Trichloroethylene Dose Response Assessment: Additional Issues Relevant for a Scientifically Credible Approach

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Abstract

Several issues associated with the hazard identification and dose response assessment of trichloroethylene are discussed. These issues include the identification of TCE's critical effect and overall cancer weight of evidence, the use of the recently harmonized TCE PBPK model for improving extrapolations from experimental animal to humans, an understanding of uncertainty in dose response assessment, and use of differing cancer slope factors in risk management decisions. Based on this discussion and analyses, we suggest research that might both ameliorate several of the uncertainties in the assessment of TCE's risk and provide a foundation for an international effort at harmonization of disparate dose response assessment values.

Introduction

Trichloroethylene (TCE) is a useful and persistent organic solvent that contaminates many environmental media. As a result, many risk groups and government agencies have focused on the assessment of its risk. These assessments do not always yield the same answer, which is troublesome, even though such differences can often be explained.

Many publications have focused on improving the science underlying the various risk assessments of TCE. For example, Scott and Cogliano (2000) describe a series of 16 papers that were sponsored by the U.S. Environmental Protection Agency, the U.S. Air Force, the U.S. Department of Energy, the National Institute of Environmental Health Sciences and the Halogenated Solvents Industry Alliance. These papers were used in part to generate a draft risk assessment text for TCE that emphasized mode of action and pharmacokinetic data to understand and characterize potential noncancer and cancer health risks (US EPA, 2001). In addition, a recent effort supported by EPA and USAF has resulted in a harmonized physiologically based pharmacokinetic (PBPK) model (*TERA*, 2004).

The purpose of this paper is to briefly highlight several issues relevant for a credible hazard identification and dose response assessment of TCE and to suggest

several avenues for additional research. The issues discussed in this paper are not exhaustive. However, these discussion highlight a number of important areas for further work and discussion, including:

1. TCE's hazard identification including critical effect and weight of evidence,
2. Use of the TCE PBPK model in a risk assessment,
3. Understanding areas of uncertainty in hazard identification and dose response assessment, and
4. Risk management decisions with different slope factors.

Issue 1: TCE's Hazard Identification Including Critical Effect and Weight of Evidence

TCE has elicited more than one effect among species, even in one species with tests of the same or different durations. Furthermore, TCE clearly shows a tumor response in experimental animals, but its tumorigenicity in humans has not been clearly established. This difference may be due in part to different modes of action between experimental animals and humans, or due in part to the difficulty in establishing causal relationships with the available epidemiology data. Perhaps because of these numerous effects, organizations (as described in the appendix) have judged the hazard identification and dose response assessment of TCE differently.

As more fully discussed by Haber et al. (2001) and EPA (1999, 2004), hazard identification and dose-response assessment depends in part on professional judgment as to whether an effect or collection of effects observed at any given dose constitutes an adverse response. Table 1 describes some key hazard identification terms, including the concept of critical effect.

A key step in identifying the critical effect for a dose response assessment is evaluation of all available data. This includes characterization of the quality of the evidence from human and animal studies, and other supportive information. Hill (1965) provided criteria for evaluating whether a causal relationship has been established in an epidemiology study, and in the overall epidemiology database (Table 2). As noted by U.S. EPA (1994) these same criteria apply in an evaluation of the weight of evidence for the entire database or when applied in the evaluation of experimental animal data (Haber et al., 2001).

Ideally, the database should include studies in humans, several experimental animal species, routes, and durations of exposure where a variety of end points are evaluated. Such variety is extremely useful in characterizing the chemical's spectrum of potential human toxicity, by identifying target organs and the dose ranges associated with adverse effects. Other supportive information includes *in vitro* data to elucidate potential mechanisms of biological activity, to evaluate the relevance to humans of the endpoint, to improve the extrapolation from animals to humans, and to characterize within-human

variability. Such information also includes studies designed to evaluate the metabolism and toxicokinetics of the chemical and elucidate its mechanism of action.

The assessment of the studies should include an evaluation of the reliability of the experimental design and toxicological interpretation of the results, as described above. In addition to the general principles described in Table 2, the strength of the overall evidence is enhanced if similar effects are observed in structurally similar compounds, and if observed differences among species sensitivity to a chemical are understood.

TCE has been extensively tested in experimental animals. Mice develop liver tumors, lung tumors, and lymphomas, and a variety of noncancer effects. Rats develop kidney tumors and testicular tumors and similar noncancer effects as mice. However, epidemiological data are limited and inconsistent. Based on a summary analysis of available epidemiological data (Wartenberg et al., 2000), sites that show the most consistent and compelling results with respect to TCE exposure and cancer in humans are the kidney and liver, followed by Hodgkin's disease, non-Hodgkin's lymphoma, and cervical cancer. As pointed out by Wartenberg et al. (2000), the occurrences of the tumors studied are relative rare; therefore, it limits the sensitivity of the studies reviewed. The statistical significance of the results of the summary analysis could change with omission of one study or another, and it is highly dependent on the selection of cohorts for each tier in their analysis.

Several different organizations, shown in Tables 3 through 6, have evaluated the noncancer and cancer toxicity of TCE and developed dose response assessment values. The critical effect has been variously judged to be liver tumors by California EPA, to be pulmonary tumors in mice and testicular tumors in rats by Health Canada, to be effects on liver, kidneys and CNS by RIVM, and to be liver, kidney, CNS, endocrine system, the immune system and developing fetus by U.S. EPA. Some organizations only derive certain types of risk values (e.g., RIVM only give values for noncancer assessment believing that the cancer response has a threshold, whereas Health Canada only gives cancer values; others, like EPA and CalEPA, give risk values for both cancer and noncancer dose response assessment. The choices of critical effect and WOE evaluations of the different organizations differ, in part to differences among their underlying methods and judgments, and in part because of the year of their evaluation (*ITER*, 2004). A brief discussion of differences in the underlying methods are summarized in the appendix; the critical effect and WOE conclusions for TCE from the various organizations are described briefly below.

CalEPA (1999) developed risk values for both cancer and noncancer toxicity. Its risk values for cancer toxicity of either 1.3 E-2 $(mg/kg\text{-}day)^{-1}$ for the oral route or 7 E-3 $(mg/kg\text{-}day)^{-1}$ for the inhalation route fall outside EPA's range of values (although the oral values are close). Its noncancer risk value of 0.5 mg/kg-day for the oral route agrees more with RIVM and less with EPA. This is true of its inhalation noncancer risk value of 0.6 mg/m^3, again agreeing more with RIVM and less with EPA.

