draft Revised Cancer Risk Assessment Guidelines Pertaining to Children, EPA-SAB-EC-00-016, September 11, 2000. Issue 6.) 3rd page of Enclosure 1
http://yosemite.epa.gov/sab/sabproduct.nsf/cf0020ec3f99320a85256eb4006b6bd1/857f46c5c8b4be4985257193004cf904/$FILE/ec00016resp.pdf

[33] Enclosure to Carol M. Browner, Administrator, U.S. Environmental Protection Agency, Correspondence to Morton Lippman, Acting Chair, Science Advisory Board Executive Chair, Enclosure I, EPA Response to Science Advisory Board Recommendation, Item 6) Narrative Summaries and the Five Hazard Descriptors.

on carcinogenic information or toxicokinetic data that indicates non-mutagens would be systematically different from mutagens for their carcinogenic response.[34]

Cal-EPA

Cal-EPA considers constraining the application of age adjustment factors to mutagenic carcinogens to be insufficiently health protective. There are several important methodological differences between the U.S. EPA and Cal-EPA regarding early life cancer potency evaluations and age weighted adjustments. These differences merit consideration when thinking about the application of the age weighted adjustment factors for early life exposures. The most noteworthy differences are:

- All treatment-related tumors observed in a given life-stage exposure experiment were accounted for in estimating cancer potency by Cal-EPA.
- The total cancer risk associated with exposure during a given life-stage was evaluated when comparing cancer potencies associated with early life versus adults exposures; (U.S. EPA compared the risk for cancers at one single site in each life-stage).
- The age groupings were different with prenatal (in utero), and distinctions between postnatal and juvenile exposures were evaluated by Cal-EPA and were not part of the evaluation performed by U.S. EPA.

Regardless of the theorized mode of action, Cal-EPA will apply weighted age adjustment factors, default age-sensitivity factors, to all carcinogens.[35] The rationale for Cal-EPA to apply weighted age adjustment factors are as follows:

- There is data that early life is a susceptible time for carcinogens that act via non-mutagenic mode of action.
- Carcinogens may have different modes of action and one mode of action may be predominant over other modes of action at different life stages.
- Not restricting the application of the weighted age adjustment factors to mutagenic carcinogens better recognizes the biological complexity of carcinogenesis.
- The factors that make individual exposure to carcinogens during an early-life-stage potentially more susceptible than those exposed during adulthood equally applies to exposures to non-mutagenic carcinogens (that is rapid growth, development of target tissues, potentially greater sensitivity to hormonal carcinogen, differences in metabolism).
- Carcinogens that that do not cause gene mutations may still be genotoxic by causing chromosomal damage.

[34] E-mail correspondence From Dr. Marcia Bailey, U.S. Environmental Protection Agency, Region 10, to Craig McCormack, Dept. of Ecology, January 20, 2009.

[35] Cal-EPA, June 2008. Air Toxics Hot Spots Program, Risk Assessment Guidelines, Part II Technical Support Document for Cancer Potency Factors, California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, June 2008 Public Review Draft.

- Many carcinogens do not have sufficient data available for determining a specific mode of action and many carcinogens may exert their biological effects, carcinogenic response, by more than one mode of action.[36]

Based on the California Office of Environmental Health Hazard Assessment (OEHHA) analysis of the potency by life-stage exposures, Cal-EPA/OEHHA proposes to weight cancer risk by a factor of 10 for exposures that occur from the third trimester of pregnancy to 2 years of age. This was based partly on research by OEHHA staff showing an increased risk of postnatal cancer following exposure to some agents in utero, but primarily on the observation that many carcinogens are associated with increased risk to neonatal rodents (which is the justification for the 10x factor during the first 2 years in humans), and the rodent at birth is at approximately the same overall point in development as the human at the start of the third trimester.

"OEHHA recognizes the limitations in the data and analyses presented, as discussed above. However, the analyses do provide some guidance on the extent to which risk may be over or underestimated by current approaches. While there is a great deal of variability across chemicals in the prenatal ASFs, the data indicate that the potency associated with prenatal carcinogen exposure is not zero. A factor of 3 is close to the median ASF, while a factor of 10 falls roughly at the 70th percentile of the prenatal ASF estimate. An ASF could be applied as a default when calculating lifetime cancer risk in humans arising from carcinogen exposures that occur in utero. In view of the considerable variability in the data for different carcinogens and the limited database available for analysis, OEHHA is not proposing the application of a specific factor to cancer potency estimates for prenatal exposures in the first and second trimesters as a default position in these Guidelines. However, given that the rodent is born at a stage of maturation similar to a third trimester fetus, it is reasonable to include the third trimester in the 10X potency weighting proposed up to age 2 years. The applicability of a cancer potency adjustment factor for first and second trimester prenatal exposure will be evaluated on a case-by-case basis, and may be used as evidence develops that supports such use. The consideration of prenatal exposures, including application of an appropriate susceptibility factor, would not make a large difference for risk estimates based on continuous lifetime exposures due to the relatively short duration of gestations. However, risk estimates for short-term or intermittent exposures would be slightly increased by inclusion of the risks to the fetus during the prenatal period. Thus, risk may be underestimated when the first and second trimesters are excluded from the analysis."[37]

[36] Cal-EPA, 2009. Technical Support Document for Cancer Potency Factors: Methodologies for derivation, listing of available values, and adjustments to allow for early life stage exposures. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment. May 2009 [http://oehha.ca.gov/air/hot_spots/2009/TSDCancerPotency.pdf]

[37] IBID, page 52

Issue 4: Further Proposed Evaluations by Ecology to Account for Uncertainty/Variability

Issue 4: What sources of scientific uncertainty and variability should Ecology consider when evaluating these issues and potential changes to the MTCA cleanup regulation?

