Commonwealth of Massachusetts
Executive Office of Energy & Environmental Affairs

Department of Environmental Protection
One Winter Street Boston, MA 02108 • 617-292-5500

DEVAL L. PATRICK
Governor

MAEVE VALLELY BARTLETT
Secretary

DAVID W. CASH
Commissioner

US EPA Trichloroethylene Toxicity Values and Office of Research and Standards Recommendations Regarding Remediation Targets and Timeframes to Address Potential Developmental Risks

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Introduction

Trichloroethylene (TCE) is a solvent used industrially and commercially. Due to its extensive use, TCE has polluted the atmosphere, ground and surface waters and soil. People may be exposed via the oral, dermal, and inhalation routes, with evidence for distribution to various tissues from each. TCE can also be transferred through the placenta, leading to fetal exposures.

Both human and animal studies have associated TCE exposure with effects on the liver, kidney, and heart, nervous, hematopoietic, immunological, reproductive, developmental, and respiratory systems. TCE is characterized by the US Environmental Protection Agency (US EPA) (2011) as "carcinogenic to humans" and US EPA has published cancer risk toxicity values for oral and inhalation exposures. Due to various non-carcinogenic health concerns, the US EPA (2011) has also published a non-cancer toxicity value for inhalation (the reference concentration, RfC) of 2 $\mu g/m^3$ (0.4 ppb) for TCE.[1] US EPA defines the RfC as an estimated continuous inhalation exposure level, with uncertainty spanning perhaps an order of magnitude, likely to be without an appreciable risk of deleterious effects to the human population (including sensitive subgroups) during a lifetime. The non-cancer inhalation toxicity value is based on multiple endpoints, including effects on heart development, raising concerns about shorter-term exposure risks during pregnancy. Based on the overall weight of the scientific evidence US EPA concluded that "*Taken together, the epidemiological and animal study evidence raise sufficient concern regarding the potential for developmental toxicity (increased incidence of cardiac defects) with in utero TCE exposure*".[2] MassDEP's Office of Research and Standards (ORS), with input from the MassDEP Health Effects Advisory Committee, concurred with US EPA's determination and concluded that is appropriate that TCE be considered a developmental toxin under the Massachusetts hazard waste site cleanup program.

[1] Integrated Risk Information System (IRIS), trichlororetheylene files.
[2] US EPA Toxicological Review of Trichloroethylene, Chapter 4: 4.8.3.3.2.3. Summary of the weight of evidence on cardiac malformations: Page 4-565

The IRIS TCE toxicity values are supported by a comprehensive toxicological review document compiled by US EPA (2011). The overall database for TCE is extensive and US EPA evaluated a large number of studies and endpoints to derive various candidate non-cancer toxicity values. This approach leads to more robust toxicity values that are less sensitive to limitations of individual studies. This methodology was supported by US EPA's Science Advisory Board (SAB). Among the candidate RfC values derived, US EPA selected two as the primary basis of the final RfC. These are based on controlled laboratory animal studies, discussed further below, where cardiac developmental effects and effects on the thymus gland (part of the immune system) were observed in animals exposed to TCE. The selection of these studies for use in deriving TCE toxicity values was also recommended by the SAB. The final RfC of 2 $\mu g/m^3$ reflects candidate RfC estimates for both effects; 1.97 $\mu g/m^3$ based on cardiac developmental effects in rats; and, 1.75 $\mu g/m^3$ based on decreased thymus weight in mice, an immunological effect (US EPA 2011).

MassDEP ORS was asked by the MassDEP Bureau of Waste Site Cleanup to assess the potential developmental risks posed by short-term exposure to TCE attributable to vapor intrusion at hazardous waste sites. This request was made because: 1) US EPA based the RfC, in part, on developmental cardiac effects; 2) these effects are serious, impact children and could result from short-term exposures during pregnancy; 3) no US EPA national guidance on how to address these short-term exposure risks is available; and, 5) inconsistent approaches have been used by US EPA Regional Offices, the Centers for Disease Control and other states to evaluate and respond to TCE short-term development risks. In response to this request, ORS completed a summary of TCE toxicity information and US EPA's assessment, with a focus on its developmental effects (MassDEP ORS 2013 a and b). With input from the MassDEP Health Effects Advisory Committee, ORS also developed recommended guidance for indoor air TCE concentration targets and response timeframes to protect public health, in particular the developing fetus.

