METHODOLOGY FOR UPDATING AIR GUIDELINES: ALLOWABLE AMBIENT LIMITS (AALS) AND THRESHOLD EFFECTS EXPOSURE LIMITS (TELS)

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List of Abbreviations

AAL	Allowable Ambient Limit
ATC	Allowable Threshold Concentration
ATSDR	Agency for Toxic Substances and Disease Registry
BMC	Benchmark concentration
BMD	Benchmark dose
BMDL	Benchmark dose lower confidence limit
BMDS	Benchmark dose software
BWP	Bureau of Waste Prevention
BWSC	Bureau of Waste Site Cleanup
CalEPA	California Environmental Protection Agency
CHEM/AAL	Chemical Health Effects Assessment Methodology and the Method to Derive Allowable Ambient Limits
DAF	Dosimetric Adjustment Factor
FIA	Facility Impact Assessment
FQPA	Food Quality Protection Act
FY10	Fiscal Year 2010
HAP	Hazardous Air Pollutant
HEC	Human Equivalent Concentration
IARC	International Agency for Research on Cancer
IPCS	International Programme on Chemical Safety
LOAEL	Lowest- Observed-Adverse-Effect-Level
MassDEP	Massachusetts Department of Environmental Protection
MCP	Massachusetts Contingency Plan codified in M.G.L. Chapter 21E
MOA	Mode of Action
MRL	Minimum Risk Level
NATA	National-scale Air Toxics Assessment
NESCAUM	Northeast States for Coordinated Air Use Management
NOAEL	No-Observed-Adverse-Effect-Level
NTEL	Non-Threshold Effects Exposure Limit
NTP	National Toxicology Program
OMB	Office of Management and Budget
ORS	Office of Research and Standards
POD	Point Of Departure
REL	Reference Exposure Level
RfC	Reference Concentration
RfD	Reference Dose
RSC	Relative Source Contribution
TEL	Threshold Effects Exposure Limit
TURA	Toxics Use Reduction Act
UF_A	Uncertainty Factor for extrapolation from animals to humans
UF_{A-k}	Uncertainty Factor for extrapolation from animals to humans accounting for cross-species differences in pharmacokinetics
UF_{A-d}	Uncertainty Factor for extrapolation from animals to humans accounting for cross-species differences in pharmacodynamics

UF_H	Uncertainty Factor accounting for human population variability in susceptibility
$UF_{H\text{-}k}$	Uncertainty Factor accounting for human population variability in susceptibility due to differences in pharmacokinetics
$UF_{H\text{-}d}$	Uncertainty Factor accounting for human population variability in susceptibility due to differences in pharmacodynamics
UR	Unit Risk
USEPA	U.S. Environmental Protection Agency
WHO	World Health Organization
WOE	Weight-of-Evidence

1.0 INTRODUCTION

This document presents a revised methodology for updating the current Massachusetts Department of Environmental Protection (MassDEP) list of Allowable Ambient Limits (AALs), Threshold Effects Exposure Limits (TELs), Non-Threshold Effects Exposure Limits (NTELs) and Allowable Threshold Concentrations (ATCs) used by the following groups within MassDEP for evaluating acceptable concentrations of chemicals[1] in air:

- Office of Research and Standards (ORS),
- Bureau of Waste Prevention (BWP) within its air permitting process, and
- Bureau of Waste Site Cleanup (BWSC) 21E Program administering the Massachusetts Contingency Plan (MCP) codified in M.G.L. Chapter 21E.

2.0 BACKGROUND

MassDEP developed the Chemical Health Effects Assessment Methodology and the Method to Derive Allowable Ambient Limits (CHEM/AAL) in the mid-1980s and established ambient air chemical exposure limits that were termed AALs, NTELs, and TELs. This methodology, developed by staff of ORS, formed the health basis of addressing air toxics in air pollution control permitting. The CHEM/AAL methodology built upon the occupational literature along with other, mostly secondary sources of information, to systematically identify and evaluate the potential adverse health effects of chemicals and to develop chemical-specific ambient air limits from this information. At the time this methodology was developed there was no consistently derived set of toxicity criteria available for ambient air inhalation exposures.

In the early 1990s, the U.S. Environmental Protection Agency (USEPA) developed a methodology for deriving chemical specific reference concentrations (RfCs) to evaluate threshold (noncancer) health effects following inhalation exposure (USEPA 1994). In the mid-1990s, MassDEP modified its CHEM/AAL process to incorporate consideration of RfCs, when available (MassDEP 1994). The basis of an RfC was reviewed, and if necessary adjusted, with the intent to provide a similar level of public health protection as intended by the CHEM/AAL process. As part of this process, other pertinent information about the chemical was also reviewed.

The most recent versions of MassDEP's lists of TELs and AALs, and ATCs are dated December 1995 (MassDEP 1995a,b). While a number of these values have been reviewed and updated since inception of the original AALs and TELs, many need to be reevaluated given the newer, widely accepted methods for deriving inhalation toxicity values and availability of new primary literature since the mid-1980's for many of the chemicals with TELs and AALs.

Thus, there is a need to update the toxicological basis of many of MassDEP's air guidance values to ensure that they reflect current science. While the CHEM/AAL method served as a guiding methodology when it was developed, the wide availability of peer-reviewed inhalation toxicity

[1] Chemical is used to mean a chemical, metal, mineral, or biological agent.

values incorporating new data and new methods for deriving inhalation toxicity values, points to the need for a restructuring of the current MassDEP methodology for deriving inhalation toxicity criteria.

To meet the needs of MassDEP's programs for updated guidance values, ORS staff have developed a new method for updating existing air guidelines. Updating and deriving guidance values is a labor-intensive process. One goal of the proposed method is to streamline the process of updating existing air guidelines by relying on inhalation guidance from other respected sources such as USEPA, California Environmental Protection Agency (CalEPA), and the Agency for Toxic Substances and Disease Registry (ATSDR).

3.0 DESCRIPTION OF EXISTING GUIDELINES

The guidelines developed using the CHEM/AAL methodology include the Threshold Effects Exposure Limit (TEL), and the Non-threshold Effects Exposure Limit (NTEL). Both are intended to be protective of public health[2] assuming a life-time of exposure. The numerically lower value of these guidelines is also designated as the AAL. The list of chemical-specific guidelines published by the MassDEP generated using this process includes the TEL and AAL for each chemical on the list. The AAL is considered to be protective for public health for both threshold and non-threshold effects over many years of exposure and is compared to annual average concentrations for compliance determination. The TEL provides additional protection from threshold-type effects in that it represents a cap on potential concentration excursions within a 24-hour time period (i.e., chemical concentrations in air averaged over a 24-hour period should not exceed the TEL, even if the concentration in air is below the AAL when averaged over a longer time period). MassDEP's air pollution control permitting program requires that the TEL and AAL be used together to protect the public from experiencing both threshold and non-threshold health effects as a result of exposure to these chemicals from facility emissions into ambient air.

TELs include a relative source contribution (RSC) factor, recognizing that people are exposed to chemicals from sources in addition to outdoor ambient air. The default value for the RSC of twenty-percent (20%) is used in the absence of better chemical-specific exposure information, under the assumption that up to twenty-percent of an individual's exposure to a chemical is from ambient air and eighty-percent may be from other potential sources of exposure, such as water, soil, food and indoor air[3]. When there is chemical specific information about the potential for additional sources, this can be used to select a RSC other than the default.

When an RfC or other inhalation toxicity values are not available for a chemical, the 21E program in the MassDEP Bureau of Waste Site Cleanup (BWSC) uses a modified TEL, called an

[2] The TEL is intended to protect the general population, including sensitive members and children, from adverse health effects over a life-time of exposure to ambient air. The NTEL is intended to permit a life-time cancer risk of no more than 1 in 1 million from exposure to ambient air.

[3] The use of a 20% default value for the RSC has its origins in the US EPA drinking water program, is used in setting MassDEP drinking water guidance values, and is consistent with derivation of standards for the MCP 21E program that include consideration of cumulative exposure and risk.

Allowable Threshold Concentration (ATC). The ATC is equivalent to the TEL with the RSC removed, i.e., a typical TEL is adjusted upwards by a factor of five to calculate an ATC. ATCs do not contain a RSC because the Method 3 risk assessment includes consideration of multiple sources of exposure from the site during calculation of total site risks (MassDEP 2007). A separate list of ATC values (MassDEP 1995b) was issued concurrently with and having the same date of issue as the most recent list of TELs and AALs (MassDEP 1995a).

For the purpose of designating a derivation methodology, use of the terms TEL or ATC are synonymous, in that they are both derived using the same approach (and differ only by a factor of 5). The ATC and USEPA's RfC are also viewed as synonymous with regard to how they are used in the MCP risk assessment process.

4.0 ADVANCES IN METHODOLOGY FOR DERIVING AIR GUIDELINES

In the years since the CHEM/AAL method was developed, research on chemical effects and methods for extrapolating from high dose studies in animals to environmental exposure levels in humans has continued. Much of the research has focused on understanding physiological interactions of the chemical with an organism, as well as variability and uncertainty in the target sites, exposure, and responses across populations.

These research efforts have led to an increased utilization of chemical-specific information on effects, exposure, and mode of action to better characterize the variability and uncertainty in the available information and to acknowledge the science policy underlying the use of default assumptions. As a result, new guidance for deriving guidance values has been developed and continues to evolve.

These advances are consistent with MassDEP's commitment to utilizing the best available scientific approaches to protecting public health (MassDEP 1990, CHEM/AAL, Vol. II, page 1).

4.1 Implementation of New Methodologies in MassDEP Air Guidelines

The advances in methodologies for deriving air guidance values related to evaluating noncancer and cancer effects are summarized in the following three sections. They are described here because many of the inhalation toxicity values that are available from USEPA, CalEPA, ATSDR and other respected sources were developed using some or all of these methods, depending on when they were derived. These methodologies are used when an inhalation toxicity value is developed *de novo* from available bioassay or epidemiologic data.

The proposed methodology for updating the TELs and AALs does not rely on deriving TELs and AALs *de novo*, except as a last resort in special cases. MassDEP intends to develop guidelines for *de novo* development of TELs and AALs in a separate initiative, described in Section 6.6. However in order to develop new MassDEP ambient air guidelines using inhalation toxicity values from different respected sources, it is important to understand the methodologies used to derive the toxicity values and their quantitative implications.

4.2 Noncancer – For Chemicals Assumed to Act by Non-Linear Mode of Action

MassDEP developed the CHEM/AAL method using occupational guidelines as the basis for deriving exposure limits. Since then USEPA has developed new methods that take advantage of the availability of animal bioassay data and incorporate the evolving understanding of toxicology and risk assessment. These methods lay the foundation for incorporating chemical-specific information when available and provide an increasingly science-informed rationale for default approaches. The methodological advances have occurred in three areas, dosimetric methods for deriving a human equivalent exposure concentration, statistical methods for characterizing a more consistent point of departure[4] using the bioassay dose-response function, and methods for characterizing of the inherent variability and uncertainty in the extrapolation from study subjects to human populations including sensitive members of the population.

4.2.1 *Dosimetric Methods – Human Equivalent Concentration*

To extrapolate from animal bioassay inhalation exposures to continuous human population inhalation exposures, USEPA developed the Reference Concentration (RfC) method (USEPA 1994). The RfC method uses animal and human respiratory anatomy and physiology parameters, and the physicochemical properties of the inhaled substance (i.e., form - particle or gas, particle size and distribution of particle sizes, reactivity and solubility of a gas or vapor) to develop a human equivalent concentration (HEC). The HEC is intended to account for cross-species differences in internal exposure dose and respiratory tract deposition patterns following exposure to the same external exposure concentration, i.e., pharmacokinetics. The HEC usually adjusts for differences between the exposure scenario in the test subjects and the general human population, under the assumption that responses are associated with cumulative exposure, calculated as the product of concentration and time (C x t).

For data-rich chemicals an internal target tissue dose could be estimated across species using physiologically-based pharmacokinetic (PBPK) models that consider the comparative physiology and structure of the respiratory system, including absorption, distribution, metabolism and excretion. In cases where chemical-specific and species-specific parameters and mode of action (MOA[5]) are not sufficiently known to parameterize a PBPK model, the HEC approach uses assumptions and default values for parameters to estimate a dosimetric adjustment factor (DAF) (USEPA 1994). Unlike a PBPK model, the HEC approach does not explicitly consider metabolism and excretion of the chemical.

The HEC methodology has been used to develop RfCs by USEPA since 1989 (USEPA 1994), by ATSDR for Minimum Risk Levels (MRL) since 1992 (Chou 2009) and by CalEPA for Reference Exposure Levels (REL) since 2000 (CalEPA 2000).

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[4] The point of departure is defined in the IRIS glossary (USEPA 2009a) as the "dose-response point that marks the beginning of a low-dose extrapolation. This point can be the lower bound on dose for an estimated incidence or a change in response level from a dose-response model (BMD), or a NOAEL or LOAEL for an observed incidence, or change in level of response."

[5] "The term "*mode of action*" is defined as a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation. A key event is an empirically observable precursor step that is itself a necessary element of the mode of action or is a biologically based marker for such an element" (USEPA 2005a). This definition also applies to noncancer effects, with the sequence of events resulting not in cancer formation, but an adverse effect.

MassDEP supports the use of the HEC method as a default approach, and PBPK models when available and sufficiently robust, for extrapolating across species and exposure patterns.

4.2.2 *Dose-Response Methods – Benchmark Dose*

The benchmark dose (BMD), or benchmark concentration (BMC), approach for estimating an effect dose, or concentration, and its confidence interval associated with a particular response rate was proposed by Crump in 1984. USEPA first proposed its use for estimating the point of departure in the 1991 *Guidelines for Developmental Toxicity* (USEPA 1991a). Use of the BMD approach became standard practice in 1996 after a series of workshops and case studies demonstrated its usefulness and comparability to the no-observed-adverse-effect-level (NOAEL) and lowest-observed-adverse-effect-level (LOAEL) approach exclusively used at the time (Allen et al. 1994; Barnes et al. 1995). ATSDR and CalEPA began using the BMD approach for their noncancer toxicity values in 2000.

