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# Interim Guidance on Human Health Risk Assessment for Short-Term Exposure to Carcinogens at Contaminated Sites



Federal  
Contaminated  
Sites Risk  
Assessment  
in Canada

Canada 

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# FEDERAL CONTAMINATED SITES RISK ASSESSMENT IN CANADA

Interim Guidance on

Human Health Risk Assessment for  
Short-Term Exposure to Carcinogens  
at Contaminated Sites

2013

Prepared by:

Contaminated Sites Division

Safe Environments Directorate



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## PREFACE

The Federal Contaminated Sites Action Plan (FCSAP) is a program of the Government of Canada designed to achieve improved and continuing federal environmental stewardship as it relates to contaminated sites located on federally owned or operated properties. Guidance documents on human health risk assessment (HHRA) prepared by the Contaminated Sites Division of Health Canada in support of the FCSAP are available on our website and may also be obtained by contacting the Contaminated Sites Division at [cs-sc@hc-sc.gc.ca](mailto:cs-sc@hc-sc.gc.ca).

This interim guidance document provides additional direction for custodial departments with respect to amortization of short-term exposure to carcinogens at contaminated sites. It is of particular importance at remote sites or sites that are accessed infrequently. The guidance is intended to be advisory in nature and will be updated periodically on the basis of revisions to current expertise, applicable standards and recommendations received from stakeholders. Readers are advised to consult with Health Canada, Contaminated Sites Division, to confirm that they are using the most recent version available on the Health Canada website and that the use of HHRAs is reflective of current and best practices. This document is not to be considered a substitute for the guidance of a qualified professional practitioner.

Work and opinions from various consultants, academics and governmental agencies were used to create this guidance. In particular, Angela Li-Muller, Margaret Yole, Norm Healey and Sanya Petrovic of Health Canada are recognized for their contribution.

Health Canada requests that any questions, comments, criticisms, suggested additions or revisions to the document be directed to the following: Contaminated Sites Division, Safe Environments Directorate, Health Canada, 269 Laurier Avenue West, 4<sup>th</sup> floor, Address Locator: 4904A, Ottawa, ON K1A 0K9. Email: [cs-sc@hc-sc.gc.ca](mailto:cs-sc@hc-sc.gc.ca).

See also: [www.hc-sc.gc.ca/ewh-semt/contamsite/index-eng.php](http://www.hc-sc.gc.ca/ewh-semt/contamsite/index-eng.php).

## ABBREVIATIONS AND ACRONYMS

A-D	Armitage-Doll
ADAF	age-dependent adjustment factors
AF	absorption factor
ASF	age sensitivity factor
BHT	butylated hydroxytoluene
BW	body weight
C	concentration
CalEPA	California Environmental Protection Agency
CSD	Contaminated Site Division
DES	diethylstilbesterol
DMBA	dimethylbenzanthracene
DNA	deoxyribonucleic acid
DQRA	detailed quantitative risk assessment
ED	exposure duration
ED <sub>01</sub>	maximum likelihood estimate of the dose corresponding to a 1% additional cancer risk
ER	exposure rate
FCSAP	Federal Contaminated Sites Action Plan
HC	Health Canada
HHRA	human health risk assessment
ILCR	incremental lifetime cancer risk
IR	intake rate
LADD	lifetime average daily dose
LMS	linearized multistage
LOAEL	lowest observed adverse effect level
MVK	Moolgavkar-Venzon-Knudson
NOAEL	no observed adverse effect level
PAHs	polycyclic aromatic hydrocarbons
PBBs	polybrominated biphenyls
PBPK	physiologically based pharmacokinetic
PQRA	preliminary quantitative risk assessment
SF	slope factor
TC	tolerable concentration
TDI	tolerable daily intake
TRV	toxicological reference value
UR	unit risk
US EPA	United States Environmental Protection Agency

## EXECUTIVE SUMMARY

This document provides guidance for application at federal contaminated sites funded under the Federal Contaminated Sites Action Plan (FCSAP). It is considered to be interim and is based on an assessment of the current scientific literature. The document does not represent the opinion of Health Canada outside the application of federal contaminated sites funded under the FCSAP.

The current approach to evaluating health risks associated with human exposure to carcinogens at contaminated sites focuses on incremental lifetime cancer risks. The approach to cancer risk assessment varies according to the mode of action at the tumour site in question. Unless there is evidence to support a threshold mode of action, the current approach assumes a linear dose-response relationship at low doses (i.e. non-threshold). The incremental lifetime cancer risk (ILCR) is calculated as a product of the lifetime daily dose (or concentration) and the toxicological reference value (TRV), expressed as cancer slope factor (or inhalation unit risk).

A threshold approach can be applied when there are sufficient data to ascertain the mode of action at the tumour site in question and to conclude that the dose-response relationship is not linear at low doses. For these carcinogenic effects, the TRVs are expressed as tolerable daily intakes (TDIs) or concentrations (TCs), the intakes or concentrations to which it is believed that a person can be exposed daily over a lifetime without deleterious effects. Human exposure is compared with these TRVs, where appropriate, to determine health risks.

Characterization of human cancer risks usually makes use of TRVs that have been derived from epidemiological or toxicological studies with comparable exposure patterns. TRVs for carcinogens are often based on the results of animal studies in which the animals were exposed on a daily basis throughout their adult lifespan. Exposures at contaminated sites may mirror these exposure patterns, but in some circumstances exposures may occur over a period of time much shorter than the lifetime of the exposed individual. In a short-term exposure scenario, short-term exceedance (or excursion) above chronic average daily exposure could occur as a result of variation in intake rates or daily fluctuation in chemical concentrations in environmental media. As a result, the health risks of short-term exposure often need to be addressed.

For contaminated site risk assessments, the current practice of characterizing ILCR associated with less-than-lifetime exposures to carcinogens that act via a non-threshold mode of action involves averaging the short period of exposure over a lifetime to calculate the lifetime average daily dose (LADD). Several issues regarding this practice of averaging the exposure have been raised:

- There is a potential for underestimating cancer risks with the practice of time-averaging of exposures (LADD).

- Variability in sensitivity among different lifestages may not be fully considered.

In addition, depending on the magnitude of exposure, carcinogenic agents may elicit other, chronic and short-term non-cancer health effects as a result of short-term exposures. At present, these effects are often not evaluated.

The Contaminated Sites Division (CSD) will continue to review information related to risk assessments for carcinogenic agents, including short-term exposure and dose averaging.

### *Cancer Risk Assessment: Non-Threshold Carcinogenic Effects*

A literature review was conducted to evaluate whether averaging short-term exposure over a lifetime would be adequate to estimate cancer risk using cancer slope factors derived from chronic animal studies. Both theoretical studies using mathematical models of carcinogenesis and empirical studies involving exposure during discrete age windows suggest that exposures in early lifestages are usually associated with a higher risk of carcinogens acting through a mutagenic mode of action. It was concluded that application of age-dependent adjustment factors to the cancer slope factor with exposure averaged over a lifetime can provide a generally conservative estimate of lifetime cancer risks. As an interim measure, the United States Environmental Protection Agency (EPA) approach has been adopted as a default recommendation for contaminated site risk assessments.

The ILCR can be estimated by summing the risk from each discrete exposure period. For non-threshold carcinogens acting through a mutagenic mode of action, it is recommended that age-dependent adjustment factors (ADAFs) be applied to the cancer slope factor (or inhalation unit risk) with exposure averaged over a lifetime to account for the sensitivity of the age-specific exposure period. We have developed default ADAFs by adjusting the US EPA's ADAFs to be consistent with the age groups recommended by CSD. These default factors can be applied when age-specific cancer slope factors (or inhalation unit risks) or chemical-specific data are not available.

When exposure periods do not match the CSD's age groupings, CSD recommends that the US EPA's ADAFs be applied. For example, if exposure occurs only between 7 months and less than 2 years of age, the adjustment factor of 10 applies. Likewise, if exposure occurs only between 12 and < 16 years of age, the ADAF of 3 applies. When chemical-specific data are available for a susceptible lifestage, these data can be used directly to evaluate risks for the chemical and the lifestage on a case-by-case basis.

## Recommended interim adjusted age-dependent adjustment factors (ADAFs) for cancer risk assessment at contaminated sites for carcinogenic effects via a mutagenic mode of action

Lifestage	Age	Adjusted age-dependent adjustment factor (ADAF) <sup>a</sup>
Infant	0–6 months	10
Toddler	7 months–4 years	5 <sup>b</sup>
Child	5–11 years	3
Teenager	12–19 years	2 <sup>c</sup>
Adult	20+	1

<sup>a</sup> US EPA (2005 a, b), except as noted.