Summary of Key TCE Toxicities

Basis of US EPA's RfC of 2 $\mu g/m^3$

The cardiac developmental effects reported by Johnson et al., 2003 and decreased thymus weight reported by Keil et al., 2009 were relied upon by US EPA to derive an RfC for TCE. Key elements of US EPA's assessment are summarized below.

Cardiac Developmental Effects

US EPA derived a candidate RfC of 1.97 $\mu g/m^3$ (0.37 ppb) based on cardiac developmental effects observed in offspring of pregnant rats exposed to TCE (USEPA, 2011). US EPA states that there is high confidence in the TCE RfC and the overall database, medium confidence in the key cardiac developmental toxicity study and moderate-to-high confidence both in the hazard and the candidate reference values for TCE developmental effects.[3]

[3] US EPA Toxicological Review of Trichloroethylene, Chapter 6.2.1.2.7. Developmental Effects, page 6-26

With respect to developmental toxicity, US EPA identified and reviewed several epidemiology and animal studies that reported cardiac developmental defects, cleft palate defects, eye/ear defects, kidney/urinary tract disorders, musculoskeletal birth anomalies, lung/respiratory tract disorders, and skeletal defects associated with exposure to TCE. The US EPA selected the cardiac developmental effects observed in laboratory rats exposed to TCE in controlled experiments as an endpoint to derive a candidate toxicity value because:

- Cardiac developmental effects occurred at lower TCE exposure levels than other developmental effects observed in animal studies[4].
- Cardiac developmental effects have been reported in several epidemiological studies that showed statistically significant increases in the incidence of cardiac defects in TCE-exposed populations compared to reference groups.
- Administration of TCE metabolites trichloroacetic acid (TCA) and dichloroacetic acid (DCA) in maternal drinking water during gestation has been reported to induce developmental effects in rat fetuses in other studies.
- *In vitro* and *in vivo* mechanistic studies support the plausibility of TCE cardiac developmental effects.

US EPA, on the recommendation of its SAB, used the Johnson et al. (2003) study on developmental effects in rats from fetal exposure to TCE to derive a candidate toxicity value. Although aspects of this and related studies have been questioned, US EPA concluded that "*In sum, while the studies by Dawson et al. (1993, 1990) and Johnson et al. (2005, 2003), have significant limitations, there is insufficient reason to dismiss their findings*."[5] ORS contacted the lead author, Dr. Paula Johnson, to further address issues relating to the experimental protocols and the data assessment methods used in the Johnson et al. (2003) publication relied upon by US EPA in its assessment of cardiac developmental effects. Dr. Johnson indicated that the: historical control data used in their assessment was consistent across experimental groups confirming that it was appropriate to combine the data to maximize the statistical strength of the study while minimizing the number of experimental animals used; experiments were conducted "blind" so the scientists determining the cardiac development effects did not know whether the tissues were from treated or untreated groups; the animal handling, dosing and other experimental procedures were consistent across the experiments; all pathology work was completed by the same experienced study pathologists (the lead authors on the paper); and, cardiac developmental effects detected were reviewed and confirmed by multiple study pathologists.

Based on the Johnson et al. (2003) publication, US EPA's assessment, and this additional clarifying information, ORS and the MassDEP Health Effects Advisory Committee concurred with US EPA's determination that the criticisms of the study raised by some groups were an insufficient basis to reject its use.

[4] However, in several inhalation studies, no cardiac developmental effects have been reported in rodent bioassays. This is unexplained but may be due to differences in study design and execution and/or route of exposure differences in TCE metabolism and pharmacokinetics.

