

**Office of Research and Standards
Department of Environmental Protection**

**Summary of Massachusetts' Methodology for
Developing Allowable Ambient Limits**

The Massachusetts methodology for deriving allowable ambient limits, known as AALs, is summarized in a document developed by the Department of Environmental Protection (DEP) entitled the Chemical Health Effects Assessment Methodology (CHEM) and the Method to Derive Allowable Ambient Limits (AAL) or CHEM/AAL. The CHEM part of the document describes the methodology used to review the scientific data for four health endpoint categories for the chemical and assigns a score to each category. In the AAL section, information derived through CHEM is used to derive the Allowable Ambient Limit (AAL) for the chemical in air. AALs derived through the CHEM/AAL methodology are purely health-based numbers conservatively derived to be protective of public health. Thus far the DEP has developed AALs for 105 chemicals which were chosen, not on the basis of hazard, but to test the methodology on representative kinds of chemicals.

The four health endpoint categories evaluated through CHEM are acute/chronic toxicity, carcinogenicity, mutagenicity and developmental/reproductive toxicity.

Acute/Chronic Toxicity:

The basis for assessing acute/chronic toxicity through CHEM/AAL is the occupational limit. Occupational limits from ACGIH, OSHA and NIOSH are reviewed along with the justification for each limit issued by the particular agency. Occupational limits from all three sources are reviewed because there are inconsistencies among these agencies as to procedures used to derive the occupational limits, (for example the criteria for identifying carcinogens is not consistent among the three agencies and sometimes even within the same agency.)

The "Most Appropriate Occupational Limit" (MAOL) is then selected from those reviewed based on selection criteria identified in CHEM/AAL. Essentially the MAOL represents that occupational limit which comes closest to the Lowest Observed Adverse Effect Level (LOAEL) for effects cited by that occupational agency without exceeding it. Specific criteria considered in selecting the MAOL include the occupational limit's degree of protection, its relevance to documented health effects, the adequacy and comprehensiveness of the toxicity data cited, self-reported limitations in the occupational limit, severity of health effects accounted for, how recently the toxicological basis for the limit was reviewed and its relevance to long-term chronic effects.

The chemical is then assigned a severity factor of from one to three points based on the severity of acute/chronic effects cited by the occupational sources. Severity of effect is used to account for the fact that effects occurring at the same level may not necessarily represent the same degree of hazard. In general, a lower severity factor is assigned to milder irritants, and chemicals producing transient, reversible effects while a

higher severity factor is assigned to chemicals producing irreversible effects, chronic effects or more widespread systemic effects involving multiple sites or organ systems.

A final letter score from A to E is then assigned to the chemical for acute/chronic toxicity based on a scoring scheme considering MAOL and severity of effect.

Carcinogenicity:

The assessment of a chemical for carcinogenicity in CHEM/AAL involves a consideration of both qualitative information (in the form of weight of evidence) and quantitative dose-response information.

Information on carcinogenicity from IARC, EPA-CAG, NTP and other sources is reviewed, along with primary sources when secondary sources are unavailable or when new data are published. A method analogous to the EPA method to assess weight-of-evidence is then used to assign a weight-of-evidence category.

Published cancer unit risk factors from EPA-CAG and others are then reviewed if available. If there has been no cancer unit risk published for a chemical or if the DEP does not agree with the EPA number, DEP will develop a cancer unit risk using the linearized multistage model if there are sufficient data.

A final letter score from A to F or ND is then assigned to the chemical based on a scoring scheme which considers weight-of-evidence and carcinogenic unit risk.

Mutagenicity:

The main information source used in CHEM/AAL to assess mutagenicity is EPA's Genetic Toxicology Program database (GENE-TOX). GENE-TOX is a peer-reviewed mutagenicity database which reports bioassay results for 73 mutagenic tests and is continuously updated. Mutagenicity information for a particular chemical is derived through GENE-TOX and is supplemented by information from IARC and primary scientific literature.