Ecology Proposal

Using Monte Carlo analysis, the Department of Ecology proposes to further evaluate the current exposure parameters used in the MTCA Cleanup Regulation in consideration of exposure factors and age adjustments that account for early life exposures to chemical carcinogens.

The YASAI simulation tool developed by Rutgers University and refined by the Environmental Assessment Program, Department of Ecology, will be used for the Monte Carlo analysis.

OPTIONS AND PROPOSED RECOMMENDATIONS

Ecology's Proposed Options and Recommendations

1. Do the current cancer risk assessment methodologies adequately address the possibility that cancer risks from early in life and adult exposure may differ?

Ecology has considered the evaluations and information developed by both the U.S. Environmental Protection Agency (U.S. EPA) and the California Environmental Protection Agency (Cal EPA) to quantitatively evaluate the effect of life-stage at exposure on the carcinogenic response in experimental animal studies. The analysis of both agencies supports the policy decision to weight risk when exposure occurs during childhood in recognition that the current cancer risk assessment methodology does not adequately account for increased susceptibility of childhood environmental exposures.

Ecology concurs with the policy decision to weight risk when exposure occurs during childhood because:

- A robust and scientifically defensible analysis conducted by two separate environmental agencies has independently concluded that exposures early in life can result in a greater lifetime risk of cancer.
- Nothing in the current risk assessment methodology specifically addresses life stage sensitivity or susceptibility.
- The majority of animal cancer bioassay data does not include exposures prior to sexual maturity.
- Most epidemiological studies of cancer have been in occupationally exposed adults, and, thus, there is nothing inherent in these studies upon which the potency estimates are based that accounts for exposures early in life.

Ecology therefore believes it is important to more accurately inform risk managers of the cancer risks posed by exposing infants and children, versus adults, to carcinogens.

2. Do differences in behavior, physiology, and anatomy between infants, children, and adults result in disproportionate exposures for infants and children?

Ecology has examined the information developed by the U.S. EPA, the California Environmental Protection Agency, international (World Health Organization, 2006), and domestic (National Research Council, 1993, 1994, and 2008) scientific agencies noting the distinguishing characteristics of children that may confer disproportionate exposures and risk to carcinogens. Some of the factors that may play a role in increased cancer risk from exposures during critical periods of development include:

- Age at exposure
- Diet
- Behavior patterns resulting in differences in exposures
- Hormonal status

  Differences in physiology and anatomy (such as differences in immunological activity, intestinal absorption, biliary and kidney excretion, blood and fat distribution, expression of enzyme systems that activate or detoxify carcinogens)

3. Does the susceptibility of infants and children from exposure to environmental contaminants confer disproportionate risks?

Various agencies (U.S. EPA, Cal-EP, WHO, NRC) have identified not only empirical evidence from humans and animals of in utero and early life susceptibility to carcinogens, there are strong multiple theoretical bases to indicate that exposures early in life can result in a greater lifetime risk of cancer. The basis to indicate early-life susceptibility includes:

- Cancer is a complex multistage process. The occurrence of cancer in the first life-stages, childhood, increases that chance that the entire carcinogenic process will be completed, and a cancer produced, within an individual's lifetime.
- Tissues undergoing rapid growth and development may be especially vulnerable to carcinogenic agents. During periods of increased cell proliferation there is rapid turnover of DNA, and more opportunity for genetic damage (that is, DNA breaks, crosslinks, adduct formations) or epigenetic alterations (that is, altered DNA methylation, histone modification) to result in permanently altered gene expressions that may ultimately lead to cancer.
- During early life-stages of development, a greater proportion of the body's cells are relatively undifferentiated stem cells, and represent a large target population of somatic cells capable of transmitting permanent changes to the DNA during future cell divisions.
- There may be greater sensitivity to hormonal carcinogen early in life since the development of many organ systems is under hormonal control (that is, male and female reproductive systems).

4. Should the application of weighted age adjustments (EPA's Age Dependent Adjustment Factors; Cal-EPA's Age Sensitivity Factors) be restricted to carcinogens with a mutagenic mode of action?

The application of age dependent adjustment factors (ADAFs) by the U.S. Environmental Protection Agency is restricted to chemicals that act to induce cancer via a mutagenic mode of action. After examining the information from the U.S EPA and assembling larger dataset to examine the application of weighted age adjustment factors for nonmutagenic carcinogens, the California Environmental Protection Agency concluded default adjustment factors should be applied for all carcinogens except where chemical-specific data indicate to the contrary.

Furthermore, the policy decision by Cal-EPA to apply the age adjustments to non-mutagenic carcinogens is reinforced based on many of the carcinogens evaluated by U.S. EPA to derive age specific adjustment factors do not have primarily a mutagenic mode of action. The independent analysis by Cal-EPA, as well as by U.S. EPA, identified several carcinogens having a non-mutagenic mode of action where increased susceptibility at younger ages was demonstrated. Also, the U.S. EPA's Science Advisory Board has noted that the U.S EPA needs to develop default adjustments for other carcinogens with other modes of actions, including hormonal.