3

Health Canada (Hughes et al., 1994) classified TCE as Group II - Probably carcinogenic to humans, and estimated a Tumorigenic Concentration of 5% (TC_{05}) of either 82 mg/m^3 in air or 200 mg/kg-day for oral exposures. The cancer classification of Health Canada is based on pulmonary and testicular tumors, as noted above, and for all routes of exposure. Health Canada did not generate separate risk values for noncancer effects.

RIVM (Baars et al., 2001) determined that trichloroethylene is a genotoxic and carcinogenic compound, although for the specific type of genotoxicity produced by trichloroethylene (only numerical chromosome aberration *in vivo*), a threshold of action was assumed to exist. Therefore, RIVM concluded that it was justified to use a threshold extrapolation method for limit value derivation, based on noncancer effects in liver, kidneys and CNS. This conclusion resulted in a provisional tolerable daily intake (TDI) for oral exposures of 0.05 mg/kg-day or a provisional tolerable concentration in air (TCA) of 0.2 mg/m^3.

U.S EPA (2001) treated the cancer toxicity of TCE as a nonthreshold event and judged that the upper 95% limit oral cancer 10^{-5} lifetime cancer risk was associated with a dose that ranged from 0.00003 to 0.0005 mg/kg-day (based on an oral slope range of 0.02 to 0.4 mg/kg-day^{-1}). EPA's cancer inhalation risk at 10^{-5} is estimated as 0.0001 to 0.002 mg/m^3. Both of these ranges dramatically differ with risk values of RIVM, primarily because of the differing judgments on whether a threshold exists for the cancer endpoint. EPA's oral value would roughly agree with CalEPA's value, if calculated, but its inhalation value would not. EPA also calculated noncancer risk values as 0.0003 mg/kg-day for the oral route and 0.04 mg/m^3 for the inhalation route. Both of these noncancer risk values differ with those of the RIVM and CalEPA.

In summary, organizations have evaluated the hazard identification and dose response assessment for TCE differently. A variety of research needs could be generated from such a list of disparate judgments. Some of these needs are shown here:
- To isolate factors that help explain the observed risks and to better quantify the risk, a meta-analysis of the available epidemiological studies would be helpful;
- Further studies of workers exposed to solvents, especially with measurement of biomarker to isolate exposures to specific solvents, could be helpful in elucidate the observed cancer risks;
- Further work is needed in identifying the key events and the doses at which tumors begin to occur in experimental animal and in the extrapolation of the relevant tumor's likely mode of action in experimental animal to humans; this will assist in the appropriate judgment of linear or nonlinear dose response assessment; and
- Additional effort is needed in the extrapolation of human response from experimental animal tumor endpoint using the recently harmonized PBPK model.

However, a first step perhaps is to further explore why such differences in hazard identification and dose response assessment exist among these organizations. For example, if these differences in judgment reflect the different years of evaluation by the various groups, then these differences are more readily understood because newer judgments reflect newer science. However, others differences might reflect different interpretations of the same data. An international effort to harmonize the dose response assessment of TCE should be included in the realm of possible approaches to this puzzle, especially in light of newly harmonized PBPK model.

Issue 2: Use of the TCE PBPK Model in a Risk Assessment

A recent effort supported by EPA and USAF has resulted in a harmonized physiologically-based pharmacokinetic (PBPK) model for TCE (*TERA*, 2004) based on the TCE models of Clewell et al. (2000) and Fisher (2000). It includes descriptions of the key target tissues for carcinogenesis, the liver, lung, and kidney, and predicts the kinetics of TCE and several key metabolites including trichloroacetic acid, chloral hydrate in the lung, trichloroethanol, and dichlorovinylcysteine in rats, mice, and humans. There is currently no data adequate to characterize the kinetics of another possible metabolite of interest, dichloroacetic acid.

The model makes is possible to perform cross-species extrapolations of internal dose metrics for use in a human health risk assessment for TCE. Internal dose metrics such as area under the curve (AUC) or amount of bioactive metabolite produced in the liver correlate much better with toxicity. Due to pharmacokinetic differences between experimental animals and humans, the same dose per kg body weight may yield very different internal doses to target tissues in humans and experimental animals. The PBPK model may be used to determine the relationship between the internal dose metric and toxic response in animals, and extrapolate to determine what level of dose in humans corresponds to toxic levels of internal dose.

The PBPK model may also be used to better evaluate human occupational exposure-response data. Data indicating possible nervous system, liver, and kidney effects are available from studies of people exposed to TCE in the air for chronic periods in the workplace. A major limitation in many of these studies is the lack of accurate exposure characterization, with data that are often limited to area measurements or urinary metabolites of the chemical of concern. Urinary metabolites have the advantage of providing a metric of individual exposures, but a method of extrapolating to parent chemical exposure levels is necessary for the data to be useful for quantitative risk assessment and regulation. While regression analysis such as that of Ikeda et al. (1972) is a reasonable approach to extrapolation, the PBPK model is capable of taking inter-individual physiological variability, temporal exposure patterns, measurement time, and high- versus low-dose kinetics into consideration.

To illustrate, the PBPK model was used to conduct a cursory examination of the effect of measurement day on TCA levels. Exposure for 8 hours a day, five days a week to a constant level of 101 mg/m^3 was simulated. As shown in Figure 1, the effect of measurement on Monday morning versus Friday afternoon can make a significant difference in the urinary concentration of TCA, from 28 to 45 mg/L for this scenario. The PBPK model predicts a mean of about 37 mg/L based on the daily variation in TCA levels in urine predicted by the PBPK model, the regression approach of Ikeda et al. (1972) predicts 52 mg/L TCA in urine, and Hansen et al. (2001) reported that the mean measured urinary TCA concentration was 40 mg/L.

There are other factors that could have a large impact on the urinary TCA levels. Variability in urine volume, variable physiological parameters such as body weight, fat content, cardiac output, and ventilation rates, and inter-individual metabolic differences could be examined using a Monte Carlo or sensitivity analysis of the PBPK model. A factor that cannot be accounted for by the TCE PBPK model alone is co-exposure to confounding chemicals, that is, chemicals other than TCE that are excreted as TCA in the urine. This would tend to increase the urinary TCA concentrations and lead to overestimation of the exposure levels of TCE in air, making it important to conduct analyses on cohorts with minimal exposure to confounding chemicals.

