

APPENDIX D

MA DEP DERIVED

TOXICITY VALUES

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BENZENE

SUBCHRONIC INHALATION REFERENCE CONCENTRATION

The subchronic inhalation Reference Concentration (RfC) equivalent value was derived from information presented in the Massachusetts DEP's Methodology to Derive Indoor Air Guidance Levels (MA DEP, 1991). The subchronic RfC is based on a 4 week study (Rosenthal, 1987) which examined the effect of inhaled benzene (6 hours/day, 5 days/week) on circulating lymphocytes. The ability of exposed mice to mount a cell-mediated immune response associated with tumor surveillance was monitored and noted to be delayed, suggesting compromised function. A Lowest Observed Adverse Effects Level (LOAEL) of 10 ppm (32.2 mg/m³) was identified by this study as a level of benzene which still resulted in significant impairment of the lymphocyte response. Based on this LOAEL and the application of standard uncertainty factors, a subchronic RfC equivalent may be calculated.

$$UF_1 = 10 = \text{LOAEL} \rightarrow \text{NOAEL}$$

$$UF_2 = 10 = \text{animal} \rightarrow \text{human extrapolation}$$

$$UF_3 = 10 = \text{sensitive subpopulations}$$

$$RfC_{\text{subchronic}} = 32.2 \text{ mg/m}^3 * 10^3 \mu\text{g/mg} * (1/10) * (1/10) * (1/10)$$

$$RfC_{\text{subchronic}} = 32 \mu\text{g/m}^3$$

SUBCHRONIC ORAL REFERENCE DOSE

The subchronic oral Reference Dose equivalent value was derived from information presented in the U.S. EPA's Benzene Health Advisory (U.S. EPA, 1987). The subchronic RfD is based on a study by Deichman (1963) who exposed Sprague-Dawley rats to benzene by inhalation (6 hrs/day, 4 days/week) at a broad range of concentrations and monitored their hematology weekly. By the second week of treatment, there was definite hematological impairment, including severe leukopenia at the 61, 65 and 831 ppm exposure concentrations and moderate leukopenia, especially in females, at the 44 and 47 ppm exposure concentrations. Leukopenia was not observed at 29 or 31 ppm.

Based on this data, and assuming 50% absorption of inhaled benzene (Nomiyama, 1974 a,b), a subchronic RfD equivalent may be calculated:

$$NOAEL_{2 \text{ wks exposure}} = 31 \text{ ppm (96 mg/m}^3)$$

$$AD_{\text{rat}} = \frac{96 \text{ mg/m}^3 \cdot 4 \text{ ev/wk} \cdot 6 \text{ hr/ev} \cdot 0.26 \text{ m}^3/\text{d} \cdot 0.5}{0.35 \text{ kg} \cdot 168 \text{ hr/l wk}}$$

$$AD_{\text{rat}} = 5 \text{ mg/kg/day}$$

Where:

AD_{rat} = The calculated Absorbed Dose in the rat study. In units: mg/kg/day
 96 mg/m^3 = No Observed Adverse Effects Level (NOAEL)
 4 events/week = dosing regimen from the study
 6 hours/day = dosing regimen from the study
 $0.26 \text{ m}^3/\text{day}$ = rat inhalation rate
 0.5 = absorption efficiency
 0.35 kg = rat body weight
 168 hrs/week = Conversion factor

The AD_{rat} may be converted to an allowable *human* absorbed subchronic reference dose equivalent through the application of standard uncertainty factors:

$UF_1 = 10$ = animal -> human extrapolation

$UF_2 = 10$ = sensitive subpopulations

$$RfD_{\text{subchronic}} = 5 \text{ mg/kg/day} \cdot (1/10) \cdot (1/10)$$

$$RfD_{\text{subchronic}} = 0.05 \text{ mg/kg/day}$$

CHRONIC ORAL REFERENCE DOSE

The chronic oral Reference Dose (RfD) equivalent was derived from the Deichman study described above. The AD_{rat} calculated above may be converted to an allowable *human* absorbed chronic reference dose equivalent through the application of standard uncertainty factors:

$UF_1 = 10$ = animal -> human extrapolation

$UF_2 = 10$ = sensitive subpopulations

$UF_3 = 10$ = subchronic -> chronic

$$RfD_{\text{chronic}} = 5 \text{ mg/kg/day} \cdot (1/10) \cdot (1/10) \cdot (1/10)$$

$$RfD_{\text{chronic}} = 0.005 \text{ mg/kg/day}$$

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CYANIDE

SUBCHRONIC INHALATION REFERENCE CONCENTRATION

A subchronic reference concentration (RfC) equivalent value and a chronic allowable threshold concentration (ATC) for cyanide have been developed based on human and animal toxicological information for all forms of inhaled cyanide. The long-term health consequences following inhalation exposure to cyanide are primarily central nervous system effects including deafness, visual deficits and loss of muscular coordination. Other organ systems involved (cardiovascular, thyroid, respiratory) are believed to be secondary responses. No evidence exists to implicate cyanide as possessing carcinogenic properties, however, it is possible that reproductive/developmental effects would result following exposure.

Few studies exist concerning health consequences of long-term cyanide inhalation. Two possible key studies have been identified from a thorough literature search. The study of El Ghawabi et al. (1975) is a human epidemiological study which examined thyroid enlargement in non-smoking workers occupationally exposed to cyanide at levels of 6.4 to 10.4 ppm for 5 to 15 years. It is possible that a chronic human LOAEL of 6.4 ppm could be identified from this study, however, it is likely that the workers were exposed to other volatiles and particulates during the course of their employment. A second key study (Hugod, 1981) involved the examination of myocardial histopathology in rabbits continuously exposed to hydrogen cyanide for 28 days. From this study a subchronic animal NOAEL of 0.5 ppm can be identified. This study is flawed since the investigator did not report a dose-response relationship and by the criticism that other cardiac indices may be more sensitive indicators of cardiac damage (O'Flaherty and Thomas, 1982). However, this study is the only inhalation study available with continuous exposure to cyanide of a subchronic nature.