<sup>b</sup>  $ADAF_{7\text{ mo-4 yr}} = (ADAF_{0- < 2} * D_{7\text{ mo-1}} / D_{7\text{ mo-4}}) + (ADAF_{2-4} * D_{2-4} / D_{7\text{ mo-4}}) = 10 * 1.5/4.5 + 3 * 3/4.5 = 5$ , and  $D_i$  = exposure duration in years

<sup>c</sup>  $ADAF_{12-19} = (ADAF_{12- < 16} * D_{12-15} / D_{12-19}) + (ADAF_{16+} * D_{16-19} / D_{12-19}) = 3 * 4/8 + 1 * 4/8 = 2$ , and  $D_i$  = exposure duration in years

When the mode of action is unknown or the burden of proof for a threshold mode of action has not been met, CSD recommends a non-threshold approach to cancer risk estimation. If chemical-specific data are available on quantitative differences between early lifestages and adults, an analysis of the differences could be used to adjust risk estimates for early life exposures. Otherwise, CSD does not recommend extending the default age-dependent potency adjustment factors to these carcinogenic effects. This position would be analogous to recommending a default ADAF of 1 for all lifestages.

### *Cancer Risk Assessment: Threshold Carcinogenic Effects*

At this time, the CSD does not recommend a default age-specific adjustment for carcinogenic effects determined to have a non-linear dose-response relationship (i.e. threshold) at low doses. Adjustment can be made on a chemical-specific basis if supported by experimental data. These substances would be included in an HHRA using a TDI (or a TC in the case of inhalation exposure).

The CSD recommends that dose averaging for short-term exposure for these types of carcinogenic effects be performed in the same way as for substances with threshold non-carcinogenic effects. It is important that dose averaging should not underestimate the potential for threshold carcinogenic effects. Without a sound basis for doing so (i.e. it cannot be a default assumption), the human health

risk assessor should not simply mathematically spread out a short-term dose over a longer period and conclude that the short-term dose is toxicologically equivalent to a lower dose over the long period. Instead, exposure should be averaged over the total actual exposure period and compared with the appropriate TRV. A scientific rationale is required to support any proposed amortization (dose averaging beyond actual exposure period) to ensure that short-term risks are not underestimated. This analysis needs to be done on a chemical-specific basis.

### *Assessment of Potential Non-Cancer Health Effects from Short-Term Exposure*

For short-term exposure, carcinogenic agents may elicit other, chronic and short-term non-cancer health effects, depending on the magnitude of exposure. Short-term effects can be evaluated for potential critical receptors/lifestages<sup>1</sup> using short-term TRVs where available (either from other regulatory agencies or derived from literature values as per the Health Canada, 2010, detailed quantitative risk assessment [DQRA] guidance) and when applicable to the exposure scenarios. If short-term TRVs are not available, such evaluation can be conducted on the basis of relevant dose-response information from toxicity studies. It is also important to consider whether the short-term exposure might elicit early biological key events that might progress to health effects at a later date.

<sup>1</sup> Including relevant receptors/lifestages with the highest exposure and receptors/lifestages associated with specific sensitivity to the toxicity of the contaminants.

## 1.0 INTRODUCTION

### 1.1 *Current Cancer Risk Assessment Approach*

Health Canada's Contaminated Sites Division (CSD) has a current risk assessment approach for carcinogenic effects that assumes a linear dose-response relationship at low doses (non-threshold) unless there are adequate data to ascertain a mode of action that is consistent with a non-linear dose-response relationship at low doses (i.e. threshold). This approach is particularly relevant for agents that are mutagenic<sup>2</sup> and DNA reactive. The incremental lifetime cancer risk is calculated as a product of the lifetime daily dose and cancer slope factor.

A threshold approach can be applied when there are sufficient data to ascertain the mode of action at the tumour site in question and to conclude that the dose-response relationship is not linear at low doses. Such a carcinogenic agent usually has not been shown to demonstrate mutagenic or other properties consistent with linearity at low doses. Endocrine disruption, cell proliferation, cytotoxicity and receptor-binding are some examples of a non-linear mode of action. For these carcinogenic effects, the CSD risk assessment approach assumes a non-linear dose-response relationship at low doses. The toxicological reference value (TRV) is derived by applying an uncertainty factor to a benchmark dose or benchmark concentration (if available)—a NOAEL (no observed adverse effect level) or a LOAEL (lowest observed adverse effect level)—as appropriate to establish a tolerable daily intake (TDI) or concentration (TC), i.e. the intake or concentration to which it is believed that a person can be exposed daily over a lifetime without deleterious effects.

In many cases, non-carcinogenic effects rather than carcinogenicity may be the main determinant of health risk from long-term exposure to the threshold carcinogenic agent. For example, the developmental effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin occur at lower exposure levels than those required for carcinogenicity and have been used to establish the TRV.

### 1.2 *Issues Related to Less-Than-Lifetime Exposure to Carcinogens at Contaminated Sites*

Short-term exposure to carcinogens at contaminated sites may be associated with activities that occur over a relatively short period of time, such as seasonal activities like camping, occasional visits to a remote site and certain occupational activities, e.g. construction and underground service installation. As a result, short-term health risks need to be addressed.

The significance of exposure to contaminants is best characterized by comparison with TRVs derived from epidemiological or toxicological studies with comparable exposure patterns (i.e. short-term exposure compared with TRVs derived from a short-term study). Otherwise, significant uncertainty could be introduced into risk characterization.

TRVs for carcinogens are often based on the results of animal studies in which the animals were exposed on a daily basis throughout their adult lifespan. Exposures to human receptors at a contaminated site may mirror this pattern of exposure, but more often exposure occurs for only a portion of the lifetime or may be intermittent. Exposures at a contaminated site may occur during childhood or in utero, lifestages not represented in standard cancer bioassays.

The current practice of characterizing incremental lifetime cancer risks (ILCR) associated with less-than-lifetime exposures to non-threshold carcinogens involves averaging the short period of exposure over a lifetime to calculate the lifetime average daily dose (LADD). The following issues related to dose averaging (sometimes referred to as dose amortization) have been raised when exposures occur over a short time frame:

1. There is a potential for underestimating cancer risks with the calculation of a LADD associated with a short exposure period.
2. The possibility of acute/subchronic non-cancer effects due to elevated exposures has not been considered and may be relevant when the exposure is elevated above the LADD over a subchronic period. For example, the physiological response will be different following a large short-term exposure as compared with the same exposure averaged over a longer period.
3. Variability in sensitivity among different lifestages may not have been fully considered. For example, the prenatal and neonatal periods, childhood, adolescence, and peri-menopausal and senior lifestages, as well as genetic predisposition, are currently not included in standard adult animal bioassays for deriving estimates of cancer potency.

This document provides a background discussion on each of these issues and presents interim guidance and supporting rationales.

<sup>2</sup> A carcinogen acts via a mutagenic mode of action if the carcinogen or its metabolite is DNA-reactive or has the ability to bind to the DNA. Mutagenicity is "the induction of permanent, transmissible changes in the amount, chemical properties or structures of the genetic material. In most cases, mutation involves changes in DNA structure that either have no effect or cause harm" (USEPA, 2005b; Schoeny, 2011).

### 1.3 Practice of Dose Averaging

Dose averaging refers to the practice of time averaging a short period of exposure or several intermittent short-duration exposure(s) over a longer duration. This practice is also referred to as exposure amortization. It assumes toxicity to be linearly proportional to the magnitude and duration of exposure. For example, it assumes an exposure of 365 µg/kg bw-day for 1 day, 36.5 µg/kg bw-day for 10 days and 1 µg/kg bw-day for 365 days to be toxicologically equivalent, which could be untrue. The risk for the shorter-term exposure could be underestimated. With this practice, daily exposures that exceed the maximum chronic acceptable daily dose (either a TDI or a risk-specific dose) may be incorrectly considered acceptable because they occur for only a short period of time. In the case of threshold carcinogens, this practice raises questions about the magnitude by which the TDI can be exceeded and for what duration before unacceptable chronic health risks (including carcinogenicity) are possible or expected. For non-threshold carcinogens, the practice raises the question of whether a high dose over a short period results in the same lifetime cancer risk as the same total dose over a lifetime. Also at issue is whether the short-term exposure could elicit adverse acute/subchronic non-carcinogenic health effects.

The answers to these questions, in part, depend on the following:

- when (at what lifestage) the excess exposure is expected to occur;
- whether there are any specific sensitivities associated with that lifestage; and
- whether these sensitivities have been accounted for (perhaps through application of uncertainty factors) in the TRV.

## 2.0 DOSE AVERAGING FOR NON-THRESHOLD CARCINOGENIC EFFECTS

The current practice of characterizing incremental cancer risks associated with less-than-lifetime exposures involves averaging the short period of exposure over a lifetime to calculate the LADD. This practice assumes that the overall incremental cancer risk is a function of the total dose received and is independent of the exposure pattern: a high dose of a carcinogen received over a short period is assumed to be equivalent to the corresponding total dose spread over a lifetime (US EPA, 1986). However, this practice is not based on firm scientific evidence or principles (Hrudey, 1998), and the US EPA (1986) has acknowledged that the approach is fraught with uncertainty; it recommends that risk assessments include a qualitative discussion of the uncertainty of this assumption.

Various groups of scientists have expressed concern that the LADD approach could underestimate cancer risk (Kodell et al., 1987, Chen et al., 1988; Murdoch et al., 1992; US EPA, 2005a; Halmes et al., 2000); the summary of some of these studies is presented in Table 2. In addition, the age at which short-term exposure occurs could influence cancer risk, as different lifestages may vary in susceptibility (Drew et al., 1983; Crump and Howe, 1984; Ginsberg, 2003; US EPA, 2005a, 2005b; Hattis et al., 2004, 2005).