[5] US EPA Toxicological Review of Trichloroethylene, 4.8.3.3.2. Cardiac malformations, page 4-561; 4.11.1.7. Developmental Toxicity, page 4-631

In the Johnson et al. study, the animals were exposed to TCE throughout gestation. Another study, by Epstein et al. (1992), provides additional insight regarding potentially critical periods of exposure during fetal development. In this study rats were treated with DCA, a metabolite of TCE, on discrete days of gestation and effects on fetal development were then assessed. The study identified gestational days (GD) 9 through 12 as a period of particular sensitivity to DCA. Exposure to fairly high levels of DCA for as short as one day during this timeframe were associated with interventricular septal defects in the heart, which have also be observed with TCE.[6] Data from similar short-term exposure experiments using TCE were not identified.

In humans, the key steps in cardiac organogenesis occur during the first 8 weeks of gestation (Kirby, 1997). Although the human epidemiological data is insufficient to assess TCE cardiac developmental risk associated with very short-term exposures, the animal bioassay data noted above, as well as the complex and sequence dependent mechanisms involved in cardiac organogenesis in animals, support concern over exposures to cardiac developmental toxins of a few days to weeks, depending on the levels and frequency of exposure.

Immunological Effects

The second candidate RfC used by US EPA, 1.75 µg/m^3 (0.33 ppb), was based on a chronic exposure study of effects on the immune system in mice. US EPA states that there is high confidence that TCE causes immunotoxicity and medium confidence in the candidate toxicity values that can be derived from the available studies. In this study, decreased thymus weight was reported at relatively low exposures in non-autoimmune-prone mice. This is a clear indicator of immunotoxicity and was therefore considered a candidate critical effect. A number of animal studies have also reported changes in other markers of immunotoxicity. Effects related to the immune system have also been associated with TCE exposure in human studies. A relationship between systemic autoimmune diseases, such as scleroderma[7], and occupational exposure to TCE has been reported in several studies. A meta-analysis of scleroderma studies resulted in a statistically significant combined effect for TCE exposure in men. Additional human evidence for the immunological effects of TCE include studies reporting TCE-associated changes in levels of inflammatory cytokines in occupationally-exposed workers and infants exposed via indoor air at concentrations typical of such exposure scenarios; a large number of case reports of a severe hypersensitivity skin disorder, distinct from contact dermatitis and often accompanied by hepatitis; and a reported association between increased history of infections and exposure to TCE contaminated drinking water.

ORS Recommendations for TCE Indoor Air Remediation Targets and Response Timeframes to Protect the Developing Fetus

Based on the weight of the scientific evidence outlined in the preceding sections, MassDEP has concluded the following.

- It is appropriate to consider TCE a developmental toxin with the potential to cause cardiac developmental effects.

[6] Gestation in humans is longer than in rodents, so a one day exposure in rats does not equate to a one day exposure in people.

[7] A disorder in which the immune system mistakenly attacks and destroys healthy body tissue.

- Because cardiac development begins early during fetal development, before a woman may realize she is pregnant, TCE exposures to women who are in the early stages of a pregnancy (the first 8 weeks) or to women who may become pregnant are of particular concern.
- Because cardiac development is completed within the first 8 weeks of pregnancy exposures after that period do not present a risk to cardiac development.
- The risk of adverse cardiac developmental effects will likely be a function of indoor air concentration and exposure duration, with greater risks at higher levels and with longer exposures.
- Depending on the concentration, exposures of a few days to weeks during critical periods of fetal cardiac development in early pregnancy are of potential concern.

The Health Effects Advisory Committee concurred with these determinations.

Because the Massachusetts Contingency Plan (MCP) Imminent Hazard (IH) provisions do not require exposures to be reduced below the IH level within the very short timeframe of concern related to TCE's potential effects on cardiac development, ORS developed recommendations regarding response timeframes and concentration targets to limit potential developmental risks for residential and typical workplace situations. This effort proceeded with input from the Health Effects Advisory Committee.