The subchronic animal NOAEL of 0.5 ppm hydrogen cyanide gas (0.55 mg/m³ cyanide) from the Hugod study was adjusted according to standard EPA RfC methodology (EPA, 1990) to derive a subchronic RfC for cyanide.

- Animal NOAEL (28-day, continuous, adult) = 0.55 mg/m³
- Human-Equivalent Concentration (x 1.8) = 0.99 mg/m³
- Human NOAEL (+ 10) = 0.099 mg/m³
- Adjustment for sensitive individuals (+ 10) = 0.0099 mg/m³
- Low confidence in database (+ 10) = 0.00099 mg/m³

$$\text{SUBCHRONIC RfC} = 1.0 \mu\text{g/m}^3$$

CHRONIC INHALATION REFERENCE CONCENTRATION

According to EPA RfC methodology for gases producing extrarespiratory effects, the air concentration should be adjusted to yield a human-equivalent concentration based on the ratio of the inhalation rate/body weight for the animal and human according to the following equation:

$$\frac{\frac{(\text{Inhalation Rate})_{\text{rabbit}}}{(\text{Body Weight})_{\text{rabbit}}}}{(\text{Inhalation Rate})_{\text{human}} / (\text{Body Weight})_{\text{human}}}$$

The confidence in the database is low since very few inhalation studies are available. Of those studies identified, all are either methodologically flawed or utilize high exposure levels.

The Chemical Health Effects Assessment Methodology (CHEM) (MA DEP, 1990) can be used to derive a threshold effects level (TEL) which is a concentration in air to which the public could be exposed for an average lifetime and experience no adverse threshold health effects. By definition, the TEL incorporates a relative source contribution factor which, when removed, results in an Allowable Threshold Concentration (ATC) (MA DEQE, 1989). The ATC, therefore, is analogous to a chronic RfC.

Occupational limits are used as the basis for a TEL rather than primary toxicity studies. The most appropriate occupational limit (MAOL) for cyanide (inorganic and gaseous forms) of 5 mg/m^3 (NIOSH/OSHA) was selected and adjusted to account for continuous exposure and for protection of children and high-risk groups to derive an adjusted MAOL of 0.07 mg/m^3 .

- MAOL = 5 mg/m^3
- Adjustment for continuous exposure (+ 4.2) = 1.2 mg/m^3
- Adjustment for childhood exposure (+ 1.75) = 0.7 mg/m^3
- Adjustment for high-risk groups (+ 10) = 0.07 mg/m^3

$$\text{Adjusted MAOL} = 0.07 \text{ mg/m}^3$$

The adjusted MAOL was further modified to account for reproductive/developmental effects and the relative source contribution which are not considered in setting the occupational exposure limit. Based on available reproductive/developmental studies, cyanide was scored as a category "B" chemical and assigned a threshold effects uncertainty factor (TEUF) of 10.

- TEUF adjustment (+ 10) = 0.007 mg/m³
- Relative source contribution (x .2) = 0.0014 mg/m³

$$\text{TEL} = 1.4 \mu\text{g}/\text{m}^3$$

Removing the relative source contribution factor of 0.2 results in the Allowable Threshold Concentration:

$$\text{ATC} = 7 \mu\text{g}/\text{m}^3$$

or,

$$\text{CHRONIC RfC} = 7 \mu\text{g}/\text{m}^3$$

REFERENCES

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1,2-DICHLOROETHANE

SUBCHRONIC ORAL REFERENCE DOSE

The subchronic oral Reference Dose equivalent value was derived from information presented in the U.S. EPA's 1,2-Dichloroethane Health Advisory (U.S. EPA, 1987). The subchronic RfD is based on a combination of three inhalation studies (Heppel, 1946; Spencer, 1951; Hofmann, 1971) in which various animal species were exposed to 1,2-dichloroethane (1,2-DCA) for up to eight months. In these studies, exposures of rats and guinea pigs to air containing 100 ppm 1,2-dichloroethane for 6 to 7 hours/day, 5 days/week resulted in no mortality and no adverse effects as determined by general appearance, behavior, growth, organ function or blood chemistry. However, similar exposures of rats, guinea pigs, rabbits, and monkeys to air containing 400 to 500 ppm 1,2-dichloroethane resulted in high mortality and varying pathological findings including pulmonary congestion, diffused myocarditis, slight to moderate fatty degeneration of the liver, kidney, adrenal and heart, and increased plasma prothrombin time.

Based on this data, and assuming 30% absorption (U.S. EPA, 1987) of inhaled 1,2-DCA, a subchronic RfD equivalent may be calculated:

$$\text{NOAEL}_{8 \text{ month exposure}} = 100 \text{ ppm (405 mg/m}^3\text{)}$$

$$\text{AD}_{\text{rat}} = \frac{405 \text{ mg/m}^3 * 5 \text{ ev/wk} * 7 \text{ hr/ev} * 0.26 \text{ m}^3/\text{d} * 0.3}{0.35 \text{ kg} * 168 \text{ hr/1 wk}}$$

$$\text{AD}_{\text{rat}} = 19 \text{ mg/kg/day}$$

Where:

AD_{rat} = The calculated Absorbed Dose in the rat study. In units: mg/kg/day
 405 mg/m^3 = No Observed Adverse Effects Level (NOAEL)
 5 events/week = dosing regimen from the study
 7 hours/day = dosing regimen from the study
 $0.26 \text{ m}^3/\text{day}$ = rat inhalation rate
 0.3 = absorption efficiency
 0.35 kg = rat body weight
 168 hrs/week = Conversion factor

The AD_{rat} may be converted to an allowable *human* absorbed subchronic reference dose equivalent through the application of standard uncertainty factors:

UF₁ = 10 = animal -> human extrapolation

UF₂ = 10 = sensitive subpopulations

$$\text{RfD}_{\text{subchronic}} = 19 \text{ mg/kg/day} * (1/10) * (1/10)$$

$$\text{RfD}_{\text{subchronic}} = 0.2 \text{ mg/kg/day}$$

CHRONIC ORAL REFERENCE DOSE

The chronic oral Reference Dose (RfD) equivalent was derived from the combination of studies described above. The AD_{rat} calculated above may be converted to an allowable *human* absorbed chronic reference dose equivalent through the application of standard uncertainty factors:

UF₁ = 10 = animal -> human extrapolation

UF₂ = 10 = sensitive subpopulations

UF₃ = 10 = subchronic -> chronic

$$\text{RfD}_{\text{chronic}} = 19 \text{ mg/kg/day} * (1/10) * (1/10) * (1/10)$$

$$\text{RfD}_{\text{chronic}} = 0.02 \text{ mg/kg/day}$$

REFERENCES

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ETHYLENE DIBROMIDE

SUBCHRONIC INHALATION REFERENCE CONCENTRATION

A subchronic reference concentration (RfC) equivalent value has been developed for ethylene dibromide (EDB) based on available human and animal toxicological information. Inhalation of EDB vapor may cause severe acute respiratory injury, central nervous system depression and severe vomiting (Sittig, 1981). Animal studies have indicated that EDB may produce liver and kidney injury (Sittig, 1981). EDB has been found to be a potent carcinogen in animals and has tested positively in a number of in vitro mutagenicity assays (NIOSH, 1977). In addition, EDB has produced developmental and reproductive effects in animals (NIOSH, 1977).

A thorough literature search was conducted for this compound. Most of the studies retrieved focused on carcinogenicity. The majority of studies located are summarized in the NIOSH Criteria for a Recommended Standard . . . Occupational Exposure to Ethylene Dibromide (NIOSH, 1977) and the Agency for Toxic Substances and Disease Registry Toxicological Profile for 1,2-Dibromoethane (ATSDR, 1991). Other noncarcinogenic studies identified which were not cited in the above publications include:

<u>Source</u>	<u>Species</u>	<u>Exp. Route</u>	<u>Duration</u>	<u>Effect</u>	<u>Exp. Level</u>
Williams et al., 1991	New Zeal. white rabbit	subcut.	5 days	incr. mortality; liver damage; signif. decr. sperm velocity; incr. sperm abnormalities	45 mg/kg/day (LOAEL)
NTP, 1982	mice, rats	inhal.	6 hr/d, 5 d/wk, 13 wks	decr. weight-male rats and male/female mice	3 ppm (LOAEL)

A critical subchronic inhalation study (NTP, 1982) was identified from this search. In this study, mice and rats were exposed to EDB by inhalation at concentrations of 0, 3, 15, or 75 ppm for 6 hours per day, 5 days per week for 13 weeks. The study produced a dose-related depression in weight in male rats and in male and female mice. A LOAEL of 3 ppm was identified from this study as the basis for developing a subchronic inhalation RfC using EPA RfC methodology (EPA, 1990). The following adjustments were made:

- Animal LOAEL (subchronic) = 3 ppm
- Corrected for continuous exposure over the subchronic period (x 6 hrs/24 hrs x 5 days/7 days) = 0.54 ppm
- Converted to mg/m³ (based on mg/m³ = ppm x M.W./24.45) = 4.1 mg/m³
(Molecular Weight, M.W. = 187.88)
- Human-Equivalent Concentration (to account for absorption: (based on comparison to a rat since yields the more conservative results of the test species used: x 2.9¹)) = 11.9 mg/m³
- Human-Equivalent Concentration (to account for distribution, metabolism and excretion: + 10) = 1.2 mg/m³
- Human NOAEL (+ 10) = 0.12 mg/m³
- Adjust for sensitive individual (+ 10) = 0.012 mg/m³
- Low confidence in database (+ 10) = 0.0012 mg/m³

$$\text{SUBCHRONIC RfC} = 1.2 \mu\text{g}/\text{m}^3$$

CHRONIC INHALATION REFERENCE CONCENTRATION

The Chemical Health Effects Assessment Methodology (CHEM) (MA DEP, 1990) can be used to derive a threshold effects exposure limit (TEL) which represents a concentration in air to which the general public can be exposed day after day for a lifetime and experience no adverse threshold health effects. The TEL incorporates a relative source contribution factor which, when removed, results in an Allowable Threshold Concentration (ATC) (MA DEQE, 1989). The ATC, therefore, is analogous to a chronic RfC.

Occupational limits are used as the basis for a TEL rather than primary toxicity studies. The OSHA occupational limit of 20 ppb (NIOSH 1978) was selected as the most appropriate occupational exposure limit (MAOL) for ethylene dibromide. The MAOL value was adjusted to account for continuous exposure and for protection of children and high-risk groups to derive an adjusted MAOL of 0.2 $\mu\text{g}/\text{m}^3$.

- MAOL = 20 ppb
- Converted to $\mu\text{g}/\text{m}^3$ (based on $\mu\text{g}/\text{m}^3 = \text{ppb} \times \text{M.W.}/24.45$) = 153.7 $\mu\text{g}/\text{m}^3$
- Adjustment for continuous exposure (+ 4.2) = 36.6 $\mu\text{g}/\text{m}^3$
- Adjustment for childhood exposure (+ 1.75) = 20.9 $\mu\text{g}/\text{m}^3$
- Adjustment for high-risk groups (+ 10) = 2.1 $\mu\text{g}/\text{m}^3$

$$\text{Adjusted MAOL} = 2.1 \mu\text{g}/\text{m}^3$$

¹ According to EPA RfC methodology for gases, the air concentration should be adjusted to yield a human-equivalent concentration based on the ratio of alveolar ventilation rate divided by the body weight of the animal species to the same parameters for humans. The following formula was used:

$$(\text{Inhalation Rate}_{\text{rat}}/\text{Body Weight}_{\text{rat}})/(\text{Inhalation Rate}_{\text{human}}/\text{Body Weight}_{\text{human}})$$

The values used in the above formula include: inhalation rate_{rat} = 0.29 m³/day; body weight_{rat} = 0.35 kg; inhalation rate_{human} = 20 m³/day; body weight_{human} = 70 kg

The adjusted MAOL was further modified to account for reproductive/developmental effects not accounted for in setting the occupational exposure limit and for relative source contribution (which is also not considered in the derivation of the occupational limit). Based on available developmental and reproductive studies, EDB was given a hazard score of "A" and assigned a threshold effects uncertainty factor (TEUF) of 10.