To further reinforce and as an extension of this comment, the National Research Council of the National Academies commented on the U.S. EPA's Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (2005) noting:[38]

> *"The 2005 guidelines and supplemental guidance that developed generic factors for early-life susceptibility was a step in the right direction. The supplemental guidance provides weighting factors for exposures to mutagenic compounds in the early postnatal and juvenile period. However, in utero periods and nonmutagenic chemicals were not covered, and in practice EPA treats the prenatal period as devoid of sensitivity to carcinogenicity, although it has funded research to explore this issue (Hattis et al. 2004, 2005). That stands in contrast with the language in the 2005 guidelines: "Exposures that are of concern extend from conception through adolescence and also include pre-conception exposures of both parents (EPA 2005b, p. 1-16). EPA needs methods for explicitly considering in cancer risk assessment in utero exposure and chemicals that do not meet the threshold of evidence that the agency is considering for judging whether a chemical has a mutagenic mode of action (EPA, 2005b). Special attention should be given to hormonally active compounds and genotoxic chemicals that do not meet the threshold of evidence requirements."*

Cancer is one of many adverse health effects that may occur in children resulting from exposures to environmental contaminants. Using different methodologies to evaluate cancer potency, the U.S. Environmental Protection Agency and the California Environmental Protection Agency have independently concluded that risks of cancer from exposures to carcinogens occurring from conception through puberty can be different than those cancer risks from exposures occurring in adulthood.

Exposure to a carcinogen early in life may result in greater lifetime risk of cancer for several reasons:[39]

- Cancer is a multi-stage process and the occurrence of the first stages of the carcinogenic process in childhood increases the chance that the entire carcinogenic process will be completed, and a cancer produced, within an individual's lifetime.
- Tissues undergoing rapid growth and development may be especially vulnerable to carcinogenic agents. During periods of increased cell proliferation there is rapid turnover of DNA, and more opportunity for misrepair of damage (that is, DNA breaks, crosslinks, adducts) or alterations resulting in permanent changes to the DNA (that is, mutations, altered DNA methylation) that may ultimately lead to cancer.

[38] NRC, 2008. Science and Decisions: Advancing Risk Assessment. National Research Council of the National Academies. Prepublication Copy November 2008, pages 103 to 104.

[39] Cal-EPA, 2008. Air Toxics Hot Spots Program, Risk Assessment Guidelines. Part II Technical Support Document for Cancer Potency Factors, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency June 2008 Public Review Draft.

- During early life-stages or development, a greater proportion of the body's cells are undifferentiated stem cells, undifferentiated stem cells represent a large target population of somatic cells capable of passing along permanent changes to the DNA during future cell divisions.
- There may be greater sensitivity to hormonal (that is, endocrine disrupting) carcinogens early in life since the development of many organ system is under hormonal control (that is, male and female reproductive systems, thyroid control of Central Nervous System development).
- Anatomical, physiological, and behavioral characteristics may influence or play a role in increased cancer risk from exposures during critical development periods such as differences in immunological activity, intestinal absorption, biliary and kidney excretion, blood and fat distribution, and expression of enzyme systems that activate or detoxify carcinogens.

For these reasons, Ecology believes that the application of default age adjustments is a policy choice informed by sound and defensible science and should be applied to all carcinogens unless there is chemical specific data that indicates to the contrary.

APPENDICES

Appendix A. Terminology

Age Dependent Adjustment Factors (ADAFs)

As a departure from the way cancer risks have historically been developed by U.S. EPA based upon the premise that risk is proportional to the daily average of the long term adult exposure (dose with a 70 year exposure duration), where age related differences in toxicity are found to occur, differences in toxicity and exposure are integrated across all relevant age intervals (life-stages) using weighted age adjustments. The table below identifies the ADAFs for different age groups where early life exposures occur for carcinogens that act via a mutagenic mode of action.

Childhood Age Groupings & Early-Life Exposure Age Adjustments With Associated Exposure Durations		
Exposure Childhood Age Group	**Exposure Duration (years)**	**Age Dependent Adjustment Factor (ADAF)**
Birth to < 1 Month	0.083	10X
1 < 3 months	0.167	10X
3 < 6 months	0.25	10X
6 < 12 months	0.5	10X
1 to <2 years	1	10X
2 to <3 years	1	3X
3 to < 6 years	3	3X
6 to < 11 years	5	3X
11 to < 16 years	5	3X
16 to < 21 years	5	1X
> 21 years (21 to < 70 yrs)	49	1X
Adapted from U.S. EPA's Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants (2005), and, Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (2005).		

Age Sensitivity Factors (ASFs)

California Environmental Protection Agency (Cal-EPA) terminology for weighted age adjustment factors that accounts for early life stage susceptibility and the time since exposure to develop the tumor, cancer. Cal-EPA will apply these ASFs to all carcinogens, regardless of the theorized mode of action.

Childhood Age Groupings & Early-Life Exposure Age Adjustments by Cal-EPA	
Exposure Childhood Age Group	**Age Sensitivity Factor (ASF)**
Birth to 2 years	10 X
> 2 to 15 years	3 X
> 15 years	1 X
Cal-EPA Air Toxics Hot Spots Program, Risk Assessment Guidelines, Part II Technical Support Document for Cancer Potency Factors, June 2008.	

Children

Children are referred to in the context of exposure assessment to include the life-stages of development from conception through adolescence. Early-life exposure refers to exposures occurring during the life-stages of development from conception through adolescence (reference framework).

