Consideration of Early Life Exposure to Chemical Carcinogens

Washington State Department of Ecology

Toxics Cleanup Program

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Contents

Introduction & Purpose **5**
Scientific Issues being Considered 5
Background Information 5
Environmental Regulatory Emphasis on Children 6
Washington Risk Policies 7

Issue 1: EPA Guidelines for Carcinogen Risk Assessment **9**
Background Information 9
Guiding Principles Used In the EPA 2005 Cancer Risk Assessment Guidance 10
MTCA Science Panel Considerations 11

Issue 2: Age Adjustments to Cancer Slope Factors for Carcinogens Acting by Mutagenic Mode of Action **12**
Lifestage Susceptibility and Cancer Risks to Children 12
Early-Life Stage Cancer Potency Adjustments 13
Other State Agencies Recognizing Children's Environmental Health 19
Questions and Issues Raised during U.S. EPA and Cal-EPA Review Process 20

Issue 3: Restricting Age Adjustments to Certain Carcinogens or all Carcinogens **22**
Application of Age Adjustment (Age Sensitivity) Factors 22
U.S. EPA 22
Cal-EPA 23

Issue 4: Sources of Uncertainty and Variability **24**
Uncertainty 24
Variability 24

Concluding Remarks **26**

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Considerations of Early Life Exposure to Chemical Carcinogens

Introduction & Purpose

This paper identifies issues relevant to the increased susceptibility of children from environmental exposures to carcinogens. These issues raise important questions as Ecology considers updates and revisions to the Model Toxics Control Act (MTCA) Cleanup Regulation. Ecology is posing a number of questions related to new scientific information and regulatory guidance being evaluated.

Scientific Issues being Considered

There has been a considerable amount of scientific information and regulatory guidance on child susceptibility to carcinogenic substances developed since 2001 when Ecology amended the MTCA Cleanup Regulation. The Department of Ecology has reviewed this information and believes it points to differences in patterns of exposure and cancer potencies based on differences in behavior, physiology, and anatomy between infants, children and adults.

Ecology is considering and analyzing a number of scientific and regulatory issues.

Issue 1: The U.S. Environmental Protection Agency (EPA) published new guidance, the Guidelines for Carcinogen Risk Assessment, in March 2005. Ecology is considering several revisions to the MTCA Cleanup Regulation 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: 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 Cleanup Regulation to incorporate methods for evaluating child exposure to carcinogens contained in this document. Is this guidance consistent with current scientific information on early life stage 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-lfe 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. Ecology plans

to review and, where appropriate, revise and update the MTCA Cleanup Regulation consistent with new scientific information and regulatory guidance.

In March 2005, EPA 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 (e.g., body weight), uptake characteristics (e.g., 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 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. The order, "Protection of Children from Environmental Health Risks and Safety Risks," 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]

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.

- EPA has a formal policy that directs all EPA programs to consider risks to infants and children consistently and explicitly as part of any risk assessment generated during its

[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

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 lifestages and subsequent outcomes that may not be expressed until later lifestages.[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 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 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 MTCA Cleanup Regulation includes policies and procedures for identifying and characterizing carcinogens. Ecology initially published these provisions in 1991. Although Ecology modified selected provisions in 2001, the current regulation largely reflects policies and procedures in the 1986 EPA cancer risk guidelines. Key features of the current MTCA Cleanup Regulation include:

- The definition of "carcinogen" reflects the terminology and policies in the 1986 EPA guidelines.

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[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.

- Cleanup levels are calculated using carcinogenic potency factors (cancer slope factors) published by EPA in the Integrated Risk Information System (IRIS) database.
- The MTCA Cleanup Regulation defines procedures for selecting cancer slope factors when values are not available in the IRIS database. This includes a hierarchy of information sources for cancer slope factors (such as the National Center for Environmental Assessment) that was added in 2001. The regulation also defines procedures for calculating cancer slope factors using the linearized multi-stage low dose extrapolation model and an animal to human scaling factors

The MTCA Cleanup Regulation does not reflect the recent advances in technical information and regulatory guidance. In particular, the risk-based policies and procedures in the MTCA Cleanup Regulation do not explicitly account for early life exposures to carcinogens with the carcinogenic response expressed later in life.