- TEUF adjustment (+ 10) = $0.2 \mu\text{g}/\text{m}^3$
- Relative source contribution ($\times 0.2$) = $0.04 \mu\text{g}/\text{m}^3$

$$\text{TEL} = 0.04 \mu\text{g}/\text{m}^3$$

Removing the relative source contribution factor of 0.2 results in the Allowable Threshold Concentration:

$$\text{ATC} = 0.2 \mu\text{g}/\text{m}^3$$

or,

$$\text{CHRONIC RfC} = 0.2 \mu\text{g}/\text{m}^3$$

SUBCHRONIC ORAL REFERENCE DOSE (RfD)

A subchronic oral reference dose (RfD) equivalent value for ethylene dibromide (EDB) has been developed based on human and animal toxicological information. Acute oral exposure to EDB has produced vomiting, abdominal pain, diarrhea, nausea, anuria and death (NIOSH, 1977). Animal studies have indicated that EDB may produce liver and kidney injury (Sittig, 1981). EDB has been found to be a potent carcinogen in animals and has tested positively in a number of in vitro mutagenicity assays (NIOSH, 1977). In addition, EDB has produced developmental and reproductive effects in animals (NIOSH, 1977).

A thorough literature search was conducted for this compound. Most of the available studies for EDB are either acute exposure studies or focus on carcinogenicity as an endpoint. The majority of studies located are summarized by NIOSH (1977) and the Agency for Toxic Substances and Disease Registry (ATSDR, 1991). Other potentially pertinent studies investigating noncarcinogenic endpoints which were not cited in the above documents include:

<u>Source</u>	<u>Species</u>	<u>Exp. Route</u>	<u>Duration</u>	<u>Effect</u>	<u>Exp. Level</u>
Williams et al., 1991	New Zeal. white rabbit	subcut.	5 days	incr. mortality; liver damage; signif. decr. sperm velocity; incr. sperm abnormalities	45 mg/kg/day (LOAEL)

Several studies (NIOSH, 1977) done by the same group of investigators which are cited in the above document focus on reproductive effects produced in bulls given oral doses of EDB. A critical subchronic study (Amir et al., 1965) was selected as the basis for developing the RfD. In this study, Israeli-Friesian bulls were given oral doses of EDB from age 4 days to 24 months. From 0 to 3 months, 2 mg/kg/day was administered via ethyl alcohol in milk. From 3-12 months, 2 mg/kg/day was dissolved in soybean oil and put into the feed. After 12 months, 4 mg/kg/day was administered orally in an oil mixture by capsule every other day. The average daily dose for this period was 2 mg/kg/day. Effects noted included abnormal spermatozoa and decreased spermatozoic density and motility. Based on the results of this study, an animal LOAEL of 2 mg/kg/day has been identified. The LOAEL has been adjusted using modified EPA RfD methodology (U.S. EPA, 1987) to derive a subchronic RfC of 0.0002 mg/kg/day.

- Animal LOAEL (subchronic) = 2 mg/kg/day
- Animal NOAEL (+ 10) = 0.2 mg/kg/day
- Human NOAEL (+ 10) = 0.02 mg/kg/day
- Adjust for sensitive individual (+ 10) = 0.002 mg/kg/day
- Low confidence in database (+ 10) = 0.0002 mg/kg/day

SUBCHRONIC RfD = 0.0002 mg/kg/day

The confidence in the database is low since there are few subchronic oral studies. Of the studies located, reproductive toxicity was the only health endpoint examined. In addition, little to no information was located regarding subchronic oral exposure in humans. No adequate dose-response data were identified. Although standard EPA RfD methodology does not include an uncertainty factor for low confidence in the database, an uncertainty factor of 10 is included in the EPA methodology for developing inhalation reference concentrations (RfCs). This factor will be adopted for development of the EDB oral RfD.

CHRONIC ORAL REFERENCE DOSE (RfD)

There were no chronic oral studies identified for EDB. Based on the approach used by EPA to extrapolate a chronic NOAEL from a subchronic NOAEL, an additional uncertainty factor of 10 was applied to the NOAEL to approximate a chronic RfD for this compound. Thus:

- Subchronic RfD = 0.0002 mg/kg/day
- Chronic RfD (+ 10) = 0.00002 mg/kg/day

CHRONIC RfD = 0.00002 mg/kg/day

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LEAD

CHRONIC AND SUBCHRONIC ORAL REFERENCE DOSES

The Office of Research and Standards currently recommends the use of the toxicity criteria for lead back-calculated from the promulgated National Primary Drinking Water Regulation *Action Level* of 15 µg/L (U.S. EPA, 1991).

It should be explicit in all reports using these criteria that they are *not* considered risk free levels. These criteria are described as *Regulatory Daily Doses* (RDDs) to distinguish them from the U.S. EPA's Reference Doses (which are assumed to result in no adverse effects) and the subjective term "Allowable Daily Intake".

The values are:

$$RDD_{\text{oral-subchronic}} = 7.5 \times 10^{-4} \text{ mg/kg/day}$$

$$RDD_{\text{oral-chronic}} = 7.5 \times 10^{-4} \text{ mg/kg/day}$$

The RDDs given here are absorbed doses.

The aim of this section was to identify surrogate toxicity values which can effectively be used in the evaluation c.21E disposal sites. It is understood that while these interim values are not considered to be without risk of harm to health, they are within the range of "acceptable risk" for this chemical. Many of the standards and guidelines (Table 1) used to develop the values listed in Table 2 have undergone extensive *national* public review, and the risk balancing/risk management decisions made are documented (federal drinking water standards). Others have undergone *statewide* review or none at all.