The uncertainty of the practice was identified as an issue “under review” in Health Canada’s (2004) guidance on Human Health Preliminary Quantitative Risk Assessment for contaminated sites. Since that publication, Health Canada’s CSD has commissioned a series of contractor reports from consulting and academic experts (Brand, 2004; GlobalTox International Consultants, 2005; Wilson Scientific Consulting Inc., 2006; Orr, 2007; Al-Zoughool and Krewski, 2008) to aid in the decision-making on this issue.

**Table 2.1 Summary of modelling studies that compare cancer risks from short-term exposure with those from lifetime-equivalent exposure (extent of under/overestimation reported quantitatively for short-term adult exposure only)**

Reference	Study type	Qualitative assessment	Range of most likely predicted LADD underestimate to overestimate of risk	Maximum predicted underestimate (overestimate) of risk
Murdoch et al., 1992	Theoretical modelling for 30-day exposures of astronauts aged 25 to 45 to hypothetical carcinogens inside the space station. Both A-D <sup>a</sup> multistage and MVK <sup>b</sup> models were used.	LADD may underestimate or overestimate risks.	-2 to +6 fold (A-D multistage model); -2 to +7 fold (MVK model)	-2 (+33) fold (A-D multistage model); -1.4 (+63) fold (MVK model)
Kodell et al., 1987	The A-D multistage model was used to model intermittent exposure to a hypothetical carcinogen starting at age 0, 10, 20 and 50 for 1, 10 and 20 years. The ratio of excess risk for intermittent dosing relative to predicted excess risk based on LADD was calculated.	LADD underestimates risk maximally when the number of cancer stages is assumed to be 6, the 1 <sup>st</sup> stage is dose-dependent and exposure occurs during years 1–10 of life.	-3 to +14 fold	-3 (> +10 <sup>5</sup> ) fold
Chen et al., 1988	The MVK model was used to calculate the ratio of excess risk for short-term exposure to a hypothetical carcinogen to predicted excess risk associated with underlying assumptions of LADD, with various input parameters, including duration of exposure and start time of exposure.	LADD underestimates risk maximally with early-stage carcinogen and exposure early in life.	-2 to +13 fold (initiator); -4.5 to +13 fold (completer); -9 to +9 fold (promoter)	-2 (> +100) fold (initiator); -5 (> +25) fold (completer); -77 (+100) fold (promoter)

<sup>a</sup> Armitage-Doll<sup>b</sup> Moolgavkar-Venzon-Knudson

## 2.1 Dose Averaging for Less-Than-Lifetime Adult-Only Exposures

The issue of dose averaging can be confounded by the potential for varied susceptibility among different lifestages. The TRV developed from studies involving adult-only exposure (e.g. occupational studies) may be inadequate to account for earlier sensitive lifestages, especially when short-duration, high-magnitude exposure is experienced during these sensitive time windows. For this reason, less-than-lifetime exposure occurring only during the adult lifestage is addressed first. In this case, the only issue leading to the potential underestimate of health risk is assumed to be the mathematical manipulation of the level of exposure. For example, daily occupational exposures occurring 5 days per week for 48–52 weeks per year are amortized to the equivalent daily dose over 7 days per week for 52 weeks per year (resulting in a lower calculated daily exposure). Amortization of this magnitude is common, as TRVs are often derived from epidemiological studies based in occupational environments. Similarly, animals are dosed 5 days per week in some toxicity studies.

Two general lines of inquiry have been explored to determine the extent to which time averaging may over or underestimate cancer risks in adult-only exposures:

1. Evidence from animal bioassays or epidemiological studies in which the cancer risks estimated from short-term exposures are compared with those derived from adult lifetime exposures.
2. Comparison of the cancer risk estimates from short-term exposures with those derived for lifetime exposures at the LADD-equivalent dose using generally accepted mathematical models of carcinogenesis.

### 2.1.1 Dose Averaging Implications from Adult Animal Bioassays

Standard carcinogenicity bioassays involve near-lifetime exposures; however, exposures of very limited duration may also result in tumour formation. A literature review by Calabrese and Blain (1999) found 426 chemicals from a broad range of chemical classes that could induce cancer after a single administration in a large number of animal models. Most of these chemicals, if not all, were found to be genotoxic. Thirty nine percent caused more tumours, 22% caused fewer tumours, and the remaining 39% showed similar tumourigenic responses when the carcinogen was administered as a single dose as compared with the same dose fractionated over a lifetime. However, Calabrese and Blain (1999) and others (Ginsberg, 2003) did not consider varied lifestage susceptibility when analyzing the available data, which involved a single exposure at different lifestages (i.e. fetal, neonatal).

Stop-exposure studies (summarized in Table 2.2) illustrate the influence of exposure schedule and duration on cancer risk. Exposures were stopped after only a portion of the animal's lifespan, and the animals were observed long enough to measure tumour development.

**Table 2.2 Summary of studies comparing cancer risks from short-term (adult-only) exposure with those from lifetime-equivalent exposure (with same total dose)<sup>a</sup>**

Reference	Study type	Qualitative assessment	Range of most likely predicted LADD underestimate to overestimate of risk	Maximum predicted underestimate (overestimate) of risk
<b>Animal experiments</b>				
Halmes et al., 2000	Animal stop-exposure—data from 11 National Toxicology Program studies (adult animals—male rats or mice). Cancer potency was estimated using 2-year continuous bioassay data with or without inclusion of stop-exposure data.	Tumour responses in the stop-exposure experiment were underpredicted by continuous exposure data at 34/59 tumour sites for 6/11 chemicals, and overpredicted at 2/59 tumour sites for 2/11 chemicals. Prediction was accurate for 26/59 tumour sites for 9/11 chemicals.	Undefined	Undefined
		Inclusion of stop-exposure data in ED <sub>01</sub> <sup>b</sup> estimation (as compared with using continuous bioassay data alone) led to a decrease for 63% of the chemical/tumour/site combinations and an increase for 17% of the chemical/site combinations, mostly within one order of magnitude. 15% (of all tumour sites examined) showed a greater than 10-fold decrease (greater risk or potency) in ED <sub>01</sub> , implying a higher risk with shorter exposure.	Undefined	Undefined
		The “equivalent averaging times” <sup>c</sup> for the stop-exposures were generally longer than the actual exposure durations but less than 104 weeks for 12 of the 14 dose groups for which this comparison was made. The median “equivalent averaging time” for all the groups was 62 weeks, indicating that averaging stop-exposure duration over a lifetime (LADD) would underestimate the risk by a median factor of 2.	–5 to +2 fold	–5 (+2) fold

Table 2.2 – cont'd →

Reference	Study type	Qualitative assessment	Range of most likely predicted LADD underestimate to overestimate of risk	Maximum predicted underestimate (overestimate) of risk
Drew et al., 1983	Animals exposed to constant concentrations of vinyl chloride (adult animals—rats, 2 strains of mice, hamsters) by inhalation. Animal age at the start of exposure and exposure duration were varied among different exposure groups.	For most of the animal species studied, exposure from months 2–8 of life produced higher tumour frequency than exposure at later lifestages for the same duration (8–14, 14–20 or 20–26 months of age), possibly because animals died before a potential tumour could be expressed in the latter groups.	Undefined	Undefined
Hattis et al., 2004	Animals—rats and mice exposed to four types of ionizing radiation at different stages of life	On the basis of a total of 138 group tumour incidence observations, dosage delivered to older animals (6–12 or 19–21 months old) appeared to be 3 fold less effective than a similar dosage delivered to young adult animals (3–3.5 months), suggesting greater sensitivity during early adulthood.	Undefined	Undefined
<b>Epidemiological studies</b>				
Hauptmann et al., 2000	Case-control study of lung cancer and smoking in adults (4300 cases). The effect of smoking pattern on lung cancer risk was examined using a linear model taking into consideration that different exposure periods vary in their contribution to the overall cancer risk.	The number of cigarettes smoked within 5–15 years prior to patient interview strongly determined lung cancer risk; the number smoked more than 20 years earlier contributed minimally to risk. The pattern corresponds to an observed decrease in risk corresponding to the time since smoking cessation. Authors concluded that use of cumulative or average dose may not be appropriate for estimating lung cancer risk.	Undefined	Undefined
Hauptmann et al., 2002	Pooled data from two German case-control studies (2652 cases) on asbestos and lung cancer were assessed in terms of various exposure metrics.	The results suggested that cancer risk increased for 5–15 years after exposure and then declined. Other studies have indicated a 20–40 year latency period for asbestos-induced lung cancer.  Dose averaging over a lifetime would underestimate the risk for people whose remaining lifespan is greater than the latency period and would overestimate the risk for people whose remaining lifespan is shorter than the latency period.	Undefined	Undefined

Table 2.2 – cont'd →

Reference	Study type	Qualitative assessment	Range of most likely predicted LADD underestimate to overestimate of risk	Maximum predicted underestimate (overestimate) of risk
Elwood et al., 1985; Elwood, 1992	Histories of exposure to sun of 595 patients with malignant melanoma in Western Canada were examined in a case-control study.	<p>Significant increase in risk was correlated with summer vacation and recreational activities with intense sun exposure. A moderate amount of total occupational exposure (likely from intermittent seasonal exposure) increased the risk; further increased exposure (&gt; 200 whole body equivalent hours of exposure per season associated with long continuous exposure) had no effect or resulted in decreased risk (for men).</p> <p>At the same total sun exposure, the relative risk of melanoma from short-term intermittent recreational exposure exceeded long-term occupational exposure by up to 2 fold.</p>	+1 to -2 fold	-2(+1)

<sup>a</sup> Adapted from Tables 4.5-1 and 4.5-2 in Orr (2007); edited to exclude studies in which juvenile exposures were compared with adult exposures.

