




UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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MEMORANDUM

OFFICE OF
SOLID WASTE AND
EMERGENCY RESPONSE

SUBJECT: Interim Recommended Trichloroethylene (TCE) Toxicity Values to Assess Human Health Risk and Recommendations for the Vapor Intrusion Pathway Analysis

FROM: 
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TO: Regional Administrators

The purpose of this memorandum is two-fold. First, consistent with OSWER's chemical toxicity hierarchy guidance we recommend interim use of existing toxicity values developed by other regulatory agencies for trichloroethylene (TCE) for evaluating potential site-specific risks from inhalation or oral exposures to protect for both cancer and non-cancer effects. Second, we recommend an approach for assessing human health risk for the vapor intrusion (VI) pathway for sites addressed under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) or the Resource Conservation and Recovery Act (RCRA). This guidance is intended to facilitate better decisions by Regions in Superfund, RCRA, and Federal Facility assessments addressing risks due to exposure to TCE from vapor intrusion, and other pathways are addressed in the EPA Regions.

The Office of Solid Waste and Emergency Response (OSWER) recommends using its 2003 Toxicity Hierarchy¹ in the development of a preliminary remediation goal (PRG) for TCE.² We generally recommend the use of the California Environmental Protection Agency's (Cal EPA's) inhalation unit risk value³ (IUR) of $2.0E-06(\text{ug}/\text{m}^3)^{-1}$

¹ *Human Health Toxicity Values in Superfund Risk Assessments* (OSWER Directive 9285.7-53, December 5, 2003), referred to in this document as the 2003 Toxicity Hierarchy, recommends using a tiered approach for identifying toxicity values. As discussed in the 2003 guidance, Tier 1 refers to IRIS, Tier 2 refers to EPA's Provisional Peer Reviewed Toxicity Values, and Tier 3 refers to other sources.
<http://www.epa.gov/oswer/riskassessment/pdf/hhmemo.pdf>

² We note that this hierarchy is generally consistent with the application of the criteria developed by the Environmental Council of the States (ECOS). Environmental Council of States (ECOS) issue paper; *Identification and Selection of Toxicity Values/Criteria for CERCLA and Hazardous Waste Site Risk Assessments in the Absence of IRIS Values*. This issue paper was developed by a task force comprised of State and DOD EPA provided technical support to the effort under the auspices of an ECOS/DOD work group on emerging contaminants.
http://www.ecos.org/files/2733_file_FINAL_ECOS_PV_Paper_4_23_07.doc

³ California Environmental Protection Agency (Cal EPA). *Air Toxics Hot Spot Program Risk Assessment Guidelines. Part II. Technical Support for Describing Available Cancer Potency Factors.*, Office of Environmental Health Hazard Assessment, December 2002. http://www.oehha.ca.gov/air/cancer_guide/TSD2.html

and oral cancer slope factor⁴ of 0.013 (mg/kg-day)⁻¹ for evaluating the carcinogenic effects of TCE in site-specific risk assessments at sites addressed under CERCLA and RCRA. Acceptable air exposure levels are generally concentration levels that represent an upper bound life-time cancer risk to an individual between 10⁻⁶ (1.2 ug/m³) and 10⁻⁴ (120 ug/m³)⁵. Consistent with the National Contingency Plan (NCP), OSWER recommends using 1.2 ug/m³ as the point of departure for determining preliminary remediation goals (see 40 CFR 300 Section 430(e)(2)(i)(A)(2)); this generally is the air concentration representing a 10⁻⁶ excess cancer risk using the Cal EPA inhalation unit risk. For assessing non carcinogenic effects of TCE, OSWER has identified two values that can be considered in evaluating systemic toxicity at sites: the 10 ug/m³ air criterion developed by the New York State Department of Health⁶ and the 600 ug/m³ Chronic Reference Exposure Level developed by Cal EPA⁷. OSWER believes that both of these values may be appropriate Tier 3 toxicity values under the OSWER Toxicity Hierarchy.

As discussed in the OSWER Toxicity Hierarchy guidance, draft toxicity assessments generally are not appropriate for use until they have been through peer review, the peer review comments have been addressed in a revised draft, and the revised draft is publicly available. The toxicity values in this guidance may be appropriate for Regions to use to assess risks at least until toxicity values for TCE are available in the Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS) database, or until further scientific analysis indicates a more appropriate value is available. When a new IRIS toxicity assessment is available, OSWER may review sites to ensure that sites addressed under this interim approach remain protective given revised toxicity values. If new scientific information representing the best available science becomes available before a new IRIS toxicity assessment is available, OSWER may revisit the toxicity values provided in this guidance.

This guidance supersedes previous guidance on TCE toxicity values found in OSWER's "Draft Guidance for Evaluating the Vapor Intrusion to Indoor Air Pathway from Groundwater and Soils" (EPA 530-D-02-004, November 2002). This guidance is consistent with our 2003 guidance on using a hierarchy of existing chemical toxicity sources; it does not represent a new, independent review of TCE toxicity, which EPA has currently underway as part of the IRIS program.

This guidance recommends an oral cancer slope factor for use in risk assessments and is designed to help provide an estimate of the cumulative risk at sites and make other cleanup decisions; this guidance does not affect or replace statutory or regulatory

⁴ California Environmental Protection Agency (Cal EPA) *Public Health Goal for Trichloroethylene*, Office of Environmental Health Hazard Assessment, Cal EPA, February 1999. http://www.oehha.ca.gov/water/phg/pdf/tce_f.pdf

⁵ These acceptable air levels (concentrations) were derived based on a residential scenario of continuous exposure (24 hrs./day and 350 d/yr), for 30 years averaged over a 70 year lifetime (equation presented in Figure 2 of appendix). Site specific exposure assumptions may be different and then could lead to different acceptable air exposure levels.