Of the seven criteria considered, the two extreme toxicity values were eliminated from further consideration: the 1991 Maximum Contaminant Level Goal was considered infeasible (the derived toxicity value is 0 mg/kg/day), and the Massachusetts Department of Public Health "*Dangerous Level in Soil*" (MA DPH) is more representative of a trigger level for a Short-Term Measure than a clean-up level (the derived value is 0.005 mg/kg/day).

Among the remaining five criteria, toxicity values range from 0.00025 mg/kg/day to 0.0025 mg/kg/day, a span of a factor of ten. Three values (from the 1985 PMCLG, the 1991 Action Level, and the ORS manipulation of the lead model) are clustered in the range 0.00075 to 0.0013 mg/kg/day (less than a factor of two). The 1991 Action Level value was chosen because:

- (1) The value is consistent with results of the back-calculation from the 1985 PMCLG and ORS manipulation of the computerized lead model,
- (2) It is back-calculated from a standard (published in its final form in the June 7, 1991 *Federal Register*) and thus represents the most recent U.S. EPA statement as to what it considers an upper limit of an "allowable" exposure,
- (3) The use of the most current drinking water standard is consistent with guidance that existing standards for lead be used to evaluate noncarcinogenic risk (U.S. EPA, 1986).

This discussion is in response to a need to include quantitative evaluations of lead in the *Residential ShortForm* pursuant to the Massachusetts Contingency Plan (MCP, 310 CMR 40). These daily intakes would be used in the absence of a U.S. EPA verified Reference Dose (RfD) or Carcinogenic Potency (Slope) Value (CPV) pending a Departmental or Bureau of Waste Site Cleanup policy addressing such exposures.

DISCUSSION

Lead is a ubiquitous environmental contaminant in Massachusetts as a result of the historical use of lead paint and leaded fuels, as well as those releases of lead regulated under the MCP. The lead problem is further complicated by its toxicity: there appears to be no concentration of lead which is free from the risk of adverse non-carcinogenic health impacts if exposure were to occur. In addition, lead is considered to be a "probable human carcinogen" (U.S. EPA, 1989a).

The problematical regulation of lead is not limited to the the *Residential ShortForm* or the Department's Bureau of Waste Site Cleanup assessment and remediation program, and should be the subject of a Department-wide strategy to reduce *all* potential exposures to lead in the Commonwealth. As with most complex issues, such a policy cannot be completed in a matter of months. In the interim, however, it is vital that the *Residential ShortForm* have some means of quantitatively assessing lead contamination at c.21E disposal sites.

Various U.S. EPA and Massachusetts regulatory actions concerning oral exposures to lead are summarized in Table 1. Given that no exposure to lead in the environment is risk-free, virtually all of the regulatory values presented in Table 1 involve risk management decisions which balance the potential health impacts with technical feasibility and cost considerations. The use of traditional methods of developing strictly health-based criteria or assessing risk is not currently an option in the case of lead for two reasons:

- (1) there is no No Observed Adverse Effect Level (NOAEL) which is used to derive a Reference Dose or Reference Concentration, the usual bases for regulating chemicals with non-carcinogenic effects, and
- (2) there is no Carcinogenic Potency Value, the usual basis for regulating chemicals considered to be carcinogenic.

In the absence of these toxicity values, a risk assessor may search the toxicological literature for alternative values, or derive such alternative values from any existing standards or guidelines for that chemical. The latter methodology is described in the Department's *Guidance for Disposal Site Risk Characterization and Related Phase II Activities - In Support of the Massachusetts Contingency Plan* (MA DEQE, 1989) and the U.S. EPA Region I *Supplemental Risk Assessment Guidance for the Superfund Program* (U.S. EPA 1989b). This process for deriving toxicity values has been chosen for this interim approach to assessing exposure to lead at c.21E disposal sites.

It should be noted that, in certain situations, the use of these toxicity values may indicate a need for remediation at c.21E disposal sites where lead concentrations are at or below "background" levels. The *Massachusetts Contingency Plan* addresses these circumstances in **40.545 (3)(j) 2., Requirements When a Remedial Response Action is Necessary**. This section states that if the evaluation of risk indicates a need for remediation and if the levels of oil or hazardous materials which would exist in the absence of the disposal site (i.e., "background") prevent achievement of guidelines, policies or total site risk limits, then the achievement of such "background" levels may, upon approval of the Department, be considered to meet the requirements for a permanent solution.

Table 2 summarizes these alternative toxicity values. The derivation for the chosen level follows.

N.B.: Many of the standards and guidelines which serve as the source for these "alternative toxicity values" incorporate risk management decisions which considered factors beyond solely the potential health impacts. These values should not be considered "safe", or "risk-free" levels.

TABLE 1

U.S. EPA and MASSACHUSETTS REGULATORY ACTIONS

WATER	U.S. EPA - <u>Proposed</u> (1985) Maximum Contaminant Level Goal for Drinking Water (PMCLG)	20 µg/L
	U.S. EPA/Massachusetts - Maximum Contaminant Level for Drinking Water (MCL)	50 µg/L
	U.S. EPA (1991) Maximum Contaminant Level Goal for Drinking Water (MCL 3)	0 µg/L
	U.S. EPA (1991) NPDWR Action Level (AL) (Measured at the tap)	15 µg/L
	U.S. EPA - Ambient Water Quality Criteria (AWQC) (Human Health)	50 µg/L
SOIL	Massachusetts - " <i>Dangerous Level in Soil</i> " (MA DPH)	1000 mg/kg
	U.S. EPA - OSWER Lead Clean-up Levels at Superfund Sites	500 - 1000 mg/kg

TABLE 2

SUMMARY OF ALTERNATIVE ABSORBED ORAL TOXICITY VALUES FOR THE EVALUATION OF LEAD IN RISK CHARACTERIZATIONS PERFORMED UNDER THE MCP