A final letter score from A to E or ND is then assigned to the chemical using a scoring matrix developed for mutagenicity. This scoring matrix was derived by assigning relative weight to the various types of mutagenicity assays, (for example, human assays are assigned greater importance than animal assays; in vivo tests, more importance than in vitro tests, etc.) and to the number and variety of tests scoring positively for mutagenicity.

Developmental/Reproductive:

CHEM/AAL defines reproductive toxicity as "any effect resulting from parental exposure to a substance which interferes with conception, gestation, birth or development of offspring to healthy adult life." Developmental toxicity is defined in CHEM/AAL as including teratogenicity, embryotoxicity, fetotoxicity, perinatal or postnatal

developmental toxicity.

The assessment of a chemical for developmental/reproductive effects in CHEM/AAL is based primarily on information derived from the primary science literature. Primary studies for both developmental and reproductive effects are reviewed and are critically evaluated (e.g. toxicologically, statistically, pharmacologically, etc.).

Weight of evidence is determined for each endpoint using a scoring scheme similar to the scoring scheme used for carcinogenicity.

A critical study is selected for developmental/reproductive toxicity. The Lowest Observed Effect Level (LOEL) is then identified from this study. A parameter developed by the DEP called the Risk Ratio is then determined. This is done by first selecting an LD50 from a toxicity study in which the species and exposure route are the same as in the study from which the LOEL is derived. The Risk Ratio is then calculated as LD50/LOEL and basically reflects the ratio of toxic doses of adult/fetus.

A final letter score from A to E or ND for developmental toxicity is then assigned based on a scoring scheme which considers weight of evidence, LOEL and Risk Ratio.

A critical study is also chosen for reproductive toxicity. Only the LOEL is identified from the study in this case and a final letter score from A to E or ND for reproductive toxicity is assigned based on a scoring scheme which considers weight-of-evidence and LOEL.

The lower of the developmental toxicity score and reproductive toxicity score is chosen as the final score for developmental/reproductive toxicity.

AAL Derivation:

The AAL is derived based on information derived in CHEM. At the end of this summary is a flowchart from CHEM/AAL outlining the steps used in deriving the final AAL. Briefly, the MAOL is adjusted for continuous exposure, adult/child differences, and high risk groups. At this point, another variable uncertainty factor of 10 called the TOX factor is applied on a case-by-case basis depending on whether it is felt that the toxicity data, as described by the occupational source, on which the selected MAOL is based, is adequate. The resulting value is now called the Adjusted MAOL.

The methodology branches here to calculate both a Threshold Effects Exposure Limit (TEL) based on threshold effects (i.e., acute/chronic toxicity and developmental/reproductive toxicity) and a Nonthreshold Effects Exposure Limit (NTEL) based on nonthreshold effects (i.e., carcinogenicity and mutagenicity.) The TEL is derived by applying an uncertainty factor known as the Threshold Effects Uncertainty Factor (TEUF) of 1, 5 or 10 to the Adjusted MAOL which is mainly based on developmental/reproductive effects not accounted for in the MAOL. (CHEM/AAL specifies in this case: if the chemical is known to have developmental/reproductive effects, and this information was not considered in the occupational limit, then the TEUF

is 5 if the CHEM toxicity score is C or D; 10 if it is A or B.) Twenty percent of the TEL is then taken to represent that portion of a person's total exposure to this chemical which can result through air. If a cancer unit risk is available, the NTEL is derived using quantitative cancer risk assessment to calculate an excess lifetime cancer risk of 1×10^{-6} . otherwise the NTEL is derived by applying an uncertainty factor known as the Nonthreshold Effects Uncertainty Factor (NTEUF) to the Adjusted MAOL, the magnitude of which is determined via a matrix which was developed to consider the scores for carcinogenicity and mutagenicity, as well as the structure-activity relationship (SAR) of the chemical (using a method which the Food and Drug Administration (FDA) uses to classify food additives, which essentially compares the structure of the chemical to the structure of other chemicals whose toxicity is better known.)