⁶ NYSDOH. 2006. Center for Environmental Health, Bureau of Toxic Substances Assessment, Trichloroethene Air Criteria Document, October.

http://www.health.state.ny.us/environmental/chemicals/trichloroethene/docs/cd_tce.pdf

⁷Chronic Toxicity Summary: Trichloroethylene. Documentation for a chronic Reference Exposure Level for Trichloroethylene, California EPA Office of Environmental Health Hazard Assessment, April 2000. www.oehha.ca.gov/air/chronic_rel.

requirements, (for example, meeting applicable or relevant and appropriate requirements (ARARs)) under CERCLA or RCRA. For example, the maximum contaminant level (MCL) for TCE, 5 ug/l, (or a lower concentration if required by a state ARAR) generally should continue to be considered as an ARAR for the cleanup under CERCLA of ground water that may be used as drinking water. OSWER recommends the same approach be taken under RCRA. However, when other ground water exposure pathways may be complete (such as vapor intrusion into indoor air) or multiple contaminants are present, site-specific conditions should be evaluated to ensure that use of the MCL would be sufficiently protective of human health and the environment.

Application of Toxicity Hierarchy for TCE

Background

As discussed in the 2003 Toxicity Hierarchy⁸, OSWER recommends using a hierarchy of sources of toxicological information that Regional risk assessors and managers should consider for site-specific risk assessments. Generally, Regions should first look for toxicity information in the Integrated Risk Information System (IRIS) developed by EPA's Office of Research and Development; as discussed in the 2003 guidance, these are considered Tier 1 values in the hierarchy. If quantitative information is not available there, generally Regions should next look to Provisional Peer Reviewed Toxicity Values (PPRTVs) developed by EPA's National Center for Environmental Assessment/Superfund Technical Health Risk Support Center (STSC); as discussed in the 2003 guidance, these are considered Tier 2 values in the hierarchy. If toxicity values are not available from either Tier 1 or 2, generally Regions should look to other high quality sources of toxicity information developed by other regulatory or health agencies that can be used for risk assessment; as discussed in the 2003 guidance, these are considered Tier 3 values in this hierarchy.

It should be noted that the 2003 Toxicity Hierarchy states:

“In general, draft toxicity assessments are not appropriate for use until they have been through peer review, the peer review comments have been addressed in a revised draft, and the revised draft is publicly available.”

Thus, the cancer and non-cancer toxicity values presented in EPA's 2001 draft risk assessment for TCE are not recommended as appropriate Tier 3 values nor are they discussed in this document based on their “draft status,” consistent with the 2003 Toxicity Hierarchy.

A consensus issue paper from the Department of Defense, EPA, and the Environmental Council of States (ECOS) supported OSWER's hierarchy and recommended a set of preferences for evaluating potential toxicity values that largely mirror EPA's. These preferences include transparent assessments that have received internal and external peer review that are derived using an established methodology, that incorporate current best scientific practice, and that consider the quality of the studies, including statistical power, as well as considering assessments that corroborate data amongst pertinent studies. In addition, both the values and supporting documentation should be publicly available and a preference should be given to toxicity values that are consistent with the duration of exposure being assessed. Selection of a toxicity value

⁸ See footnote 1

should include an understanding of the available sources of toxicity data and the strengths and weaknesses of each source in order to select the most appropriate toxicity value for use in a risk assessment. Because there is no toxicity value for TCE either in IRIS (Tier 1) or as a PPRTV (Tier 2), EPA evaluated other high quality sources of toxicity information (Tier 3) developed by other regulatory or health agencies.

Consistent with CERCLA and the NCP, protection of human health and the environment is a threshold requirement for selected remedies (see e.g., 40 CFR §300.430(f)(1)(i)(A)). In the CERCLA remedy selection process, preliminary remediation goals (PRGs) typically are developed as a site-specific tool when setting cleanup levels. At CERCLA sites, PRGs typically are “statements of the desired endpoint concentrations or risk levels” (see e.g., 55 Fed. Reg. 8713; March 8, 1990); generally they are conservative, default endpoint concentrations used in screening and initial development of remedial alternatives before consideration of more detailed information from the site-specific risk assessment.

The NCP states:

Remediation goals shall establish acceptable exposure levels that are protective of human health and the environment and shall be developed by considering the following:

(A) Applicable or relevant and appropriate requirements under federal environmental or state environmental or facility siting laws, if available, and the following factors:

(1) For systemic toxicants, acceptable exposure levels shall represent concentration levels to which the human population, including sensitive subgroups, may be exposed without adverse effect during a lifetime or part of a lifetime, incorporating an adequate margin of safety;

(2) For known or suspected carcinogens, acceptable exposure levels are generally concentration levels that represent an excess upper bound lifetime cancer risk to an individual of between 10^{-4} and 10^{-6} using information on the relationship between dose and response. The 10^{-6} risk level shall be used as the point of departure for determining remediation goals for alternatives when ARARs are not available or are not sufficiently protective because of the presence of multiple contaminants at a site or multiple pathways of exposure;

(3) Factors related to technical limitations such as detection/quantification limits for contaminants;

(4) Factors related to uncertainty; and

(5) Other pertinent information.”

40CFR§300.430(e)(2)(i)(A).