	<u>SOURCE</u>	<u>VALUE</u>
ORAL	back-calculated from PMCLG = 20 µg/L	0.001 mg/kg/day
	back-calculated from MCLG = 0 µg/L	0 mg/kg/day
	back-calculated from MCL = 50 µg/L	0.0025 mg/kg/day
	back-calculated from Action Level = 15 µg/L	0.00075 mg/kg/day
	back-calculated from UPTAKE/BIOKINETIC MODEL	0.0013 mg/kg/day
	back-calculated from MA DPH "Dangerous Level in Soil"	0.005 mg/kg/day
	back-calculated from EPA OSWER Directive Levels	0.0025 mg/kg/day

DOSE ESTIMATES FROM EXISTING STANDARDS AND GUIDELINES

In the absence of a U.S. EPA verified reference dose and/or reference concentration, or equivalent published toxicity values which could be used to evaluate risk of harm to human health, guidance has been provided (MA DEQE, 1989; U.S. EPA, 1989b) to assist a risk assessor in the development of acceptable alternative dose. These alternative doses are generally back-calculated from existing standards and guidelines. While this methodology is relatively straight-forward, it is important to remember that standards and guidelines may consider other factors (such as cost and feasibility) in addition to health impacts. Alternative toxicity values calculated in this manner must be accompanied by a discussion of the basis of the standard or guideline used as a starting point.

Action Level (AL)

An Interim Maximum Contaminant Level of 0.05 mg/L was promulgated for lead by the U.S. EPA in 1980. On June 7, 1991, the U.S. EPA promulgated the National Primary Drinking Water Regulation for Lead (40 CFR Part 141 and 142, Federal Register Vol. 56 No. 110)

which established an *Action Level* of 0.015 mg/liter. The *Action Level* is triggered if more than 10% of the targeted tap samples is greater than 0.015 mg/l. [An *Action Level* is defined as that concentration of lead in water that determines, in some cases, whether a water system must install corrosion control treatment, monitor source water, replace lead service lines, and undertake a public education process.] The *Action Level* is a standard based on health considerations, but which also considers risk management issues such as technological or economic feasibility. The following calculations detail the derivation of an Regulatory Daily Dose (RDD) the AL (the RDD_{AL}).

$$ARDD = STND * VI \div BW$$

Where:

ARDD = Applied Regulatory Daily Dose (mg/kg/day) back-calculated from the Action Level
 STND = the 1991 Action Level (AL: 0.015 mg/L)
 VI = Daily Intake of Water for a Child, 1 L/day
 BW = A Child's Body Weight, 10 kg

$$ARDD_{AL} = 0.015 \text{ mg/L} * 1 \text{ L/day} \div 10 \text{ kg}$$

$$ARDD_{AL} = 0.0015 \text{ mg/kg/day}$$

Assuming that 50% of the lead ingested in the drinking water is absorbed in the gastrointestinal tract, the *absorbed* Regulatory Daily Doses based upon the Action Level would be:

$$RDD_{AL} = 0.0015 \text{ mg/kg/day} * 0.5$$

$$RDD_{AL} = 0.00075 \text{ mg/kg/day}$$

$$\frac{0.015 \text{ mg}}{\text{L}} \times \frac{\text{L}}{\text{day}} \times \frac{1}{10 \text{ kg}} = 0.0015 \frac{\text{mg}}{\text{kg} \cdot \text{day}}$$

REFERENCES

Guidance for Disposal Site Risk Characterization and Related Phase II Activities - In Support of the Massachusetts Contingency Plan. Massachusetts Department of Environmental Quality Engineering [Policy No. WSC/ORS-141-89] (1989).

The Massachusetts Contingency Plan. Massachusetts Department of Environmental Protection, 310 CMR 40.000.

Lead Poisoning Prevention and Control. Massachusetts Department of Public Health, 105 CMR 460.

Health Effects Assessment For Lead. U.S. Environmental Protection Agency, NTIS PB # 86 134665/AS (1986).

LEAD, U.S Environmental Protection Agency, *Integrated Risk Information System* (IRIS) file (1989a).

Supplemental Risk Assessment Guidance for the Superfund Program. U.S. Environmental Protection Agency, Region I (1989b).

National Primary Drinking Water Regulation for Lead, 40 CFR Part 141 and 142, U.S. Environmental Protection Agency, *Federal Register* 56(110).

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METHYL TERTIARY BUTYL ETHER (MTBE)

SUBCHRONIC ORAL REFERENCE DOSE

The subchronic oral Reference Dose equivalent value was derived from information presented in the U.S. EPA's Methyl-t-Butyl Ether Health Advisory (U.S. EPA, 1989). The subchronic RfD is based on a 13-week inhalation study (Greenough, 1980) in which rats were exposed for 6 hours/day, 5 days/week for 13 weeks to 0, 250, 500 or 1,000 ppm MTBE. No effects were seen on survival, body weight, hematological, clinical chemistry or urinalysis values, or gross or microscopic appearance of tissues or organs. A slight reduction in absolute and relative lung weight was observed in females exposed to 1,000 ppm MTBE. The only other effect noted by the investigators was an increasing depth of anesthesia with increasing exposure concentration. Exposure-effect relationships for anesthesia were not further delineated. Accordingly, 250 ppm is considered a LOEL for anesthetic effects.

Based on this data, and assuming 50% absorption of inhaled methyl tert-butyl ether, a subchronic RfD equivalent may be calculated:

$$\text{LOEL}_{13 \text{ week exposure}} = 250 \text{ ppm (901 mg/m}^3\text{)}$$

$$\text{AD}_{\text{rat}} = \frac{901 \text{ mg/m}^3 \cdot 5 \text{ ev/wk} \cdot 6 \text{ hr/ev} \cdot 0.217 \text{ m}^3/\text{d} \cdot 0.5}{0.336 \text{ kg} \cdot 168 \text{ hr/1 wk}}$$

$$\text{AD}_{\text{rat}} = 52 \text{ mg/kg/day}$$

Where:

AD_{rat} = The calculated Absorbed Dose in the rat study. In units: **mg/kg/day**
 901 mg/m^3 = Lowest Observed Adverse Effects Level (LOEL)
5 events/week = dosing regimen from the study
6 hours/day = dosing regimen from the study
 $0.217 \text{ m}^3/\text{day}$ = rat inhalation rate (based on measured body weight)
0.5 = absorption efficiency
0.336 kg = rat body weight from study
168 hrs/week = Conversion factor

The AD_{rat} may be converted to an allowable *human* absorbed subchronic reference dose equivalent through the application of standard uncertainty factors:

$\text{UF}_1 = 10 = \text{animal} \rightarrow \text{human extrapolation}$
 $\text{UF}_2 = 10 = \text{sensitive subpopulations}$
 $\text{UF}_3 = 10 = \text{LOEL} \rightarrow \text{NOEL}$

$$\text{RfD}_{\text{subchronic}} = 52 \text{ mg/kg/day} * (1/10) * (1/10) * (1/10)$$

$$\text{RfD}_{\text{subchronic}} = 0.052 \text{ mg/kg/day}$$

CHRONIC ORAL REFERENCE DOSE

The chronic oral Reference Dose (RfD) equivalent was derived from the Greenough study described above. The AD_{mt} calculated above may be converted to an allowable *human* absorbed chronic reference dose equivalent through the application of standard uncertainty factors:

$\text{UF}_1 = 10 = \text{animal} \rightarrow \text{human extrapolation}$

$\text{UF}_2 = 10 = \text{sensitive subpopulations}$

$\text{UF}_3 = 10 = \text{subchronic} \rightarrow \text{chronic}$

$\text{UF}_4 = 10 = \text{LOAEL} \rightarrow \text{NOAEL}$

$$\text{RfD}_{\text{chronic}} = 52 \text{ mg/kg/day} * (1/10) * (1/10) * (1/10) * (1/10)$$

$$\text{RfD}_{\text{chronic}} = 0.0052 \text{ mg/kg/day}$$

REFERENCES

Methyl tertiary-butyl ether (Driverton) three month inhalation toxicity in rats. Greenough, R.J., P. Mc Donald, P. Robinson, J.R. Cowie, W. Maule, F. Macnaughton, and A. Rushton, Project No. 413038. Unpublished report submitted to Chemische Werke Hols, AG. Marl, West Germany. 230pp. (1980)

Methyl-t-Butyl Ether Health Advisory. U.S. Environmental Protection Agency, Office of Drinking Water (1989).

POLYCHLORINATED BIPHENYLS

CHRONIC ORAL REFERENCE DOSE

The chronic oral reference dose equivalent value for polychlorinated biphenyls (PCBs) was developed with information contained in the (DRAFT) Toxicological Profile for Selected PCBs (ATSDR, 1991). One study (Tryphonas et al., 1989) looked at several immunological parameters in monkeys fed dietary doses of Aroclor 1254 ranging from 0.005 to 0.08 mg/kg/day over a period of 133 weeks (27 months). All doses tested induced a significant and dose-related decrease in antibody levels (IgG and IgM) in response to immunization with SRBC-7, 14 and 21 days after immunization. The ATSDR calculated a "Minimal Risk Level" (MRL) of 0.005 $\mu\text{g}/\text{kg}/\text{day}$ based upon this study in a manner similar to that described below.

$$\text{LOAEL} = 0.005 \text{ mg/kg/day}$$

$$\text{UF}_1 = 10 = \text{LOAEL to NOAEL extrapolation}$$

$$\text{UF}_2 = 10 = \text{animal} \rightarrow \text{human extrapolation}$$

$$\text{UF}_3 = 10 = \text{sensitive subpopulations}$$

$$\text{RfD}_{\text{oral-chronic}} = 0.005 \text{ mg/kg/day} * (1/10) * (1/10) * (1/10)$$

$$\text{RfD}_{\text{oral-chronic}} = 5 \times 10^{-6} \text{ mg/kg/day}$$

SUBCHRONIC ORAL REFERENCE DOSE

The chronic oral RfD equivalent derived above is based upon immunological effects which have been demonstrated following shorter exposures periods (Loose et al., 1978a, 1978b; Thomas and Hinsdill, 1978; Truelove et al., 1982) without the demonstration of a NOAEL. As a result, the chronic oral RfD equivalent has been adopted as the subchronic oral RfD equivalent.

$$\text{RfD}_{\text{oral-subchronic}} = 5 \times 10^{-6} \text{ mg/kg/day}$$

REFERENCES

DRAFT Toxicological Profile for Selected PCBs, Agency for Toxic Substances and Disease Registry, U.S. Public Health Service (1991).

Loose, L.D., Silkworth, J.B., Pittman, K.A., et al. (1978a) *Impaired host resistance to endotoxin and malaria in polychlorinated biphenyl- and hexachlorobenzene-treated mice*. **Infection and Immunity** 20:30-35.

Loose, L.D., Pittman, K.A., Benitz, K.F., et al. (1978b) *Environmental chemical-induced immune dysfunction*. **Ecotoxicol Environ Safety** 2:173-198.

Thomas, P.T. and Hinsdill, R.D. (1978) *Effect of polychlorinated biphenyls on the immune responses of rhesus monkeys and mice*. **Toxicol Appl Pharmacol** 44:41-51.

Truelove, J., Grant, D., Mes, J. et al. (1982) *Polychlorinated biphenyl toxicity in the pregnant cynomolgus monkey: A pilot study*. **Arch Environ Contam Toxicol** 11:583-588.

Tryphonas, H., Hayward, S., O'Grady, L., et al. (1989) *Immunotoxicity studies of PCB (Aroclor 1254) in the adult rhesus (*Macaca mulatta*) monkey -- preliminary report*. **Int J Immunopharmacol** 11:199-206.