Figure 1. Dose Response Curve Illustrating the Benchmark Dose and the Lower Confidence Level on the Benchmark Dose, the BMDL

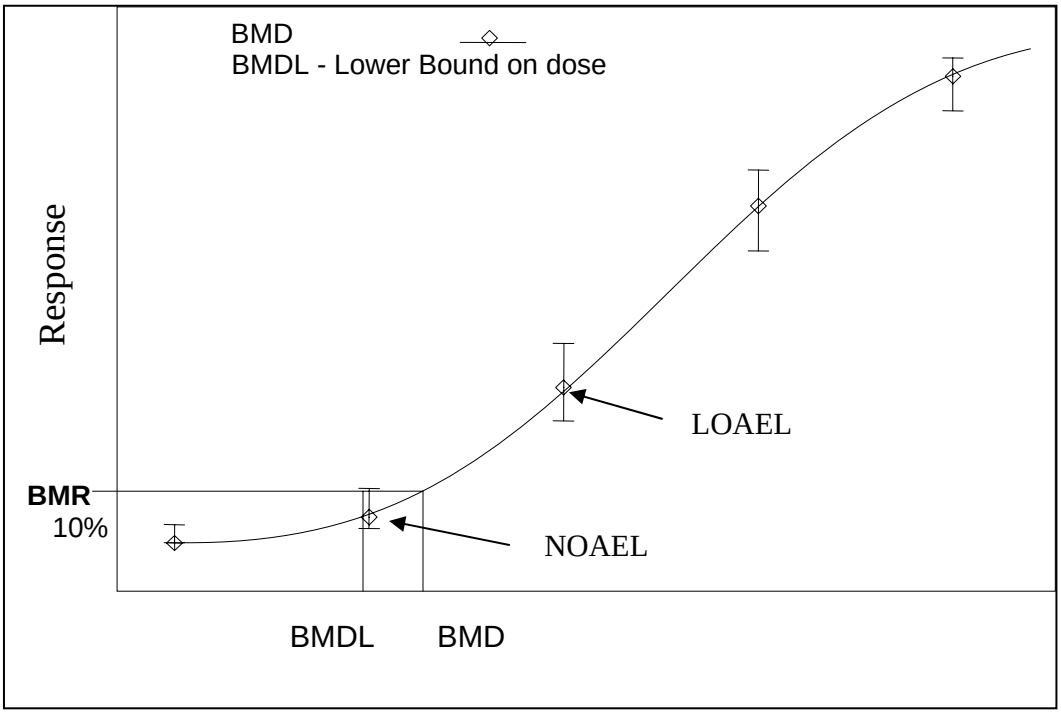

Figure generated using software available at USEPA Website: http://epa.gov/ncea/bmds.htm

The BMD method fits a dose-response curve to the effect data across all doses as shown in Figure 1, estimates the dose associated with a defined benchmark response[6], and calculates the statistical 95% lower confidence limit on the estimate of the dose, the BMDL. The BMDL is used as the POD in the next step of the extrapolation (USEPA 1991a; 1995; 2000). The BMD

[6] Benchmark Response (BMR): An adverse effect, used to define a benchmark dose from which an RfD (or RfC) can be developed. The change in response rate over background of the BMR is usually in the range of 5-10%, which is the limit of responses typically observed in well-conducted animal experiments (USEPA 2009a).

method can be implemented using the BMDS software developed and supported by USEPA (2009b). The BMD approach requires more data than the NOAEL/LOAEL approach but provides a more consistent estimator for the POD because it makes use of all of the dose-response data, uses an identified response rate and accounts for uncertainty in the estimate of the dose-response function.

Prior to the development and acceptance of the benchmark dose approach for quantitative characterization of an explicit effect level as the POD, treated groups in a study were identified as a NOAEL or a LOAEL. The disadvantages of using the NOAEL and LOAEL for developing toxicity values are that they do not provide a consistent point of departure (effect level) as the no effect or lowest effect level may be under- or over-estimated depending on the dose spacing used in the study, and they are sensitive to the quality of the study and its power to detect effects because the LOAEL is the dose where the response is statistically (or biologically) different from the control response.

MassDEP supports the use of the BMD methodology for characterizing the dose-response and the point of departure for the TEL and the NTEL when data are sufficient, and the NOAEL/LOAEL approach for other cases.

4.2.3 ***Extrapolation Methods – Uncertainty Factors***

Once the point of departure is determined for a response, it is adjusted to extrapolate from the study population to the human population including susceptible populations. The goal is to use all available scientific information for the extrapolation from the study population to the human population. Ideally chemical-specific MOA information and biologically-based models (e.g., PBPK models) would be used to inform the extrapolation. However, available information is usually too limited, so the biologically supported USEPA HEC method described in Section 4.2.1 and default uncertainty factors are used for the extrapolation in most cases.

The reference concentration is derived using the equation,

$$RfC = \frac{\text{POD (BMDL or NOAEL or LOAEL)}}{UF_A \times UF_H}$$

Default uncertainty factors, usually a factor of 10 each, are applied to account for the extrapolation from animals to humans (UF_A) and to account for susceptible individuals in the human population (UF_H) (Lehman and Fitzhugh 1954; USEPA 1994).

Additional default uncertainty factors are applied to the POD in cases when the database is limited, including:

- UF_S to extrapolate from a subchronic (less than life-time) study to chronic study duration;
- UF_L to extrapolate from a LOAEL to a NOAEL, when adverse effects different from control were seen at the lowest dose tested (and a BMDL could not be calculated); and

- UF_D to account for an incomplete database (e.g., missing studies evaluating developmental or reproductive effects).

The rationale and data supporting the selection and application of these uncertainty factors can be found in Dourson and Stara (1983), Barnes and Dourson (1988), and USEPA (1994) among others.

Since the publication of the RfC methodology by USEPA in 1994, research has continued on the theoretical and empirical underpinnings of the uncertainty factors. Researchers including, Hattis et al. (1999), Baird et al. (1996), and Renwick and Lazarus (1998) have evaluated the theoretical constructs supporting the uncertainty factors and developed and evaluated empirical databases to quantify variability and uncertainty in the estimates of the uncertainty factors.

This research has led to the recommendations from USEPA (2002a), WHO (2005) and CalEPA (2008) that UF_A and UF_H both be explicitly considered as comprised of two components, pharmacokinetics and pharmacodynamics. Chemical-specific information can be used to determine the values for each component, or in the absence of such data, default values can be used.

The application of uncertainty factors during the development of a toxicity value has evolved over time based on research described above. Table A-1 in Appendix A summarizes changes by USEPA, CalEPA and ATSDR over time. The following sections, describe the current understanding of the uncertainty factors.

4.2.3.1 UF_A – Animal to Human Extrapolation

The uncertainty factor, UF_A, is applied to account for cross-species extrapolation and the uncertainty in that extrapolation, and can be thought of as comprised of two components accounting for cross-species differences in pharmacokinetics ($UF_{A\text{-}k}$) and pharmacodynamics ($UF_{A\text{-}d}$).

As described in Section 4.2.1, the HEC method is intended to account for pharmacokinetic differences between the test animal and human populations based on physiology and structure of the respiratory systems and physico-chemical properties of the chemical. However, as currently developed the HEC method does not account for differences in metabolism or excretion of a chemical at the point of exposure in the respiratory system or systemically, potentially important components of pharmacokinetics.

USEPA (1994; 2002a) considers the HEC method sufficiently conservative for estimating the animal to human extrapolation such that they conclude that there is no need for an uncertainty factor to account for the uncertainty in the pharmacokinetics component of the animal to human extrapolation (i.e., $UF_{A\text{-}k}$=1). However, CalEPA (2008) recommends that a factor of 2 be applied for $UF_{A\text{-}k}$ to account for uncertainty in pharmacokinetics related to metabolism and excretion that is not quantitatively accounted for by the HEC method.

The HEC method does not address pharmacodynamic differences between the test animal and human populations, i.e., differences in the target tissues, function, susceptibility to perturbation,

or ability to recover from an insult. USEPA (1994) recommends that when the HEC method is used for dosimetric adjustment, that instead of the default factor of 10 for UF_A, a partial factor ($10^{0.5}$ rounded to 3)[7] be used to account for the potential differences in pharmacodynamics (UF_{A-d}) in the extrapolation from the test animal to human population. ATSDR uses USEPA's approach for both components of UF_A. The CalEPA (2008) value for UF_{A-d} is consistent with USEPA (1994).

4.2.3.2 UF_H – Human Variability

The uncertainty factor, UF_H, is applied to account for human population variability in response and can also be thought of as comprised of two components accounting for differences in pharmacokinetics (UF_{H-k}) and pharmacodynamics (UF_{H-d}).

Unless there are data to support a chemical-specific value for population variability in metabolism or response, USEPA (1994; 2002a) recommends using the default factor of 10 for UF_H (covering both UF_{H-k} and UF_{H-d}). However, values greater than 10 are not excluded and it is acknowledged that children were not specifically considered when estimating the range of variability (USEPA 2002a). ATSDR uses USEPA's approach for both components of UF_H.

To investigate if the existing risk assessment practice of using a factor of 10 for UF_H is protective of children, CalEPA (2008) conducted a review of the literature evaluating variability in pharmacokinetics in infants, children and adults. In addition, they investigated interindividual variability using existing PBPK models for chemicals with sufficient chemical-specific and age-specific pharmacokinetic information. Their results indicate that interindividual variability in pharmacokinetics is greater than a factor of 3. Based on these results, CalEPA (2008) recommends default values of 10 for UF_{H-k} "to allow for diversity, including infants and children, when there are no human kinetic data," a value of 3 for UF_{H-d} if there is no reason to suspect that children are particularly susceptible, and a value of 10 for UF_{H-d} if there is a reason to suspect that children are particularly susceptible.

MassDEP supports explicit consideration of separating pharmacokinetic and pharmacodynamic variability from uncertainty when adjusting the point of departure observed in a study to a concentration for lifetime exposure of the human population.

4.3 Cancer – For Chemicals Assumed to Act by a Linear Mode of Action

USEPA released updated cancer guidelines in 2005 along with supplemental guidance for evaluating the potential for increased susceptibility following early-life exposure (USEPA 2005a,b). The major thrust of the updated guidelines is shifting the focus of the evaluation to using chemical-specific information as much as possible, and default approaches only in cases where specific information is inconclusive or not available. The overall structure of the approach for developing a cancer toxicity estimate (e.g., cancer slope factor for oral exposures and inhalation unit risk for inhalation exposures) in the new guidelines is the same as that in the original cancer guidelines (USEPA 1986) informed by the National Research Council 1983 and 1994 reports on risk assessment including, hazard identification, dose-response, human exposure and risk characterization.

[7] A partial factor of 10, the square root of 10 ($10^{0.5}$) is typically rounded from 3.16 to 3 when applied singly, but when 2 partial factors of 10 are applied, they are combined into a factor of 10.

Most of the cancer toxicity values currently in use are based on versions of USEPA's cancer guidelines that pre-date the 2005 guidelines. Cancer toxicity values developed prior to the 2005 cancer guidelines are still considered valid by USEPA. The major revisions in the 2005 cancer guidelines are summarized in the following four sections with attention given to their potential to influence the development of NTELs.

4.3.1 *Hazard Identification*

Within the hazard identification step of the risk assessment all available data are collected and evaluated for evidence of carcinogenic or mutagenic effects, the MOA, and the overall weight-of-evidence (WOE) for carcinogenic potential. The WOE is summarized in a narrative and by using one of the five new standard descriptors of carcinogenic potential,

"Carcinogenic to Humans,"
"Likely to be Carcinogenic to Humans,"
"Suggestive Evidence of Carcinogenic Potential,"
"Inadequate Information to Assess Carcinogenic Potential," and
"Not Likely to be Carcinogenic to Humans" (USEPA 2005a).

These descriptors replace the letter designations for WOE introduced in the 1986 Cancer Guidelines that were used during the development of the NTELs in the CHEM/AAL method,

"A - Human carcinogen,"
"B1 – Probable Human Carcinogen based on limited evidence in humans and sufficient evidence of carcinogenicity in animals,"
"B2 - Probable Human Carcinogen based on sufficient evidence of carcinogenicity in animals,"
"C – Possible human carcinogen,"
"D – Not classifiable as to human carcinogenicity," and
"E – Evidence of non-carcinogenicity for humans" (USEPA 1986).

International Agency for Research on Cancer (IARC) (WHO 2006) and National Toxicology Program (NTP) (NTP 2005) also evaluate the WOE for chemicals in their programs. Table A-2 in Appendix A provides the WOE descriptors for USEPA, IARC and NTP; matching the interpretation of the descriptors across agency and changes over time by USEPA.

The USEPA 2005 cancer guidelines now permit more than one WOE descriptor to be applied to a chemical by exposure route. For example, a chemical could be judged by the WOE as "Likely to be Carcinogenic to Humans," from inhalation exposure, and as "Inadequate Information to Assess Carcinogenic Potential" from oral exposure.

The 2005 cancer guidelines focus on the need to understand the MOA of a chemical as the key feature for evaluating its carcinogenic potential by different routes of exposure, across exposure levels, for extrapolating from animals to humans, and for identifying susceptible populations. These guidelines request that explicit consideration be given to the possibility that multiple modes of action can be involved with development of a single type of tumor, at different levels of exposure, by different routes of exposure and for different species depending on the characteristics of the chemical (USEPA 2005a).

The MOA of a carcinogenic chemical determines the method used to extrapolate cancer toxicity from the observed doses in the studies to the lower environmentally relevant doses. If there is evidence that a chemical acts through a mutagenic MOA or the information about MOA is too limited to determine the MOA, the chemical is assumed to have a linear dose-response at low levels (i.e., some risk is assumed at any dose above zero), then the dose-response and low dose extrapolation methods described in Section 4.3.2 are used. If there is sufficient scientifically defensible evidence that a chemical acts through a non-linear mode of action (i.e., assumes that there is a dose with no risk), then the method used to derive an RfD/RfC is used. In addition, the 2005 cancer guidelines (USEPA 2005a) specify that chemicals determined to act through a mutagenic MOA are evaluated for increased susceptibility from exposures during early-life.

MassDEP supports the use of MOA data as a key feature for evaluating carcinogenic potential and for estimating cancer potency.