Cancer Toxicity Values for TCE

After analyzing potential Tier 3 human health toxicity values using the preferences described in the ECOS paper, OSWER believes that the Cal EPA IUR of $2.0E-06$ ($\mu\text{g}/\text{m}^3$)⁻¹ presented in the Air Toxics Hot Spots Program (Cal EPA, 2002) and an

oral cancer slope factor of $0.013 \text{ (mg/kg-day)}^{-1}$ presented in the “Public Health Goal for Drinking Water” (Cal EPA, 1999) generally are appropriate for use in site specific risk assessments at least until a revised IRIS value is available or until further scientific analysis identifies a more appropriate value. These values were developed specifically for use in risk assessments and are consistent with the 2003 Toxicity Hierarchy

The Cal EPA IUR is derived from the geometric mean of the unit risks from four inhalation studies on mice and includes liver cancers, lung cancer, and lymphoma endpoints⁹ (see appendix for a more detailed discussion). The Cal EPA oral cancer slope factor was based on the geometric mean of four values based on the occurrence of hepatocellular carcinomas and adenocarcinomas in mice in two studies, in both sexes, by inhalation and oral routes of administrations and a linear dose response approach.¹⁰ OSWER believes the IUR and oral cancer slope factor developed by Cal EPA are reasonably consistent with values developed by other researchers and regulators, also discussed in more detail in the appendix. OSWER believes the Cal EPA IUR and oral cancer slope factor provide an appropriate interim approach, based on information currently available. These recommended toxicity values can be used to evaluate lifetime excess cancer risk from TCE exposure at least until toxicity values for TCE are available in EPA’s IRIS database or until further scientific analysis indicates a more appropriate value is available.

Consistent with the National Contingency Plan (NCP) (40 CFR §300.430(e)(2)(i)(A)(2)), OSWER recommends using a concentration of 1.2 ug/m^3 , corresponding to the 10^{-6} cancer risk level using the Cal EPA IUR, as the point of departure for determining remediation goals. OSWER also recommends using 1 ug/m^3 to 120 ug/m^3 as the generally acceptable concentration levels corresponding to 10^{-6} to 10^{-4} cancer risk (See footnote 5).

Systemic, Non cancer Toxicity Value for TCE

After analyzing existing potential Tier 3 human health toxicity values, OSWER has identified two values as appropriate for consideration: Cal EPA’s reference exposure level (REL) and NYSDOH’s non-cancer air criterion. The National Research Council (NRC, 2006), in its comments on the non cancer studies analyzed in EPA’s 2001 draft risk assessment noted that several neurotoxicity studies reported common effects in humans and rats at similar concentrations. The studies included reports in humans of changes in trigeminal nerve function and motor incoordination (Ruijten et al. 1991; Rasmussen et al. 1993) and symptoms including nausea, drowsiness, and fatigue (Okawa and Bodner 1973; Vandervort and Polakoff 1973). Studies in rats showed changes at similar levels (adjusted for human equivalence) in heart rate and wakefulness (Arito et al. 1994). Furthermore, the NRC also noted that new information on neurological effects of TCE published since 2001 “is limited and thus may offer little in the way of amendment” to the current understanding of non cancer effects. These comments support the studies cited in the development of these values as representing noteworthy and current

⁹ Trichloroethylene. In: Technical Support Document for Describing Available Cancer Potency Factors., California EPA Office of Environmental Health Hazard Assessment., December 2002. pp 522-530.

¹⁰ Public Health Goal for Trichloroethylene in Drinking Water, California EPA Office of Environmental Health Hazard Assessment, February 1999.. www.oehha.ca.gov

understanding regarding these systemic effects.

The Cal EPA reference exposure value (REL) is based on a pre-2000 review of literature and used the 1973 Vandervort and Polakoff study to develop a chronic REL¹¹ (similar to a reference concentration) of 600 ug/m³ based on self reported neurological effects (drowsiness, fatigue, headache) and eye irritation in workers. This study looked at self-reported symptoms in 19 workers, who had an average of 8 years of exposure, with exposure concentrations extrapolated from one day of personal air concentration measurements. The lack of reproductive and developmental toxicity studies and the lack of a no effect level were identified by Cal EPA as major areas of uncertainty. In addition, OSWER identified the use of self-reported symptoms as a limitation of the study. Cal EPA used an estimated LOAEL of 60 mg/m³ and an uncertainty factor of 100 to account for intraspecies differences and the use of an LOAEL.

NYSDOH is based on a pre-2007 review of the literature on the non-cancer health effects of TCE and includes studies published more recently than those cited in the Cal EPA REL. NYSDOH used the 1993 Rasmussen et al. study to derive a potential non-cancer air criterion (similar to a reference concentration) of 10 ug/m³ based on neurological effects (as measured by coordination tests) among 99 Danish metal degreasers exposed for 11 years. Limitations of the study include some uncertainty about the actual long-term exposure levels of the workers to TCE during their employment, and that 25 of 99 subjects were exposed primarily to CFC 113. The appendix provides further discussion of these points.

The NYS DOH assessment is limited by gaps in the data on developmental effects and immunotoxicity, and concerns about adequacy of methods for evaluating health risks to children (limitations it shares with the CalEPA assessment). NYSDOH used an estimated LOAEL of 11 mg/m³ and an uncertainty factor of 1000 to account for intraspecies differences, use of an LOAEL, and extrapolation from 11 years of exposure to a lifetime. The NYSDOH analysis also indicated that this air criterion of 10 ug/m³ is only slightly lower than the air criterion of 20 ug/m³ they estimated based on developmental and reproductive effects.

Both CalEPA and NYS DOH had an external peer review process and allowed for public comment before finalizing their respective assessments. The NYS DOH assessment was finalized in 2006 and the CalEPA assessment was finalized in 2000, but only the NYSDOH assessment discussed the Rasmussen et al. study. Comparing the Rasmussen et al. study underlying the NYSDOH air criterion to the Vandervort and Polakoff study underlying the Cal EPA REL, the LOAEL for the Rasmussen et al. (1993) study is about 1/6th of the LOAEL from the study Cal EPA used. OSWER also found that the Rasmussen study was based on a significantly larger number of subjects (99 compared to 19) and used objective clinical neurological measurements compared to self-reported symptoms.

While both the NYSDOH value and the Cal EPA REL should be considered as Tier 3 toxicity values under the OSWER Toxicity Hierarchy, OSWER notes that the

¹¹ Chronic Toxicity Summary: Trichloroethylene. Documentation for a chronic Reference Exposure Level for Trichloroethylene, California EPA Office of Environmental Health Hazard Assessment, April 2000. http://www.oehha.ca.gov/air/chronic_rels/pdf/79016.pdf,

NYSDOH criterion is based on a more extensive presentation of health endpoints and a more recent evaluation of the available health effects literature.