Data Gaps in PBPK Model

Several uncertainties remain in the modeling of TCE kinetics. A peer consultation for the TCE PBPK model was held and several key data gaps and research needs were identified (*TERA*, 2004). Additional studies should be designed to address the following, high priority data gaps to improve the model most efficiently.

The current PBPK model describes the kinetics of glutathione conjugates in the kidney based on a rat model. However, recent studies by Lash et al. (2003) suggest that metabolism of glutathione conjugates in the kidney may be dominated by different enzymes in humans and rats, and the current model description of metabolism in the kidney may be lacking an important consideration for interspecies extrapolation. There are currently no data which enable quantitative modeling of the bioactivation step in humans. Further research examining the activation of the glutathione conjugate and measurement of the relevant metabolites in humans is needed to improve kidney dosimetry.

Further investigation into the kinetics of chloral hydrate production and clearance would reduce uncertainty in the modeling and interspecies extrapolation of lung dose metrics. The current model of chloral hydrate in the lung has been developed based on the trichloroethylene data. While this is a reasonable approach for assessing chloral hydrate production, these data cannot inform the clearance of chloral hydrate from the lung. Because of the reverse reaction from trichloroethanol (TCOH) to chloral hydrate, the impact of TCOH clearance on chloral hydrate kinetics may potentially be an important consideration of the model. More research is needed to fully characterize the

production and clearance of chloral hydrate in order to compute lung dose metrics with more confidence.

It is unclear whether dichloroacetic acid (DCA) plays a role in liver tumor formation, and the existing data on DCA kinetics cannot be relied upon to develop a model. Further mode of action studies to determine the potential contribution of DCA to TCE induced tumorigenesis would help to determine the degree to which more detailed modeling of DCA kinetics should be pursued. Assuming that DCA is important in liver tumor formation, there are other uncertainties regarding the metabolic pathway leading to the production of DCA, and additional studies in microsomal preparations are needed. Further uncertainties exist regarding the accuracy of DCA measurements in existing studies because DCA is formed as an artifact of *ex vivo* conversion of trichloroacetic acid (TCA) to DCA. Although an improved analytical method for DCA is under development, DCA has yet to be accurately determined in the presence of TCA.

Issue 3: Understanding Areas of Uncertainty
In Hazard Identification and Dose response Assessment

As stated previously, a derivation of a noncancer risk value involves identification of critical effect and a corresponding point of departure followed by application of an uncertainty factor. Based on U.S. EPA methodology, uncertainty factors are used to cover the uncertainties involved in extrapolation from animal to human (A), human variability (H), subchronic to chronic or LOAEL to NOAEL extrapolation if applicable, as well as a database completeness. Therefore, the uncertainties involved in the TCE assessment can be better discussed based on each of the uncertainty factors used by various agencies in each area. In this section, we will discuss the uncertainties in these areas in order to identify data needed for improving the confidence in TCE assessment.

Interspecies extrapolation

For a human risk assessment, human data are more reliable and relevant than animal data. EPA's policy when developing RfDs and cancer slope factors in many of its program offices, regional offices, and ORD has been to use human data first and foremost in the determination of critical effect and choice of uncertainty factors and extrapolation models. Because of this policy, EPA risk assessment guidelines and guidance documents have consistently supported the preferred use of adequate human data over that from laboratory animal data in the estimation of risk values such as RfDs (US EPA 1989, 1991, 1993, 1998, 1999; Barnes and Dourson, 1988; Dourson, 1994) and RfCs (US EPA, 1994; Jarabek, 1994, 1995). This preference for human data can also be found in methods texts of other countries, such as Canada (Meek et al., 1994) and The Netherlands (Rademarker and Linders, 1994), international groups such as the International Programme o Chemical Safety (IPCS, 1994; Meek et al., 2001), other U.S. government organizations such as the Agency for Toxic Substances and Disease Registry (ATSDR) (Pohl and Abadin, 1995) and the Food and Drug Adminstration, and independent groups (e.g., Dourson et al., 2001).

Information on humans is available from studies of people exposed to TCE in the air for chronic periods in the workplace. These studies indicate that the nervous system may be the most sensitive target. Other studies of workers occupationally exposed to TCE for chronic periods indicate that liver and kidneys are targets of TCE. A major limitation in these studies is exposure assessment. Some of the occupational studies didn't have any exposure data while others might have exposure data, but these studies are limited by the absence of information on the joint distribution of the variety solvents and other agents in each workplace. As the result, the analysis of TCE induced toxicity could not control for the confounding effects due to exposure to these solvents and agents. More data with better-defined exposure matrix would be very helpful in human-based inhalation assessment.

Information on chronic human exposure to TCE via the oral route is largely from studies of people who consumed TCE and other solvents in their drinking water for several years. The effects associated with TCE in these studies included cardiovascular effects, dermal effects, immunological effects, neurological effects, an increase in birth defects, and cancer. The greatest limitation to these studies is the difficulty in estimating dose, and exposure to multiple chemicals. There is a potential of inhalation exposure to contaminated drinking water due to the volatilization of TCE during showering and other uses. In addition, dermal absorption is another likely exposure route for TCE exposure from contaminated drinking water. Exposure to TCE from drinking water is typically accompanied by co-exposure to multiple solvents, making it difficult to attribute observed results to only one agent. Additionally, exposure generally is assessed at a community level rather than the individual. Therefore, improved exposure assessment is need in future epidemiology studies.

However, due to lack of reliable quantitative information from human studies, the dose-response analysis for all groups (as in the appendix) are largely based on information from experimental animal studies. Based on newly developed scheme on Chemical Specific Adjustment Factors (IPCS, 2001), each of interspecies and intraspecies variability can be divided into two subfactors for toxicokinetic and toxicodynamic variations.

In terms of toxicokinetics, a significant progress in quantitative analysis of toxicokinetics of TCE and its metabolites in the body has been made recently. A workgroup consisted of scientists from U.S. AirForce, U.S. EPA, academia and private consulting group developed a harmonized PBPK model (http://www.tera.org/vera/TCEwelcome.htm). This new model was developed based on the latest data and our knowledge on TCE kinetics in animals and humans; therefore, it provides a most updated tool for quantitative estimation of TCE and its metabolites kinetics after oral and inhalation exposure in humans and animals (rats and mice). In developing this model, several areas of uncertainties have been identified as listed below. New data to address these uncertainties would significantly enhance the certainty of using the harmonized PBPK model.