The TEL is designated as a 24-hr. average concentration; the NTEL is assigned an annual average. The lower of the TEL and the NTEL is designated as the AAL.

The AAL and TEL must be used together to be protective of public health for both threshold and nonthreshold effects.

ASSUMPTIONS USED IN DERIVATION OF FACTORS USED IN CHEM/AAL:

1. **4.2 factor to adjust for continuous exposure:**

$$\text{occupational exposure} = \frac{8 \text{ hrs}}{\text{day}} \times \frac{5 \text{ days}}{\text{wk}} = \frac{40 \text{ hrs}}{\text{wk}}$$

$$\text{continuous exposure} = \frac{24 \text{ hrs}}{\text{day}} \times \frac{7 \text{ days}}{\text{wk}} = \frac{168 \text{ hrs}}{\text{wk}}$$

$$\text{ratio determined} = \frac{168 \text{ hrs}}{40 \text{ hrs}} = 4.2$$

2. **1.75 factor to adjust for adult to child differences:**

$$\text{adult breathing rate:} \quad 20 \text{ m}^3/\text{day}$$

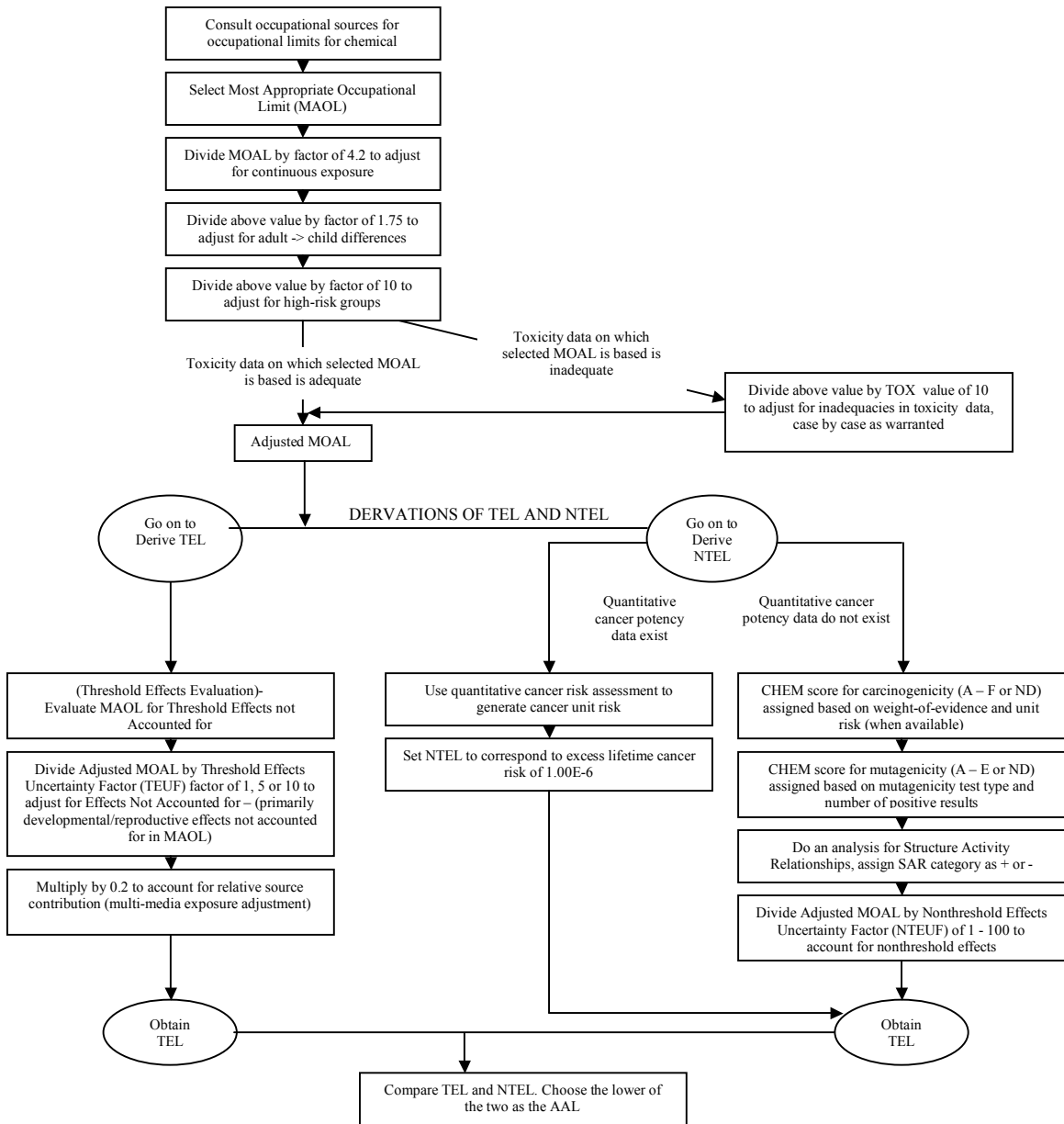
$$\text{child breathing rate:} \quad 10 \text{ m}^3/\text{day}$$