4.3.2 ***Dose-response***

The USEPA 2005 cancer guidelines (USEPA 2005a) recommend adjusting exposure concentrations and doses to human equivalent concentrations (HEC) prior to conducting the dose-response assessment. Standard practice is to use the chemical-specific approaches to adjust exposure concentrations or doses using biologically based models or PBPK models to the extent possible especially for data-rich chemicals. In the absence of chemical-specific information, inhalation exposures are extrapolated using the HEC methods (USEPA 1994).

In a shift from the USEPA 1986 cancer guidelines (USEPA 1986) that used the linearized multi-stage dose-response model to model down to low doses, the USEPA 2005 cancer guidelines (USEPA 2005a) recommend carrying out the dose-response assessment in two parts. The first step is to evaluate the dose-response function in the range of the bioassay responses using benchmark dose methods (BMD). The dose associated with the benchmark response, e.g., the effective response rate of 5 % (ED05) or 10% (ED10) and the 95% lower confidence limit on the estimate of the dose (BMDL) is used as the point of departure (POD). The second step is to extrapolate from the point of departure to estimate an acceptable human population exposure level. As described in Section 4.3.1, information about the mode of action of the chemical determines the method used to extrapolate to lower exposure levels. Non-linear extrapolation from the POD, i.e., the method for deriving an RfC or RfD, is used when "there are sufficient data to ascertain the mode of action and conclude that it is not linear at low doses and the agent does not demonstrate mutagenic or other activity consistent with linearity at low doses" (USEPA 2005a). A linear extrapolation from the POD to the origin is used when the data indicate that the chemical acts by a mutagenic mode of action or as the default if there is insufficient evidence to support a non-linear mode of action. If a biologically based dose-response model is available, it can be used to extrapolate to lower levels.

When there are data on more than one tumor type or precursor, all tumors and precursor responses are carried through the full process and a judgment is made at the end about what data best represent the human cancer toxicity.

MassDEP supports the use of BMD analysis of the dose-response data to establish the POD and use of MOA to determine the method of low dose extrapolation for carcinogens.

4.3.3 *Risk Characterization*

The 2005 cancer guidelines include explicit language related to expressing the uncertainty in the risk estimates citing the Office of Management and Budget Circular A-4 (OMB 2003) emphasizing that agencies should present a probability distribution of the risk or at a minimum present central estimate and upper and lower bounds of the risk estimate (USEPA 2005a; OMB 2003).

The lower bound on the dose or upper bound on the risk are typically used for estimating risk in a human health risk assessment and deriving guideline values. However, the central estimate and the range of the upper and lower bounds on the risk estimate are useful for characterizing the uncertainty in the cancer toxicity estimate.

MassDEP supports characterizing and presenting the uncertainty in the toxicity values, however the currently available point estimates of cancer toxicity based on upper bound estimates of potency will be used until probability distributions of the risk estimates are widely available.

4.3.4 *Early-life Exposure to Carcinogens*

USEPA released the Supplementary Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (USEPA 2005b) in conjunction with the 2005 cancer guidelines (USEPA 2005a). As described in Section 6.6, implementation of USEPA's guidelines by MassDEP will be addressed in a separate document describing MassDEP guidelines for protecting children's health.

MassDEP supports explicit consideration of increased susceptibility to cancer from early-life exposure when characterizing cancer risk to human populations.

4.4 Children's Health

Evidence showing the potential for increased susceptibility in children from environmental exposures was initially summarized by the Committee on Pesticides in the Diets of Infants and Children (NRC, 1993). Since then, regulatory guidance has been developed in order to protect children including,

- Food Quality Protection Act (FQPA) (FQPA 1996),
- Supplementary Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (USEPA 2005b),
- Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants (USEPA 2005c),
- Framework for Assessing Health Risks of Environmental Exposures to Children (USEPA 2006a).

The TELs and NTELs developed using the CHEM/AAL method include a factor of 1.75 to protect children from increased exposure compared to adults by explicitly accounting for the increased daily average ventilation rate on a volume per body weight basis (MassDEP 1990). At this time, CalEPA and Minnesota Department of Health, and to a lesser extent USEPA, but not

ATSDR have developed toxicity values and regulatory values that incorporate assumptions about exposure and increased susceptibility of children. During the process of updating the toxicity values to include explicit consideration of children's susceptibility, the existing toxicity values are still considered valid by these agencies.

MassDEP is in the process of developing guidelines for use in deriving guidance values that incorporate consideration of the special characteristics of children that increase susceptibility. The MassDEP Children's Guidelines, to be developed in a separate document as discussed in Section 6.6, will be applied to the approach described in Section 5 for updating the air guideline values.

MassDEP supports explicit consideration of the potential for increased exposure and susceptibility of children to chemicals in the environment.

5.0 APPROACH FOR UPDATING EXISTING AIR GUIDELINES

Updating AALs or any toxicity guidance value is an iterative process informed by new data and methods. A number of approaches were considered in light of the new guidance described above. The goals considered when selecting an approach for updating the existing air guidelines are that the method must be:

- Scientifically defensible;
- Efficient, i.e., minimize the amount of effort spent to develop a high quality air guideline;
- Adequate for meeting program manager's needs for regulating ambient air; and
- Intended to provide public health protection from health effects from chronic exposure.

Developing guidelines and the underlying toxicity basis is a time intensive process. In order to provide an efficient and scientifically defensible means of revising existing air guidance, existing peer reviewed toxicity values from respected sources will be used as the basis of the new MassDEP air guideline values.

The overall approach to updating the guideline values is similar for both noncancer (TEL) and cancer (NTEL) effects, shown in Figures 3 and 4, respectively. The intended level of protection for life-time exposure remains the same as with CHEM/AAL, i.e., the TEL is intended to prevent noncancer health effects and includes a relative source contribution (RSC) factor to account for exposures from sources other than ambient air; the NTEL uses 1 in a million (10^{-6}) excess lifetime cancer risk as the target cancer risk.

The potential for increased susceptibility in children will be considered during the derivation of all toxicity values using the methods described in the MassDEP Children's Guidance, Section 6.6.1, once it is completed.

5.1 Step 1 - Database of Available Inhalation Toxicity Values

Inhalation toxicity values from USEPA, e.g., RfCs and URs from IRIS, and their equivalents from other reputable peer-reviewed sources, including CalEPA, ATSDR, states that are part of Northeast States for Coordinated Air Use Management (NESCAUM); and other agencies that have a peer reviewed guideline value will be collected and serve as the basis of the new MassDEP air guidelines[8]. Weight of evidence evaluations for carcinogenic potential will be collected from USEPA, International Agency for Research on Cancer (IARC) and National Toxicology Program (NTP).

The database will include the fields listed in Table A-3 in Appendix A. The chemicals included in the database are described in Section 6.1.

5.2 Step 2 - Approach for Chemicals with Available Toxicity Values

The approach for chemicals that have peer reviewed toxicity values is described in the sections below and in Figures 2, 3 and 4 for weight of evidence evaluation, noncancer and cancer toxicity values, respectively.

If there are no toxicity values available for a chemical that is currently on the AAL list and has been identified as a high priority by MassDEP programs, the chemical will be considered later in the process using the approach described in Section 5.3.

5.2.1 *Weight of Evidence (WOE) for Carcinogenic Potential*

For each chemical, the WOE evaluations conducted for carcinogenic potential will be reviewed. WOE evaluations conducted by IARC, NTP and USEPA use different terminology to describe the evidence available for classifying carcinogenic potential of a chemical. Table A-2 in Appendix A provides a comparison of evidence and cancer classification terminology across the groups evaluating WOE and changes in terminology across time. Different agencies may assign different cancer classifications for the same chemical because the evaluations were done at different times, with different data, with different criteria, and by different experts.

When the WOE evaluations from different agencies yield different WOE classifications for the same chemical, the dates and rationale of the available WOE classifications will be reviewed. In the absence of newer definitive evidence in a WOE evaluation that supports otherwise, the cancer classification suggesting a greater potential for carcinogenicity will be used for the chemical.

A chemical will be considered to have carcinogenic potential when the WOE evaluation results in a chemical being classified as Group C or higher using 1986 terminology (USEPA 1986) or equivalent. As illustrated in Figure 2, if a unit risk is available, it will be used to estimate the NTEL. If there is no UR available, but there are noncancer toxicity values available for deriving a TEL, the TEL will be divided by a factor of 10 to account for the potential for carcinogenic effects. This approach was consistent with that used in CHEM/AAL and by the USEPA Office of Water for Group C chemicals (USEPA 2002b).

[8] Selection of a particular value derived by sources other than MassDEP is not intended to imply that the methods and data used for derivation of the value are those that would have been used by MassDEP. Values selected through the updating process are viewed by MassDEP as the best of those available.

5.2.2 *Noncancer*

For each chemical, the most recent RfC or equivalent will be adopted if available toxicity values for the chemical are within a factor of three[9] of each other (Figure 3). Chemical-specific information about basis of the selected toxicity value will be documented in the database using the data fields listed in Appendix A, Table A-3.

If the available RfC and equivalents are different by more than a factor of three from each other, indicating uncertainty about the best value, the basis of each value will be documented using the data fields listed in Appendix A, Table A-3. The toxicity value that will serve as the basis of the TEL for the chemical will be decided from among the available values based on the quality of the data evaluated and the approach used to extrapolate to the general human population. Weight will be given to values based on newer studies, studies with greater ability to detect effects, studies where more sensitive effects were evaluated and studies where dosimetric and dose-response extrapolation methods were most consistent with current methods. If one value cannot be identified as superior to another, the more health protective value will be selected.

The RfC, or equivalent, selected as the basis of the TEL will be adjusted by the relative source contribution factor (RSC) to derive a TEL. The default RSC of 0.2, used by CHEM/AAL methodology[10], will be used unless there is evidence to support a different RSC. The application of a RSC to a TEL was re-evaluated; a description of the process of the evaluation and conclusions are included in Appendix B. Once the MassDEP children's guidance document is completed, additional steps to evaluate consideration of children susceptibility included in the RfC may be incorporated into calculation of the TEL.

5.2.3 *Cancer*

For each chemical, the most recent unit risk (UR) will be adopted if available toxicity values for the chemical are within a factor of three of each other (Figure 4). Chemical-specific information about the basis of the selected toxicity value will be documented in the database using the data fields listed in Appendix A, Table A-3.

If the available URs are different by more than a factor of three from each other the basis of each value will be documented using the data fields listed in Appendix A, Table A-3. As for the TEL, the toxicity value that will serve as the basis of the NTEL for the chemical will be decided from among the available values based on the quality of the data evaluated and the approach used to extrapolate to the general human population. Weight will be given to values based on newer studies, studies with greater ability to detect effects, studies where more sensitive effects were evaluated and studies where dosimetric and dose-response extrapolation methods were most consistent with current methods. If one value cannot be identified as superior to another, the more health protective value will be selected.

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[9] The value of three was chosen for this criteria (rather than 1 or 10 or some other value) recognizing that there is uncertainty in all toxicity values, that professional judgment plays a role in determining the value to assign to each uncertainty factor, and because three is one-half the value of a full uncertainty factor default value of 10 and is the smallest incremental difference in uncertainty factor value that is typically applied.

[10] The RSC of 0.2 (20%) was used for deriving TELs for all chemicals evaluated by CHEM/AAL. A RSC of 1 was applied to ammonia, hydrochloric acid and hydrogen sulfide when TELs were updated in 1995 (MassDEP 1995).