In terms of toxicodynamics, there is very limited information about toxicodynamic variations between animals and humans. As the result, in two assessments conducted by CalEPA (1999) and RIVM (Baars et al., 2001), a default 10-fold uncertainty factor was used without a quantitative adjustment for toxicokinetic difference. In EPA (2001) assessment, after adjusting for TCE metabolites' toxicokinetics, a default value of $10^{1/2}$ was used for interspecies toxicodynamic subfactor. Thus, data on quantitative difference in effective doses at target organs, such as the CNS, liver, kidney and immune system, between animals and humans, would significantly improve our confidence in estimating TCE noncancer dose response assessment values from experimental animal data.

Intraspecies variation

Similar to the interspecies extrapolation, the intraspecies variation can also be attributed to two areas of variations: toxicokinetics and toxicodynamics. While this area is generally not considered in the dose response assessment of cancer endpoints due to the general conservative nature of the low dose extrapolation, the toxicokinetics might be addressed by the newly developed harmonized TCE PBPK model for noncancer endpoints. Unfortunately, very limited information exists about toxicodynamic variations between human subpopulations. As the result, the two assessments conducted by CalEPA (1999) and RIVM (Baars et al., 2001) used a default 10-fold uncertainty factor. EPA (2001) assessment, after adjusting for TCE metabolites' toxicokinetics, used a default value of $10^{1/2}$ for toxicodynamic subfactor. Therefore, data on quantitative difference in effective doses at target organs, such as the CNS, liver, kidney and immune system, between human subpopulations, could also significantly improve our confidence in estimating TCE noncancer dose response assessment values.

Subchronic to chronic extrapolation

As summarized by EPA (2001) and ATSDR (1997), several critical effects have been identified from animal studies. Following oral treatment, eye malformations, liver weight changes, immune function and kidney toxicity were observed. The critical effects following inhalation exposure to TCE were central nervous system toxicity, heart rate and electroencephalographic changes, increased liver weight, and endocrine effects. The available database includes acute, short-term, subchronic and chronic studies. However, all the lifetime studies with TCE have predominantly focused on cancer at high doses (>= 500 mg/kg/day for rats and >= 1000 mg/kg/day for mice). These studies consistently report noncancer kidney toxicity in rodents at the lowest doses tested which in turn is much higher than the threshold doses identified from subchronic studies; therefore, while these chronic studies are helpful for dose response assessment of cancer endpoints, they are not helpful in defining noncancer end points in humans following long-term exposure. The only chronic oral study used relatively low doses of TCE (50 and 250 mg/kg/day) has numerous limitations because of unusual reporting methods, such as failure to indicate the number of surviving animals and the absence of GLP. This lack of threshold data from chronic studies and duration-response trends observed in both oral and inhalation studies resulted in a selection of a subchronic-chronic extrapolation factors by EPA (2001) for both RfD and RfC estimations. Additional chronic-duration oral and inhalation studies of TCE in animals focusing on the responses in the sensitive target organs at low dose are necessary to further define the thresholds of chronic toxicity.

LOAEL to NOAEL extrapolation

While this area is generally not considered in the dose response assessment of cancer endpoints, EPA (2001) used a LOAEL to NOAEL uncertainty factor of $10^{1/2}$ to estimate a RfD. This factor was used because the point of departure is a subchronic LOAEL in one study, and a NOAEL in another, and an LED10 in a third study, indicating the point of departure at the boundary where effect can begin to be observed. Again, this uncertainty about the point of departure can be alleviated by a well-designed chronic study. This further emphasizes the importance of having a new chronic study designed to identify the threshold dose for non-cancer toxicity.

Completeness of database

While this area is generally not considered in the dose response assessment of cancer endpoints, a database uncertainty factor should be discussed for noncancer toxicity. The major limitation of the current database is lack of definite threshold value for noncancer toxicity from chronic studies as indicated above. Animal studies regarding developmental effects have been completed using both inhalation and oral exposure. Studies for oral exposure indicate no adverse reproductive effects, however, available inhalation studies in animals do not fully characterize the reproductive effects following inhalation exposure. Thus, additional animal studies are needed to further characterize reproductive effects of inhalation exposure to TCE. Immunotoxicity studies are also available, and indicate that the immune system may be a sensitive end point for toxic

effects from low-level exposure to TCE. Nevertheless, no firm conclusions can be drawn from the available data. Thus, additional human and animal studies are needed to better characterize this end point.

Due to aforementioned uncertainties, ATSDR considered that the database is not strong enough to support a chronic value for oral or inhalation exposure to TCE, while EPA developed RfD and RfC by using a 3,000-fold UF for RfD and a 1,000-fold UF for RfC. The major uncertainty in TCE assessment is the relative lack of chronic studies, which resulted in reliance on subchronic studies and corresponding UFs in the dose-response assessment. Additional chronic-duration oral and inhalation studies of TCE in animals focusing on the responses in the sensitive target organs at low dose are necessary to provide a more confident point-of-departure for deriving RfD and RfC.

Issue 4: Risk Management Decisions With Different Slope Factors

Risk managers depend on clear science in order to make decisions about public health protection. Clarity is often achieved by estimating single risk values for a chemical for both the oral and inhalation routes of exposure. Unfortunately, science is not always clear and decisions have to be made in the face of uncertainties. U.S. EPA recently drafted risk values for TCE's carcinogenicity as a range of values for both the inhalation and oral routes. While EPA's decision has the advantage of reflecting the uncertainties in the underlying science, it is a fair question to ask risk managers whether a range of risk values is helpful. Another important consideration is whether a range in factors impedes consistent application of risk assessment methodologies across federal programs.

EPA and others routinely use hazard identification and dose response assessment information from the oral and inhalation routes to derive route specific guidance. Numerous examples of this exist for ATSDR, EPA, Health Canada, RIVM on *ITER* (2004). For TCE specifically, EPA developed route specific guidance for TCE's noncancer toxicity, but did not develop route specific guidance for TCE's cancer toxicity. In contrast, Health Canada developed route specific guidance for TCE's cancer toxicity as stated above. So too did RIVM with route specific guidance for TCE's cancer and noncancer toxicity with a provisional TDI and TDA (see Tables 3 through 6).