The recommendations that follow are based on the principle that the risk of adverse effects typically increases with higher concentration and longer exposure duration. These apply to the sensitive subgroups, including pregnant women through the first 8 weeks of pregnancy and women who may become pregnant. The recommendations are intended to provide guidance to MassDEP staff, LSPs, public health officials and others responding, under the MCP, to hazardous waste sites that have associated TCE contamination of indoor air. The recommendations regarding short-term remediation target levels and response timeframes to limit TCE developmental risks are summarized below.

Guidance for Residential Exposure Situations

- **Residential RfC = 2 µg/m^3**

  MassDEP considers the US EPA TCE RfC published on IRIS as an appropriate chronic, long-term exposure limit for TCE that is protective of immunological, cardiac development and other potential effects. Based on its review of US EPA's TCE assessment, ORS considers the RfC of 2 µg/m^3 to be very health protective with respect to cardiac developmental effects. The Health Effects Advisory Committee concurred with this determination.

  The RfC of 2 µg/m^3 is the ultimate remediation target for residential exposure situations. Under the MCP, residential exposure situations constitute a Critical Exposure Pathway, which triggers immediate response actions to reduce indoor air concentrations more quickly. Because of the nature of the endpoint of concern, when concentrations exceed 2

µg/m^3 in a residential situation remediation efforts to reduce concentrations should proceed expeditiously.

- **Residential Imminent Hazard Level > 6 µg/m^3**

  For chemicals exhibiting developmental toxicity, the MCP requires that an Imminent Hazard (IH) level, with its associated regulatory requirements, be established using a Hazard Quotient (HQ) of 1 to characterize risk. Based on the US EPA RfC, this would result in an IH level of 2 µg/m^3 for residential situations. However, for TCE, ORS considers risks due to short-term exposures between 2 and 6 µg/m^3 to be very low. Therefore, MassDEP established the TCE IH level at 6 µg/m^3. This value was derived by reducing the uncertainty factor (UF) for pharmacodynamics[8] applied by US EPA to the HEC_{99} in the RfC derivation by the square root of 10. This was deemed appropriate for deriving the Imminent Hazard concentration because the RfC is based on animal data from the most sensitive life-stage and cardiac development is well conserved across species.

  Indoor air levels in excess of the IH concentration trigger immediate response actions that are required under the MCP, including 2 hour notification to MassDEP; immediate notification to sensitive subgroups of the potential risk; and the initiation of response actions to eliminate the IH condition. At levels above 6 µg/m^3 efforts to reduce exposures to the sensitive subgroups should proceed as quickly as possible. Women who are concerned about potential risks while remediation efforts are underway may want to consult with their physician. Depending on the specific situation there may be ways to lower exposures, for example by minimizing time spent in areas with higher TCE levels or using an appropriate air filter.

Residential More Urgent Concern Level[9] > 20 µg/m^3

Although well below the exposure level where effects were observed in the animal cardiac developmental studies, 20 µg/m^3 is close to the air concentration that would result in a dose of metabolized TCE[10] in about 1% of people equivalent to that associated with a modeled 1% risk in the laboratory animal study.[11]

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[8] US EPA accounted for differences in pharmacokinetics (how animals absorb, metabolize and excrete TCE) using physiologically based pharmacokinetic (PBPK) modeling; pharmacodynamic (differences in animal responses to TCE) uncertainties were addressed using an uncertainty factor of 10 to account for potential inter- and intra-species differences in sensitivity.

[9] The More Urgent Concern Levels do not trigger any additional regulatory requirements. They are intended to provide guidance to MassDEP staff, Licensed Site Professionals and others responding to situations where TCE concentrations well exceed the IH.

[10] US EPA concluded that metabolites are likely responsible for the developmental effects of TCE.