Stages in Human Development Defined (Working Definitions)	
Developmental Stage/Event	**Time Period Defined**
Preconception	Prefertilization
Preimplantation embryo	Conception to implantation
Postimplantation embryo	Implantation to 8 weeks of pregnanacy
Fetus	8 weeks of pregnancy to birth
Preterm birth	24-37 weeks of pregnancy
Normal - term birth	40 ± 2 weeks of pregnancy
Perinatal stage	29 weeks of pregnancy to 7 days after birth
Neonate	Birth to 28 days of age
Infant	28 days of age to 1 year
Child	
Young child	1-4 years of age
Toddler	2-3 years of age
Older child	5-12 years of age
Adolescent	Beginning with the appearance of secondary sexual characteristics to achievement of full maturity (usually 12 to 18 years of age)
Adapted from Table 1, page 10, Principles for Evaluating Health Risks in Children Associated with Exposure to Chemicals, Environmental Health Criteria 237, World Health Organization, 2006.	

Developmental Exposure

Developmental life-stage exposures from preconception through adolescence.[40]

Life-stage

A distinguishable time frame in an individual's life characterized by unique and relatively stable behavioral and/or physiological characteristics that are associated with development and growth. Age groups recommended by environmental organizations are life-stages relevant to environmental exposure.[41] Also, life-stage is defined by U.S. EPA, as "temporal stages of life that have distinct anatomical, physiological, and behavioral or functional characteristics that contribute to potential differences in vulnerability to environmental exposures. A life-stage approach to risk assessment considers the relevant periods of exposure in developmental life-stages and subsequent outcomes that may not be expressed until later life-stages."[42]

[40] U.S. EPA, 2006. A Framework for Assessing Health risks of Environmental Exposures to Children. U.S. Environmental Protection Agency, National Center for Environmental Assessment. September 2006. EPA/600/R-05/093F.

[41] U.S. EPA, 2005. Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants. U.S. Environmental Protection Agency, Risk Assessment Forum. November 2005. EPA/630/P-03/003F.

[42] U.S. EPA, 2006. A Framework for Assessing Health risks of Environmental Exposures to Children. U.S. Environmental Protection Agency, National Center for Environmental Assessment. September 2006. EPA/600/R-05/093F. (page 1-1)

Sensitivity

In the context of early life-stages, sensitivity refers to children having a reduced capacity to detoxify environmental chemicals and, therefore, may exhibit effects at lower doses and environmental concentrations, than their adult counterparts.[43]

Susceptibility

An increased likelihood of an adverse effect, often discussed in terms of relationship to a factor that can be used to describe a human subpopulation (that is, life-stage, demographic feature, or genetic characteristics).[44] The capacity of a person to be affected based on characteristics as age, sex, genetic attributes, socioeconomic status, prior exposure to harmful agents, and stress. A variation in risk may reflect s susceptibility.[45]

Vulnerability

An intrinsic predisposition of an exposed person, community, population, or ecologic entity to suffer harm from external stresses and perturbations (exposures) based on variations in disease susceptibility, psychological and social factors, exposures, and adaptive measures to anticipate and reduce future harm, and to recover from an insult.[46]

[43] NRC, 1993. Pesticides in the Diets of Infants and Children. National Research Council of the National Academies. 1993

[44] U.S. EPA, 2005. Supplemental Guidance for Assessing Susceptibility from Early-life Exposure to Carcinogen. U.S. Environmental Protection Agency, Risk Assessment Forum. March 2005. EPA/630/R-03/003F.

[45] NRC, 2008. Science and Decisions: Advancing Risk Assessment. National Research council of the National Academies. Prepublication Copy November 2008.

[46] NRC, 2008. Science and Decisions: Advancing Risk Assessment. National Research Council of the National Academies. Prepublication Copy November 2008.

Appendix B: A Brief Review of Carcinogenic Response/Process

Carcinogenesis is a complex multistage process that involves the genome both directly and indirectly. The multistage process of carcinogenesis is a series of events that must transpire during the transformation of a normal cell into a malignant tumor. The multistage nature of carcinogenesis is understood from both epidemiological and experimental data.

The carcinogenesis process is conceptualized as comprising three different processes: initiation, promotion, and progression. Initiation is the event that transforms a normal cell into a pre-cancerous intermediate (initiated) cell. Promotion is the proliferation of a single initiated cell into a group, or clone, of many initiated cells. Progression is the transformation of one of the initiated cells into a malignant cell, which may proliferate into a malignant tumor. These stages may involve epigenetic and genetic cellular alterations either singularly or in combination with one another.

The stages of the carcinogenic response may be influenced, to varying degrees, by a large number of variables including:

- Age at exposure
- Diet
- Hormonal status
- Intra- and interspecies variability[47 & 48]

Cancer Risks in Children

The World Health Organization (WHO) noted in the 2006 Environmental Health Criteria 237, *Principles For Evaluating Health Risks in Children Associated With Exposure To Chemicals*, that "There is direct evidence that children are more susceptible than adults to at least some kinds of carcinogens, including certain chemicals and various forms of radiation. Data from controlled experimental studies in animals also support the concept that susceptibility to some chemical carcinogens and to various forms of ionizing radiation is greatest during the early stages of life, both before and after birth."[49] There are several examples of adult cancers related to childhood exposures to carcinogens. Examples include:

- Tumors of the brain, cranial nerves, and meninges
- Thyroid carcinoma

[47]Chemical Carcinogens: Review of the Science and Its Associated Principles, Office of Science and Technology Policy, Federal Register Notice, Volume 50, No. 50, February 1985, pages 10372 – 10442.
[48] Perspectives on Biologically Based Cancer Risk Assessment. Edited by Vincent James Cogliano, E. Georg Luebeck, and Giovanni A Zapponi. Kluwer Academic/Plenum Publishers, 1999. NATO-Challenges of Modern Society-Volume 23.
[49] WHO, 2006. World Health Organization 2006. Environmental Health Criteria 237. Principles for Evaluating Health Risks in Children Associated with Exposure to Chemicals, page 115.