The development of route specific guidance often reflects the true differences in target organ toxicity that a chemical displays. In other situations, the toxicity of the chemical is independent of either route and a harmonized hazard identification and dose response assessment is possible. For TCE, differences exist among risk assessment groups on how the route is treated for the cancer endpoint. This is an area for future study, debate and harmonization.

The Indiana Department of Environmental Management conducted a survey of states asking the following questions:

- What slope factor are you currently using for TCE?
- Do you use the same slope factor for residential and industrial?
- Do you anticipate changing the slope factor you use in the near future?
- Do you use a hierarchy of toxicology sources?
- What is the hierarchy?

Figures 2 and 3 show the results for the first question. States are using a 30-fold range in the oral, and a 70-fold range in the inhalation, slope values for TCE. Thirteen out of 15 states use the same value for residential and industrial risk assessment. The remaining 2 states take into account the risk goals and/or the likelihood of future use in this determination. All of the states indicated that they do not plan on changing the slope factor they are using unless EPA/NCEA or IRIS makes a change. All of the states indicated that they do use a hierarchy, but 2 of the 15 states do not use a formal rule or policy. Nine different hierarchies were given by the 15 states. These were:

- 1 out of 15 states uses CA OEHHA, then IRIS, HEAST, and NCEA.
- 2 out of 15 states use weight of evidence determination if no IRIS value exists.
- 4 out of 15 states use the OSWER Directive dated Dec. 5, 2003.[1]
- The remainder of the states use some variation of IRIS, HEAST, NCEA, ATSDR, Cal EPA, *ITER* and other (not specified) with IRIS being the first choice for all of them.

These and other questions were also addressed in part during a recent TCE workshop entitled "Approaches for Selecting Single Values from a Range of Cancer Risk Potency Factors - TCE as a Case Study" (Midwestern States, 2004). The goal of this workshop was to provide discussion and generate suggestions from TCE and risk assessment experts on approaches and considerations in selecting among ranges of cancer potency estimates. Topics for discussion included:

1. How does knowledge of cancer mode of action or use of mechanistic data inform the choice of cancer potency estimate derived from different data sets?
2. Can the level of confidence in the data for a specific endpoint inform the choice of cancer potency estimate? Issues might include assessing reliability of a reported outcome, assessing human relevance of a critical endpoint, and determining impacts on sensitive subpopulations.
3. How do patterns of exposure in the affected population impact the choice of the cancer potency estimate? Issues might include the impact of temporal patterns of exposure, and the potential for co-exposures or cumulative exposure.

If the underlying science cannot deliver single dose response assessment values for the inhalation and oral routes of exposure, then difficulties emerge in the current process of risk management decisions, as exemplified by Figures 2 and 3. Few folks

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[1] OSWER Directive 9285.7-53Memorandum revises the hierarchy of human health toxicity values generally recommended in risk assessments. The new hierarchy is:
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> Tier 1 – EPA's IRIS
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> Tier 2 – EPA's Provisional Peer Reviewed Toxicity Values (PPRTVs)
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> Tier 3 – Other Toxicity Values (use similar methods and procedures as Tier 1 and 2 values), such as Cal EPA, ATSDR, HEAST, and other publicly available peer reviewed values

would believe that states should manage the risk from the inhalation of TCE differently by 70-fold. And yet the fact that states are managing risk of TCE by this difference demonstrates large implications for public health protection. How will risk mangers choose between slope factors and defend them to stakeholders? What possible strategies might a risk manager use for applying a range of these factors? How does a risk manager decide among many values?

The implications of such a series of questions is far beyond the ability of this paper to offer solutions, but clearly, more effort is needed in understanding whether a range of values is helpful in risk management decisions, without further clarification from risk assessment scientists.

Acknowledgement

References

Anttila A, Pukkala, E, Sallmen, M, Hernberg, S, and Hemminki, K. 1995. Cancer Incidence Among Finnish Workers Exposed to Halogenated Hydrocarbons. J Occup Environ Med. 37(7): 797-806.

ATSDR (Agency for Toxic Substances and Disease Registry). 1997. Toxicological Profile for trichloroethylene. U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA. Available at: http://www.atsdr.cdc.gov/toxprofiles/tp19.html.

Axelson, O, Selden, A, Andersson, K, Hogstedt, C. 1994. Updated and Expanded Swedish cohort Study on Trichloroethylene and Cancer Risk. J Occup Med. 36(5): 556-562.

Baars, AJ, Theelen, RMC, Janssen, PJCM, Hesse, JM, van Apeldoorn, ME, Meijerink, MCM, Verdam, L, and Zeilmaker, MJ. 2001. Re-evaluation of human-toxicological maximum permissible risk levels. National Institute of Public Health and the Environment, Bilthoven, The Netherlands. RIVM report no. 711701025. March. pp 9-11 and 162-170. Available at: http://www.rivm.nl/bibliotheek/rapporten/711701025.pdf.

Barnes, DG and Dourson, ML. 1988. Reference Dose (RfD): Description and use in Health risk Assessment. Regul Toxicol Pharmacol. 8: 471-486.

CalEPA (California Environmental Protection Agency). 1999. Public Health Goal for Trichloroethylene in Drinking water. Office of Environmental Health Hazard Assessment, Oakland, CA. February.

CalEPA (California Environmental Protection Agency). 2001. Proposition 65: Process for Developing Safe Harbor Numbers. Office of Environmental Health Hazard Assessment, Oakland, CA. February.

CalEPA (California Environmental Protection Agency). 2000. Air Toxics Hot Spots Program Risk Assessment Guidelines: Part III, Technical Support Document for the Determination of Noncancer Chronic Reference Exposure levels. Office of Environmental Health Hazard Assessment, Oakland, CA. February.

Clewell, HJ, Gentry, PR, Covington, TR, Gearhart, JM. 2000. Development of a physiologically based pharmacokinetic model of trichloroethylene and its metabolites for use in risk assessment. Environ Health Perspect. 108(suppl. 2): 283-305.

Dourson, ML. 1994. Methods for Establishing Oral Reference Doses (RfDs). In: Risk Assessment of Essential Elements, W. Mertz, CO Abernathy and SS Olin, Ed. ILSI Press, Washington DC. Pp. 51-61.