<sup>b</sup> ED<sub>01</sub> is the maximum likelihood estimate of the dose corresponding to a 1% additional cancer risk.

<sup>c</sup> Equivalent averaging time is the length of time over which stop-exposure doses have to be averaged so that the observed response falls exactly on the fitted dose-response curve developed from the continuous exposure (i.e. 104 weeks) data.

Halmes et al. (2000) evaluated cancer data from 12 similar United States National Toxicology Program animal bioassays in which both chronic lifetime and stop-exposure dosing protocols (using male rats except for 1,3-butadiene, to which male mice were exposed) were followed. The Weibull Model was fitted first to the chronic data only and then to the combined chronic and stop-exposure data adjusted to average lifetime exposure. Tumours developed following exposure to 11 chemicals (acting through different modes of action), some at multiple sites, totalling 59 chemical/site combinations. The same response rate was observed for 44% of the chemical/tumour site combinations. However, for 46% of the chemical/tumour site combinations, the response rate was higher in the stop-exposure groups than the chronic lifetime exposure groups. About 5% showed a lower response in the stop-exposure groups than the chronic lifetime exposure groups. Therefore, the assumption of equivalent cancer risk at equivalent total doses (i.e. that the product of concentration and time is constant independent of the exposure pattern) was incorrect at least half of the time. Combining stop-exposure and continuous exposure data in ED<sub>01</sub><sup>3</sup> estimation showed varied effect. Inclusion of responses from the stop-exposure groups led to a decrease in the ED<sub>01</sub> (greater risk or potency) for 63% of the chemical/tumour/site combinations and an increase in the ED<sub>01</sub> (lesser risk or potency) for 17% of the chemical/site combinations, mostly within one order of magnitude. While the overall change was less than 2-fold (in either direction) for 36% of the tumour sites examined, approximately 15% (of all tumour sites examined) showed a greater than 10-fold decrease (greater risk or potency) in ED<sub>01</sub>, implying a higher risk with shorter exposure. The largest reduction was 102-fold for lymphomas following 1,3-butadiene exposure.

Halmes et al. (2000) also evaluated dose averaging by determining the “equivalent averaging time”. Equivalent averaging time is the length of time over which stop-exposure doses have to be averaged so that the observed response falls exactly on the fitted dose-response curve developed from the continuous exposure (i.e. 104 weeks) data. This method of evaluation has a direct implication for cancer risk assessment. The stop-exposure studies exposed animals for varying durations that ranged from 13 weeks to 66 weeks. For most endpoints, the “equivalent averaging times” were generally longer than the actual exposure durations but less than 104 weeks for 12 of the 14 dose groups for which this comparison was made. The median “equivalent averaging time” for all the groups was 62 weeks, indicating that averaging the stop-exposure dose over a lifetime (i.e. LADD) would underestimate cancer risk by a median factor of 2 (ranging from an overestimation of 2-fold to an underestimation of 5-fold).

In addition to duration-related variability (i.e. short-term versus long-term exposures), carcinogenic sensitivity may not be constant throughout the adult period. On the basis of their

analysis of animal (rats and mice) experimental data involving four different types of ionizing radiation, Hattis et al. (2004) demonstrated that the dosage delivered to older animals (6–12 months or 19–21 months old) appeared to be several-fold less effective than a similar dosage delivered to young adults (3–3.5 months old), suggesting greater sensitivity for exposures in early adulthood.

In summary, experimental data with animals suggest that averaging short-term exposure over a lifetime results in uncertainties and may overestimate or underestimate the risk when exposure occurs during adulthood. The level of underestimation or overestimation is generally within an order of magnitude for the substances studied. However, many carcinogens found at contaminated sites have not been studied in this manner.

### 2.1.2 Dose Averaging Implications from Adult Exposures in Epidemiological Studies

The available epidemiological data on the effect of exposure patterns on cancer risks (summarized in Table 2.2) are limited, lung and skin cancer being the most frequently studied.

A review (Wilson Scientific Consulting Inc., 2006) of the literature on cancer risk from smoking indicates a general scientific consensus that cancer risk decreases for individuals who quit smoking when compared with those who continue to smoke, the extent of the reduction lessening as the age of quitting increases. The review concluded that an appreciable amount of cancer risk is removed 10 years after smoking cessation. However, although smoking reduction may also lead to reduced lung cancer risk, the conclusion did not consider the intensity of smoking or the age of the smoker. Smoking is a unique activity that involves inhaling a high dose of a mixture of carcinogenic and non-carcinogenic chemicals, which include irritants and pharmacologically active levels of nicotine. The effects of both psychological and physical addiction as well as other socioeconomic factors may not have been accounted for in the analyses. Therefore, the exposure–risk relationship observed for smoking may not be applicable to carcinogens and exposures typical of contaminated sites. In addition, the available analysis of the smoking data lacks a quantitative comparison of the cancer risks predicted by LADD and alternative approaches with the observed cancer risks as a function of smoking intensity (dose) and duration.

Hauptmann et al. (2002) investigated lung cancer risk associated with occupational exposure to asbestos in two German case-control studies. The data suggest that an individual’s lung cancer risk increased for 5–15 years after exposure and then declined. The risk declined to about one-half after more than 20 years from the final exposure. When individual risks were modelled and compared, the risk was higher and peaked earlier at high exposure rates as

<sup>3</sup> Maximum likelihood estimate of the dose corresponding to a 1% additional cancer risk.

compared with lower exposure rates (5 fiber-yrs/yr for 5 years versus 0.5 fiber-yrs/yr over 50 years). The result suggests that dose averaging over a lifetime would underestimate the risk, especially for people whose remaining lifespan is longer than the latency period. On the other hand, the risk would be overestimated for people whose remaining lifespan is shorter than the latency period.

Case control studies of the incidence of melanoma or basal cell carcinoma involving patients 20–79 years of age with a recent diagnosis in Western Canada (Elwood et al., 1985) found an individual's total dose alone did not determine cancer risk, as the intensity of exposure also played a role. Activities that likely involved more intense sun exposure (vacation and recreation) conferred a greater level of risk (by up to 2-fold) than if the same dose had been achieved by predominantly occupational exposure. A moderate amount of occupational sun exposure (likely from intermittent seasonal exposure) increased the risk, but further increase in exposure (typical of chronic occupational exposure) either had no effect or resulted in decreased risk (for men) (Elwood, 1992). Other major studies showed a similar pattern following intermittent exposures, although results from the northern hemisphere studies are more definitive than from Australian studies (Kricker et al., 1995), partly because the total dose received in Australia is so much greater (Elwood, 1992).

The limited human data associated with short-term or intermittent exposure support the notion that averaging short-duration or intermittent exposure over a longer time period may not be appropriate for predicting cancer risk.

### 2.1.3 Theoretical Cancer Modelling Studies of Less-Than-Lifetime Exposure

Mathematical models of cancer, such as the A-D multistage model and MVK model (the latter model is also known as the two stage birth-death-mutation model), are generally compatible with the current understanding of the mechanism of carcinogenesis. The A-D multistage model assumes cancer to be the end result of a normal cell going through a finite number (e.g.  $k$ ) of irreversible independent transitions (stages) that must take place in a specific order (Armitage, 1985; Al-Zoughool and Krewski, 2008). The MVK model assumes that the clonal expansion of cancer involves two discrete phases: initiation (due to genetic damage) and malignant conversion with progression (Al-Zoughool and Krewski, 2008). Although these models have not been validated (United Kingdom Department of Health, 2004), they have been used to describe the age-dependent rate of cancer formation and to explore the extent to which the LADD approach could over or underestimate cancer risk resulting from less-than-lifetime exposure scenarios (Kodell et al., 1987; Murdoch and Krewski, 1988; Chen et al., 1988; Murdoch et al., 1992; Al-Zoughool and Krewski, 2008). These analyses may

provide insight into the upper bound estimate of the level of over or underestimation of the risk.

Using the A-D multistage time-to-tumour model, a number of publications (Murdoch et al., 1992; Al-Zoughool and Krewski, 2008; Kodell et al., 1987) have demonstrated the propensity of LADD to over or underestimate cancer risk under certain exposure scenarios. The theoretical upper bound of underestimation by the LADD approach was also estimated. The consensus is that the LADD approach can over or underestimate cancer risks for less-than-lifetime exposures depending on the exposure. The greatest extent of underestimation was postulated for two general scenarios: short-term exposures in early life to initiators (carcinogens that increase the rate of the first stage of carcinogenesis) and short-term exposures late in life to completers (carcinogens that increase the rate of the last stage of carcinogenesis, Chen et al., 1988). In both cases, LADD can underestimate cancer risk by up to a factor of 6. When short-duration exposure occurs in an adult's mid-life period, the extent of underestimation is less than 2- to 3-fold. Depending on the mode of action, cancer risk from short-term exposure may also be overestimated by up to several orders of magnitude.