Other exposure scenarios (e.g., commercial/industrial) may result in a different concentration range based on different exposure assumptions. OSWER recommends that the Regions implementing RCRA corrective action take this analysis into consideration for those settings as well.

Vapor Intrusion Recommendations

The Agency often evaluates TCE inhalation risks arising from the vapor intrusion pathway; this is a potentially significant exposure pathway associated with volatile contaminants at wastes sites. While this guidance focuses on TCE, the following recommendations relating to vapor intrusion are relevant and useful for other volatile organic compounds as well.

Considerable information, primarily empirically-based, has been generated regarding evaluation of the VI pathway since the pathway emerged as a national issue in the late 1990s and especially since publication of EPA's draft vapor intrusion guidance in November 2002.¹² . Our experience with vapor intrusion investigations indicates that no single media data set, whether it be ground water, soil gas, sub-slab gas or indoor air, can be used reliably to fully evaluate the potential for risks from VI above health risk-based levels due to the large number of variables affecting the transport of vapors from the subsurface to indoor air and the confounding influence of indoor sources of common subsurface contaminants. Our investigations have found that spatial and temporal impacts on volatile organic chemical (VOC) concentrations are highly variable. Some of this variability is due to vertical and horizontal differences in subsurface conditions and the differences in structural conditions, such as foundation cracks, and ventilation rates from one building to another. Variation in weather conditions, such as rainfall and barometric pressure, can also have a significant impact. All these factors strongly suggest that multiple lines of evidence are important to evaluate VI as an exposure pathway of concern at sites where hazardous VOCs have been released to the subsurface¹³.

Lines of evidence to evaluate the VI pathway may include: site history and geology, groundwater data, soil gas data, sub-slab soil gas data, crawlspace sample data, preferential pathway sample data, indoor air data, outdoor air data, tracer compound data, chemical ratio data, modeling results, building/home surveys, chemical use inventory, and other supporting information, as appropriate. By using the multiple lines of evidence approach, project managers usually have been successful in determining whether the VI exposure pathway for TCE is complete and whether any elevated levels of TCE in indoor air are likely caused by subsurface VI, an indoor source (consumer product), or an

¹² OSWER Draft Guidance for Evaluating the Vapor Intrusion to Indoor Air Pathway from Groundwater and Soils (Subsurface Vapor Intrusion Guidance), EPA 530-D-02-004, November 2002.

¹³ We note that based on an evaluation of the evidence and experience at numerous sites with VI, the Interstate Technology and Regulatory Council also recommended a multiple lines of evidence approach in their document entitled, Vapor Intrusion Pathway: A Practical Guideline (January 2007) Interstate Technology and Regulatory Council, Vapor Intrusion Pathway: A Practical Guideline, VI-1. Washington, DC., January 2007. www.itrcweb.org

outdoor source. Generally, site conditions will determine the number of lines of evidence that provide enough information for decision making. For example, where ground water and sub-slab soil gas concentrations are low, project managers could determine that the VI exposure pathway is not complete with relatively few lines of evidence. Coordination with a risk assessor and hydrogeologist generally will be very useful in evaluating the multiple lines of evidence.

OSWER believes it is often useful to collect sufficient data to evaluate two or more of these lines of evidence in parallel. For example, Regions should consider, it may be more expeditious and cost-effective to sample indoor air for TCE directly where there is existing ground water or sub-slab soil gas data that suggest the potential for a VI problem. If the decision is made to sample indoors for TCE, we generally recommend the collection of sub-slab soil gas samples along with indoor and outdoor air samples. Collecting sub-slab samples along with air samples often can provide a more complete evaluation and allow a more definitive conclusion to be drawn regarding the VI pathway for TCE at a particular site. However, sub-slab sampling may not be necessary when collecting indoor air samples for degradation products, such as cis-1,2-dichloroethene or 1,1-dichloroethene, that have few or no indoor or outdoor sources. Also, when a building is built on concrete reinforced with pressure tension cables, sub-slab sampling may not be feasible.

We recognize that some states and facilities have found it expeditious in some situations to implement remediation rather than do extensive indoor air sampling; however, the cost of oversight, monitoring, operations, and maintenance should be factored into the decision to remediate.

The potential for VI should be considered at sites that may involve new development projects overlying contaminated soil or shallow ground water. Property developers, regulators, city planners and others involved in redevelopment and Brownfields projects and sites addressed under the Base Realignment and Closure Act (BRAC) should consider designing engineering controls to mitigate for the potential of VI before new buildings are constructed. This recommended approach can have multiple benefits:

- Engineering controls may be used to address the uncertainty in both site characterization and the toxicity of contaminants;
- It is often more cost-effective to mitigate potential VI in advance of construction than to conduct the extensive sampling necessary to determine whether VI might result in unacceptable health risk at the site, and
- It is typically more cost-effective to incorporate VI mitigation measures during the design/build phase than to retrofit an existing building.

Conclusion

We recommend that Regions use the approach described in this guidance to evaluate sites with potential VI of TCE and monitor developments with regard to TCE. If you have any questions, please contact Jayne Michaud at 703-603-8847 or Mary Cooke at 703-603-8712.

APPENDIX

Supplemental Information and Discussion

The US Environmental Protection Agency's (EPA's) Office of Research and Development (ORD) developed a draft health risk assessment in 2001 (U.S. EPA, 2001); however, external peer review commenters raised several important issues. As a result, ORD developed a series of issue papers on various aspects of trichloroethylene (TCE) toxicology based on the comments from the external peer reviewers, which were then submitted as background information to the National Academy of Science (NAS) for review (U. S. EPA, 2005 a, b, c, d). NAS was asked to examine issues critical to developing an objective, realistic, scientifically based health risk assessment for TCE. The National Research Council (NRC) released their report in 2006 (NRC, 2006), providing ORD with further insights as they develop a revised health risk assessment. Given the Office of Solid Waste and Emergency Response's (OSWER's) policy not to use draft toxicology values until peer review comments have been addressed in a publicly available document and the further effort that ORD is continuing, OSWER will not rely upon the 2001 draft risk assessment and recommends that the Regions and others not utilize the 2001 draft risk assessment for quantifying the toxicity of TCE.