Issue 1: EPA Guidelines for Carcinogen Risk Assessment

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

Background Information

In 1983, The National Academy of Sciences' National Research Council (NRC) published Risk Assessment in the Federal Government: Managing the Process.[12] The publication of this book established the basis for defining the potential health effects that may result from exposure of individuals or populations to hazardous chemicals. The NRC supported the use of risk assessment as the regulatory tool or paradigm to be used by Federal regulatory agencies to evaluate the health effects (toxicity) and assess the risks from chemical exposures. Furthermore, the NRC also recommended that federal regulatory agencies establish guidelines to promote consistency and technical quality in risk assessments and that the risk assessment process should be a separate scientific effort from the risk management decisions.

As a result of the 1983 National Research Council publication, between 1986 and the early 1990's, EPA published risk assessment guidelines with a technical focus on five major areas:

- Carcinogenicity[13]
- Mutagenicity[14]
- Chemical mixtures[15]
- Developmental toxicants[16]
- Estimating exposures.[17]

[12] NRC (National Research Council). (1983) Risk Assessment in the Federal Government: Managing the Process. Committee on the Institutional Means for Assessment of Risks to Public Health, Commission on Life Sciences, NRC. Washington, DC: National Academy Press.

[13] U.S. EPA (U.S. Environmental Protection Agency). (1986) Guidelines for Carcinogen Risk Assessment. Federal Register 51 (185):33992-34003. Available at: http://epa.gov/ncea/raf/.

[14] U.S. EPA (U.S. Environmental Protection Agency). (1986) Guidelines for Carcinogen Risk Assessment. Federal Register 51 (185):34006-34012. Available at: http://epa.gov/ncea/raf/recorddisplay.cfm?deid=23160.

[15] U.S. EPA (U.S. Environmental Protection Agency). (1986) Guidelines for the Health Risk Assessment of Chemical Mixtures. Federal Register 51 (185):34014-34025. Available at: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=22567.

[16] U.S. EPA (U.S. Environmental Protection Agency). (1991) Guidelines for Developmental Toxicity Risk Assessment. Federal Register 56 (234):63798-63826. Available at: http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=23162.

[17] U.S. EPA (U.S. Environmental Protection Agency). (1992) Guidelines for Exposure Assessment. Federal Register 57 (104):22888-22938. Available at:http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=15263.

These U.S. EPA guidelines formed the basis for regulatory decision making to help protect the public from exposures to environmental contaminants.

Guiding Principles Used In the EPA 2005 Cancer Risk Assessment Guidance

EPA continues to publish regulatory risk assessment guidance to promote high technical quality, agency-wide consistency, and transparency in risk management decision making. With the advancement of knowledge regarding the biological processes of carcinogenicity and the continued need for regulatory guidance to reflect these advancements, in March 2005, EPA published the Guidelines for Carcinogen Risk Assessment. [18]

The major guiding principles that EPA employed for the revisions to the 1986 cancer risk assessment regulatory guidance was to be protective of public health and scientifically defensible. To be health protective, EPA noted that risk assessment practice should consider a range of susceptibilities among the human population. In addition, in the absence of complete knowledge or chemical-specific information by the scientific or regulatory communities, assumptions should be employed that reflect the risks to susceptible individuals.

To be scientifically sound, the EPA's 2005 Guidelines for Carcinogen Risk Assessment reflects a greater use of the increasing scientific understanding of the modes of action associated with the carcinogenic process. Several interrelated issues have been the focus of EPA's 2005 cancer guidelines and result in a set of guiding principles.