- Leukemia and solid tumors in adult survivors of Hiroshima and Nagasaki atomic bombs
- Skin cancer due to childhood exposures to solar radiation
- Tumors of female reproductive tract in adolescent and young adult women due to treatment of their mothers with synthetic non-steroidal estrogens.[50]

In recognition of children's potentially increased susceptibility to environmental contaminants, there have been growing concerns regarding children's environmental health. According to the National Cancer Institute:

> *Cancer among children is a substantial public concern. Each year in the United States, approximately 12,400 children and adolescents younger than 20 years of age are diagnosed with cancer. Approximately 2,300 children and adolescents die of cancer each year, which makes cancer the most common cause of disease-related mortality for children 1-19 years of age.* [51]

Exposures to environmental carcinogens during fetal development and in early childhood have been suggested as possible causal factors responsible for the increases in leukemia, lymphoma, brain and testicular cancers.[52 & 53]

There has been a moderate and steady increase in the incidence of childhood cancers (ages 0 to 20 years) since the 1970s. Each year, approximately 150 out of every million children will be diagnosed with cancer. The most common cancers among children are leukemias, lymphomas and brain tumors; among adolescent children germ cell and testicular tumors are common.[54] Over the past 20 years:

- Leukemia in children under 15 years increased by one percent per year
- Hodgkin's lymphoma has been declining by about one to two percent per year, but non-Hodgkin's lymphoma increased from 11 to 16 per million among 15 to 19 year olds and has remained constant for children under 15
- Incidences of central nervous system cancers among children under 15 have increased
- Germ cell, trophoblastic, and other gonadal cancers have increased among both males and females aged 14 to 19

The World Health Organization estimates that at least three million children under five die annually due to environmentally-related diseases. Approximately 30% of the global burden of

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[50] IBID, page 120.

[51] Ries LAG, Smith MA, Gurney JG, Linet M, Tamra T, Young JL, Bunin GR (eds). *Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995*, National Cancer Institute, SEER Program. NIH Pub. No. 99-4649. Bethesda, MD, 1999 (Quoted from Forward provided by Richard D Klausner, Director, NCI, page iii). [http://seer.cancer.gov/publications/childhood/foreword.pdf]

[52] Ries LAG, Smith MA, Gurney JG, Linet M, Tamra T, Young JL, Bunin GR (eds). *Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995*, National Cancer Institute, SEER Program. NIH Pub. No. 99-4649. Bethesda, MD, 1999. [http://seer.cancer.gov/publications/childhood/]

[53] Cal-EPA, 2001. Prioritization of Toxic Air Contaminants Under the Children's Environmental Health Portection Act. Final. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment. October 2001.

[54] IBID, Introduction [http://seer.cancer.gov/publications/childhood/introduction.pdf]

disease may be attributed to environmental factors; 40% of this burden is associated with children under five.

Estimates of disease incidence rates in children due to exposure from environmental contaminants are not well documented. There is, however, clear evidence that exposure to environmental chemicals during different developmental stages can result in a number of adverse effects in children including increased incidence of selected childhood diseases.[55]

Factors Influencing Children's Increased Susceptibility

The development of cancer is one of many adverse health effects that may occur in children from exposure to environmental contaminants. A number of factors, related to both biology and exposure, have been shown to influence children's increased susceptibility.

Critical Biological Systems and Periods of Development

Certain physiological systems have critical periods during their development when they are vulnerable, susceptible to lasting adverse effects from exposure to chemicals. These complex physiological systems include the central nervous, the endocrine, the respiratory, and the immune systems. In humans these physiological systems work together to control and protect the organism. Each of these systems is genetically programmed as it develops, and chemical contaminants can potentially interfere with the programming of these critical systems. Also, adverse effects of one system can be expected to have collateral adverse effects on other physiological systems.[56 & 57 & 58]

Developmental Toxicants

Chemicals can act on developmental events that occur prenatally, postnatally, or both. Development is a biological continuum that begins at conception and continues through adolescence. Chemicals may exhibit a range of developmental effects at different dose levels and periods of development and durations of exposure.

Central Nervous System

Critical stages in the development of the central nervous system occur during embryogenesis and development of the fetus and postnatally through adolescence. Exposures to chemicals can have profound permanent effects on all stage of neurologic development.

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[55] WHO, 2006. World Health Organization 2006. Environmental Health Criteria 237. Principles for Evaluating Health Risks in Children Associated with Exposure to Chemicals.

[56] Cal-EPA, 2001. Prioritization of Toxic Air Contaminants Under the Children's Environmental Health Protection Act. Final. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment. October 2001.

[57] WHO, 2006. World Health Organization 2006. Environmental Health Criteria 237. Principles for Evaluating Health Risks in Children Associated with Exposure to Chemicals.

[58] Faustman et. al., 2000. Elaine M. Faustman, Susan M. Silbernagel, Richard A. Fenske, Thomas M. Burbacher, and Rafael A. Ponce. Mechanisms Underlying Children's Suscptibility to Environmental Toxicants. Environmental Health Perspectives Vol 108, Supplement 1, March 2008, pages 13-21.