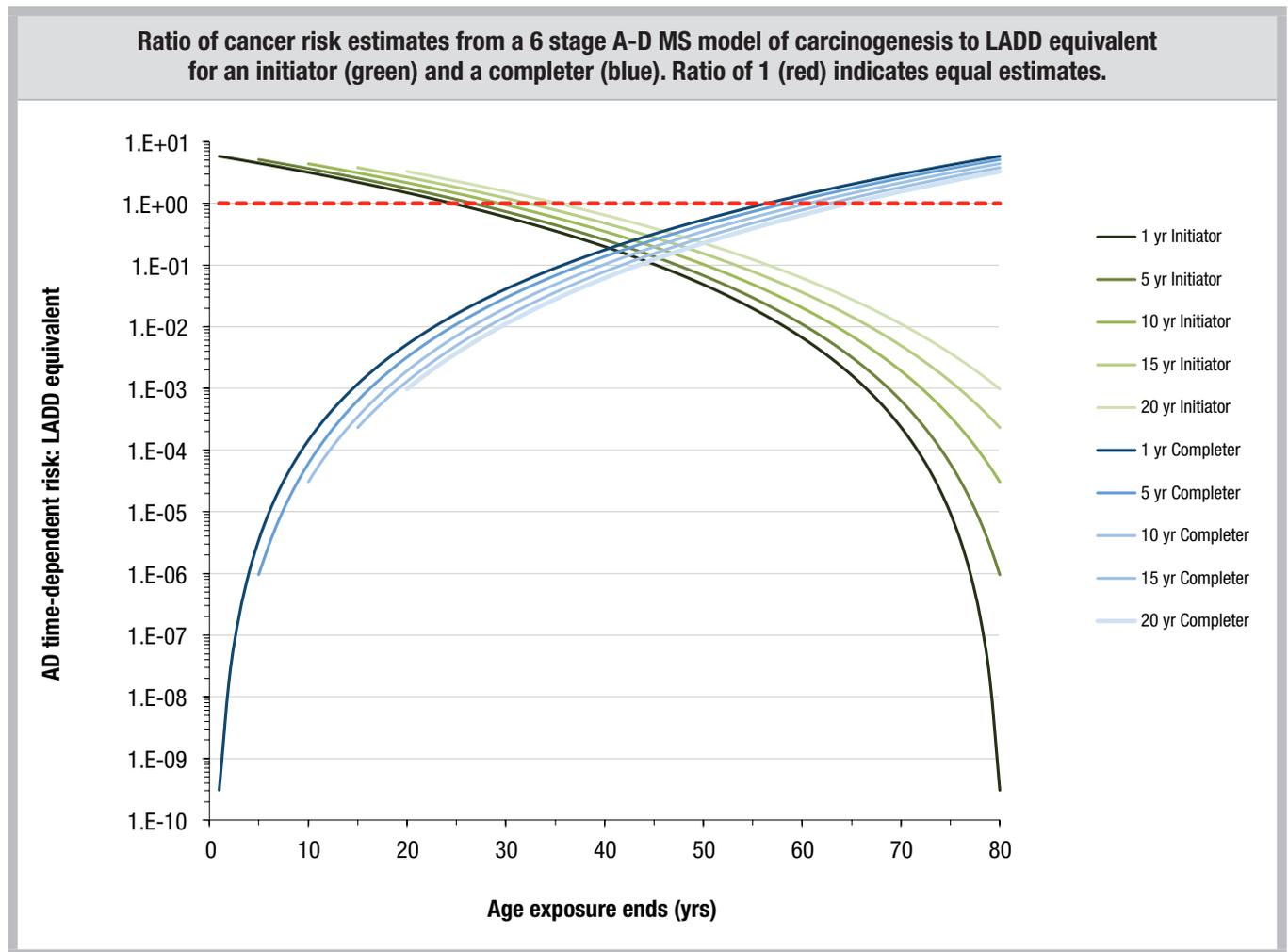
The relationships between the prevalence and magnitude of potential under and overestimates of cancer risk using the LADD approach are illustrated in Figure 2.1. This figure compares the relative risk estimates generated using a 6-stage A-D multistage model (to estimate cancer risks for time-dependent exposure patterns) with those calculated using an "equivalent" LADD (a time-weighted average dose assuming constant lifetime exposure). The value of 1 on the Y axis represents equivalent risk estimates. Values greater than 1 represent cases in which LADD underestimates cancer risks relative to the time-dependent risk model, and values smaller than 1 represent cases in which LADD overestimates those risks. The figure illustrates that, except for the specific cases discussed above, the LADD is more likely to overestimate cancer risk, and the magnitude of potential overestimation is much greater than the magnitude of underestimation.

It is important to note that the difference in cancer risk estimates between the models is dependent on the number of stages considered in the A-D multistage model, which stage is affected and the age at first exposure. Figure 2.1 illustrates a comparison using the 6-stage A-D multistage model and an assumption that only one stage (i.e. first or last stage) is dose-related. The difference between the models in cancer risk estimates will be smaller if one uses a lower number of cancer stages in the A-D multistage model. The modelled cancer risk estimates become approximately equivalent with a 2-stage A-D model (assuming carcinogenesis has only two stages).

The results from the MVK model generally parallel those from the A-D multistage model exercises (Chen et al., 1988; Murdoch et al., 1992). The model predicts LADD may over or underestimate cancer risks depending on the cell growth rate, time of first exposure, duration of exposure and the type of carcinogen. The maximum underestimate of risk reported by Chen et al. (1988) using the LADD approach would occur with early-life, shorter

exposures to an initiator (maximum 7-fold underestimate) or with longer duration, late-life exposures to a completer (maximum 4.5-fold underestimate). When exposure takes place during mid-life, the degree to which LADD can underpredict cancer risk (up to 2-fold) for initiators using the MVK model is generally quite comparable with the A-D multistage model prediction (Chen et al., 1988; Murdoch et al., 1992).

**Figure 2.1 Relative cancer risk estimates for various ages and durations of adult exposure calculated using a 6-stage Armitage-Doll multistage (MS) model for estimating cancer risks for time-dependent exposure patterns versus lifetime average daily dose (LADD). Only one stage was assumed to be dose-related in the modelling, the first stage for “initiators” and the last (or kth) stage for “completers”. A value of 1 on the Y axis (indicated by the red horizontal dotted line) represents equivalent risk estimates. Values greater than 1 represent cases in which LADD underestimates cancer risks, and values smaller than 1 represent cases in which LADD overestimates risks.**



### 2.1.4 Summary for Dose Averaging for Less-Than-Lifetime Adult Exposure

Evidence from animal experiments, epidemiological studies and theoretical modelling studies supports the conclusion that exposure pattern has an effect on lifetime cancer risk. Averaging less-than-lifetime exposure over a lifetime using LADD may underestimate or overestimate cancer risks, depending on the timing of exposure and the mode of action of the carcinogen. The degree of underestimation seems generally to be confined to within an order of magnitude and is approximately 2-fold for short exposure during all but the very late stages of adulthood. Theoretical modelling predicts up to a 6-fold underestimation of risk for exposure to a completer only late in life; however, most chemicals act through multiple mechanisms, and few exclusive completers have been identified. The original multistage A-D model assumes that cancer incidence increases with age at a constant rate. The review by Al-Zoughool and Krewski (2008) indicates that this assumption does not apply to the incidence of prostate and breast cancers, which increase until age 40 and 50 and decline thereafter; the incidence of most cancer types declines after the age of 80. The multistage model may therefore overestimate cancer rates in the elderly, and LADD may not underpredict cancer risk from less-than-lifetime exposure to (theoretical) completers late in life as much as the model suggests.

Overall, the limited evidence currently available suggests dose averaging over a lifetime (LADD) overestimates as frequently as it underestimates cancer risk for short-term exposure. However, for adult exposures to mutagenic carcinogens (e.g. initiators), the underestimation of cancer risk is insignificant in most cases. Adjustment to correct for underestimation of cancer risk resulting from using the LADD approach for less-than-lifetime exposures in adults is therefore not recommended (i.e. the status quo is maintained).

## 2.2 Dose Averaging for Less-Than-Lifetime Early-Life Exposure

Cancer slope factors are generally derived from adult human epidemiological studies or standard chronic adult rodent bioassays. The US EPA (2005a) conducted a comprehensive review of cancer risk associated with early-life exposure to determine whether specific age-dependent adjustments of adult cancer slope factors were needed when assessing cancer risk from early-life exposure.

The review found limited cancer epidemiological data involving childhood exposure to radiation and chemotherapeutic agents. A review of available animal studies (Barton et al., 2005; Chhabra et al., 1993; Peto et al., 1984; Vesselinovitch et al., 1979) indicated that early-life exposures (i.e. perinatal) usually resulted in a higher tumour incidence later in life than standard adult-only exposures.