$$\text{average adult weight:} \quad 70 \text{ kg}$$

$$\text{average child weight:} \quad 20 \text{ kg}$$

$$\begin{aligned} \text{ratio of child parameters} & \quad \frac{10 \text{ m}^3/\text{day}}{20 \text{ kg}} \\ \text{over adult parameters:} & \quad \frac{20 \text{ m}^3/\text{day}}{70 \text{ kg}} \end{aligned} = 1.75$$

Figure III - 1. Derivation of AAL



Incorporation of Inhalation Reference Concentrations into the CHEM/AAL Process

The Chemical Health Effects Assessment Methodology and the Method to Derive Allowable Ambient Limits (CHEM/AAL) (ORS, 1990) represents Massachusetts' current methodology to derive health-based exposure limits for chemical compounds in ambient air. At the time this methodology was developed, there was no consistently derived set of toxicity criteria available for inhalation exposures such as there was in the form of the Environmental Protection Agency (EPA) Reference Doses (RfDs) for ingestion exposures. The occupational literature was the only relatively consistent source of inhalation information available and was thus used as the starting point for the derivation of air limits. The CHEM/AAL documentation acknowledges that the use of occupational limits as starting points does have certain limitations since these levels are often not based only on health considerations but also incorporate such factors as technical feasibility and cost. Nevertheless, the occupational literature represented the best available source of information at the time.

With the development of EPA's methodology to derive inhalation Reference Concentrations (RfCs), a consistent source of air exposure criteria became available. Because RfCs are toxicologically more current and are based only on toxicity considerations, they are more appropriate starting points for the derivation of ambient air guidance than are occupational limits. The following is a discussion of ORS' policy to incorporate inhalation RfCs into the guideline-derivation process for those compounds for which RfCs are available. The traditional method of deriving air limits as presented in the CHEM/AAL methodology document will continue to be used for those compounds without RfCs.

Inhalation Reference Concentrations

Inhalation Reference Concentrations (RfCs) represent benchmark air concentrations to which a receptor can be exposed chronically through inhalation and expect to suffer no adverse effects. The EPA defines an RfC as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The methodology to derive inhalation RfCs, developed by the U.S. Environmental Protection Agency (EPA), is similar to EPA's methodology to derive oral Reference Doses (RfDs). The same general principles are used in both methodologies, but the RfC methodology is expanded to account for the dynamics of the respiratory system as the portal of entry, in addition to extrapulmonary effects. As is discussed in Interim Methods for Development of Inhalation Reference Concentrations (EPA, 1990), the major difference between the two methods is that the inhalation RfC methodology includes dosimetric adjustments to account for species-specific relationships of inhaled concentrations and deposited/delivered doses. Particles and gases are treated separately and the site of the observed toxic effect (respiratory and extrapulmonary) is considered in applying the

dosimetric adjustments.