Dourson, M, Andersen, M, Erdreich, L, MacGregor, J. 2001. Using human data to protect the public's health. Regul Toxicol Pharmacol. 33:234-256.

Fisher, JW. 2000. Physiologically based pharmokinetic models for trichloroethylene and its oxidative metabolites. Environ Health Perspect. 108(suppl. 2): 265-273.

Haber, LT, Dollarhide, JS, Maier, A, and Dourson, ML. 2001. Noncancer Risk Assessment: Principles and Practice in Environmental and Occupational Settings. In: Patty's Toxicology, 5th ed. Bingham, E., Cohrssen, and Powell, CH Eds. Wiley and Sons, Inc., New York, NY.

Hansen, J, Raaschou-Nielsen, O, Christensen JM, Johansen, I, McLaughlin JK, Lipworth, L, Blot, WJ, Olsen JH. 2001. Cancer Incidence Among Danish Workers Exposed to Trichloroethylene. J Occup environ Med. 43(2): 133-139.

Health Canada. 1996. Health-Based Tolerable Daily Intakes/Concentrations and Tumorigenic Doses/Concentrations for Priority Substances. Environmental Health Directorate, Health Protection Branch, Ottawa, Ontario.

Hill, AB. 1965. The environment and disease: Association or causation? Proc Royal Soc Med. 58: 295-300.

Howd, R. 2004. Personal communication.

Hughes, K., Meek, ME, and Windle, W. 1994. Trichloroethylene: Evaluation of Risks to Health from Environmental Exposure in Canada. Environ Carcin Ecotoxicol Rev, Part C J Environ Sci Health. C12(2): 527-543.

IARC (International Agency for Research on Cancer). 1999. IARC Monographs Evaluations and Introduction. Available at: http://www.inchem.org/documents/iarc/monoeval/eval.html.

Ikeda M, Otsuji H, Imamura T, and Komoike Y. 1972. Urinary Excretion of Total Trichloro-Compounds, Trichloroethanol, and Trichloroacetic Acid as a Measure of Exposure to Trichloroethylene and Tetrachloroethylene. Br J Ind Med. 29(3): 328-333.

IPCS (International Programme on Chemical Safety). 1994. Environmental Health Criteria 170, Assessing Human Health Risks of Chemicals: Derivation of Guidance Values for Health-Based Exposure Limits. World Health Organization, Geneva, Switzerland. Available at: http://www.inchem.org/documents/ehc/ehc/ehc170.htm.

ITER (International Toxicity Estimates for Risk) database. 2004. Trichloroethylene. Available at: http://toxnet.nlm.nih.gov.

Jarabek, AM. 1994. Inhalation RfC methodology: Dosimetric adjustments and dose-response estimation of noncancer toxicity in the upper respiratory tract. Inhal Toxicol. 6(suppl): 301-325.

Jarabek, AM. 1995. The application of dosimetry models to identify key processes and parameters for default dose response assessment approaches. Toxicol Lett. 79: 171-184.

Lash, LH, Putt, DA, Hueni, SE, Krause, RJ, Elfarra, AA. 2003. Roles of necrosis, Apoptosis, and mitochondrial dysfunction in S-(1,2-dichlorovinyl)-L-cysteine sulfoxide-induced cytotoxicity in primary cultures of human renal proximal tubular cells. J Pharmacol Exp Ther. 305(3): 1163-1172.

Meek, ME, Newhook, R, Liteplo, RG and Armstrong, VC. 1994. Approach to Assessment of Risk to Human Health for Priority Substances Under the Canadian Environmental Protection Act. Environ Carcino Ecotox Revs. C12(2): 105-134.

Meek M, Renwick A, Ohanian E, Dourson M, Lake B, Naumann B, and Vu V. 2001. Guidelines for application of compound specific adjustment factors (CSAF) in dose/concentration response assessment. Comm Toxicol. 7: 575-590.

Midwestern States Risk Assessment Symposium. 2004. Held in Indianapolis, Indiana on August 25th. Available at: www.spea.indiana.edu.

Pohl, HR and Abadin, HG. 1995. Utilizing uncertainty factors in minimal risk levels derivation. Regul Toxicol Pharmacol. 22: 180-188.

Rademaker, BC and Linders, JBHJ. 1994. Estimated-Concentrations-of-no-Concern of Polluting agents in Drinking Water and Air for Humans. National Institute of Public Health and Environmental Protection, Bilthoven, The Netherlands. May.

Renwick, AG. 1993. Data-Derived Safety Factors for the Evaluation of Food Additives and Environmental Contaminants. Food Addit Contam. 10(3): 275-305.

Scott, CS and Cogliano, VJ. 2000. Introduction: Trichloroethylene Health Risks – State of the Science. Environ Health Perspect. 108(suppl 2): 159-160.

TERA (Toxicology Excellence for Risk Assessment). 2004. Report of Peer Consultation of Harmonized PBPK Model for Trichloroethylene. Peer Consultation Meeting Organized by Toxicology Excellence for Risk Assessment, Cincinnati, OH. June. Available at: http://www.tera.org/vera/TCEwelcome.htm.

US EPA (U.S. Environmental Protection Agency). 1989. Risk Assessment Guidance for Superfund, Volume 1, Human Health Evaluation Manual (Part A). Office of Emergency and Remedial Response, Washington, DC. EPA/540/1-89/002.

US EPA (U.S. Environmental Protection Agency). 1991. Guidelines for Developmental Toxicity Risk Assessment. Fed Reg 56(234): 63798-63826. December 5.

US EPA (U.S. Environmental Protection Agency). 1993. Reference Dose (RfD): Description and Use in Health Risk Assessments. Background Document 1A, Integrated Risk Information System. March. Available at: http://www.epa.gov/iris. (also published as Barnes and Dourson, 1988).

US EPA (U.S. Environmental Protection Agency). 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. Office of Research and Development, Washington, DC. EPA/600/8-90/066F.

US EPA (U.S. Environmental Protection Agency). 1998. Guidelines for Neurotoxicity Risk Assessment. Fed Reg. 63: 26926-26954. May 14.

US EPA (U.S. Environmental Protection Agency). 1999. Guidelines for Carcinogen Risk Assessment. Draft. Risk Assessment Forum, Washington, DC. NCEA-F-0644. Available at: http://www.epa.gov/iris/cancer_gls.pdf.