Because no Tier 1 (Integrated Risk Information System (IRIS)) or Tier 2 (Provisional Peer-Reviewed Toxicity Values (PPRTVs)) toxicity values are currently available, typical Tier 3 sources were inventoried and toxicity values evaluated. Typical Tier 3 sources include other federal agencies¹⁴ and states that may develop toxicity values that would be useful for site-specific risk assessments. We identified three States (California, New York, and Indiana) with potentially relevant values. In addition, we identified one scientific research paper (Lewandowski and Rhomberg (2005)) that addressed the question of TCE toxicity and that had some form of cancer assessment for TCE.¹⁵ These are discussed in the paragraphs below.

Cancer Assessments

To inform their development of an air guideline for TCE, NYSDOH developed an array of cancer slope factors and potential air criteria for kidney tumors in rats (Maltoni et al., 1986), liver tumors in mice (Maltoni et al., 1986), lung tumors in mice (Maltoni et al., 1986, Fukuda et al. 1983), testes tumors in rats (Maltoni et al., 1986), and lymphomas in mice and humans (Henschler et al., 1980, Hansen et al., 2001).

The NYSDOH analysis provides a good overview of the current data available on the carcinogenicity of TCE. From the available studies, they identified five cancer endpoints for which they developed potency factors. These five endpoints were rat kidney tumors, rat testes tumors, mouse lung tumors, mouse liver tumors, and mouse lymphoma, in order of increasing toxicity. These data are arrayed in Figure 1 at the end of the Appendix. NYSDOH also looked at human epidemiological data to check the relevance of the cancer endpoints to humans. If humans and animals develop cancer in the same target organs, then the endpoint is more relevant than if humans do not develop

¹⁴ ATSDR has neither cancer toxicity values nor chronic minimal risk levels in their Toxicological Profile for TCE (ATSDR, Dec 1997).

¹⁵ We include the research paper of Lewandowski and Rhomberg for comparison and completeness only.

cancer in that organ. Human epidemiologic data do not support the conclusion that TCE is a risk factor for lung cancer, so this health endpoint was given less weight in the NYSDOH assessment (NYSDOH, 2006). NYSDOH also incorporated an age adjustment factor to account for potential increased susceptibility of children to the effects of TCE exposure, where their analysis determined it was appropriate. Figure 1 graphs their age adjusted cancer risk ranges for kidney and liver tumors.

Cal EPA has an inhalation unit risk (IUR), an oral cancer slope factor, and an inhalation cancer slope factor presented on the Office of Environmental Health Hazard Assessment website. <http://www.oehha.ca.gov/risk/ChemicalDB/cancerpotency.asp?name=Trichloroethylene&number=79016>. The IUR and the inhalation cancer slope factor represent the same analysis expressed in different units. Cal EPA based their oral cancer slope factor of $0.013 \text{ (mg/kg-day)}^{-1}$ on slope factors derived from liver tumor data for mice exposed orally (National Cancer Institute, 1976) or by inhalation (Maltoni et al., 1986, 1988) and from lung tumor data for mice exposed by inhalation (Fukuda et al., 1983). Human equivalent doses were calculated with three different dose metrics using physiologically-based pharmacokinetic (PBPK) modeling. The slope factor based on liver tumor incidence using a total TCE metabolism dose metric (AMET dose metric) was selected as the most appropriate based on model fitting criteria (Cal EPA, 1999).

The Cal EPA IUR of $2.0\text{E-}06 \text{ (ug/m}^3\text{)}^{-1}$ was based on the geometric mean of the 95% upper confidence limit potency estimates from four inhalation studies (Bell et al., 1978; Henschler et al., 1980; Fukuda et al., 1983; and Maltoni et al., 1986) based on mouse liver carcinoma, mouse malignant lymphoma, mouse lung adenocarcinoma, and mouse hepatoma, respectively (Cal EPA, 1990).

Cal EPA looked at many of the same studies as NYS to develop their cancer potency values. The California evaluation is older, so some later studies were not available to them. California chose to calculate their IUR from four inhalation studies (Bell et al., 1978; Henschler et al., 1980; Fukuda et al., 1983; and Maltoni et al., 1986) based on mouse liver carcinoma, mouse malignant lymphoma, mouse lung adenocarcinoma, and mouse hepatoma, respectively. They determined that approach would result in the most protective and supportable cancer potency factor. Their IUR incorporates several of the more potent potential IURs identified by NYSDOH. Air concentrations associated with the 10^{-6} to 10^{-4} lifetime excess cancer risk range using the Cal EPA IUR can be found on Figure 1.

The Indiana Department of Environmental Management (IDEM) conducted a focused review of the toxicity studies cited in the 2001 ORD draft TCE risk assessment, with the primary goal of selecting a single cancer slope factor from within the range of slope factors presented in the 2001 ORD draft TCE risk assessment. IDEM did not consider studies published after 2001; although their review was peer reviewed, it is not recommended because of its more limited focus. Because of the specific, narrow focus of the IDEM review (i.e., a predetermined range of cancer potency values derived from studies considered in the 2001 ORD draft TCE risk assessment) and its reliance on the 2001 ORD draft TCE risk assessment, which as we noted earlier is still considered a draft document, we determined that the IDEM review was not the best source for establishing an interim Tier 3 toxicity value. However, their analysis is germane and we will present

the results of their analysis for comparison. IDEM (2005) based their cancer potency value on mouse bioassays (NCI, 1976; NTP, 1990) and developed an oral cancer slope factor of $0.034 \text{ (mg/kg-day)}^{-1}$ adjusted to $0.1 \text{ (mg/kg-day)}^{-1}$ to protect children. For inhalation exposures, they developed an inhalation cancer slope factor of $0.018 \text{ (mg/kg-day)}^{-1}$ adjusted to $0.054 \text{ (mg/kg-day)}^{-1}$ to protect children, based on the same studies.