- Use of Default Options: Default exposure options are appropriate when scientific information about the effects or exposures of a substance is unavailable, limited, or of insufficient quality.
- Consideration of Modes of Action: The EPA's 2005 guidelines indicate that mode-of-action data, when available and of sufficient quality, may be useful in determining the carcinogenic potency of a chemical, its potential effects at low doses, whether findings in animals are relevant to human populations, and which populations or life-stages may be particularly susceptible.
- Fuller Characterization of Carcinogenic Potential: The EPA's 2005 guidelines describe a chemical's human carcinogenic potential as a weight-of-evidence narrative. This narrative summarizes the range of evidence and conditions associated with the risk-based conclusion about the agent's carcinogenic potential. For example, the carcinogenic hazard may be attributed to exposures during sensitive life-stages of development but not at other times during a person's life.
- Consideration of Differences in Susceptibility: The EPA's 2005 guidelines explicitly recognize that variation exists among people in their susceptibility to exposures to carcinogens. Some populations may experience increased susceptibility to carcinogens throughout their life, such as those who have inherited a predisposition to certain cancer types or a reduced capacity to repair genetic damage. The guidance also recognizes that during certain lifestages entire populations may experience increased susceptibility from

[18] Guidelines for Carcinogen Risk Assessment. U.S. Environmental Protection Agency, Risk Assessment Forum, 2005. EPA/630/P-03/001F. Located at: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=116283.

exposure to chemical carcinogens. Technical information in consideration of differences in susceptibility was sufficient that EPA published the Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens concurrent with the publication of the 2005 cancer risk assessment guidelines.

MTCA Science Panel Considerations

Ecology has carefully reviewed the EPA 2005 Guidelines for Carcinogen Risk Assessment and believes that the new cancer guidelines reasonably reflect the current state of knowledge to evaluate the toxicity and assess the risks from exposure to chemical carcinogens.

- Does the MTCA Science Panel agree with the guiding principles used by EPA in the development of new 2005 cancer risk assessment guidelines?
- Should Ecology consider additional information or other guiding principles in support of the MTCA Cleanup Regulation Update to evaluate the toxicity and assess the risks from exposure to chemical carcinogens?

Issue 2: Age Adjustments to Cancer Slope Factors for Carcinogens Acting by Mutagenic Mode of Action

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 Cleanup Regulation to incorporate methods for evaluating child exposure to carcinogens contained in this document. Is this guidance consistent with current scientific information on early life stage exposure to carcinogens with a mutagenic mode of action?

Lifestage 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 (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 (e.g., DNA breaks, crosslinks, adducts) or alterations resulting permantent changes to the DNA (e.g., 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 (e.g., endocrine disrupting) carcinogens early in life since the development of many organ system is under hormonal control (e.g., 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, 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)[19]; for Cal-EPA the age adjustment factors are termed Age Sensitivity Factors (ASFs)[20].

An expert panel workshop was held in 2000 by 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 [21] and then used to develop the associated EPA guidance for applying the early life-stage age groupings. [22]

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 Lifestages & Age Groups

Lifestage 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
	3 to < 6 years
	6 to < 11 years
Adolescent	11 to < 16 years
	16 to < 18 years
	18 to < 21 years

[19] 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.

[20] 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.

[21] 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.

[22] 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.

Derivation of Age Adjustment Factors

Brief descriptions are provided of the methodologies used by EPA and Cal-EPA to derive lifestage-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 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.[23]

Selection criteria was established for studies to be included in EPA's analysis to quantitatively evaluate the effect of lifestage 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.

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. Of those 18 chemicals, there were overlapping subsets of 11 chemicals involving repeated exposures during early postnatal and adult lifestages and 8 chemicals using acute exposures at different ages.

[23] 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.

Table 2. Chemicals having animal cancer study data available with early-life and adult exposures in the same experiment[24]	
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

For each of the studies, differences in susceptibility between early life and adult exposure were calculated as the estimated ratio of cancer potency from early life exposure over the cancer potency from adult exposure.

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

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

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 lifestages. 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 EPA

The 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 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[25]

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 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.

[25] 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.

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 type of studies evaluated by Cal-EPA are multi-lifestage exposure studies which have at least two groups of animals exposed during different lifestages of their development. These studies had one dose group exposed to a chemical only during the prenatal lifestage (from conception to birth), the postnatal lifestage (from birth to weaning), or the juvenile lifestage (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 life stage, either prenatal, postnatal, juvenile, or adult.