US EPA (U.S. Environmental Protection Agency). 2001. Trichloroethylene Health Risk Assessment: Synthesis and Characterization. External Review Draft. Office of Research and Development, Washington, DC. August.

US EPA (U.S. Environmental Protection Agency). 2002. A review of the Reference Dose (RfD) and Reference Concentration (RfC) processes. Risk Assessment Forum, Washington, DC. EPA/630/Patricia-02/002F. December.

US EPA (U.S. Environmental Protection Agency). 2004. Integrated Risk Information System (IRIS) Glossary. National Center for Environmental Assessment, Washington, DC. Available at: http://www.epa.gov/iris/gloss8.htm.

Wartenberg, D, Reyner, D, Siegel Scott, C. 2000. Trichloroethylene and cancer: Epidemiologic evidence. Environ Health Perspect. 108(suppl. 2): 161-176.

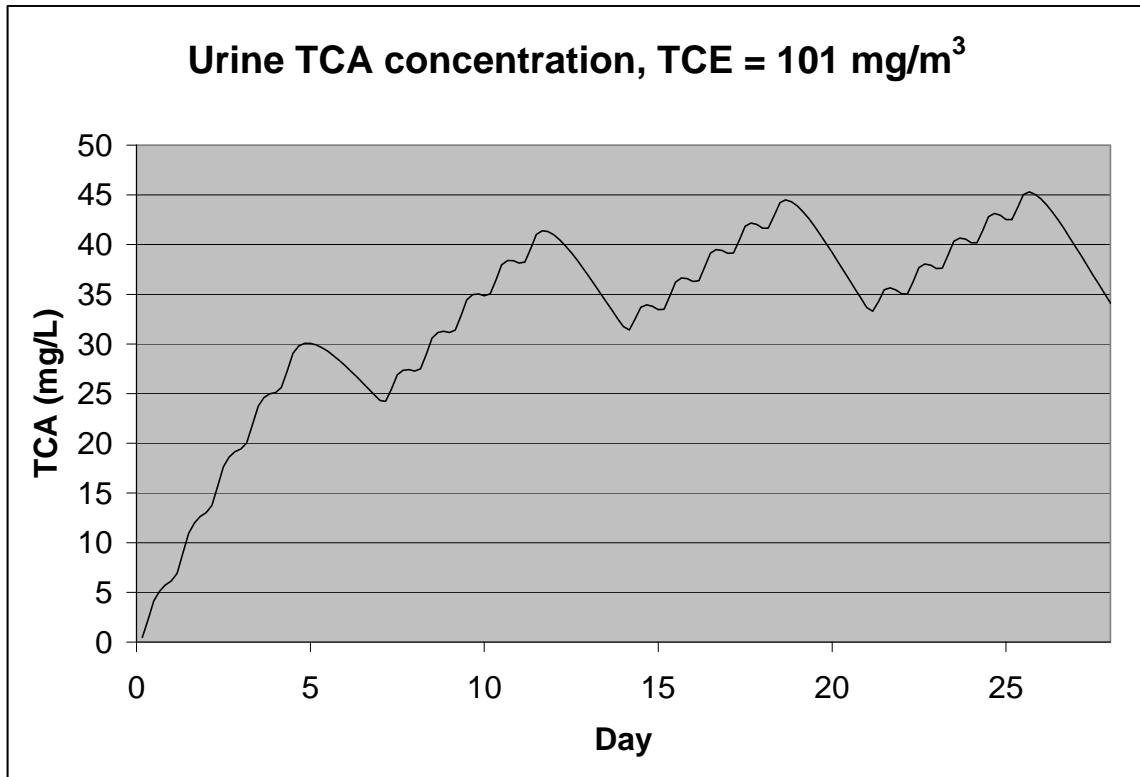Figure 1. PBPK Model Simulation of Urinary TCA predictions.