IDEM based their inhalation cancer slope factor on an evaluation of mouse liver tumors. They developed cancer slope factors independently for each sex from the NCI (1976) and NTP (1990) studies of the mouse liver tumor endpoint. From PBPK modeling and a goodness of fit analysis, IDEM determined that the data were best represented as a lognormal distribution, from which they calculated the harmonic mean of the four datasets for their inhalation cancer slope factor. To this inhalation cancer slope factor, they applied a factor of three to account for children's exposure. Figure 1 includes the air concentrations associated with the cancer risk range using the IDEM cancer slope factor. The 1×10^{-6} cancer risk equates to a concentration of 0.15 ug/m^3 .

Finally, Lewandowski and Rhomberg (2005) undertook an analysis to derive an interim unit cancer risk for low-dose inhalation exposure based on available scientific information. Based on accepted principles for evaluating scientific studies, they identify the most appropriate interim unit risk for low-level inhalation exposure as $9.0\text{E-}7 \text{ (ug/m}^3\text{)}^{-1}$ based on epidemiological data. The authors do not represent a regulatory agency, which typically EPA would rely on for Tier 3 assessments. However, we included the results of this paper for comparison and completeness.

Lewandowski and Rhomberg arrayed the available cancer studies, both human and animal, with the goal of identifying a plausible interim cancer endpoint. They asserted that the uncertainty introduced by using a human study with uncertain exposures was preferable to the uncertainty of interspecies extrapolation. As a result, they chose the Antilla (1995) study from which they quantified an IUR based on human liver cancers. Using this approach, they derived an IUR marginally less potent than, but within the rounding range of the Cal EPA IUR. A 1×10^{-6} cancer risk equates to 2.7 ug/m^3 using the Lewandowski and Rhomberg recommendation and 1.2 ug/m^3 using the Cal EP IUR, which is close concordance in this field. However, the NAS indicated in their review that the available human exposure data were more uncertain than the interspecies extrapolation, which argues for using the animal data as the basis for quantification.

Non Cancer Assessments

Cal EPA also has a chronic inhalation reference exposure level of 600 ug/m^3 . Cal EPA developed this value for risk assessment using established methodology. These values are peer-reviewed and are publicly available.

After thorough analysis, the Cal EPA chronic reference exposure level (REL) of 600 ug/m^3 was based on neurological effects (drowsiness, fatigue, headache) and eye irritation in workers (Vandervort and Polakoff, 1973). This study analyzed self-reported symptoms of 19 workers employed for an average of 8 years working with TCE as a degreaser, and included drowsiness, heart palpitations, weakness, and dizziness. Time-weighted 8-hour exposures to TCE, extrapolated from 1-day personal breathing zone and area samples ranged from $172\text{-}419 \text{ mg/m}^3$. The lack of reproductive and developmental

toxicity studies and the lack of a no effect level were identified by Cal EPA as major areas of uncertainty. In addition, OSWER identified the use of self-reported symptoms as a limitation of the study.

NYSDOH also derived a number of potential air criteria based on studies of the non-cancer effects of TCE. After thorough analysis, NYSDOH selected 10 ug/m³ as the most appropriate criterion to assess noncancer effects of TCE. (NYSDOH, 2006, page 81). The critical study for non-cancer endpoints that NYSDOH identified was a study by Rasmussen et al. (1993) which investigated clinical neurological effects among Danish metal degreasers. This study examined clinical neurological effects in 99 metal degreasers after long-term exposure to TCE. For 70 of the workers, the dominant exposure was to TCE for 35 hours/week, with a mean exposure duration of 7.1 years, while for 25 of the workers, dominant exposure was to 1,1,2-trichloro-1.2.2-trifluoroethane (CFC113) for 15.1 hours/week, with a mean exposure duration of 4.2 years. Evidence of air exposure was extrapolated from measurement of urinary metabolite TCA. Clinical measures of effect (as measured by coordination tests) show significant increase with increasing exposure duration. Limitations of the study include some uncertainty about the actual long-term exposure levels of the workers to TCE during their employment, and that 25 of 99 subjects were exposed primarily to CFC 113. However, as NYSDOH notes,

“However, a separate, earlier report by the same investigators on the same cohort indicated that only 3 of the 99 workers showed slight signs of psychoorganic syndrome (i.e., reduced performance on tests evaluating motor coordination, psychomotor speed and memory) that the authors attributed solely to CFC 113 (Rasmussen et al., 1988). In limited short-term tests, CFC 113 has also been shown to be less potent than TCE in causing effects on psychomotor performance in humans, with the reported effect levels being about 12-fold higher (2500 ppm versus 200 ppm) (Stopps and McLaughlin et al., 1967). The greater potency of TCE compared to CFC 113, and the finding that only a small percentage of the Rasmussen et al. (1993) cohort was identified as having neurological deficits attributable to CFC 113, suggest that the observed deficits in motor coordination observed by Rasmussen et al. (1993) are primarily due to TCE exposure.”