[11] The 99th percentile human equivalent concentration (HEC_{99}) in the air derived by US EPA is 21 µg/m^3. This is the predicted high-end TCE metabolized dose, generated in about 1% of people, associated with a 1% response in the rat. This value was derived by US EPA using the most up-to-date physiologically based pharmacokinetic (PBPK) modeling. The US EPA's modeling addressed: 1) human variability in the capacity to generate the TCE metabolites likely to be responsible for the developmental effects (those with "high" capacity being more sensitive); 2) differences in how TCE is metabolized in rats following an ingestion exposure vs. in humans following an inhalation exposure; and, 3) statistical uncertainty in the data. This value *does not* account for

The value of 20 µg/m^3 is also close to the median and about 7 times lower than the upper end, indoor TCE air concentration reported in the Endicott, N.Y. epidemiological study (Forand, 2012). In this study, the risk of developmental heart abnormalities was about 2% vs. the background rate of about 1%. Although this study supports concern over TCE developmental toxicity, individual indoor air TCE levels in the homes of affected individuals during pregnancy could not be ascertained limiting its usefulness in quantitatively assessing risk. Some other epidemiologic studies have also reported developmental effects associated with TCE exposure while others have not.

At levels above 20 µg/m^3 the potential risk is of higher concern and ORS recommends notification to sensitive subgroups that they consider taking immediate steps to reduce or eliminate exposures. Depending on the specific situation these steps could include avoiding areas of the house with higher TCE levels or temporarily living with family or friends while measures are taken to reduce indoor air concentrations.

Guidance for Typical Workplace Exposure Situations

- **Workplace RfC = 8 µg/m^3**

The workplace RfC of 8 µg/m^3 is the ultimate remediation target for situations where workplace indoor air has been impacted by vapor intrusion and is equivalent to the residential RfC value adjusted for a typical workplace exposure pattern of 8 hours a day, five days a week. Because of the nature of the endpoint of concern, when concentrations exceed 8 µg/m^3 in a typical workplace situation remediation efforts to reduce concentrations should proceed expeditiously.

- **Workplace Imminent Hazard Level > 24 µg/m^3**

As with the residential value, this value is equivalent to workplace RfC adjusted upwards by a factor of three, reflecting the use of a reduced pharmacodynamic uncertainty factor.

Indoor air levels in excess of the IH concentration trigger immediate response actions that are required under the MCP, including 2 hour notification to MassDEP; immediate notification to sensitive subgroups of the potential risk; and the initiation of response actions to eliminate the IH condition. At levels above 24 µg/m^3, efforts to reduce exposures to the sensitive subgroups should proceed as quickly as possible. Women who are concerned about potential risks while remediation efforts are underway may want to consult with their physician. Depending on the specific situation there may be ways to lower exposures, for example by minimizing time spent in areas with higher TCE levels.

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potential differences in individual and cross-species *responses* to an equivalent dose of metabolized TCE (i.e. differences in pharmacodynamics). Uncertainty about pharmacodynamic differences is typically accounted for by applying an uncertainty factor of 3-10. Because pharmacodynamic uncertainty is not accounted for in the 21 µg/m^3 value, the potential risk at this level among those most sensitive to TCE could be higher than 1% in the 1% of the most sensitive individual exposed. Specific individuals who may be particularly sensitive to TCE cannot be identified.

- **Workplace More Urgent Concern Level > 60 µg/m^3**

  This value was derived from the residential value of 20 µg/m^3 by adjusting the exposure duration to 8 hours a day. Because some members of the Health Effects Advisory Committee expressed concerns about the potential for developmental effects attributable to higher levels of exposure in the workplace over a few days, this value was not adjusted to reflect a 5 day workweek. This provides additional protection against potential peak exposure risks, which may not be entirely mitigated by intermittent cessation of exposures while employees are away from the workplace on days off (e.g. the weekend).

  In typical workplace situations (8 hours a day) where workplace concentrations of TCE attributable to vapor intrusion exceed this value, the potential risk is of higher concern and ORS recommends notification to sensitive subgroups that they consider taking immediate steps to reduce or eliminate the exposure. For example it may be possible for sensitive subgroups to avoid areas of the workplace that have TCE levels above 60 µg/m^3 or temporarily relocate to another workspace.

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