These findings are consistent with the current understanding of biological processes involved in carcinogenesis and are supported by other reviews (McConnell, 1992; Miller et al., 2002; US EPA, 1996), which found the following:

- Tumours usually occur at the same sites following either perinatal or adult exposure.
- Perinatal exposure followed by adult exposure usually increases the percentage of treated animals bearing tumour or reduces the latency period before tumours are observed as compared with adult-only exposures.

The US EPA (2005a) identified several factors that may contribute to increased susceptibility to carcinogens in early life:

- Differences in the capacity to metabolize and clear chemicals at different ages can result in larger or smaller internal doses of the active agent(s), either increasing or decreasing risk (Ginsberg et al., 2002; Renwick, 1998).
- More frequent cell division during development can result in enhanced fixation of mutations because of the reduced time available for repair of DNA lesions, and clonal expansion of mutant cells results in a larger population of mutants (Slikker et al., 2004).
- Some embryonic cells, such as brain cells, lack key DNA repair enzymes.
- Some components of the immune system are not fully functional during development (Holladay and Smialowicz, 2000; Holsapple et al., 2003).
- Hormonal systems operate at different levels during different lifestages (Anderson et al., 2000).
- Induction of developmental abnormalities can result in a predisposition to carcinogenic effects later in life (Anderson et al., 2000; Birnbaum and Fenton, 2003; Fenton and Davis, 2002).
- While tumour promotion processes can be very dependent upon the duration of promotion, initiation processes can occur in relatively brief periods.
- Most tumours take extended periods to develop, which means that damage occurring earlier in life is more likely to result in tumours before death than would exposures that occur later in life.

The US EPA (2005a) compared the cancer potencies from early-life exposure with the cancer potencies from adult exposure in repeated (continuous) dosing studies taken from the published literature. Studies included in the analysis involved a) exposure of animals either only during the juvenile or adult period and followed through adulthood to assess tumour incidence; or b) exposure of animals beginning either in the juvenile or adult period, but once begun continuing through life. Cancer potencies were estimated by fitting the one-hit model, or a restricted form of the Weibull model, to the data for each age group. The analysis for the six carcinogens

(benzidine, diethylnitrosamine, 3-methylcholanthrene, safrole, urethane and vinyl chloride) with a mutagenic mode of action is most informative. The results indicate that the early lifestages can be, but are not always, much more susceptible to cancer development than when exposure occurs in the adult lifestage. The ratio of tumour incidence from early life to adult exposure varies by chemical, sex and species with the weighted geometric mean ratio estimated at 10.4.

The US EPA (2005a) performed a similar analysis of acute dosing studies (which generally compared a single exposure during the juvenile period with identical or similar exposure in adult animals). The results<sup>4</sup> supported the concept that early-lifestage exposure to carcinogenic chemicals with a mutagenic mode of action leads to increased tumour incidence when compared with adult exposure of a similar dose and duration.

On the basis of the analysis involving repeated (continuous) dosing studies, the US EPA (2005a) recommended adjusting the adult cancer slope factor by a factor of 10 for exposures to mutagenic carcinogens occurring during the first 2 years of life. Pharmacokinetic and pharmacodynamic differences between children and adults are greatest during the first 2 years of life (World Health Organization, 2006), which corresponds to the period of birth to weaning in laboratory rodents (Hattis, 2005; WHO, 2006).

The US EPA (2005a) considered the available data insufficient to calculate a specific adjustment factor for the period from 2 through 15 years of age, which represents middle adolescence and follows the period of rapid developmental changes during puberty. The US EPA therefore selected a 3-fold adjustment as it is the geometric mean between the 10-fold adjustment for the first 2 years of life and a unity adjustment for adult exposure. The US EPA recommends that these default age-dependent adjustment factors be applied only when chemical-specific data on early-life exposure are absent.

Although the limited data for carcinogens with a non-mutagenic mode of action (e.g. hormonally mediated) suggest increased susceptibility when exposure occurs perinatally, the US EPA (2005a) considered the data inadequate to derive a generic adjustment of cancer response. More research is needed, particularly because it was observed that tumours arising from hormonally active chemicals appeared to involve different sites when exposure occurred during early life versus adulthood.

The California Environmental Protection Agency (CalEPA, 2009) released its findings on a similar study it undertook to address age-related cancer. This study compared cancer potencies (estimated by applying the linearized multistage [LMS] model to the dose-response data from animal experiments) from

early-life exposures (exposed during the prenatal, postnatal or juvenile period) with exposure at an older age, preferably during adulthood. CalEPA used the full distribution of the cancer slope to derive the ratios of cancer potencies from early-life to adult exposures with adjustment for time to manifest tumour (i.e. to account for the longer available time the young animals had from exposure to tumour development). Each chemical was represented by a single distribution based on cancer potencies estimated from one or more studies and from all tumour sites.

The medians of the postnatal age sensitivity factor (ASF), estimated from data on 18 carcinogens (55 distributions), and the juvenile ASF, estimated from data on 5 carcinogens (7 distributions), were reported as 13.5 and 4.5 respectively. Because of the limited database and the broad distributions of results for different chemicals, CalEPA found no basis for specifying a default ASF with greater than half-log precision (i.e. values of 1, 3, 10, 30, etc). Further, rodents are born at a stage of maturity that approximates that of a third-trimester human foetus. Therefore, in the absence of chemical-specific data, CalEPA recommended applying a default ASF of 10 for the third trimester to age 2 years (totalling 2.25 years) and a factor of 3 for ages 2 through 15 years to account for potential higher sensitivity during early lifestages. While the same values were selected by US EPA (2005a) to be applied only to carcinogens with a mutagenic mode of action, CalEPA will apply these factors to all carcinogens. CalEPA (2009) included in its analysis three non-genotoxic carcinogens and found evidence that early life is a susceptible time for a carcinogen thought to act through a non-mutagenic mode of action, e.g. diethylstilbestrol (DES). CalEPA's rationale for not restricting ASF to chemicals acting via a mutagenic mode of action includes the potential problems of defining "mutagenic mode of action" when applied narrowly and the possibility of carcinogens with multiple modes of action that dominate at different lifestages (CalEPA, 2009).

### 2.3 Dose Averaging for Prenatal Exposure (Transplacental Carcinogenesis)

A number of agents are suspected to be transplacental carcinogens, i.e. in utero exposure to these agents leads to cancer development later in life, involving either a mutagenic or a non-mutagenic mode of action. Most data are from animal studies, such as those involving DES, genistein, tamoxifen, polycyclic aromatic hydrocarbons (PAHs), polybrominated biphenyls, polychlorinated dibenzo-p-dioxins (dioxin; reviewed in Birnbaum and Fenton, 2003), arsenic (Waalkes et al., 2004) and nitrosamines (Mohr et al., 1983). In humans, only radiation and DES have been shown to cause cancer following in utero exposures (Anderson et al., 2000; Barton et al., 2005; and Birnbaum and Fenton, 2003). Other chemicals suspected to be transplacental carcinogens

<sup>4</sup> Based on acute dosing carcinogenic data for eight chemicals with a mutagenic mode of action: benzo[a]pyrene, dibenzanthracene, diethylnitrosamine, dimethylbenzanthracene, dimethylnitrosamine, ethylnitrosourea, methylnitrosourea, urethane.

on the basis of human data include aflatoxin B1 and the hormones used for assisted reproduction (in vitro fertilization). These substances are not typically found at federal contaminated sites; moreover, for many substances that are found at contaminated sites, the data on transplacental carcinogenesis are available only from animal studies.

Some chemicals may be acting as initiators following in utero exposures or prezygotic exposure of the male parent, with cancer formed only upon subsequent postnatal promotion and/or additional exposures (i.e. in utero exposure creates altered susceptibility to cancer later in life). This effect has been seen experimentally with various chemicals, including dioxin/dimethylbenzanthracene (DMBA; Brown et al., 1998), 3-methylcholanthrene/butylated hydroxytoluene (Gressani et al., 1999), genistein or atrazine/DMBA (Hilakivi-Clarke et al., 1999; Fenton and Davis, 2002) and N-methyl-N-nitrosourea or PAHs/phenobarbital (Diwan et al., 1989). In utero initiation/postnatal promotion has been demonstrated in humans only for DES and radiation (Yamasaki et al., 1992).

The prenatal to adult cancer potency ratio has not been considered in the US EPA (2005a) supplemental guidance. The CalEPA (2009) has conducted a probabilistic analysis of the prenatal to adult potency ratio. The prenatal age window showed an increased sensitivity to the majority of the 14 carcinogens (22 potency ratio distributions) analyzed. The median of the prenatal ASF distribution was 2.9. However, because of the limited database and the considerable variability in available data, no recommendation on a default adjustment factor was proposed for prenatal exposures in the first and second trimesters. As rodents are born at a stage of maturation similar to that of a third-trimester human foetus, the trimester is included in the default ASF of 10 proposed for up to 2 years of age (i.e. total duration of 2.25 years). No other major regulatory agency has a default position for adjustment of risk calculations for prenatal exposures. While CalEPA (2009) illustrated how an ASF of 10 can be applied when the daily exposure (mg/kg-d) is known, the agency has not provided sample risk calculations for human exposure from known environmental concentrations.