Inhalation RfCs are derived by applying a series of uncertainty factors to an effect level derived from a toxicological study. This toxicological level is either a No Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect Level (LOAEL) which has been dosimetrically adjusted to estimate a human-equivalent concentration (HEC). Inhalation RfCs are defined by the equation:

$$\text{RfC}_{[\text{HEC}]} = \text{NOAEL}_{[\text{HEC}]} / (\text{UF} \times \text{MF})$$

where $\text{NOAEL}_{[\text{HEC}]}$ represents a human-equivalent No Observed Adverse Effect Level (corrected for continuous exposure), UF designates the series of uncertainty factors applied and MF designates a modifying factor which is applied based on professional judgment about the adequacy of the entire data base of the chemical.

The uncertainty factors applied are generally of an order of magnitude (i.e., 10). They are used to account for intra- and inter- species differences, differences in exposure time and to extrapolate from a LOAEL to a NOAEL. Occasionally, EPA uses one uncertainty factor of 10 to adjust for more than one parameter. The magnitude of the modifying factor can range from 0-10.

RfCs represent a consistently derived source of toxicity criteria for inhalation exposures. The basic philosophy behind the derivation of these numbers is very similar to the approach used by the Department of Environmental Protection (DEP) to derive Threshold Effects Exposure Limits (TELS) from occupational limits as described in the Chemical Health Effects Assessment Methodology and the Method to Derive Allowable Ambient Limits (CHEM/AAL) (DEP, 1990). In both cases, a starting toxicological value is adjusted to be made applicable to exposures experienced by the general population and to account for effects not accounted for by that value. Both types of criteria are developed to be protective for chronic, continuous exposure and are developed to account for adverse threshold or noncarcinogenic health effects.

However, the toxicological studies used to derive inhalation RfCs are more current than the toxicological bases for many of the occupational limits used to derive TELs. The RfCs are derived using a consistent quantitative approach and are not simply established as consensus values by a group of experts as is the case with many occupational limits. In addition, RfCs consider a range of health effects and are not primarily based on irritant or short-term effects as many occupational exposure limits are.

Incorporation of RfCs into the CHEM/AAL Process

Because inhalation RfCs are inherently more comprehensive, more applicable to the general public and toxicologically more current than occupational limits, a decision was made to incorporate the consideration of inhalation RfCs, when available, into the CHEM/AAL process. The intent of this change is not to abandon the CHEM/AAL methodology but to build upon and improve it. In the same way that adequate cancer potency data are incorporated into the CHEM/AAL methodology when available,

adequate inhalation RfCs will be included in the process when available. The overall CHEM/AAL methodology will thus remain the same with the exception that inhalation RfCs will be incorporated into the process on a case-by-case basis.

Compound-specific hazard scores for carcinogenicity, mutagenicity and developmental/reproductive toxicity will be derived using the same process described in CHEM/AAL, relying as much as possible on peer-reviewed secondary sources of information. These scores will be used, if necessary, to assign uncertainty factors in the derivation process.

Revised hazard scores will not be developed for acute/chronic toxicity when RfCs are available. The scheme for deriving a hazard score for acute/chronic toxicity is partially based on the magnitude of the compound's occupational limit. In addition, acute/chronic hazard scores have never served as the basis for assigning uncertainty factors in the CHEM/AAL system. Thus, derivation of hazard scores for acute/chronic toxicity will not be conducted as part of the revised AAL-derivation process when RfCs are being used. An updated scheme for deriving compound-specific hazard scores based on indicators other than occupational limits may be developed as a separate project. This scheme may be incorporated in the CHEM/AAL process at a later date. However, the information provided by the acute/chronic hazard scores will have a qualitative function only in the AAL-derivation process.