Figure 2. Weight of Evidence Evaluation

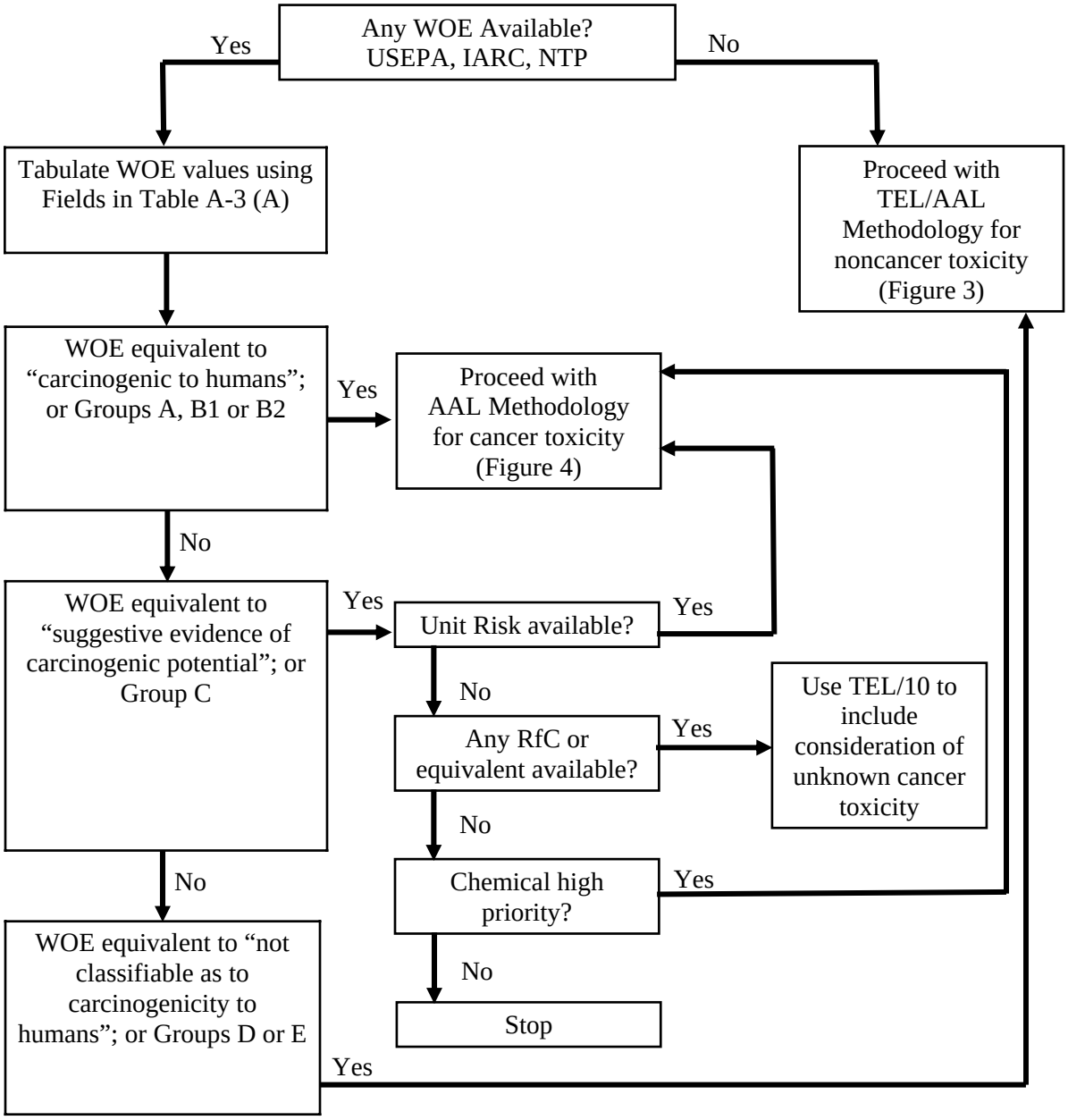


Figure 3. TEL/AAL Methodology for Noncancer Toxicity

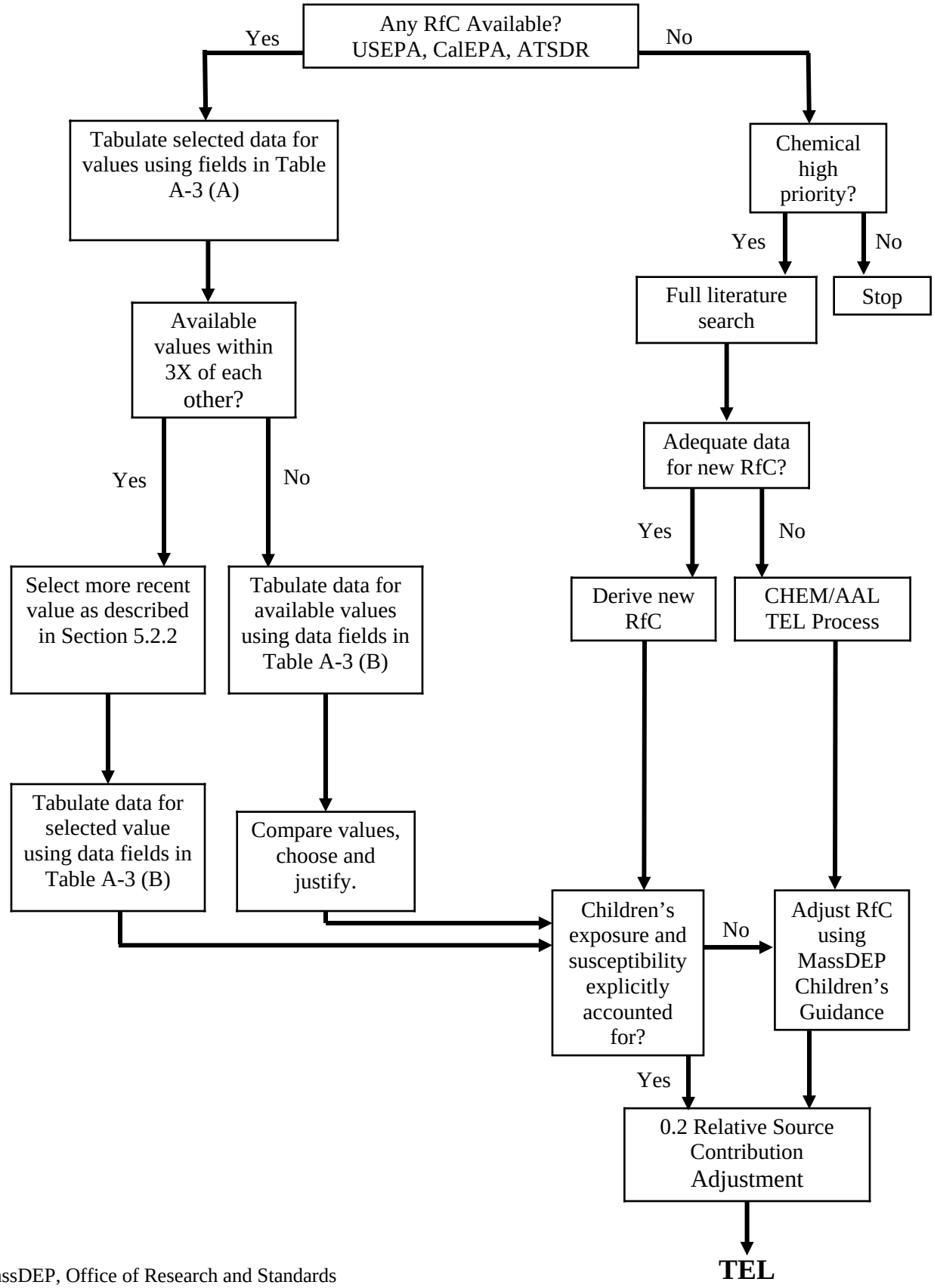
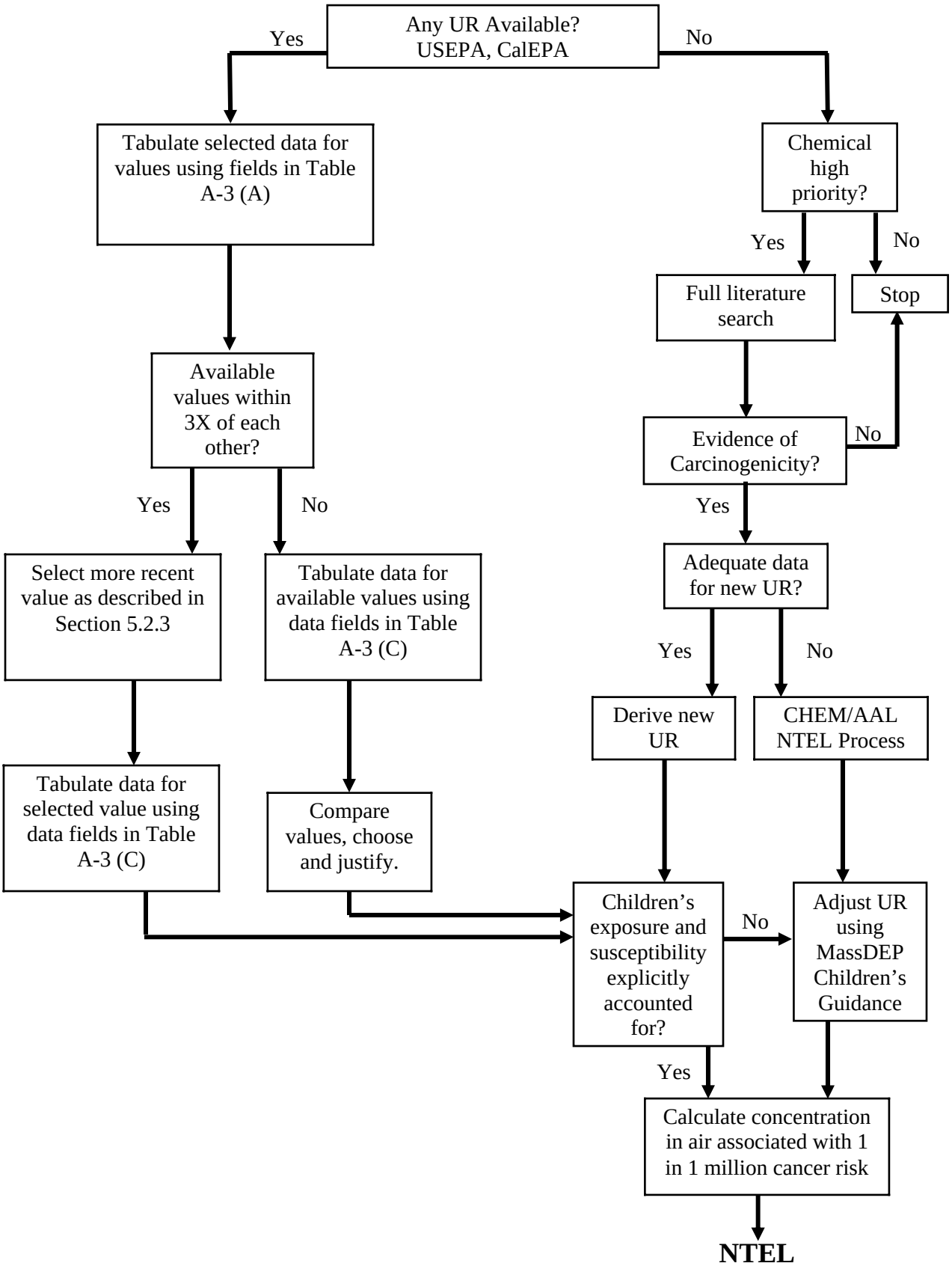


Figure 4. NTEL/AAL Methodology for Cancer Risk



The UR selected as the basis of the NTEL will be used to calculate the concentration associated with a 1 in 1 million excess lifetime cancer risk to derive a NTEL. Chemicals identified by USEPA as mutagenic and with increased susceptibility associated with early-life exposures will be adjusted as indicated by USEPA Cancer Guidelines (2005a,b) and associated directives. Once the MassDEP children's guidance document is completed, additional steps to evaluate consideration of children susceptibility included in the UR may be incorporated into calculation of the NTEL.

5.3 Step 3 - Approach for Chemicals without Existing Toxicity Values

For chemicals that are determined to be high priority for MassDEP without available peer reviewed toxicity values other than from CHEM/AAL, toxicity values will be derived *de novo* as indicated in Figures 3 and 4, TEL and NTEL respectively. Deriving a value *de novo* is a labor intensive process, thus will be limited to chemicals that are determined to be a high priority to the Department.

The process to derive a toxicity value *de novo* begins with a literature search for toxicological information. If the literature search produces data that are judged to be adequate to support the derivation of toxicity values, RfC or UR, then the toxicity values are derived using the MassDEP guidelines for *de novo* development of TELs and AALs. The MassDEP *de novo* Guidelines are under development and will incorporate aspects of the new methodologies employed by USEPA and CalEPA as described in Section 4.

Given the level of effort required for *de novo* derivation of a toxicity value, for chemicals with peer reviewed oral toxicity values, inhalation toxicity values may be developed using cross-route extrapolation methods if the effects are expected to occur systemically. The uncertainty associated with the cross-route extrapolation will be considered in the context of the uncertainty associated with not accounting for potential toxic effects if the chemical is not included in the health evaluation. Like-wise, structurally related chemicals may be used as surrogates for chemicals without toxicity values.

5.4 Step 4 - Peer Review

Air guidelines developed using this methodology will be peer reviewed by scientists within ORS.

6.0 IMPLEMENTATION OF THE UPDATING APPROACH

6.1 Chemicals for Air Guidelines

The current list of air guidelines, TELs/AALs and ATCs, contain inhalation toxicity criteria information for 109 chemicals. Since the list was originally established additional chemicals have been recognized as of interest to MassDEP programs. Also, the original chemical list contained chemicals included for the purpose of validating CHEM/AAL method development rather than program needs. Thus the number of chemicals needing air guidance values has expanded, but some chemicals on the current list would be a low priority for the re-evaluation process based on program needs.

The current list of chemicals with air guidelines was compared to the lists of chemicals regulated under the Bureau of Waste Prevention (BWP) and Bureau of Waste Site Cleanup (BWSC) programs including:

1) the Clean Air Act Hazardous Air Pollutant (HAP) list (regulated by BWP), including chemicals identified as important contributors to risk in Massachusetts by the 1999 National-scale Air Toxics Assessment (NATA) (USEPA 2006b);
2) the AP-42 list, including landfill gases, used as a reference list for conducting facility impact assessments (FIA) under the BWP solid waste facility site assignment and permitting program (MassDEP 2006a, Table 6);
3) the list of Groundwater-2 (GW-2) standards (i.e., groundwater concentrations back-calculated from acceptable indoor air concentrations based on vapor intrusion modeling) regulated under BWSC (MassDEP 2006b); and
4) chemicals identified as priority chemicals by the Toxics Use Reduction Act (TURA) program (MassDEP 2005).

Chemicals that appear on a program chemical list, but not on the air guideline list were put on a list of proposed additions. BWP program managers and regional air permit chiefs were given the opportunity to review and comment on the proposed additions.

The program managers and permit chiefs identified the following chemicals as high priority for review:

- Acrolein
- Arsenic
- Ammonia
- Cadmium
- Formaldehyde
- Hydrogen Sulfide
- Organics in gasoline:
    - Benzene
    - Ethanol
    - Toluene
    - Xylene
- Other combustion by-products (not otherwise specified)
- Tetrachloroethylene

As shown on Table 1, most of the eleven chemicals identified as high priority by BWP have toxicity values available to derive TELs and NTELs. Acrolein, ammonia, hydrogen sulfide, toluene and xylene do not have toxicity values for evaluation of cancer toxicity because they are not considered carcinogens at this time. Ethanol does not have any available toxicity values from USEPA, CalEPA or ATSDR.

Table 1. Availability of Toxicity Values from USEPA, CalEPA and ATSDR for Chemicals Identified as High Priority by BWP

		Toxicity Value Available to Support TEL		Toxicity Value Available to Support NTEL	
CAS Number	**Pollutant Name**	**Yes**	**No**	**Yes**	**No**
107028	Acrolein[a]	X			NC[b]
7664417	Ammonia	X			NC
7440382	Arsenic (inorganic)	X		X	
N/A	Arsenic Compounds (inorganic, may include arsine)	X		X	
7784421	Arsine	X		X	
71432	Benzene	X		X	
7440439	Cadmium (including compounds)	X		X	
64175	Ethanol		X		X
50000	Formaldehyde	X		X	
7783064	Hydrogen Sulfide	X[c]			NC
127184	Tetrachloroethylene	X		X[c]	
108883	Toluene	X			NC
1330207	Xylenes (isomers and mixture)	X			NC

[a] Acrolein is a new chemical that will be added to the list of chemicals with air guideline values.
[b] NC indicates that the chemical is not considered a carcinogen.
[c] MassDEP has developed *de novo* guideline values for this chemical.

6.2 Prioritizing Chemical Review

The air guidelines will be updated in groups of chemicals based on prioritization by MassDEP programs and availability of toxicity values. MassDEP programs will be included in the ongoing process of identifying priority chemicals, development of guidelines, and process for implementing new guidelines within the respective programs.