Endocrine System

The endocrine system secretes hormones directly into the circulatory system from glands and other organs in the body. The endocrine system influences most bodily functions including growth and metabolism. The endocrine system works to coordinate and control the development of the organism. Glands or organs with endocrine functions include pituitary, thyroid, parathyroid, adrenal glands, pineal body, the gonads, and the pancreas. The endocrine system plays critical roles in the development of the organism during the first few years of life, and during puberty.

Immune System

One of the many functions of the immune system is to protect against infections. The development of the immune system occurs during embryonic, fetal, and early postnatal life. Chemicals that affect the immune system can influence the organism's ability to respond to environmental challenges. Increasing evidence indicates that exposure of pregnant animals to immunotoxic chemicals at doses causing only transient effects in adults produces long lasting or permanent immune deficits in their offspring.[59&60]

Differences in Exposures (Infants, Children, and Adults)

There are a number of different physiological and behavioral factors between children and adults that influence biological responses and patterns of exposure to chemicals. Children's behavior and physiological factors influence exposure at each portal of entry. Pharmacokinetic / toxicokinetic differences between children and adults influence absorption, distribution, metabolism and excretion of chemicals. Also, infants and children may have different responses from exposures to chemicals due to different target tissue sensitivities during windows of susceptibility during their development.

Selected examples of differences in children affecting exposures are provided here.[61 & 62]

Water Ingestion Exposure Pathway

Children and adults have significantly different fluid requirements. Water consumption rates decrease with age, reaching adult consumption rates during adolescence. Infants have a greater requirement for fluids than older children. Infants may receive formula as a source of calories in combination with breast milk for the first few months of life. Formula fed infants may receive greater doses (mg/kg body weight basis) of water-borne contaminants than older children and adults because formula may be an infant's sole source of fluids and nutrients. Infants consume more fluids on a body weight basis than do older children or adults.

[59] IBID
[60] WHO, 2006. World Health Organization 2006. Environmental Health Criteria 237. Principles for Evaluating Health Risks in Children Associated with Exposure to Chemicals.
[61] IBID
[62] U.S. EPA, 2000. Summary Report of the Technical Workshop on Issues A Associated with Considering Developmental Changes in Behavior & Anatomy When Assessing Exposure to Children. U.S. Environmental Protection Agency, Risk Assessment Forum. December 2000. EPA/630/R-00/005.

Breast Milk Exposure Pathway

Breast milk is an exposure pathway unique to infants and represents repeated doses to contaminants present in the mother's breast milk. For lipophilic chemicals, the breast-fed infant may receive from the mother a significant portion of the total maternal contaminant body burden over time.

Soil Ingestion Exposure Pathway

Under most circumstances, children ingest more soil than adults due to their frequency of contact with soil and with objects that have contacted soil. Young children receive greater doses than older children because mouthing behavior is more frequent, and differences in personal hygiene, crawling activities, and play behaviors result in greater soil contact.

Children's Behavior and Immediate Environment

Children are more physically active than adults with high energy expenditure and energy requirements requiring more food and fluids on a body weight basis than adults. Infants and children spend more time in single environments as opposed to moving about as older children and adults. An infant or toddler may have a greater exposure to contaminants in a single environment than an older child or adult who moves in and out of that environment.

Dermal Exposure

Infants and children have a greater body surface area to body weight ratio than adults. The infant's greater body surface results in increased exposures to chemicals from the dermal route of exposure. Also, as an infant or child matures the skin's permeability and absorption changes. And, child behavior can influence skin permeability when the child's skin moisture content is increased with increased activities.

Childhood Differences in Absorption, of Environmental Chemicals

A number of factors affect differences in absorption rates:

- Lower gastric acidity in neonates
- Slower gastric emptying in neonates
- Lower intestinal absorption in neonates compared to children
- Higher breathing rates in infants and children than adults
- Higher surface area/body weight ratio
- More permeable skin surface

Childhood Differences in Distribution of Environmental Chemicals

A number of factors affect differences in how chemicals are distributed in children relative to adults:

- Higher total body water/body weight
- Lower body fat/body weight
- Lower mass of skeletal muscle/body weight
- Higher relative brain and liver weights vs. adult

- Albumin and other proteins that bind chemicals are found at decreased levels during the newborn period and early in life
- Fetal hemoglobin present in neonates
- Blood pH is lower in neonates
- Increased permeability of the blood brain barrier in early-life

Childhood Differences Affecting Metabolism:

- Children have increasing maximum oxygen consumption/basal metabolic rate
- Enzyme activities are different, usually lower, in neonates
- Blood esterases are lower at birth and rise gradually during the first year of life
- Pancreatic enzymes are lower at birth
- Difference in protein binding between infants and adults results in difference in availability of a chemical for metabolism

Childhood Difference Affecting Excretion:

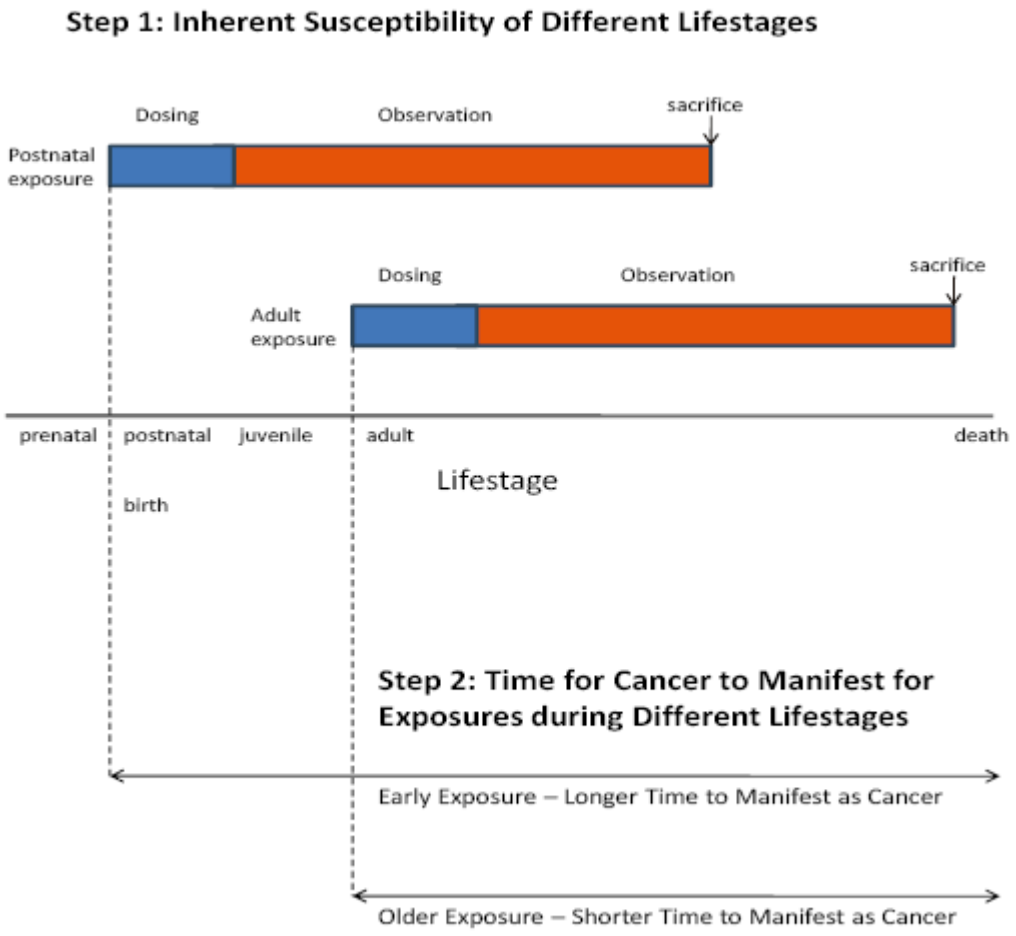
- Lower renal function in neonates and young children
- Slowly developing biliary function of the liver
- Generally greater intestinal function of the child

Appendix C: A Brief Review of the California Environmental Protection Agency Analysis for Early Life Exposure Factors

Evaluation of Early Life Exposure Susceptibility[63]

Age sensitivity factors (ASFs) account for the susceptibility of early life exposures, step 1, and the time from exposure to develop cancer, step 2, noted in the diagram below. The derivation of the ASF evaluates (step 1) differences in various life-stages in age sensitivity for individuals characterizing the susceptibility of the early life-stage to the carcinogen. Step 2 diagrams the longer period of time that a carcinogen exposure to the fetus, infant, or child has to exhibit a carcinogenic response.

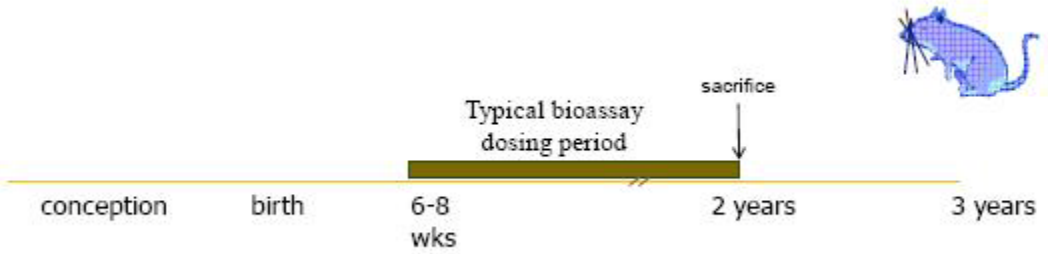
Age Sensitivity Factors (ASFs): Susceptibility & Time to Tumor Response



[63] Information & Diagrams adapted from In Utero and Early Life susceptibility to Carcinogen: The Derivation of Age-at-Exposure Sensitivity Measures, California Environmental Protection Agency, Office of Environmental Health Hazard Assessment. December 2008.

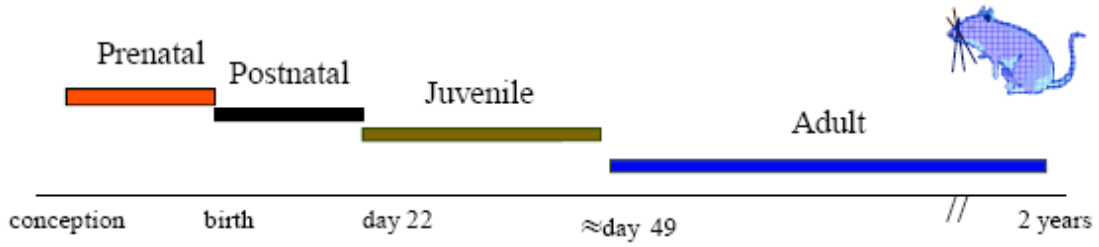
Typical National Toxicology Program (NTP) cancer bioassays conducted with rats and mice start a dosing regimen at six to eight weeks of age, which is the time these animals reach sexual maturity (late teenagers relative to humans). The animal experiments are conducted for two years, ending when the animal is sacrificed in late middle age. Early and very late life exposures, dosing regimens, are not part of the typical NTP rodent bioassay protocol.