Physiologically based pharmacokinetic (PBPK) modeling of transplacental transfer could theoretically better define the magnitude of increased susceptibility in the foetus. However, validated PBPK models are unlikely to become available in the near future, as the necessary data for modelling and reliable markers of foetal exposure are lacking, and the models themselves require further refinement (Anderson et al., 2000). Efforts to advance knowledge on issues such as the temporal profile and gene polymorphism in enzymes involved in carcinogen activation/detoxification and DNA repair enzymes in the foetus would facilitate development of better PBPK models. More work with animal models is needed to identify transplacental carcinogens and their mechanism of action, including interaction with target genes.

## 2.4 Dose Averaging for Less-Than-Lifetime Exposure during Puberty

Mutagenic carcinogens are generally more effective in rapidly dividing tissues. The higher rates of cell division provide more opportunities for carcinogens to interact with DNA and less time for DNA repair prior to cell division, which results in increased probability of initiation activity. During puberty, there is dramatic growth in reproductive and other related organs, including some parts of the brain, potentially making them more susceptible to mutagenic carcinogens acting at those sites.

Changes in physiological and biological processes during puberty could also alter susceptibility to the effects of some non-mutagenic carcinogens (e.g. endocrine-disrupting chemicals). On the basis of its analysis of the limited available data, the US EPA Science Advisory Board (US EPA, 2004) concluded that altered sensitivity to the development of cancer may occur when exposure takes place during puberty as compared with other exposure time windows.

### 3.0 PROPOSED INTERIM MEASURE FOR HUMAN HEALTH RISK ASSESSMENT FOR LESS-THAN-LIFETIME EXPOSURE TO CANCER-CAUSING AGENTS AT CONTAMINATED SITES

The CSD provides this interim guidance with regard to HHRA of carcinogenic agents, including short-term exposure and dose averaging. Risk assessments submitted to CSD should provide a rationale taking into consideration the mode of action at the tumour site in question.

#### 3.1 Assessment of Cancer Risk for Non-Threshold Carcinogenic Effects

##### 3.1.1 Carcinogenic Effects Acting Through a Mutagenic Mode of Action

The US EPA (2005 a, b) provides one of the most comprehensive analyses of the available data related to increased sensitivity when exposure to a carcinogen with a mutagenic mode of action occurs at early lifestages. As an interim measure, CSD has adapted the US EPA approach for contaminated site risk assessments.

The US EPA's default adjustment factor of 10 is supported by LMS modelling studies (Al-Zoughool and Krewski, 2008) indicating that a default factor of 6 should be applied to LADD-based cancer risk estimates for mutagens (i.e. to account for potential increased effectiveness of early-life exposure to an initiator). An additional factor of 1.6 may be applied to slope factors derived from rodent bioassays in which exposure begins in early adulthood (6–8 weeks of age), to give a total adjustment of 10 (6 × 1.6). This additional factor (1.6) is needed to account for the neonatal/infant period (i.e. from birth to 6–8 weeks of age).

This cancer risk assessment approach takes into account the varying sensitivity of different lifestages to cancer effects. The ILCR is estimated by summing the risk from each discrete exposure period. For non-threshold carcinogens acting through a mutagenic mode of action, it is recommended that ADAFs be applied to the cancer slope factor (or inhalation unit risk) with exposure averaged over a lifetime, to account for the sensitivity of the age-dependent exposure period. This approach can be illustrated by the equations below.

**ILCR from oral exposure can be estimated using the following equation:**

$$\begin{aligned} \text{ILCR} &= \sum_i (\text{LADD}_i * \text{SF}_i) \\ &= \sum_i (\text{LADD}_i * \text{SF} * \text{ADAF}_i) \end{aligned}$$

Where: LADD<sub>i</sub> = dose received during lifestage i averaged over a lifetime  
 SF<sub>i</sub> = age-specific slope factor  
 SF = adult cancer slope factor (per mg/kg-d)  
 ADAF<sub>i</sub> = age-dependent adjustment factors for lifestage i

For exposure by inhalation, the following equation applies:

$$\text{ILCR} = \sum_i (\text{C}_{\text{ai}} * \text{TR}_i * \text{UR} * \text{ADAF}_i)$$

Where: C<sub>ai</sub> = concentration in air during lifestage i (mg/m<sup>3</sup>)  
 TR<sub>i</sub> = fraction of time exposed (yr/80 yr)  
 UR = adult cancer unit risk (per mg/m<sup>3</sup>)  
 ADAF<sub>i</sub> = age-dependent adjustment factors for lifestage i

**LADD is defined by the following equation:**

$$\text{LADD (mg/kg-d)} = [\text{ER} * \text{ED}] / \text{Lifetime} \quad \text{or}$$

$$\text{LADD (mg/kg-d)} = [\text{C} * \text{IR} * \text{AF} * \text{ED}] / [\text{BW} * \text{Lifetime}]$$

Where: ER = exposure rate (mg/kg-d)  
 C = chemical concentration in the media (mg/m<sup>3</sup> or mg/kg)  
 IR = intake rate of medium (m<sup>3</sup>/day or kg/day)  
 AF = medium-specific absorption factor  
 ED = exposure duration (days)  
 BW = body weight (kg)  
 Lifetime = days in a lifetime = 365 d/yr \* 80 yr

LADD<sub>i</sub> is defined as the dose received during lifestage i averaged over a lifetime and can be represented by the following equation:

$$\text{LADD}_i \text{ (mg/kg-d)} = [\text{C}_i * \text{IR}_i * \text{AF} * \text{ED}_i] / [\text{BW}_i * \text{Lifetime}]$$

Where: C<sub>i</sub> = chemical concentration in the media a person is exposed to during lifestage<sub>i</sub> (mg/m<sup>3</sup> or mg/kg)  
 IR<sub>i</sub> = intake rate of medium during lifestage<sub>i</sub> (m<sup>3</sup>/day or kg/day)  
 AF = medium-specific absorption factor  
 ED<sub>i</sub> = exposure duration during lifestage<sub>i</sub> (days)  
 BW<sub>i</sub> = body weight during lifestage<sub>i</sub> (kg)  
 Lifetime = days in a lifetime = 365 d/yr \* 80 yr

The US EPA's ADAFs have been adjusted to fit the age groups presented in the PQRA (Health Canada, 2004). Table 3.1 summarizes the default adjusted ADAFs that CSD recommends for contaminated site risk assessments of non-threshold carcinogens with a mutagenic mode of action. These default factors can be applied when age-specific cancer slope factors, age-specific inhalation unit risks or chemical-specific data are not available. In scenarios where exposure periods do not match the CSD's age groups, CSD recommends that the US EPA's ADAFs be applied. For example, if exposure occurs only between 7 months and less than 2 years of age, the adjustment factor of 10 would apply. Likewise, if exposure occurs only between 12 and < 16 years of age, the ADAF of 3 would apply. Worked examples are illustrated in Section 4.

When age-specific cancer slope factors, age-specific inhalation unit risks or chemical-specific data are available for a susceptible lifestage, it is preferable to use these data directly to evaluate risks for the chemical and the lifestage on a case-by-case basis. In these cases, such as vinyl chloride, application of default ADAFs would not be appropriate. The US EPA recommends twice the adult inhalation unit risk to be applied for estimating incremental cancer risk from continuous exposure to vinyl chloride from birth.

For intermittent exposures, the total cancer risk will be the sum of each discrete exposure with lifestage-specific potency and exposure averaged over a lifetime.

**Table 3.1 Recommended interim adjusted age-dependent adjustment factors (ADAFs) for cancer risk assessment at contaminated sites for carcinogenic effects via a mutagenic mode of action**

Lifestage	Age	Adjusted age-dependent adjustment factor (ADAF) <sup>a</sup>
Infant	0–6 months	10
Toddler	7 months–4 years	5 <sup>b</sup>
Child	5–11 years	3
Teenager	12–19 years	2 <sup>c</sup>
Adult	20+	1

<sup>a</sup> US EPA (2005 a, b), except as noted.

<sup>b</sup>  $\text{ADAF}_{7\text{ mo}-4\text{ yr}} = (\text{ADAF}_{0-2} * \text{D}_{7\text{ mo}-1} / \text{D}_{7\text{ mo}-4}) + (\text{ADAF}_{2-4} * \text{D}_{2-4} / \text{D}_{7\text{ mo}-4}) = 10 * 1.5/4.5 + 3 * 3/4.5 = 5$ , and D<sub>i</sub> = exposure duration in years

<sup>c</sup>  $\text{ADAF}_{12-19} = (\text{ADAF}_{12-16} * \text{D}_{12-15} / \text{D}_{12-19}) + (\text{ADAF}_{16+} * \text{D}_{16-19} / \text{D}_{12-19}) = 3 * 4/8 + 1 * 4/8 = 2$ , and D<sub>i</sub> = exposure duration in years

The prenatal period (in utero) may be a sensitive window of exposure for some cancers, and an ADAF of 3 (or 2) may not be sufficient to address increased sensitivity during puberty, but further study is needed to delineate more accurately the magnitude of increased sensitivity. CSD will continue to evaluate the issue as new research data become available and as other regulatory agencies consider this issue. In the interim, CSD recommends addressing the risks associated with mutagenic carcinogen exposure during these lifestages on a case-by-case basis.