Group I Chemicals

Group I chemical are those that have inhalation toxicity values derived by IRIS, CalEPA, ATSDR or other agency. Of the 163 Group I chemicals, 86 have an AAL/TEL, while 77 chemicals do not but were identified as of interest to one or more MassDEP program. Group I chemicals that currently have an AAL are listed in Table C-1 of Appendix C and those that do not currently have an AAL are listed in Table C-2 of Appendix C.

Group I chemicals will be updated in batches selected in consultation with BWP to coordinate with MassDEP program priorities.

Group II
Group II chemicals are the chemicals that do not have published inhalation toxicity values, but are of interest to the air toxics and 21E programs. Seven of the 20 Group II chemicals currently have an AAL/TEL, while the remaining 13 do not. In Appendix C, Table C-3 lists chemicals with an AAL and Table C-4 lists chemicals without an AAL. These chemicals would require *de novo* development of toxicity values. These chemicals will be selected for updating when program managers determine that the chemical is needed for decision making in their programs.

Group III
Group III chemicals consists of 50 chemicals that do not have published inhalation toxicity values and are a low priority for MassDEP programs. The 16 chemicals with an AAL/TEL that are not used in MassDEP programs are listed in Table C-5 and the 34 chemicals included in NATA without an AAL/TEL are listed in Table C-6 of Appendix C. These chemicals would require *de novo* development of toxicity values. Group III chemicals with an existing AAL/TEL are unlikely to be updated unless they become Group II chemicals based on program needs. In the future, they could be considered for removal from the air toxics list.

6.3 Presentation of Values

The presentation of the air toxicity guidance values is intended to be transparent. For each chemical, the list of guidelines will present the TEL (an ambient air concentration), NTEL (an ambient air concentration), AAL (an ambient air concentration), and the date of the last time the guidelines were evaluated, as illustrated in Figure 5.

Figure 5. Proposed Table Format for New ORS Air Guidelines

CHEMICAL NAME Chemicals with summaries have links to MS Word files directly below.	Threshold Effects Exposure Limit TEL	Allowable Ambient Limit AAL	Year Evaluated
	24-hour average	annual average	
	ug/m^3 ppb	ug/m^3 ppb	

NTEL, TEL and AALs will be presented to one significant figure in units of ug/m^3. This is consistent with the general rule for calculations involving multiplication and division, that the final number of the calculation is rounded to the same number of significant figures as the least precise parameter used in their calculation, i.e., the toxicity values. Values will also be presented in units of ppb for the convenience of users. Values in units of ppb will be calculated from the NTEL, TEL and AAL in ug/m^3 after it has been round to one significant figure. Concentrations measured in units of ppb can be transformed to ug/m^3 using all significant figures applicable to the measured concentration in ppb, assuming the molecular conversion factor has an infinite number of significant figures, and then rounded to one significant figure for comparison to the Air Guidelines.

The single new list of MassDEP Air Guidelines will include the newly derived values and existing AAL/TELs that have not yet been revised. Over time, AALs/TELs will be updated

following their review. The Air Guideline list will be updated with new values as they are completed in coordination with the Air Program.

The air guidelines will be posted on the MassDEP web. A description of the health basis underlying each type of guideline will be developed to accompany the air guidelines. An email alert will be sent to programs and interested parties when new values are updated.

6.4 Plan for Ongoing Review

Once a majority of Air Guidelines have been revised, an annual review process will be put in place. The annual review process will involve searching USEPA, CalEPA, ATSDR, and other databases to check for revised toxicity values. If revised values are located, then the Air Guideline for that chemical will be flagged for possible review and revision.

6.5 Updating Process and Use of Current AALs

The updating process will be conducted on batches or groups of chemicals over time. Existing AALs and TELs will be considered valid while they are waiting to be reviewed.

6.6 Plan for Future Guidance

MassDEP plans to develop additional guidance in the future to address children's health, less than lifetime exposure, and *de novo* derivation of guidance values. Once drafted, the guidance documents will be peer reviewed.

6.6.1 ***Children's Health***

MassDEP is developing guidance to incorporate quantitative consideration of increased susceptibility of children in future guidance values. MassDEP's guidance will build on the work by USEPA, CalEPA and others.

6.6.2 ***Less than Lifetime Exposure***

MassDEP plans to develop guidance for developing toxicity values for less than lifetime exposure to residents including children.

6.6.3 ***Guidance for Development of de novo Toxicity Values***

MassDEP plans to develop guidance for developing *de novo* inhalation toxicity values for high priority chemicals without peer reviewed toxicity values.

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Appendix A

Supporting Documentation

Appendix A
Supporting Documentation

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Table A-1. Current and Historical Application of Uncertainty Factors by Agency

Agency	Year	Animal to Human Extrapolation (UF_A)	Human Population Variability (UF_H)	Rationale
USEPA		10	10	Historical for oral exposure, Lehman and Fitzhugh (1954)
USEPA	1989	UF_{AK} = 1 (with HEC)* UF_{AD} = 3 (= $10^{0.5}$)	10	Inhalation exposure extrapolated from animal to human with Human Equivalent Concentration (HEC) methodology (draft 1989, final 1994). HEC methodology is intended to account for animal to human pharmacokinetics. UF_{AK} = 1 assumes that HEC provides cross-species extrapolation of pharmacokinetics with sufficient protection that uncertainty in extrapolation is included in HEC. The UF_{AD} of 3 accounts for pharmacodynamic differences between animals and humans.
ATSDR	1992			ATSDR begins using HEC; adopts EPA UF approach
CalEPA (OEHHA)	1999			OEHHA begins using HEC, adopts EPA UF approach.
USEPA	2002	UF_{AK} = 1 (with HEC) UF_{AD} =3 (=$10^{0.5}$)	UF_{HK} = 3 (= $10^{0.5}$) UF_{HD} = 3 (= $10^{0.5}$)	USEPA (2002) recommends explicitly considering the contribution of pharmacokinetics and pharmacodynamics to uncertainty in each extrapolation.
WHO - IPCS (International Programme on Chemical Safety)	2005	UF_{AK} = 4 (= $10^{0.6}$) UF_{AD} =2.5 (=$10^{0.4}$)	UF_{HK} = 3 (= $10^{0.5}$) UF_{HD} = 3 (= $10^{0.5}$)	WHO (2005) does not explicitly suggest a value for UF_{AK} when the HEC method is used, but this could be considered a type of pbpk model.
CalEPA (OEHHA)	2008	UF_{AK} = 2 if HEC = 1 if pbpk model = 3 if no other extrapolation UF_{AD} =3 (= $10^{0.5}$)	UF_{HK} = 10 to protect infants and children variability = 3 (= $10^{0.5}$) if direct contact mechanism UF_{HD} = 3 (= $10^{0.5}$) unless the endpoints are those that suggest children may be more susceptible, then use 10.	

* This nomenclature, UF_{AK} for pharmacokinetics and UF_{AD} for pharmacodynamics, was not used in the HEC methodology description but has become the standard of practice so is used here to facilitate comparison across agencies and time. The nomenclature is consistent with intent of the HEC methodology which describes the default dosimetry (HEC) as accounting for variability in disposition (pharmacokinetics) and the residual uncertainty "envisioned to address species differences in pharmacodynamics (USEPA 1994)."

Table A-2. Mapping of Cancer Classification Language

1986 EPA Cancer Guidelines	1996 EPA Draft Cancer Guidelines	1999 EPA Draft Cancer Guidelines	2005 EPA Cancer Guidelines[1]	NTP[2]	2006 WHO - IARC[3]
Group A: Human carcinogen	Known/likely human carcinogen	Carcinogenic to humans	Carcinogenic to humans	Known to be human carcinogen	Group 1: Carcinogenic to humans
Group B1: Probable human carcinogen – based on limited evidence in humans and sufficient evidence of carcinogenicity in animals	Known/likely human carcinogen	Likely to be carcinogenic to humans	Likely to be carcinogenic to humans	Reasonably anticipated to be a human carcinogen	Group 2A: Probably carcinogenic to humans
Group B2: Probable human carcinogen – based on sufficient evidence of carcinogenicity in animals					Group 2B: Possibly carcinogenic to humans
Group C: Possible human carcinogen (n=39 on IRIS)		Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential (n=1 on IRIS)	Suggestive evidence of carcinogenic potential		
Group D: Not classifiable as to human carcinogenicity	Carcinogenic potential cannot be determined (n=15 on IRIS)	Data are inadequate for an assessment of human carcinogenic potential	Inadequate information to assess carcinogenic potential (n=10 on IRIS)		Group 3: Not classifiable as to carcinogenicity to humans
Group E: Evidence of non-carcinogenicity for humans	Not likely to be carcinogenic to humans	Not likely to be carcinogenic to humans	Not likely to be carcinogenic to humans		Group 4: Probably not carcinogenic to humans

[1] EPA 2005 Cancer Guidelines, http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=116283
[2] Report on Carcinogens, 11th Edition, National Toxicology Program. http://ntp.niehs.nih.gov/ntp/roc/eleventh/intro.pdf
[3] International Agency for Research on Cancer. http://monographs.iarc.fr/ENG/Preamble/currentb6evalrationale0706.php

Table A-3. List of Database Fields for Toxicity Values

A. Identifying Availability of Toxicity Values

CAS Number
Chemical Name
TEL (ug/m3)
AAL (ug/m3)
Noncancer Values
- IRIS RfC (mg/m^3)
- IRIS RfC (ug/m^3)
- Date RfC finalized
- New Data Identified by IRIS Lit. Search (Y/N)
- Date of Lit Search by IRIS
- IRIS in process of updating Tox Review (Y/N)
- HEAST (ug/m^3)
- CalEPA chronic REL (ug/m^3)
- CalEPA Date
- ATSDR chronic MRL (ppm); (if *, then mg/m^3)
- ATSDR chronic MRL (ug/m^3)
- ATSDR Date
- Others as available – EU, HC, ITER database

Cancer Values
- IARC WOE
- IARC Date
- NTP WOE
- NTP date
- EPA WOE
- IRIS Unit Risk (per ug/m^3)
- EPA Date
- HEAST (per ug/m^3)
- CalEPA Unit Risk (per ug/m^3)
- CalEPA Date

Date of Entry
Date Reviewed
Reviewer

B. Noncancer Toxicity Values

Name of Toxicity Value
Agency
Date
Value (ug/m^3)
Value (ppb)
Relative Source Contribution
Test Species
Study Type and Length (critical study)
Route
Study Ref.
Study Date
Study NOAEL (ug/m^3)
Study LOAEL (ug/m^3)
Study BMDL (ug/m^3)
Study BMD (ug/m3)
BM Response (%)
Human Equivalent Conc. (24 hours/day) (ug/m^3)
HEC method
Critical Effects
Target Organs
Point of Departure (ug/m^3)
POD source (e.g., NOAEL, BMDL5)
Uncertainty factor total
- UFA
- UFH
- UFL
- UFS
- UFD

Explicitly adjusted for Children (Y/N)?
Method of adjustment for children
Value of quantitative adjustment for children?
Confidence Level from derivation agency
Respiratory tract toxicity data available?
Developmental tox data available?
Reproduction tox data available?
Neurotoxicity data available?
Immunotoxicity data available?
Exposure data available for RSC?
Comments

C. Cancer Toxicity Values

Name of Value
Agency
Date
NTEL Value (ug/m^3)
NTEL Value (ppb)
Unit Risk(per ug/m^3)
Test Species
Study Type and Length (critical study)
Route
Study Ref.
Tumor Type
Cross-species dose extrapolation method
Dose-Response Model
Explicitly adjusted for Children? (Y/N)
Method of adjustment for children
Value of quantitative adjustment for children?
Confidence Level
Comments

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Appendix B

Re-Evaluation of the Application of Relative Source Contribution Factors to TELS

Appendix B
Re-Evaluation of the Application of Relative Source Contribution Factors to TELS

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Re-Evaluation of the Application of Relative Source Contribution Factors to TELS

The relative source contribution (RSC) factor and its application to Threshold Effects Exposure Limits (TELs) were reviewed as part of the process of updating the method for deriving TELs.

1.0 INTENT OF RELATIVE SOURCE CONTRIBUTION (RSC)

The RSC was originally incorporated into the CHEM/AAL process (MassDEP 1990) to account for the potential for an individual to be exposed to the same chemical from multiple sources in addition to ambient air, such as water, soil and food. It was intended to take into account the potential for cumulative exposure to a chemical that could increase the potential for adverse effects. The inclusion of an RSC in the derivation of the TEL represents a science policy decision that air guidance values should consider other sources of exposure to chemicals in addition to ambient air (MassDEP 1990).

As part of the process of updating the MassDEP TEL derivation methodology that replaces CHEM/AAL (MassDEP 1990) the following questions were considered about the use of an RSC;

- Should an RSC still be applied when deriving a TEL using the new approach?
- If yes, when is it needed?
- Should the default value of the RSC remain 0.2 (twenty-percent)?

To answer these questions, we;

- looked back at the description, methods and application of the RSC in the CHEM/AAL process;
- reviewed CalEPA's use of RSCs for drinking water (Howd et al. 2004); and,
- considered comments from members of the MassDEP/DPH Advisory Committee on Health Effects, the peer reviewers of the "Updating Methodology."

The history and intent of the use of relative source contribution factors in CHEM/AAL, and the considerations for use of the RSC in the context of the updated guideline values are described in the next two sections.

2.0 HISTORY OF RSC IN CHEM/AAL

The TEL is a chemical-specific guidance value defining an allowable concentration of a chemical in ambient air intended to protect the general population from noncancer health effects and is used to guide the permitting of facilities that release chemicals into ambient air and for evaluating potential health concerns in various MassDEP programs. The TEL is compared to the 24-hour average ambient air concentration at the fence line of the facility.

The CHEM/AAL process assumes that the portion of the exposure from the particular chemical that an individual receives via inhalation should be no greater than one-fifth (or 20-percent) of the person's total exposure to that chemical (including exposure through other routes such as ingestion of drinking water and food, dermal exposure, etc.). This factor has historically been applied as a default value in the derivation of TELs in the absence of more chemical-specific information. The twenty-percent (or 0.2 factor) has its origins in the USEPA Drinking Water Program, is used in MassDEP's methodology for determining drinking water guidance values and is consistent with the consideration of cumulative risk from four media/pathways (ground water ingestion and volatilization into indoor air, soil ingestion and dermal contact) employed in setting standards in the MCP 21E program.