The basis of an individual RfC and the uncertainty factors incorporated in its derivation will be reviewed in the context of the available toxicity information from EPA and other pertinent sources. A determination will be made as to its appropriateness for use in setting a guideline. The assumptions used in deriving the RfC will be compared to the assumptions used in deriving a TEL to assure that the RfC-based number provides the same degree of protection to the public health as the TEL.

In general, RfCs have already been corrected for continuous exposure. Thus, the 4.2 factor used to adjust for continuous exposure in CHEM/AAL is not applicable for this purpose. An uncertainty factor of 10 is incorporated into the derivation of the RfC that already accounts for differences in sensitive individuals and children. The factors of 10 and 1.75, respectively, which account for these parameters in the CHEM/AAL process, do not need to be applied. The TOX and TEUF factors are applied on a case-by-case basis as needed. A multi-media exposure factor to account for relative source contribution via air exposures is not applied in the RfC derivation methodology. Thus, the 20% factor used in CHEM/AAL is usually applied to the RfC, except in the case of water soluble gases (such as NH₃, H₂S and HCl) since it is assumed that chronic exposure to these compounds would be largely via inhalation. Although each RfC will be reviewed on a case-by-case basis, the following general guidelines presented in Table 1 will be used for the application of adjustment factors and uncertainty factors to the RfC:

Table 1. Guidelines for the Application of Adjustment and Uncertainty Factors for the Derivation of a TEL from an RfC and Comparison with Present MAOL-Based Methodology.

<u>MAOL as basis:</u>	<u>Inhalation RfC as basis:</u>
<ul style="list-style-type: none"> ○ divide by 4.2 to adjust for continuous exposure ○ divide by 1.75 to account for differences between adults and children ○ divide by 10 to account for high-risk groups ○ divide by 10 on a case-by-case basis to account for inadequate toxicity data (TOX factor) 	<ul style="list-style-type: none"> ○ do not divide by 4.2; already accounts for continuous exposure ○ do not divide by 1.75; factor of 10 applied for sensitive individuals already accounts for ○ do not divide by 10; factor of 10 applied for sensitive individuals already accounts for ○ divide by 10 on a case-by-case basis to account for inadequate toxicity data (TOX factor) not already accounted for in the RfC derivation process
<u>"ADJUSTED MAOL"</u>	<u>"ADJUSTED RfC"</u>
<ul style="list-style-type: none"> ○ divide by 1, 5 or 10 to account for threshold effects not accounted for in the MAOL (TEUF factor) ○ multiply by 20% to account for relative source contribution 	<ul style="list-style-type: none"> ○ divide by 1,5 or 10 to account for threshold effects not already accounted for in the RfC derivation process (TEUF factor) ○ multiply by 20%, if appropriate, to account for relative source contribution

The value estimated above represents the TEL since it considers only threshold effects. To derive an AAL, the same approach would be used as described in the CHEM/AAL document. When adequate cancer potency data exist, then these data are used to derive a value which corresponds to a one in 1,000,000 cancer risk. If these data do not exist, then the approach described in CHEM/AAL for developing a limit based on nonthreshold effects, the Non Threshold Effects Exposure Limit (NTEL), is used. The information (reflected in the hazard scores) for carcinogenicity and mutagenicity, together with information on the structure-activity relationship for that chemical are used to assign a Non Threshold Effects Uncertainty Factor (NTEUF) which is applied to the Adjusted RfC in this case (see above). The final AAL will continue to be determined as at present, being the lower of the TEL and NTEL values. When an Inhalation RfC is not available for a chemical, the CHEM/AAL process based on the MAOL will continue to be used.

The attached worksheets are used to record compound-specific hazard scores, to evaluate the basis for the RfC and to calculate the TEL.