From this epidemiological data presented by Rasmussen et al., NYSDOH derived an air criterion for evaluating the non-cancer effects from exposure to TCE in ambient air (analogous to a reference concentration) of 10 ug/m³. Ultimately, NYSDOH supported their evaluation by looking at the weight of scientific evidence, observing:

“Several other factors increased confidence in the CNS criterion as the basis of the TCE criterion for non-carcinogenic effects:

- (1) inhaled TCE is unequivocally an animal and human neurotoxicant;
- (2) comparison of the points-of-departure for the various endpoints indicates that CNS may be more sensitive to the toxic effects of inhaled TCE than other organ, systems, or lifestages;
- (3) the characteristics of children were specifically addressed in the derivation;
- (4) it is based on a good epidemiologic study (Rasmussen et al., 1993) for use in dose response assessment because although it had a relatively small cohort (n = 99), it did have an extended exposure duration, a dose-response relationship, and concurrent

biological monitoring data;

(5) a limitation of the study (the concomitant exposure to CFC 113) is not considered a major confounding factor because of its lower CNS potency compared to TCE and because only a small percentage of the cohort was identified as having effects related to CFC 113 exposure; and

(6) it is similar or lower than the potential criteria based on CNS effects, including effects in adult animals (Arito et al., 1994) and neurobehavioral effects in young animals (e.g., Isaacson and Taylor, 1989).”

The NYSDOH analysis indicates that 10 ug/m^3 is only slightly lower than potential criteria based on other non-cancer endpoints (e.g. developmental effects (Isaacson and Taylor, 1989; NTP, 1986) and reproductive effects (Land et al., 1981; Kumar et al., 2000, 2001). The NYS DOH assessment is limited by gaps in the data on developmental effects and immunotoxicity, and concerns about adequacy of methods for evaluating health risks to children (limitations it shares with the CalEPA assessment).

All of the studies discussed above were considered in developing the NYSDOH air guideline, but none were specifically selected as the best study upon which to base a toxicity value, since that was not their ultimate goal. However, they did identify the Rasmussen study as the critical study for CNS effects and stated “the recommended criterion for evaluating the risks of non-carcinogenic effects from chronic exposure to TCE in ambient air is 10 ug/m^3 ” (NYSDOH, 2006, page 81). Ultimately, their air guideline was set at 5 ug/m^3 , as a risk management decision, “based partly on residual concerns in three toxicologic areas: (1) gaps on the non-carcinogenic effects of TCE, including gaps in the data on developmental effects and immunotoxicity, (2) concerns about adequacy of methods for evaluating health risks to children, and (3) concerns about human carcinogenicity of TCE.” (NYSDOH, 2006).

The NYSDOH analysis was based on current science, was peer-reviewed, and is publicly available. However, because NYSDOH’s final TCE air guideline is a risk management value that considers factors other than systemic toxicity, such as practicality and analytical sensitivity, EPA has focused on its toxicity values, i.e., cancer slope factors and air criteria, in this review.

With respect to non-cancer endpoints, both Cal EPA and NYSDOH based their assessments on epidemiological studies. Cal EPA based their reference exposure level on Vandervort and Polankoff (1973). This study looked at self-reported endpoints in 19 subjects, who had an average of 8 years of exposure, with exposure concentrations extrapolated from one day of concentration measurements. The NYSDOH assessment identified Rasmussen et al. (1993) as their critical study. Rasmussen et al. is a more recent study, had a significantly larger number of subjects than Vandervort and Polankoff (99 compared to 19), had objective clinical neurological endpoints compared to a self-reported symptoms, and an LOAEL $1/6^{\text{th}}$ that of the Cal EPA study. The NYSDOH report described the strengths and limitations of the Rasmussen study as follows: “Strengths of the Rasmussen et al. (1993) study include the fact that it evaluated TCE-related CNS effects in a reasonably-sized human cohort (which eliminates the uncertainty associated with interspecies extrapolation), the extended exposure duration (as long as 35 years), a statistically significant trend for increasing severity of a sensitive CNS effect (motor coordination deficits) with increasing exposure duration, and concurrent

biological monitoring data (urinary TCA) that can be used with pharmacokinetic modeling to estimate a TCE air concentration at the LOEL. A limitation of the Rasmussen et al. (1993) study is the concomitant exposure to CFC 113, which, based on its lower neurological potency compared to TCE and that only a small percentage of the cohort was identified as having effects related to CFC 113 exposure, is not considered a major confounding factor.”

Conclusions

As noted earlier, the purpose of this guidance is to recommend an appropriate interim toxicity value for TCE from among those developed by other regulatory agencies and specifically using the preferences described in the 2003 Toxicity Hierarchy and consistent with the ECOS white paper (*Identification and Selection of Toxicity Values/Criteria for CERCLA and Hazardous Waste Site Risk Assessments in the Absence of IRIS Value* (ECOS, 2007)). The following criteria were recommended in that paper:

1. There should be a preference for transparent assessments (in which toxicity values are derived), that clearly identify the information used and how it was used.
2. There should be a preference for assessments which have been externally and independently peer reviewed, where reviewers and affiliations are identified. Other things being equal, there should also be a preference for assessments with more extensive peer review. Panel peer reviews are considered preferable to letter peer reviews.
3. There should be a preference for assessments that were completed with a previously established and publicly available methodology. Methodologies that themselves were externally peer reviewed are preferred over those that were not externally peer reviewed.
4. While there should be a preference for assessments using established methodologies to derive toxicity values, these methodologies should also be informed by the current best scientific information and practices. New assessment methodologies should provide reproducible results and meet quality assurance and quality control requirements.
5. There should be a preference for assessments that consider the quality of studies used, including the statistical power or lack thereof to detect effects; that corroborate data amongst pertinent studies; and that make best use of all available science.
6. There should be a preference for assessments and values which are publicly available or accessible. There may be a further preference for toxicity assessments that invited and considered public comment (as well as, but not in lieu of, external peer review).
7. Other things being equal, there should be a preference for toxicity values that are consistent with the duration of human exposure being assessed. For example, an externally peer reviewed subchronic reference dose (RfD) should be preferred to an externally peer reviewed chronic RfD when assessing an exposure of 2 years for non-cancer toxicity.

These recommendations formed the criteria against which the identified values were evaluated. The ECOS paper also recommends against the use of risk management values for use in risk assessment.