In 1994, when the TEL-derivation process was updated to incorporate USEPA inhalation Reference Concentrations (RfCs) (MassDEP 1994), a number of TEL values were revised for inclusion in the 1995 list of TELs and AALs (MassDEP 1995). Three of the TEL values that were revised during this time were for reactive gases, hydrogen chloride, hydrogen sulfide and ammonia. Reactive gases are those that may react to form corrosive products, such as acids or bases.

Based on an evaluation of these compounds, it was recognized that such gases have a unique set of characteristics. These gases produce adverse health effects almost exclusively on the respiratory tract. Specifically, the compounds hydrolyze in the moist lining of the respiratory mucus membranes to produce acids or bases that irritate the respiratory tract. Because of their tendency to rapidly hydrolyze, these compounds undergo a transformation from the gas phase to an acid or base in water. Thus, they are not present in drinking water and they are also not present in food. The only exposure pathway into the human body for these gases is inhalation.

The properties of these compounds as discussed above influence their potential for multi-media exposure and upon this basis, ORS adopted an informal policy for assigning the RSC to reactive gases in CHEM/AAL: for any such compound that undergoes a physical/chemical transformation in media other than air, which targets the respiratory system with adverse health effects and for which inhalation is the only exposure route to the human body, a decision was made to incorporate an RSC of 1.0 in the final TEL value. To date, the three compounds noted above are the only chemicals for which an RSC other than the 0.2 default has been applied. Although this policy was never documented, it persists with regard to these three chemicals. It has not been applied to additional chemicals since 1995, but there have also been no additional updates to the TELs since then.

3.0 RE-EVALUATION OF THE INTENT AND GOAL OF THE RSC

The stated goal of the RSC in CHEM/AAL (MassDEP 1990) is to account for exposure to the chemical from other exposure pathways, e.g., ingestion (water, food, soil), and dermal (water, soil).

In the years since CHEM/AAL was created, research evaluating chemicals in indoor air has found that people can have significant inhalation exposures to chemicals originating from

sources other than ambient air that are present in indoor air (Wallace 1991). Thus inhalation of indoor air could be added to the stated goal of the RSC.

4.0 REVIEW OF PROCESS AND TECHNICAL CONSIDERATIONS FOR APPLICATION OF RSC

Having decided that it is appropriate to continue including a RSC in the updated methodology for deriving TELs (MassDEP 2011, section 5.2.2) and to expand the goal of the RSC to include indoor air, a number of options for assigning RSCs were evaluated, considering the work effort involved and the qualitative benefits and costs.

The options considered for assigning the RSC were:

1) Continue the CHEM/AAL method of applying the RSC factor of 0.2 for all chemicals (except hydrogen sulfide, ammonia, and hydrochloric acid) (MassDEP 1994, 1995);
2) Stop applying the RSC – other states do not include a factor like the RSC in their ambient air guidance values.
3) Evaluate the need for an RSC on a chemical by chemical basis considering all other potential sources of exposure as described in the next section. If an RSC is determined to be needed, the default value of 0.2 will be used. When available information is insufficient to determine the need, the default RSC value of 0.2 will be used. This process was applied to 6 chemicals to evaluate the types of information available, and the effort required to gather the information and assess whether an RSC was needed;
4) Develop and apply an approach to derive chemical-specific RSC values other than 0.2. Application of an RSC value of 0.2 will be retained as the default value when data are not sufficient to determine a need or to support a chemical-specific value.

Of these options, Option 3, evaluating the need for an RSC on a chemical by chemical basis, was considered in more detail as described in the next section.

5.0 RE-EVALUATION OF THE POTENTIAL FOR EXPOSURE TO SOURCES IN ADDITION TO AMBIENT AIR

The uses and physical/chemical characteristics of individual chemicals determine the potential for and extent of exposure from different sources. To re-evaluate the potential for exposure from sources in addition to ambient air relevant characteristics were identified and a structured approach was created for evaluating whether an individual chemical merits an RSC on its TEL.

The information necessary to evaluate the need for an RSC consists of:

- Chemical sources – natural, anthropogenic - industry, consumer products, food, water, soil;
- Chemical behavior – chemical form at normal temperature and pressure, solubility in water, volatility, sorption to soil; and,

- Chemical effects from inhalation, ingestion and dermal exposure to primary chemical and other available forms (i.e., dissociated in water, salts, parent chemical and metabolites – considering first pass effects following ingestion).

The structured approach for determining the need for an RSC includes three steps, framed as questions, explicitly including consideration of the potential for exposure to sources in addition to air, the potential for effects from multiple sources, and the potential for exposure from indoor air sources.

Step 1.

Is there potential for *exposure* from sources in addition to air? i.e., is the chemical present in water, soil, or food, and are people likely to be exposed from multiple sources?

a. If yes, go to step 2.
b. If no, go to step 3.

Step 2.

Are the *effects* from the chemical, in the chemical form that it is available in from the multiple sources, such that the effects arising from exposure to 'Source A' (e.g., air) and 'Source B' (e.g., drinking water) have the potential to occur in the same organ systems?

a. If yes, apply RSC of 20%.
b. If no, go to step 3.
c. If not known, apply RSC of 20%.

Step 3.

Is there potential for *exposure* from air sources in addition to *ambient* air? i.e., is the chemical relatively common (typically present) in consumer products such that people could be exposed to it in indoor air on an ongoing basis? Chemicals that off-gas and remain in the indoor air environment at some steady level would be of greater concern than chemicals with episodic peaks in indoor air that dissipate within a few hours.

a. If yes, apply RSC of 20%.
b. If no, do not apply RSC.
c. If not known, apply RSC of 20%.

5.1 Application of the Proposed Process for Evaluation of a Chemical-specific RSC

Six chemicals, ammonia, maleic anhydride, 2,4-toluene diisocyanate, formaldehyde, benzene and arsenic, were selected as case study chemicals to evaluate the proposed three step process. The level of effort required to complete the evaluation and the potential for concluding that the value of the RSC should be different from the default of 0.2 were both evaluated. Please note that these examples are not intended to reflect a final decision about the RSC value for the individual chemical.

5.1.1 ***Ammonia***

Step 1 – Potential for exposure - Ammonia is naturally occurring in the environment, humans, animals, water, plants and soil. It is created endogenously as the product of breakdown of

proteins and is an important component of the nitrogen cycle (ATSDR 2004). Its concentration in water is limited as it is thought to break down quickly under aerobic conditions to nitrate or to volatilize into the air as a gas. It is present in soil at higher concentrations after application of fertilizer or decomposing manure, and adsorbs to soil. There is very limited potential for significant exposure to sources other than air. Go to Step 3.

Step 2 – Potential for same effects from different sources – n/a

Step 3 – Potential for exposure in addition to ambient air – People can be exposed to ammonia in indoor air during the use of cleaning products containing ammonia in solution; concentrations are highest when used in closed spaces without ventilation. Because the use of ammonia cleaning products is episodic, ammonia is not expected to accumulate, and is expected to dissipate once cleaning is completed, a relative source contribution factor is not needed for derivation of the TEL.

Conclusion: Use an RSC factor of 1 in the TEL for ammonia.

5.1.2 *Arsenic*

Step 1 – Potential for exposure - Arsenic is present in the environment from natural and anthropogenic sources. Arsenic is a naturally occurring element in the earth's crust. It is found in the environment as the metal, elemental arsenic, or in mineral form as inorganic arsenic when combined with sulfur, oxygen or chlorine, and as organic arsenic when combined with carbon and hydrogen. Arsenic is present in water, soil, air, and food. Anthropogenic sources include smelting, mining, coal combustion, wood combustion, waste incineration, past uses as a pesticide in orchards and CCA treated wood. In parts of Massachusetts and other New England states, arsenic is naturally present in groundwater used for drinking water. There is significant potential for exposure to sources in addition to air. Go to Step 2.

Step 2 – Potential for same effects from different sources – Inhaled and ingested arsenic are available systemically, and both routes of exposure are associated with the adverse effects in the same organ systems, including skin, respiratory, gastrointestinal, peripheral and central nervous system and cardiovascular system. For more information see ATSDR (2007a). There is potential for effects in the same organ systems from exposure to arsenic from sources other than ambient air.

Step 3 – Potential for exposure in addition to ambient air – n/a

Conclusion: Include an RSC factor of 0.2 in TEL for arsenic.

5.1.3 *Benzene*

Step 1 – Potential for exposure - Benzene is released to the environment from natural and anthropogenic sources, with anthropogenic sources dominating (ATSDR 2007b). Benzene is released into ambient air from gasoline vapors, auto exhaust, chemical production and use, and cigarette smoke (ATSDR 2007b). It is released into water from leaking underground gasoline storage tanks, industrial effluent and landfill leachate (ATSDR 2007b). Benzene in water will

volatilize to air. Benzene in soil and water can undergo biodegradation. Most exposure to benzene is from the air. However, exposure can occur through ingestion of contaminated food and water. There is potential for exposure to sources in addition to air. Go to Step 2.

Step 2 – Potential for same effects from different sources – Inhaled and ingested benzene are readily available systemically, and both routes of exposure are associated with the adverse effects in the same organ systems, including hematopoeitic and neurologic. (For more information see ATSDR 2007b.) There is potential for effects in the same organ systems from exposure to benzene from sources other than ambient air.

Step 3 – Potential for exposure in addition to ambient air – There is potential for indoor air exposure from consumer products (i.e., gasoline stored in a garage, nail polish, cigarette smoke) and from volatilization from contaminated drinking water. The available information indicates that benzene is likely to be present in indoor air and to contribute to human exposure (Wallace 1996).

Conclusion: Include an RSC factor of 0.2 in TEL for benzene.

5.1.4 ***Formaldehyde***

Step 1 – Potential for exposure - Formaldehyde is produced by endogenous and anthropogenic sources. Cellular concentrations of endogenous formaldehyde are tightly controlled. Most formaldehyde entering the environment is found in ambient air from combustion sources such as exhaust from motor vehicles, power plants, refineries, wood stoves, kerosene heaters, cigarettes, and forest fires (ATSDR 1999). Another important source is photochemical production of formaldehyde in the atmosphere from NOx and volatile organic compounds, particularly in the warmer summer months. It is unstable in water, when released to water it degrades in a few days; it is not expected to be in drinking water (ATSDR 1999). Formaldehyde is not expected to adsorb to soil or sediment. There is very limited potential for significant exposure to sources other than air. Go to Step 3.

Step 2 – Potential for same effects from different sources – n/a

Step 3 – Potential for exposure in addition to ambient air – There are many sources of formaldehyde in indoor air including furniture and cabinets made of particle board and pressed wood, permanent press fabrics, fiberglass products, decorative laminates, paper goods, paints, wallpaper, and cosmetics (CARB 1996). Combustion sources indoors also contribute, including stoves, heaters, or burning cigarettes (ATSDR 1999). The available information indicates that formaldehyde is likely to be present in indoor air and to contribute to human exposure.

Conclusion: Include an RSC factor of 0.2 in TEL for formaldehyde.

5.1.5 ***Maleic Anhydride***

Step 1 – Potential for exposure - Maleic anhydride is produced and used as a chemical reactant and intermediate, with 50% of it being used in the manufacture of polyester and alkyd resins or

unsaturated polyester resins (UPR) that are used to produce fiberglass reinforced plastics for pleasure boats, bathroom fixtures, cars, tanks, pipes and electrical products. Maleic anhydride is also used as an additive in lubricating oils such as gasoline and diesel engine crankcase oil as a dispersant, and in lacquers as a drying agent. It can be released from agricultural chemicals and pharmaceuticals. Maleic anhydride can be released to water, soil and air. Maleic anhydride released to the soil is expected to have high mobility and to hydrolyze: it is not expected to volatilize. When released to water maleic anhydride rapidly hydrolyses with a half-life of 0.37 minutes at 25 deg C (HSDB 2010) and is not expected to bioaccumulate in aquatic organisms. There is very limited potential for significant exposure to sources other than air. Go to Step 3.

Step 2 – Potential for same effects from different sources – n/a

Step 3 – Potential for exposure in addition to ambient air – Maleic anhydride is used in products that could be found in residences, such as artificial sweeteners, flavor enhancers, paper sizing, detergents, water treatment chemicals, hair sprays, adhesives, floor polishes, textile sizing and printing ink. No information was located that evaluated concentrations of maleic anhydride in indoor air. The available information is too limited to determine the magnitude of the contribution of indoor sources to human exposure.

Conclusion: Include an RSC factor of 0.2 in TEL for maleic anhydride.

5.1.6 *2,4-Toluene Diisocynate*

Step 1 – Potential for exposure - 2,4-Toluene diisocyanate is one of the two isomers in the mixture toluene diisocyanate, the other is 2-6 toluene diisocyanate. Toluene diisocyanate (TDI) is widely used in polyurethane foam, elastomers and coatings, as a cross-linking agent in nylon, and as a hardener in polyurethane adhesives and finishes. At temperatures greater than 20.5^{o}C, 2,4-Toluene diisocyanate exists as a liquid that readily volatilizes to ambient air (HSDB 2010). Toluene diisocyante rapidly hydrolyses in water; thus drinking water is not likely to be a source of exposure and it is unlikely to be present in food (HSDB 2010). It is not known if TDI that volatizes from polyurethane foam products reacts with other substances that remain in the indoor environment as dust (CARB 1997). There is very limited potential for significant exposure to sources other than air. Go to Step 3.

Step 2 – Potential for same effects from different sources – n/a

Step 3 - Potential for exposure in addition to ambient air – 2,4-Toluene diisocyanate is used in the manufacture of consumer products that may be used indoors, including flexible polyurethane foam used in mattresses, carpet pads, and air filters, foam plastics, polyurethane foam coated fabrics, rigid insulation, lacquers, wood finishes, polyurethane varnishes, paints, coating materials and adhesives. While the studies evaluating the amount and rate of release of TDI from new polyurethane foam are limited, one available study (Hugo et al. 2000) reports that under their study conditions, TDI off-gases quickly from products; TDI was not detected above the detection limit of 0.7 ug/m^3 from foam made 3 days prior to being extracted for 3 days at 37^{o}C, 30% humidity. California Air Resources Board (CARB) (1997) tested 39 different readily available polyurethane consumer products. Using extreme screening conditions of 50^{o}C (i.e.,

122°F), 50% humidity to maximize off-gassing, the concentration of TDI released was estimated to be equivalent to an indoor air concentration of less than 0.1 ug/m^3 (CARB 1997). The one commercial product tested, a concrete stop leak product, containing 4% w/w mixed isomers of TDI, released the TDI rapidly when applied, with emissions reaching non-detect levels within 1 hour at 21°C, 50% relative humidity (CARB 1997).