Dosing Period for the Typical NTP Rodent Bioassay – Figure Below



The Cal-EPA evaluated published animal cancer bioassay studies where life-stage dosing regimens could be identified. Two types of animal cancer bioassays where early life-stage exposures were identified were used in their evaluation. The first types of studies are multi-life-stage exposure studies with at least two groups of animals exposed during different life-stages; one group is exposed to a chemical only during one of the following life-stages (see figure below): prenatal, postnatal, and juvenile life-stages. The second type of cancer bioassay has a dose regimen for some period of time at an older life-stage-this group served as the reference group. Studies where groups of animals were exposed that spanned multiple life stages were not included in Cal-EPA's evaluation. Cal-EPA evaluated the patterns of early life-stage susceptibility for carcinogens by defining the rodent life-stage, figure below, and calculating life-stage potency ratio distributions. The life-stage potency ratios characterize the susceptibility of early life-stages to a carcinogen exposure by comparing potencies for individuals followed for similar periods of time and similarly exposed, but exposed during different life-stages.

Defined Rodent Life-stages Adopted by Cal-EPA for Early-Life Susceptibility Evaluations



Appendix D: Characteristics Considered in Deriving the Recommended Set of Childhood Age Groups

Age Group	Characteristics
Birth to <1 month	*Behavior-Related:* Time spent sleeping or sedentary; breast and bottle feeding *Physiology-Related:* Rapid growth and weight gain; increasing proportion of body fat; high skin permeability; high oxygen requirements (increased breathing rate); deficiencies in hepatic enzyme activity; immature immune system; more alkaline stomach; increases in extracellular fluid; renal function less than predicted by body surface area
1 to <3 months	*Behavior-Related:* time spent sleeping or sedentary; breast and bottle feeding *Physiology-Related:* Rapid growth and weight gain; increasing proportion of body fat; high oxygen requirements (increased breathing rate); deficiencies in hepatic enzyme activity; immature immune system; more alkaline stomach; increases in extracellular fluid; renal function less than predicted by body surface area
3 to <6 months	*Behavior-Related:* Solid foods may be introduced into diet, especially toward the end of this stage; contact with surfaces increases; mouthing of hands and objects increases; more time spent in breathing zone close to floor *Physiology-Related:* Rapid growth and weight gain; increasing proportion of body fat; deficiencies in hepatic enzyme activity; immature immune system functions; increases in extracellular fluid; renal function less than predicted by body surface area
6 to <12 months	*Behavior-Related:* Food consumption expands; floor mobility increases (surface contact); children are increasingly likely to mouth nonfood items; children develop personal dust clouds *Physiology-Related:* Rapid growth and weight gain; body fat increases begin to moderate; deficiencies in hepatic enzyme activity; immature immune system; rapid decrease in extracellular fluid; can begin predicting renal function by body surface area
1 to <2 years	*Behavior-Related:* Full range of foods consumed; participation in increased play activities coupled with extreme curiosity and poor judgment; breast and bottle feeding cease; children walk upright, run, and climb; children occupy a wider variety of breathing zones and engage in more vigorous physical activities; frequency of mouthing hands and objects is high *Physiology-Related:* Some hepatic enzyme activities peak at a level exceeding that of adults; most immune system functions have matured; extracellular fluid becomes more consistently related to body size
2 to <3 years	*Behavior-Related:* Frequency of mouthing hands and objects begins to moderate; occupancy of outdoor spaces increases; children begin to wear adult-style clothing *Physiology-Related:* Hepatic enzyme activity level falls back to the adult range
3 to <6 years	*Behavior-Related:* Continued increases in the occupancy of outdoor spaces *Physiology-Related:* Entering a period of relatively stable weight gain and skeletal growth (as opposed to a period marked by growth spurts)
6 to <11 years	*Behavior-Related:* Decreased oral contact with hands and objects as well as decreased dermal contact with surfaces; children spend time in school environments and begin playing sports *Physiology-Related:* Period of relatively stable weight gain and growth but may be entering period of rapid reproductive and endocrine system changes (especially for females)
11 to <16 years	*Behavior-Related:* Smoking may begin; increased rate of food consumption; increased independence (more time out of home); workplace exposures can begin *Physiology-Related:* Rapid skeletal growth; rapid reproductive and endocrine system changes
16 to <18 years	*Behavior-Related:* High rate of food consumption; independent driving begins; expanded work opportunities *Physiology-Related:* Rapid skeletal growth (may see epiphyseal closure); rapid reproductive and endocrine system changes
18 to <21 years	*Behavior-Related:* High rate of food consumption; increased time in work environments; may move away from home environment *Physiology-Related:* Reproductive growth continues (especially for males); epiphyseal closure may take place

Appendix D table: Adapted from Summary Report of the Technical Workshop on Issues Associated with Considering Developmental Changes in Behavior and Anatomy when Assessing Exposure to Children. December 2000. EPA/630/R-00/005. [http://www.epa.gov/raf/publications/sum-report-wrkshp-development-changes-behavior.htm]; and Firestone et. al., 2007.; Firestone, Michael; Jacqueline Moya; Elaine Cohen-Hubal; Valerie Zartarian; and Jianpin Xue. Identifying Childhood Age Groups for Exposure Assessments and Monitoring. Risk Analysis, Volume 27, No. 3, 2007, page 701 – 714. See Table IV, page 705. [http://www.epa.gov/teach/docs/firestone%20etal%202007-age%20grouping.pdf]]