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 3). 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-lifestage exposure studies. Eighteen carcinogens were included in the postnatal multi-lifestage exposure studies. Five carcinogens were included in the juvenile multi-lifestage exposure studies.

Table 4: Carcinogens for Which Studies With Multi-Lifestage 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 lifestage 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 lifestage were taken into account in estimating cancer potency from a particular experiment.

The sensitivity of the different lifestages was quantitatively estimated by Cal-EPA from the ratio of cancer potency derived from an early lifestage exposure experiement(s) compared to that derived from an experiment(s) conducted from adult animals. The potency distributions for individual lifestage exposures were used to derive the ratios. The lifestage potency ratios characterize the susceptiblilty of early lifestages 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 lifestages.

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 lifestage 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 lifestage potency ratio (addresses the susceptibility of early lifestages relative to adult of the 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 **California**, other state environmental agencies have adopted policies and procedures to account for these differences in exposures and cancer potencies including:

- In March 2007, **Oregon** Department of Environmental Quality (Oregon DEQ) provided guidance that requires the consideration of early-life exposure for all human health risks assessments for sites where childhood exposure is likely. Oregon DEQ requires consideration of early-life exposure for carcinogens acting by a mutagenic mode of action.[26]
- The **Michigan** Department of Environmental Quality, Toxics Steering Group, agreed that the April 2005 EPA Supplemental Guidance for Assessing Susceptibility From Early-Life Exposure should be used to better account for children's differential risks.[27]
- Proposed revisions to **Connecticut's** remediation standards are designed to account for increased exposure and susceptibility of children to carcinogens.[28]
- 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.[29]
- Similar to the Washington Department of Ecology, the **Massachusetts** Department of Environmental Protection is currently evaluating the incorporation of 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.[30]

According to the National Conference of State Legislators (a bipartisan organization that serves legislators and staff 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 are 124 bills pending in 10 different states and 32 bills enacted in 18 different states related to children's environmental health.[31]

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[26] State of Oregon, Department of Environmental Quality Memorandum. March 14, 2007. Subject: Incorporation of Early-Life Exposure in Human Health Risk Assessments. To: Interested Parties; From: DEQ Toxicology Workgroup. Located at: http://www.deq.state.or.us/lq/rbdm.htm

[27] 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

[28] 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

[29] 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.

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

[31] 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

Questions and Issues Raised during U.S. EPA and Cal-EPA Review Process

Prior to the publication of their respective guidance documents, both the U.S. EPA and Cal-EPA responded to comments from the public and from their science advisory panels.[32 & 33]

The text box below summarizes common themes that emerged during the review processes.

Themes and Concerns Related to Early – Life Stage Evaluations

- Chemical risk assessments should use the best available scientific information.
- 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 should they also be 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?
- Is there sufficient information to support early-life stage age adjustments factors based on age groupings to represent critical periods of human growth and development?

Both the U.S. EPA and Cal-EPA addressed a large range of issues and concerns and conducted extensive review of the scientific literature. There is a single substantial point of difference between the Cal-EPA's recommended policies and procedures and those of the U.S. EPA regarding evaluating and assessing cancer susceptibility from early-life exposure to carcinogens.

U.S. EPA and Cal-EPA disagree on whether to apply the age dependent adjustment factors for all carcinogens, (the Cal-EPA approach), or only to carcinogens with a hypothesized mutagenic mode of action (the U.S. EPA approach).

[32] Review of EPA's Draft Supplemental Guidance for Assessing Cancer Susceptibility 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]

[33] 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] This document has been provided for the MTCA science panel discussions on November 23, 2009.

Based on informed science, the U.S. EPA Science Advisory Board agrees with the Cal-EPA approach that early-life sensitivity to carcinogen exposure should be incorporated when estimating lifetime cancer risks.