Concentrations of total isocyanates (a measure of all isocyanates including TDI) following short-term air sampling in car body repair shops from stationary samplers ranged from 0.01 to 0.03 ug/m^3; personal sampling monitors of workers spraying or sanding isocyanate containing materials ranged from 0.001 to 5.38 ug/m^3 with a median of 0.07 ug/m^3 (Pronk et al. 2006). The median concentrations of total isocyanates in auto repair and refinishing shops ranged from 206 ug/m^3 for spray operations, 0.93 ug/m^3 on the shop floor near spray area, 0.17 ug/m^3 for mixing and spray gun cleaning operations, and 0.05 ug/m^3 in offices or work spaces adjacent to the spray area, considered workplace background (Woskie et al. 2004). The median workplace background concentration is lower than the TEL and AAL. The available information suggests that 2,4-toluene diisocyanate is not likely to be present in indoor air from consumer products, and thus indoor air is not likely to be a source of human exposure.

Conclusion: Use an RSC factor of 1 for deriving the TEL for 2,4-toluene diisocyanate.

5.2 Evaluation of the Proposed Process for Deriving Chemical-specific RSCs

Six chemicals served as case study chemicals to evaluate the proposed process for deriving chemical specific RSCs. The current RSC is 0.2, the default, for all except ammonia that had earlier been assigned an RSC of 1. After deriving chemical-specific RSCs using the proposed 3-step process one chemical, 2,4-toluene diisocyanate, was recommended for an RSC different from the current default RSC of 0.2. The evaluation for 2,4-toluene diisocyanate was unusual in that there was a study available that specifically evaluated the off-gassing of 2,4-toluene diisocyanate from products and the levels of 2,4-toluene diisocyanate in the air of workplaces where 2,4-toluene diisocyanate was expected to be present.

The process of collecting and evaluating the available chemical specific information took at minimum a half day for each chemical; in some cases more. Documentation of the process added more time.

Although the number of chemicals evaluated was limited, the chemical-specific RSCs derived for these case study chemicals were consistent with the default RSC in all but one case for 2,4-toluene diisocyanate, which was data rich. The level of effort required to complete the chemical-specific evaluation appears to be greater than the potential benefit.

6.0 CONCLUSIONS

After evaluating the intent of CHEM/AAL, considering the new information about sources of chemicals in indoor air, and evaluating the possible benefits of deriving chemical-specific RSCs, the following conclusions were reached:

- It remains appropriate to apply an RSC factor to the TEL.
- New data on exposure to chemicals in indoor air supports extending the intent of the RSC, i.e., to include consideration of indoor air as a having the potential to be a separate source of exposure when considering cumulative exposure from sources that are in addition to ambient air.
- The RSC could continue to be applied to all chemicals with TELs, with the exception of the three chemicals, hydrogen sulfide, hydrochloric acid, and ammonia, that were assigned an RSC value of one (1) in the update to CHEM/AAL (MassDEP 1995).
- The default value of the RSC should remain 0.2 because data are not available in most cases to identify a chemical specific value or categories of values, and because the effort to develop defensible chemical specific values is greater than the resources available in relation to other priorities.

7.0 RECOMMENDATION

After evaluation of the RSC process, its influence on choice of RSC (0.2 or 1) and the effort involved with each of the options, we decided that the most reasonable option at this time is, Option 1) continuation of the application of an RSC of 0.2 to all chemicals, except those already using an RSC of 1. However, if specific chemicals are identified that might benefit from a more extensive evaluation they can be considered on a chemical by chemical basis if resources permit.

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Appendix **C**

Priority Lists of Chemicals for AAL/TEL Review

Appendix **C**
Priority Lists of Chemicals for AAL/TEL Review

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Appendix C. Table C-1.
Chemicals with AAL and Inhalation Toxicity Information

Identified as High Priority by BWP (n=8[a])

CAS Number	Pollutant Name	On 21E List	On Landfill AP-42 List	On NATA 1999 List	NATA 1999 Risk Driver (C/NC)[b]
7664417	Ammonia	0	0	0	0
7440382	Arsenic (inorganic)	1	0	1	C/NC[c]
N/A	Arsenic Compounds (inorganic, may include arsine)	0	0	1	C/NC[c]
7784421	Arsine	0	0	1	0[c]
71432	Benzene	1	1	1	C[c]
7440439	Cadmium (including compounds)	1	0	1	C/NC
50000	Formaldehyde	0	0	1	NC (not eval for Cancer)
127184	Tetrachloroethylene	1	1	1	C[c]
108883	Toluene	1	1	1	0
1330207	Xylenes (isomers and mixture)	1	1	1	0

Priority not specified by BWP (n=78)

CAS Number	Pollutant Name	On 21E List	On Landfill AP-42 List	On NATA 1999 List	NATA 1999 Risk Driver (C/NC)
75070	Acetaldehyde	0	0	1	NC[c]
67641	Acetone	1	1	0	0
107131	Acrylonitrile	0	1	1	0
62533	Aniline	0	0	1	0
7440360	Antimony	1	0	0	NC
N/A	Antimony Compounds (trioxide)	1	0	1	NC
1332214	Asbestos	1	0	1	0
100447	Benzyl Chloride	0	0	1	0
7440417	Beryllium (including compounds)	1	0	0	0
117817	Bis(2-ethylhexyl)phthalate (Di(2-ethylhexyl)phthalate	1	0	1	0
106990	1,3-Butadiene	0	0	1	C/NC[c]
13765190	Calcium Chromate	0	0	0	0
75150	Carbon Disulfide	0	1	1	0
56235	Carbon Tetrachloride	1	1	1	C[c]
463581	Carbonyl Sulfide	0	1	1	0
57749	Chlordane (alpha & gamma isomers)	1	0	1	0
7782505	Chlorine	0	0	1	NC
108907	Chlorobenzene	1	1	1	0
75003	Chloroethane (Ethyl Chloride)	0	1	1	0
67663	Chloroform	1	1	1	0
126998	Chloroprene	0	0	1	0

CAS Number	Pollutant Name	On 21E List	On Landfill AP-42 List	On NATA 1999 List	NATA 1999 Risk Driver (C/NC)
7738945	Chromic Acid (mist Cr VI)	0	0	0	0[c]
18540299	Chromium VI	1	0	1	C/NC[c]
7440473	Chromium metal	1	0	0	0
7440508	Copper	0	0	0	0
106445	p-Cresol	0	0	0	0
1319773	Cresols_Cresylic acid (isomers and mixture) (p-cresol for AAL/TEL)	0	0	1	0
110827	Cyclohexane	0	0	0	0
106467	p-Dichlorobenzene	1	1	1	0
75354	1,1-Dichloroethylene (Vinylidene Chloride)	1	1	1	0
75092	Dichloromethane (Methylene Chloride)	1	1	1	0
78875	1,2-Dichloropropane (Propylene dichloride)	1	1	1	0
68122	Dimethyl Formamide	0	0	1	0
123911	1,4-Dioxane	1	0	1	0
106898	Epichlorohydrin	0	0	1	0
140885	Ethyl Acrylate	0	0	1	0
100414	Ethyl Benzene	1	1	1	0
107062	Ethylene Dichloride (1,2-Dichloroethane)	1	0	1	0
107211	Ethylene Glycol	0	0	1	0
16984488	Fluoride	0	0	0	0
76448	Heptachlor	1	0	1	0
77474	Hexachlorocyclopentadiene	0	0	1	0
67721	Hexachloroethane	1	0	1	0
302012	Hydrazine	0	0	1	C/NC
7647010	Hydrochloric Acid (Hydrogen Chloride)	0	0	1	NC
7664393	Hydrofluoric Acid (Hydrogen Fluoride)	0	0	1	0
10035106	Hydrogen Bromide	0	0	0	0
74908	Hydrogen Cyanide	0	0	0	0
7783064	Hydrogen Sulfide	0	1	0	0
7439921	Lead	1	0	0	0
N/A	Lead Compounds	0	0	1	0
1335326	Lead Subacetate	0	0	0	0
58899	Lindane (all isomers) (HCH)	1	0	1	0
108316	Maleic Anhydride	0	0	1	NC
7439976	Mercury (elemental)	1	1	0	0
N/A	Mercury (inorganic)	1	1	0	0
22967926	Mercury (methyl)	1	0	0	0
N/A	Mercury Compounds	0	1	1	0
67561	Methanol	0	0	1	0

CAS Number	Pollutant Name	On 21E List	On Landfill AP-42 List	On NATA 1999 List	NATA 1999 Risk Driver (C/NC)
109864	2-Methoxy Ethanol (ethylene glycol methyl ether)	0	0	0	0
74839	Methyl Bromide (Bromomethane)	1	0	1	0
71556	Methyl Chloroform	1	1	1	0
78933	Methyl Ethyl Ketone	1	1	1	0
108101	Methyl Isobutyl Ketone	1	1	1	0
80626	Methyl Methacrylate	0	0	1	0
91203	Naphthalene	1	0	1	C[c]
7440020	Nickel (metal)	1	0	1	NC
N/A	Nickel compounds	1	0	1	NC
1313991	Nickel Oxide	1	0	0	0
98953	Nitrobenzene	0	0	1	0
87865	Pentachlorophenol	1	0	1	0
108952	Phenol	1	0	1	0
7664383	Phosphoric Acid	0	0	0	0
85449	Phthalic Anhydride	0	0	1	0
1336363	Polychlorinated Biphenyls (PCBs)	1	0	1	0
75569	Propylene Oxide	0	0	1	0
7782492	Selenium	1	0	0	0
N/A	Selenium Compounds	0	0	1	0
7446346	Selenium Sulfide	0	0	0	0
100425	Styrene	1	0	1	0
7664939	Sulfuric Acid	0	0	0	0
79345	1,1,2,2-Tetrachloroethane	1	1	1	0
584849	2,4-Toluene Diisocyanate	0	0	1	NC
95534	o-Toluidine	0	0	1	0
79005	1,1,2-Trichloroethane	1	1	1	0
79016	Trichloroethylene	1	1	1	0
88062	2,4,6-Trichlorophenol	1	0	1	0
121448	Triethylamine	0	0	1	NC
108054	Vinyl Acetate	0	0	1	0
75014	Vinyl Chloride	1	1	1	0

[a]Multiple forms of metals are counted as one chemical.
[b]Identified by1999 National Air Toxics Assessment as a national or regional risk driver; C – for cancer risk; NC for noncancer toxicity.
[c]Identified by 2002 National Air Toxics Assessment as a risk driver in Massachusetts; C/NC indicators as above.

Appendix C. Table C-2.
Chemicals without AAL but of Interest to MassDEP Programs
with Inhalation Toxicity Information

Identified as High Priority by BWP (n=1)					
CAS Number	**Pollutant Name**	**On 21E List**	**On Landfill AP-42 List**	**On NATA 1999 List**	**NATA 1999 Risk Driver (C/NC)[b]**
107028	Acrolein	0	0	1	NC[c]

Currently on 21E List (n=14[a])					
CAS Number	**Pollutant Name**	**On 21E List**	**On Landfill AP-42 List**	**On NATA 1999 List**	**NATA 1999 Risk Driver (C/NC)**
75343	1,1-Dichloroethane (Ethylidene Dichloride)	1	1	1	0
106934	Ethylene Dibromide	1	1	1	0
75252	Bromoform	1	0	1	0
10105831	Chromium III	1	0	1	0
N/A	Cyanide Compounds	1	0	1	0
91941	3,3-Dichlorobenzidene	1	0	1	0
111444	Dichloroethyl Ether (Bis-2(chloroethylether)	1	0	1	0
542756	1,3-Dichloropropene	1	0	1	0
121142	2,4-Dinitrotoluene	1	0	1	0
1746016	Dioxins/Furans (TCDD and equivalents)	1	0	1	0
118741	Hexachlorobenzene	1	0	1	0
87683	Hexachlorobutadiene	1	0	1	0
1634044	Methyl tert Butyl Ether	1	0	1	0
62759	Nitrosodimethylamine	1	0	1	0

Currently on AP-42 List (but not 21E) (n=12)					
CAS Number	**Pollutant Name**	**On 21E List**	**On Landfill AP-42 List**	**On NATA 1999 List**	**NATA 1999 Risk Driver (C/NC)**
124389	Carbon Monoxide (evaluated under 310 CMR 16.00)	0	1	0	0
75456	Chlorodifluoromethane (Freon 22)	0	1	0	0
75718	Dichlorodifluoromethane (Freon 12)	0	1	0	0
75434	Dichlorofluoromethane (Freon 21)	0	1	0	0
75081	Ethyl Mercaptan	0	1	0	0
75694	Fluorotrichloromethane (Freon 11)	0	1	0	0
74931	Methyl Mercaptan	0	1	0	0
67630	2-Proponal (Isopropyl Alcohol)	0	1	0	0

CAS Number	Pollutant Name	On 21E List	On Landfill AP-42 List	On NATA 1999 List	NATA 1999 Risk Driver (C/NC)
74873	Chloromethane (Methyl Chloride)	0	1	1	0
156605	trans-1,2-Dichloroethane (on 21E list as mixed enantiomers)	0	1	0	0
77781	Dimethyl Sulfate	0	1	1	0
110543	Hexane	0	1	1	0

Risk Drivers in NATA 1999 Evaluation (but not evaluated by 21E or AP-42) (n=6)

CAS Number	Pollutant Name	On 21E List	On Landfill AP-42 List	On NATA 1999 List	NATA 1999 Risk Driver (C/NC)
92875	Benzidine	0	0	1	C
N/A	Coke Oven Emissions	0	0	1	C
N/A	Diesel Particulate Matter	0	0	1	NC (not eval for Cancer) [c]
75218	Ethylene Oxide	0	0	1	C
822060	Hexamethylene-1,6-diisocyanate	0	0	1	NC
N/A	Manganese Compounds	0	0	1	NC