In summary, the goal of this analysis is to choose the most appropriate interim toxicity values for assessing site-specific risks of TCE exposure from among available assessments. OSWER recommends that the Cal EPA values provide the most appropriate interim cancer potency factors for risk assessment. Specifically, Cal EPA developed them expressly for use in risk assessment. In addition, the Cal EPA assessment was based on a full review of the literature, unlike IDEM's assessment, which IDEM undertook specifically to determine an appropriate cancer slope factor within the draft ORD risk range, which narrowed the focus of their analysis. As can be seen from Figure 1, the Cal EPA IUR is consistent with many of the other assessments and other IURs that could be developed on individual cancer endpoints. Lymphoma, which was the effect that occurred at the lowest concentration identified in the NYSDOH analysis, was one of the cancers incorporated into the calculation of the Cal EPA IUR. The Cal EPA value is consistent with relevant age-adjusted IURs that were developed in the NYSDOH analysis. Because EPA's risk assessment for TCE is currently being developed, EPA has not determined that the weight of evidence for TCE supports a mutagenic mode of action for carcinogenicity as described in EPA's "Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens." Therefore, OSWER is not recommending any specific adjustments for childhood susceptibility in site-specific risk assessments for TCE.

OSWER recommends using the criteria in the 2003 Toxicity Hierarchy in developing a preliminary remediation goal (PRG) for assessing systemic non-carcinogenic effects of TCE exposure. OSWER notes that both the NYSDOH value and the CAL EPA REL should be considered as Tier 3 toxicity values under the OSWER Toxicity Hierarchy. OSWER also notes that the NYSDOH analysis presented evaluation of more and different studies than the Cal EPA REL evaluation including the critical study NYSDOH identified (Rasmussen et al. (1993)) which was based on more subjects and had more objective endpoints than Vandervort and Polakoff (1973) and an LOAEL 1/6th that of the Cal EPA study.

Disclaimer

This guidance presents current OSWER technical and policy recommendations regarding the TCE human health values for site-specific risk assessments. While OSWER developed this guidance for facility response actions under CERCLA and RCRA corrective action, other regulators, including the states, may find it useful in their programs, although they may choose to develop alternative assessments, consistent with their own programs and policies. In addition, EPA may use and accept other technically sound approaches after appropriate review, either at its own initiative or at the suggestion of other interested parties. This guidance does not impose any requirements or obligations on EPA, the states, other federal agencies, or the regulated community. It is important to understand that this document does not substitute for statutes EPA administers or their implementing regulations, nor is it a regulation itself. Thus, this document does not impose legally binding requirements on EPA, the states, or the regulated community, and may not apply to a particular situation based upon the specific

circumstances. Rather, the document suggests approaches that may be used at particular sites as appropriate, given site-specific circumstances.

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Figure 1: Air Concentrations associated with the 1 E-06 to 1E-04 lifetime excess cancer risk range for variety of Inhalation Unit Risks. This graph includes the risk range calculated for five cancer endpoints developed by NYSDOH, the Cal EPA IUR, the IDEM inhalation cancer slope factor converted to an IUR, the IUR recommended by Lewandowski and Rhomberg (2005), and U.S. EPA for comparison. OSWER recommends that the Cal EPA values provide the most appropriate interim cancer potency factors for risk assessment.

1E-06 to 1E-04 Risk-Based TCE Indoor Air Concentrations

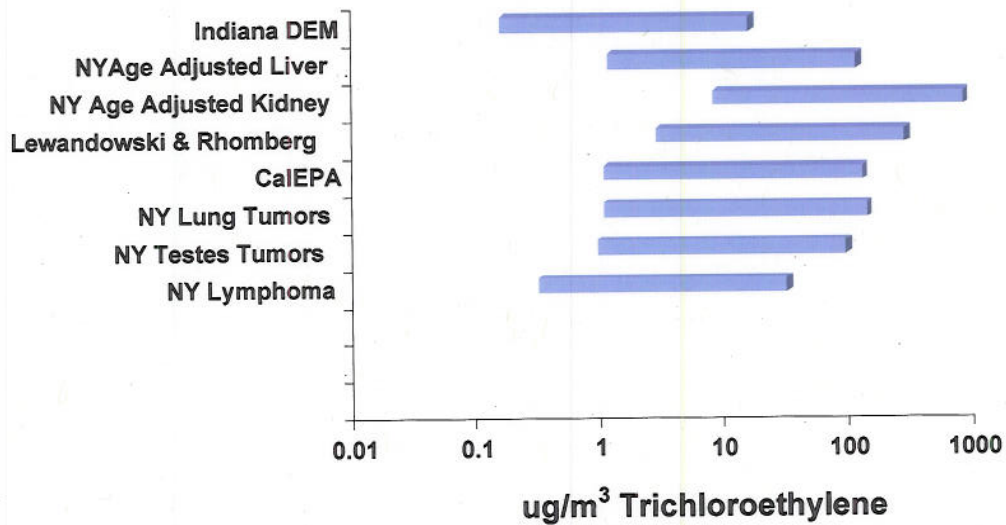


Figure 2: Example calculation of acceptable air level (concentration), or screening level, for a continuous residential exposure to a carcinogen.

$$SL_{\text{res-air-ca}} (\mu\text{g}/\text{m}^3) = \frac{TR \times AT_r \left(\frac{365 \text{ days}}{\text{year}} \times LT (70 \text{ years}) \right)}{EF_r \left(\frac{350 \text{ days}}{\text{year}} \right) \times ED_r (30 \text{ years}) \times ET_{ra} \left(\frac{24 \text{ hours}}{\text{day}} \right) \times \left(\frac{1 \text{ day}}{24 \text{ hours}} \right) \times IUR \left(\frac{\mu\text{g}}{\text{m}^3} \right)^{-1}}$$

Where: $SL_{\text{res-air-ca}}$ = residential air for a carcinogen

TR = target risk (e.g., 10^{-6})

AT_r = averaging time - residential

LT = lifetime

EF_r = exposure frequency - residential

ED_r = exposure duration – residential

ET_{ra} = exposure time – residential air

IUR = inhalation unit risk