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

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 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 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."* [34]

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." [35]

Ecology consulted with 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 on

[34] 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 for 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

[35] 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.

carcinogenic information or toxicokinetic data that indicates non-mutagens would be systematically different from mutagens for their carcinogenic response.[36]

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 lifestage exposure experiment were accounted for in estimating cancer potency by Cal-EPA.
- The total cancer risk associated with exposure during a given lifestage was evaluated when comparing cancer potencies associated with early life versus adults exposures; (EPA compared the risk for cancers at one single site in each lifestage)
- 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.[37] 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-lifestage potentially more susceptible than those exposed during adulthood equally applies to exposures to non-mutagenic carcinogens (e.g., 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.

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

[37] 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.[38]

Issue 4: Sources of Uncertainty and Variability

4. What sources of scientific uncertainty and variability should Ecology consider when evaluating toxicity of human carcinogens?

Ecology acknowledges the need to recognize both uncertainty and variability in evaluating the toxicity and assessing the risks from exposures to chemical carcinogens. The uncertainty and variability may lead to either an underestimation or an overestimation of potential health threats and risks.

Uncertainty

Uncertainties in the process of risk assessment to evaluate the toxicity of chemicals may be associated with some of the following:

- Lack of data or information related to a chemical's toxicity
- Extrapolation of toxicity data in animals to humans
- Lack of epidemiologic information, human data
- Type of animal models used to evaluate toxicity
- Interactive effects of different chemicals
- Metric used to evaluate dose-response information
- Type of model used to extrapolate to zero to estimate carcinogenic potency.

Generally speaking, these uncertainties (or unknowns) can be reduced with further scientific investigation.

Variability

In addition to uncertainty, there is a range or "variability" that exists in the human population. This variability may be among individuals and different populations. Types of variability may be attributed to different patterns of exposure, susceptibility to toxic insults related to age, lifestyle, genetic background, sex, ethnicity, and other factors. For example, there is variability in exposure factors related to body weight, body surface area exposed, and susceptibility to chemical toxicants.

[38] 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. 2008

Scientific studies with representative individuals and a large enough sample size can help characterize variability. However, variability can be characterized but not reduced or eliminated with further scientific study.

Cal-EPA examined the biological variability in cancer potency responses from early life exposure compared to that from later-life exposure. They compared the quotient of the cancer potency distribution for those animals exposed in early life and those animals exposed in later life for 14 selected carcinogens. This ratio of distribution for multi-lifestage exposure studies is termed the lifestage potency (LP) ratio distribution.[39] These ratios are derived as distributions, representing the uncertainty in cancer potency and variability in sensitivity of the different animal strains on which these potencies are based. The LP ratio characterizes the inherent differences in susceptibility of the young animals compared to older animals exposed to the carcinogen. An LP ratio distribution that primarily lies above the value of 1.0 indicates early life exposure to a carcinogen result in a stronger tumor response compared to adult exposure. For the carcinogens examined, taking into account both the inherent sensitivity of prenatal animals and the time since exposure to develop cancer, Cal-EPA found that there is substantial susceptibility early in life.[40]

[39] In Utero and Early Life Susceptibility to Carcinogens: The Derivation of Age-at-Exposure Sensitivity Measures. May 2009, page 28-40.

[40] IBID, See Appendix J, page 39, Figure 8.

Concluding Remarks

Following the recommendations of the National Academy of Sciences' National Research Council, state and federal environmental regulatory and public health agencies are adopting policies and procedures that recognize early-life stage susceptibilities from exposure to carcinogens. These risk-based policies and procedures are in recognition of several important factors:

- Distinguishing characteristics of children may confer disproportionate exposures and risk to carcinogens.
- The current cancer risk assessment methodology does not adequately account for increased susceptibility of childhood environmental exposures.
- Exposure to a carcinogen early in life may result in greater lifetime risk of cancer.
- State and federal agencies have made the policy decision to weight risk, using age dependent adjustment factors, when exposure occurs during childhood to help account for increased susceptibility of childhood environmental exposures.

As part of the MTCA Cleanup Regulation update, and similar to other state environmental agencies, Ecology is in the process of evaluating policies and procedures that recognize early-life stage susceptibilities from exposure to carcinogens.

Ecology welcomes feedback, opinions, and perspectives related to the science behind these issues.