Currently on NATA List (but not 21E or AP-42 Lists) (n=44)

CAS Number	Pollutant Name	On 21E List	On Landfill AP-42 List	On NATA 1999 List	NATA 1999 Risk Driver (C/NC)
60355	Acetamide	0	0	1	0
75058	Acetonitrile	0	0	1	0
53963	2-Acetylaminofluorene	0	0	1	0
79061	Acrylamide	0	0	1	0
79107	Acrylic Acid	0	0	1	0
107051	Allyl Chloride	0	0	1	0
92671	4-Aminobiphenyl	0	0	1	0
90040	o-Anisidine	0	0	1	0
57578	beta-Propiolactone	0	0	1	0
542881	Bis(chloromethyl)ether	0	0	1	0
133062	Captan	0	0	1	0
532274	2-Chloroacetophenone	0	0	1	0
107302	Chloromethyl Methyl Ether	0	0	1	0
N/A	Cobalt Compounds	0	0	1	0
98828	Cumene	0	0	1	0
96128	1,2-Dibromo-3-chloropropane	0	0	1	0
62737	Dichlorvos	0	0	1	0
111422	Diethanolamine	0	0	1	0
79447	Dimethyl Carbamoyl Chloride	0	0	1	0
60117	p-Dimethylaminoazobenzene	0	0	1	0
122667	1,2-Diphenylhydrazine	0	0	1	0

CAS Number	Pollutant Name	On 21E List	On Landfill AP-42 List	On NATA 1999 List	NATA 1999 Risk Driver (C/NC)
106887	1,2-Epoxybutane	0	0	1	0
51796	Ethyl Carbamate	0	0	1	0
151564	Ethylene Imine (Aziridine)	0	0	1	0
96457	Ethylene Thiourea	0	0	1	0
N/A	Fine Mineral Fibers	0	0	1	0
78591	Isophorone	0	0	1	0
624839	Methyl Isocyanate	0	0	1	0
101144	4,4'-Methylene Bis(2-chloroaniline)	0	0	1	0
101688	Methylene Diphenyl Diisocyanate (MDI)	0	0	1	0
101779	4,4'-Methylenedianiline	0	0	1	0
7439987	Molybdenum	0	0	0	0
79469	2-Nitropropane	0	0	1	0
59892	N-Nitrosomorpholine	0	0	1	0
684935	N-Nitroso-N-methylurea	0	0	1	0
75445	Phosgene	0	0	1	0
7803512	Phosphine	0	0	1	0
1120714	1,3-Propane Sultone	0	0	1	0
123386	Propionaldehyde	0	0	1	0
96093	Styrene Oxide	0	0	1	0
7550450	Titanium Tetrachloride	0	0	1	0
95807	2,4-Toluene Diamine	0	0	1	0
8001352	Toxaphene	0	0	1	0
593602	Vinyl Bromide	0	0	1	0

[a]Multiple forms of metals are counted as one chemical.
[b]Identified by1999 National Air Toxics Assessment as a national or regional risk driver; C – for cancer risk; NC for noncancer toxicity.
[c]Identified by 2002 National Air Toxics Assessment as a risk driver in Massachusetts; C/NC indicators as above.

Appendix C. Table C-3.
Chemicals with AAL and of Interest to MassDEP Programs but No Inhalation Toxicity Information

Identified as High Priority by BWP (n=1)					
CAS Number	**Pollutant Name**	**On 21E List**	**On Landfill AP-42 List**	**On NATA 1999 List**	**NATA 1999 Risk Driver (C/NC)[b]**
64175	Ethanol	0	1	0	0
Priority not specified by BWP (n=6[a])					
CAS Number	**Pollutant Name**	**On 21E List**	**On Landfill AP-42 List**	**On NATA 1999 List**	**NATA 1999 Risk Driver (C/NC)**
	Alkanes/alkenes	1	0	0	0
92524	Biphenyl (Diphenyl)	1	0	1	0
95501	o-Dichlorobenzene	1	0	0	0
540590	1,2-Dichloroethylene	1	1	0	0
91576	2-Methylnaphthalene	1	0	0	0
1314621	Vanadium	1	0	0	0
1314621	Vanadium Pentoxide	1	0	0	0

[a]Multiple forms of metals are counted as one chemical.
[b]Identified by1999 National Air Toxics Assessment as a national or regional risk driver; C – for cancer risk; NC for noncancer toxicity.

Appendix C. Table C-4.
Chemicals without AAL but of Interest to MassDEP Programs and without Inhalation Toxicity Information

Identified as High Priority by BWP (n=1[a])

CAS Number	Pollutant Name	On 21E List	On Landfill AP-42 List	On NATA 1999 List	NATA 1999 Risk Driver (C/NC)[b]
N/A	Polycyclic Organic Matter (POM)	0	0	1	C[c]
N/A	POM Group 1: Unspeciated	0	0	POM	0
N/A	POM Group 2: no URE data	0	0	POM	0
N/A	POM Group 3	0	0	POM	0
N/A	POM Group 4	0	0	POM	0
N/A	POM Group 5	0	0	POM	0
N/A	POM Group 6	0	0	POM	0
N/A	POM Group 7	0	0	POM	0
N/A	POM Group 8	0	0	POM	0

Currently on 21E List (n=7)

CAS Number	Pollutant Name	On 21E List	On Landfill AP-42 List	On NATA 1999 List	NATA 1999 Risk Driver (C/NC)
75274	Bromodichloromethane	1	1	0	0
131113	Dimethyl Phthalate	1	0	1	0
51285	2,4-Dinitrophenol	1	0	1	0
72435	Methoxychlor	1	0	1	0
114261	Propoxur	1	0	1	0
120821	1,2,4-Trichlorobenzene	1	0	1	0
95954	2,4,5-Trichlorophenol	1	0	1	0

Currently on AP-42 List (but not 21E) (n=5)

CAS Number	Pollutant Name	On 21E List	On Landfill AP-42 List	On NATA 1999 List	NATA 1999 Risk Driver (C/NC)
106978	Butane	0	1	0	0
75183	Dimethyl Sulfide	0	1	0	0
74840	Ethane	0	1	0	0
109660	Pentane	0	1	0	0
74986	Propane	0	1	0	0

[a]Multiple forms of metals are counted as one chemical.
[b]Identified by1999 National Air Toxics Assessment as a national or regional risk driver; C – for cancer risk; NC for noncancer toxicity.
[c]Identified by 2002 National Air Toxics Assessment as a risk driver in Massachusetts; C/NC indicators as above.

Appendix C. Table C-5.
Chemicals with AAL but No Inhalation Toxicity Information

Chemicals with AALs Not Currently Evaluated in MassDEP Programs (n=16[a])					
CAS Number	**Pollutant Name**	**On 21E List**	**On Landfill AP-42 List**	**On NATA 1999 List**	**NATA 1999 Risk Driver (C/NC)[b]**
109897	Diethylamine	0	0	0	0
122394	Diphenylamine	0	0	0	0
141786	Ethyl Acetate	0	0	0	0
60297	Ethyl Ether	0	0	0	0
110009	Furan	0	0	0	0
591786	2-Hexanone	0	0	0	0
123922	Isoamyl Acetate	0	0	0	0
110190	Isobutyl Acetate	0	0	0	0
78831	Isobutyl Alcohol	0	0	0	0
108214	Isopropyl Acetate	0	0	0	0
96333	Methyl Acrylate	0	0	0	0
71238	Propyl Alcohol	0	0	0	0
108463	Resorcinol	0	0	0	0
76120	1,1,2,2-Tetrachloro-1,2-difluoroethane	0	0	0	0
109999	Tetrahydrofuran	0	0	0	0
71363	n-Butyl Alcohol	0	0	0	0

[a]Multiple forms of metals are counted as one chemical.
[b]Identified by1999 National Air Toxics Assessment as a national or regional risk driver; C – for cancer risk; NC for noncancer toxicity.

Appendix C. Table C-6.
Chemicals without AAL and without Inhalation Toxicity Information on NATA List

Currently on NATA List (but not evaluated by MassDEP Programs) (n=34[a])					
CAS Number	Pollutant Name	On 21E List	On Landfill AP-42 List	On NATA 1999 List	NATA 1999 Risk Driver (C/NC)[b]
98862	Acetophenone	0	0	1	0
98077	Benzotrichloride	0	0	1	0
156627	Calcium cyanamide	0	0	1	0
63252	Carbaryl	0	0	1	0
120809	Catechol	0	0	1	0
79118	Chloroacetic Acid	0	0	1	0
510156	Chlorobenzilate	0	0	1	0
94757	2,4-D, salts and esters	0	0	1	0
334883	Diazomethane	0	0	1	0
132649	Dibenzofurans	0	0	1	0
84742	Dibutylphthalate	0	0	1	0
64675	Diethyl Sulfate	0	0	1	0
119904	3,3-Dimethoxybenzidine	0	0	1	0
119937	3,3-Dimethyl Benzidine	0	0	1	0
57147	1,1-Dimethyl Hydrazine	0	0	1	0
534521	4,6-Dinitro-o-cresol, and salts	0	0	1	0
N/A	Glycol Ethers	0	0	1	0
680319	Hexamethylphosphoramide	0	0	1	0
123319	Hydroquinone	0	0	1	0
60344	Methyl Hydrazine	0	0	1	0
74884	Methyl Iodide	0	0	1	0
121697	N,N-Diethyl Aaniline	0	0	1	0
92933	4-Nitrobiphenyl	0	0	1	0
100027	4-Nitrophenol	0	0	1	0
56382	Parathion	0	0	1	0
82688	Pentachloronitrobenzene	0	0	1	0
106503	p-Phenylenediamine	0	0	1	0
75558	1,2-Propylenimine	0	0	1	0
91225	Quinoline	0	0	1	0
106514	Quinone	0	0	1	0
1582098	Trifluralin	0	0	1	0
540841	2,2,4-Trimethylpentane	0	0	1	0
7440315	Tin	0	0	0	0
7440666	Zinc	0	0	0	0

[a]Multiple forms of metals are counted as one chemical.
[b]Identified by1999 National Air Toxics Assessment as a national or regional risk driver; C – for cancer risk; NC for noncancer toxicity.

REFERENCES

MassDEP (Massachusetts Department of Environmental Health). 2009. Memorandum: U.S. EPA's 2002 National Air Toxics Assessment (NATA). June 24, 2009.

USEPA (U.S. Environmental Protection Agency). 2006. Results of the 1999 National-scale Air Toxics Assessment. Available: http://www.epa.gov/ttn/atw/nata1999/index.html (accessed September 15, 2006).

USEPA (U.S. Environmental Protection Agency). 2009. Results of the 2002 National-Scale Air Toxics Assessment. Office of Air and Radiation. Available: http://www.epa.gov/ttn/atw/nata2002/index.html (accessed June 5, 2009).

Appendix D

Decision Rules for Applying Updating Methodology

Appendix D
Decision Rules for Applying Updating Methodology

Table of Contents

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Decision Rules for Applying Updating Methodology

Informal suggestions for applying updating methodology and consistency of formatting.

1.0 SELECTION OF VALUES

Use the official published peer review value, even if the agency has updated the inhalation value in the context of preparing other assessments (e.g., drinking water number is based on newer evaluation of inhalation data, but inhalation toxicity value has not been updated).

Use the official published peer reviewed value, even if rounding was done in a manner inconsistent with ORS practice. While ORS and the Review Committee agreed that issues of rounding could be addressed and corrected in our method, further discussions among ORS staff concluded that rounding differences constitute a small quantitative difference relative to the factor of 3 we have determined to be within the range of uncertainty for purposes of selecting among values. Thus, the rounding approach used for development of the peer reviewed value will be retained.

Do not use **draft** values if there are final peer reviewed values available.

If a range of values is presented for a UR/RfC (or equivalent), select the more conservative value as the agency's value.

If one value cannot be identified as superior to another, the more health protective value will be selected.

1.1 Values within three-fold (3X)

The **most recent** RfC/UR or equivalent will be adopted if available toxicity values for the chemical are within a factor of three[11] of each other

1.2 Values differing by more than three-fold (3X)

If the available RfC/UR and equivalents are **different by more than a factor of three** from each other, the toxicity value that will serve as the basis of the TEL/NTEL for the chemical will be decided from among the available values based on,

- the **quality of the data** evaluated, and
- the **approach used to extrapolate** to the general human population.

Weight will be given to values based on,

- newer studies,
- studies with greater ability to detect effects,

[11] The value of three was chosen for this criteria (rather than 1 or 10 or some other value) recognizing that there is uncertainty in all toxicity values, that professional judgment plays a role in determining the value to assign to each uncertainty factor, and because three is one-half the value of a full uncertainty factor default value of 10 and is the smallest incremental difference in uncertainty factor value that is typically applied.

- studies where more sensitive effects were evaluated,
- dosimetric extrapolation methods most consistent with current methods, and
- dose-response characterization methods most consistent with current methods.

2.0 SUMMARY DOCUMENT DESCRIPTION

2.1 Content

Focus summary of a chemical's toxicity on critical effects. We decided that we do not need include a review, or indicate lack of information, for all possible types of health effects. A footnote is included on each summary document stating that the document is not intended to be a comprehensive summary of all toxicity information.

2.2 Formatting

Do not include in-text citations in the **Critical Effects** and **Potentially Susceptible Populations** sections if the same information is presented in the sections describing the basis for the TEL and/or AAL.

Lists of available values should be listed in the following order. If a value is not available from an organization listed, omit the name of the organization. Include date value was derived, date of publication by organization and date downloaded from website.

TEL and NTEL list	WOE list
USEPA	USEPA
CalEPA	IARC
ATSDR	NTP

2.3 References

List references from the same source in chronological order.

Cite IRIS using the date of the file (last update – if different dates for RfC and UR, use newer of the 2 dates for the citation. Include date file downloaded in the citation

> USEPA (U.S. Environmental Protection Agency). 1998. Integrated Risk Information System (IRIS). Available: http://www.epa.gov/iris/ (accessed June 6, 2011).

For references that we have not read, but are used to describe what was evaluated by an agency, include "as cited in" in the reference:

> Jarup L, Pershagen G and Wall S. 1989. Cumulative arsenic exposure and lung cancer in smelter workers: a dose-response study. Am. J. Ind. Med. 15:31-41 (as cited in Viren and Silver, 1994).