TRICHLOROETHYLENE

SUBCHRONIC ORAL REFERENCE DOSE

The subchronic oral Reference Dose equivalent value was derived from information presented in the U.S. EPA's Trichloroethylene Health Advisory (U.S. EPA, 1987). The subchronic RfD is based on a subacute inhalation study (Kimmerle, 1973). In this study rats were exposed to 55 ppm trichloroethylene for 8 hours/day, 5 days/week for 14 weeks. Indices of toxicity include hematological investigation, liver and renal function tests, blood glucose and organ/body weight ratios. Liver weights were shown to be elevated while other test values were not different from controls. The elevated liver weights could be interpreted to be the result of hydropic changes or fatty accumulation. The no-observed-effect level was not identified since only a single concentration was administered

Based on this data, and assuming 30% absorption of inhaled trichloroethylene, a subchronic RfD equivalent may be calculated:

$$\text{LOAEL}_{14 \text{ week exposure}} = 55 \text{ ppm (300 mg/m}^3\text{)}$$

$$\text{AD}_{\text{rat}} = \frac{300 \text{ mg/m}^3 * 5 \text{ ev/wk} * 8 \text{ hr/ev} * 0.26 \text{ m}^3/\text{d} * 0.3}{0.35 \text{ kg} * 168 \text{ hr/1 wk}}$$

$$\text{AD}_{\text{rat}} = 16 \text{ mg/kg/day}$$

Where:

AD_{rat} = The calculated Absorbed Dose in the rat study. In units: mg/kg/day
 300 mg/m^3 = Lowest Observed Adverse Effects Level (LOAEL)
5 events/week = dosing regimen from the study
8 hours/day = dosing regimen from the study
 $0.26 \text{ m}^3/\text{day}$ = rat inhalation rate
0.3 = absorption efficiency
0.35 kg = rat body weight
168 hrs/week = Conversion factor

The AD_{rat} may be converted to an allowable *human* absorbed subchronic reference dose equivalent through the application of standard uncertainty factors:

$\text{UF}_1 = 10 = \text{animal} \rightarrow \text{human extrapolation}$
 $\text{UF}_2 = 10 = \text{sensitive subpopulations}$
 $\text{UF}_3 = 10 = \text{LOAEL} \rightarrow \text{NOAEL}$

$$\text{RfD}_{\text{subchronic}} = 16 \text{ mg/kg/day} * (1/10) * (1/10) * (1/10)$$

$$\text{RfD}_{\text{subchronic}} = 0.02 \text{ mg/kg/day}$$

CHRONIC ORAL REFERENCE DOSE

The chronic oral Reference Dose (RfD) equivalent was derived from the Kimmerle study described above. The AD_{oral} calculated above may be converted to an allowable *human* absorbed chronic reference dose equivalent through the application of standard uncertainty factors:

$\text{UF}_1 = 10 = \text{animal} \rightarrow \text{human extrapolation}$

$\text{UF}_2 = 10 = \text{sensitive subpopulations}$

$\text{UF}_3 = 10 = \text{subchronic} \rightarrow \text{chronic}$

$\text{UF}_4 = 10 = \text{LOAEL} \rightarrow \text{NOAEL}$

$$\text{RfD}_{\text{chronic}} = 16 \text{ mg/kg/day} * (1/10) * (1/10) * (1/10) * (1/10)$$

$$\text{RfD}_{\text{chronic}} = 0.002 \text{ mg/kg/day}$$

REFERENCES

Kimmerle, G. and Eben, A. (1973) *Metabolism, excretion and toxicology of trichloroethylene after inhalation. 1. Experimental exposure on rats. Arch. Toxicol.* 30:115.

Trichloroethylene Health Advisory, U.S. Environmental Protection Agency, Office of Drinking Water (1987).

VINYL CHLORIDE

CHRONIC ORAL REFERENCE DOSE

The chronic oral Reference Dose equivalent value was derived from information presented in the U.S. EPA's Vinyl Chloride Health Advisory (U.S. EPA, 1987). The chronic RfD is based on a lifetime feeding study (Til, 1981). In this study Til extended earlier work (Feron, 1981) to include lower doses with basically the same protocol used in the latter study. Carcinogenic and noncarcinogenic effects were evident with a vinyl chloride dietary level of 1.3 mg/kg/day. At dietary levels of 0.014 and 0.13 mg/kg/day, increased incidences of basophilic foci of cellular alteration in the liver of female rats were evident. However, basophilic foci by themselves are concluded not to represent an adverse effect on the liver in the absence of additional effects indicative of liver lesions such as those found in the 1.3 mg/kg/day group; and a dose-related increase in basophilic foci was not evident. Therefore, the dose of 0.13 mg/kg/day is identified as the NOAEL for noncarcinogenic effects.

Based on this data, a chronic RfD equivalent may be calculated:

$$\text{NOAEL}_{\text{rat-lifetime exposure}} = 0.13 \text{ mg/kg/day (applied dose)}$$

The $\text{NOAEL}_{\text{rat-lifetime}}$ may be converted to an allowable *human* applied chronic reference dose equivalent through the application of standard uncertainty factors:

$\text{UF}_1 = 10 =$ animal -> human extrapolation

$\text{UF}_2 = 10 =$ sensitive subpopulations

$$\text{RfD}_{\text{chronic}} = 0.13 \text{ mg/kg/day} * (1/10) * (1/10)$$

$$\text{RfD}_{\text{chronic}} = 0.001 \text{ mg/kg/day (applied dose)}$$

SUBCHRONIC ORAL REFERENCE DOSE

The chronic oral RfD is assumed to be protective of subchronic exposures, and the subchronic oral RfD is set equal to the chronic oral RfD.

$$\text{RfD}_{\text{subchronic}} = 0.001 \text{ mg/kg/day (applied dose)}$$

REFERENCES

Feron, V.J., Hendrikson, C.F.M., Speek, A.J., Til, H.P. and Spit, B.J. (1981) *Lifespan oral toxicity study of vinyl chloride in rats*. *Fd. Cosmet. Toxicol.* 19:317-331.

Til, H.P., Immel, H.R. and Feron, V.J. (1983) *Lifespan oral carcinogenicity study of vinyl chloride in rats*. Final Report, Civo Institutes TNO. Report No. V 83.285/291099.

Vinyl Chloride Health Advisory, U.S. Environmental Protection Agency, Office of Drinking Water (1987).