To date, among the carcinogens for which CSD provides TRV values, the US EPA (2009, 2011a) has identified carcinogenic PAHs, trichloroethylene and vinyl chloride as acting through a mutagenic mode of action. After a toxicological review, the US EPA (2010) proposed that chromium (VI) is “likely carcinogenic to humans” via the oral route of exposure and hypothesized a mutagenic mode of action for its carcinogenicity. This US EPA report is currently undergoing review (US EPA, 2011b).

### 3.1.2 *Carcinogenic Effects Acting Through an Unknown Mode of Action*

For carcinogenic effects with an unknown mode of action or for which the burden of proof for a threshold mode of action has not been met, CSD recommends treating the effect as non-threshold. The mathematical equations used to estimate cancer risk for mutagenic carcinogens can be applied in these situations. If chemical-specific data are available on quantitative differences between early lifestages and adults, an analysis of the differences could be used to adjust risk estimates for early life exposures. Otherwise, CSD does not recommend extending the default age-dependent potency adjustment factors to these carcinogenic effects. This position would be analogous to recommending a default ADAF of 1 for all lifestages.

The non-threshold approach for carcinogenicity risk assessment arises initially from the mechanistic, one-hit model, which assumes that only one-hit is required for the cell to be altered. The role of the body's defence mechanism (e.g. repair, apoptosis), which has an influence on the health outcome, is not considered. CSD considers the use of the linear low-dose extrapolation approach (without further adjustment) to be sufficiently conservative and to provide adequate public health protection for carcinogenic effects with a mode of action that is not mutagenic.

## 3.2 *Assessment of Health Risk from Threshold Carcinogens*

The CSD does not recommend a default age-specific adjustment for carcinogenic effects found to have a non-linear dose-response relationship (i.e. threshold) at low doses at this time. An adjustment can be made on a chemical-specific basis if supported by experimental data. These substances would be included in an HHRA using a TDI (or a TC in the case of inhalation exposure).

The CSD recommends that dose averaging for short-term exposure for these types of carcinogenic effects be performed in the same way as for other substances with threshold effects. It is important that dose averaging does not underestimate the potential for threshold carcinogenic effects. Without a sound basis for doing so (i.e. it cannot be a default assumption), the human health risk assessor should not simply mathematically spread out a short-term dose over a long period and conclude that the short-term dose is toxicologically equivalent to a lower dose over the long period. In short, CSD recommends that the exposure be averaged over the total actual exposure period and compared with the appropriate TRV. A scientific rationale is required to support any proposed amortization (dose averaging beyond actual exposure period) to ensure that short-term risks are not underestimated. This analysis needs to be done on a chemical-specific basis.

## 3.3 *Assessment of Health Risk from Non-Cancer Health Effects*

For short-term exposure, carcinogenic agents may elicit other chronic and short-term non-cancer health effects, depending on the magnitude of exposure. Short-term effects can be evaluated for potential critical receptors/lifestages<sup>5</sup> using short-term TRVs where available (either from other regulatory agencies or derived from literature values, as per Health Canada, 2010, guidance) and applicable to the exposure scenarios. If short-term TRVs are not available, such evaluation can be conducted according to relevant dose-response information from toxicity studies. It is also important to consider whether the short-term exposure might elicit early biological key events that might progress to health effects at a later date. In many cases, both the short-term and chronic non-carcinogenic effects, rather than carcinogenicity, may be the main determinant of the risk from short-term exposure. For example, keratosis rather than carcinogenicity could drive a risk assessment for exposure to high levels of arsenic in soil (e.g. 100 mg/kg) in a less-than-lifetime exposure scenario.

<sup>5</sup> Including relevant receptors/lifestages with the highest exposure and receptors/lifestages associated with specific sensitivity to the toxicity of the contaminants

## 4.0 WORKED EXAMPLES

### 4.1 Assessment of Lifetime Risk Associated with Exposure to a Carcinogen with a Mutagenic Mode of Action

When assessing cancer risk, it is important to consider both the difference in exposure and the increased susceptibility for early lifestages. ADAFs in dose-response (i.e. slope factors) need to be combined with age-specific exposure estimation.

The following examples illustrate how to integrate potential lifestage differences in exposure and susceptibility in risk estimation for both lifetime and less-than-lifetime exposure during a specific period in life. The examples consider risk from oral exposure. Risks associated with inhalation exposure to mutagenic carcinogens can be calculated in a similar manner by applying the appropriate ADAFs with the corresponding inhalation unit risk estimates using appropriate estimates of exposure concentrations.

These calculations assume that the available slope factor does not specifically consider early-life exposure. In the case of carcinogens for which age-specific (and in particular early-life) slope factors are available, these factors should be used instead of adjusting the adult slope factor.

#### 4.1.1 Example 1: Exposure Occurs Over a Lifetime

Consider a scenario of exposure to a hypothetical carcinogen with a mutagenic mode of action present in drinking water. The oral slope factor derived from a typical animal study (i.e. in which dosing begins after puberty) is estimated to be  $2 \text{ (mg/kg-d)}^{-1}$ . The absorption factor of the carcinogen from drinking water is 1. The carcinogen is present in drinking water at  $0.001 \text{ mg/L}$ .

To calculate lifetime risk for a population with average life expectancy of 80 years, sum the risk associated with each of the time periods, applying recommended ADAFs to the relevant time periods:

- risk for the infant—first 6 months of life (where ADAF = 10),
- risk for toddler—6 months through 4 years of life (ADAF = 5),
- risk for child—ages 5 through 11 (ADAF = 3),
- risk for teenager—ages 12 through 19 (ADAF = 2) and
- risk for adult—ages 20 to 80 (ADAF = 1)

Thus, the ILCR equals the sum of the various age groups:

- Risk for infant  

$$= \text{slope factor} \times \text{ADAF} \times \text{LADD}_{0-6 \text{ mo}}$$

$$= 2 \text{ (mg/kg-d)}^{-1} \times 10 \times [(0.001 \text{ mg/L} \times 0.3 \text{ L/d} / 8.2 \text{ kg}) \times 0.5 \text{ yr/80yr}]$$

$$= 5 \times 10^{-6}$$

- Risk for toddler  

$$= \text{slope factor} \times \text{ADAF} \times \text{LADD}_{7 \text{ mo}-4}$$

$$= 2 \text{ (mg/kg-d)}^{-1} \times 5 \times [(0.001 \text{ mg/L} \times 0.6 \text{ L/d} / 16.5 \text{ kg}) \times 4.5 \text{ yr/80yr}]$$

$$= 2 \times 10^{-5}$$
- Risk for children  

$$= \text{slope factor} \times \text{ADAF} \times \text{LADD}_{5-11}$$

$$= 2 \text{ (mg/kg-d)}^{-1} \times 3 \times [(0.001 \text{ mg/L} \times 0.8 \text{ L/d} / 32.9 \text{ kg}) \times 7 \text{ yr/80yr}]$$

$$= 1 \times 10^{-5}$$
- Risk for teenager  

$$= \text{slope factor} \times \text{ADAF} \times \text{LADD}_{12-19}$$

$$= 2 \text{ (mg/kg-d)}^{-1} \times 2 \times [(0.001 \text{ mg/L} \times 1 \text{ L/d} / 59.7 \text{ kg}) \times 8 \text{ yr/80yr}]$$

$$= 8 \times 10^{-6}$$
- Risk for adult  

$$= \text{slope factor} \times \text{ADAF} \times \text{LADD}_{20+}$$

$$= 2 \text{ (mg/kg-d)}^{-1} \times 1 \times [(0.001 \text{ mg/L} \times 1.5 \text{ L/d} / 70.7 \text{ kg}) \times 60 \text{ yr/80yr}]$$

$$= 3 \times 10^{-5}$$

Total ILCR

$$= 5 \times 10^{-6} + 2 \times 10^{-5} + 1 \times 10^{-5} + 8 \times 10^{-6} + 3 \times 10^{-5}$$

$$= 7 \times 10^{-5}$$

#### 4.1.2 Example 2: Exposure Occurs at Less Than 2 Years of Age

Consider a scenario in which exposure to the same hypothetical carcinogen only takes place for a limited period of time, e.g. in a family that lives near a source of contamination for a short time and then moves away. The exposure may occur with a child aged from 1 to less than 2 years of age. It is important to consider lifestage-specific differences in exposure. The carcinogen has an oral cancer slope factor of  $2 \text{ (mg/kg-d)}^{-1}$  derived from a typical animal study, and the concentration in drinking water is  $0.001 \text{ mg/L}$ .

As this exposure period does not match CSD age groupings, the US EPA's ADAF applies<sup>6</sup>.

$$\text{Risk} = \text{slope factor} \times \text{ADAF} \times \text{LADD}_{1-<2}$$

$$\text{Risk} = 2 \text{ (mg/kg-d)}^{-1} \times 10 \times 0.001 \text{ mg/L} \times 0.6 \text{ L/d/16.5 kg} \times 1 \text{ yr/80 yrs}$$

$$= 9 \times 10^{-6}$$

Thus, the incremental lifetime cancer risk from 1 year of exposure to a carcinogen with a mutagenic mode of action assuming initial exposure at 1 year of age is estimated at  $9 \times 10^{-6}$ .

<sup>6</sup> Please note that when the exposure period matches a CSD age grouping, CSD recommends that its ADAFs be used.

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