Urine TCA concentration, TCE = 101 mg/m^3

Figure 2. What Oral Slope Factor Are You Currently Using for TCE?
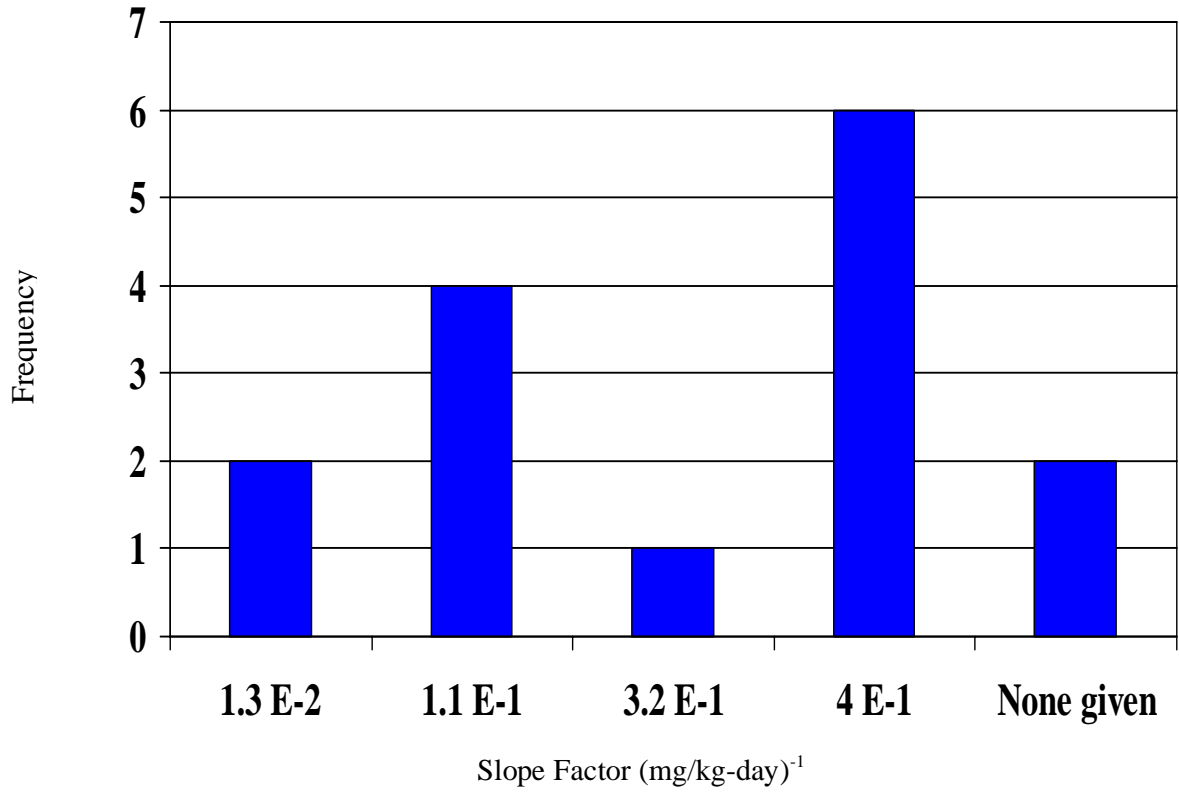
Figure 3. What Inhalation Slope Factor Are You Currently Using for TCE?
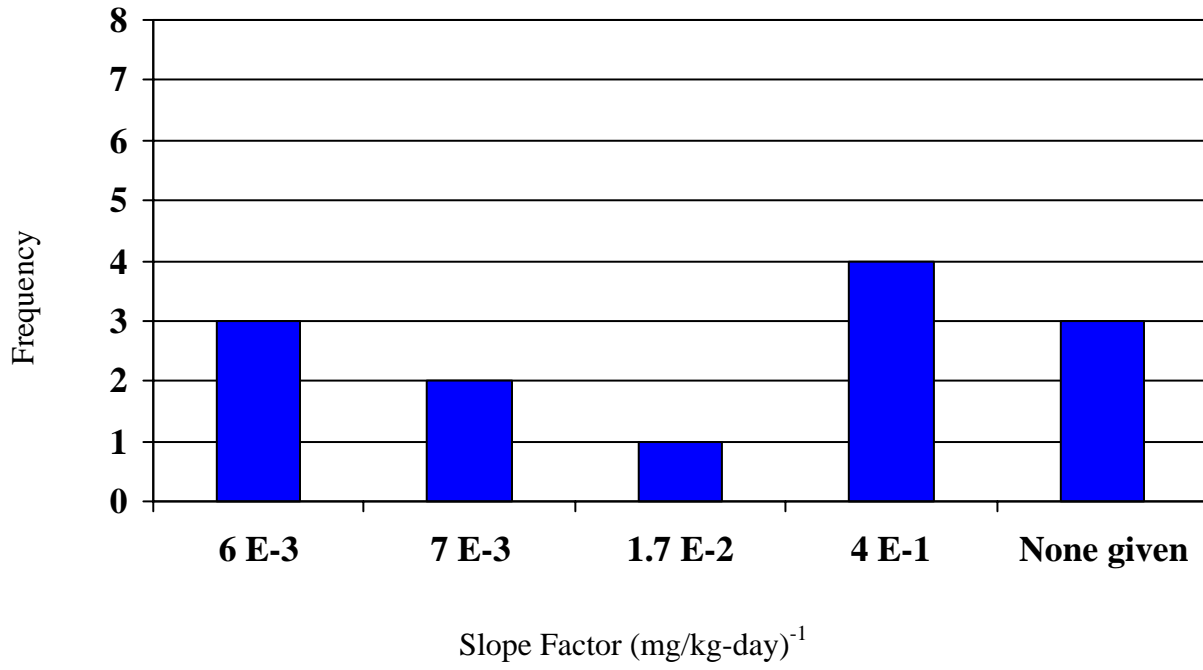

Slope Factor (mg/kg-day)$^{-1}$

Table 1. Some Key Definitions for Hazard Identification (US EPA, 2004)

ADAPTIVE EFFECT enhances an organism's performance as a whole and/or its ability to withstand a challenge. An increase in liver weight due to an increase in hepatic smooth endoplasmic reticulum is an example of an adaptive effect, if hepatic metabolism reduces the chemical's toxicity.

COMPENSATORY EFFECT maintains overall function without enhancement or significant cost. Increased respiration due to metabolic acidosis is an example of a compensatory effect.

CRITICAL EFFECT is the first adverse effect, or its known precursor, that occurs as dose rate or exposure level increases. One or more effects may be critical.

ADVERSE EFFECT is a biochemical change, functional impairment, or pathologic lesion that impairs performance and reduces the ability of an organism to respond to additional challenge. The determination of such effects may require special tests or observation, such as preparation of slides for histological analysis.

FRANK EFFECT is an unmistakable adverse effect, such as convulsions or mortality. The determination of such effects can be done by clinical observation, and normally does not require special tests.

SEVERITY connotes the toxicological significance attached to the continuum of effects, including adaptive, compensatory, critical, adverse and frank effects, potentially associated with exposure of xenobiotics.

Table 2. Criteria for Establishing Causal Significance

The strength of the association is enhanced when:

- Consistent results are obtained by different investigators under a variety of circumstances

- The association is stronger (larger relative risk or odds ratio)

- The association is specific, with the exposure is associated with a specific effect, and that effect is specific to the exposure

- Exposure occurs prior to the development of the effect (temporality)

- The association is consistent with what is known about the chemical's effects and mechanism based on clinical or animal studies (coherence and biological plausibility)

- A dose-response relationship is observed

Table 3. Summary of Noncancer Oral Risk Values for Trichloroethylene (adapted from *ITER*, 2004)

	ATSDR	HEALTH CANADA	RIVM	CALEPA	US EPA
Risk Value Name	Chronic MRL (Minimal Risk Level)	NA	TDI (Tolerable Daily Intake)	RfD Equivalent	RfD (Oral Reference Dose)
Risk Value (mg/kg-day)	NA	NA	5 E-2 [a]	5 E-1	3 E-4
Year	1997	1992	1999	1999	2001 [b]
Uncertainty Factor	NA	NA	1000	100	3000
Critical Organ or Effect	NA	NA	multiple	kidney	Liver, kidney, fetus
Species	NA	NA	Rat, mouse	rat	mouse

[a] TDI is provisional because the total database on oral toxicity is limited and lacks adequate (sub) chronic studies.
[b] – US EPA, 2001

Table 4. Summary of Noncancer Inhalation Risk Values for Trichloroethylene (adapted from *ITER*, 2004)

	ATSDR	HEALTH CANADA	RIVM	CALEPA	US EPA
Risk Value Name	Chronic MRL (Minimal Risk Level)	NA	TCA (Tolerable Concentration in Air)	REL (Reference Exposure Levels)	RfC (Inhalation Reference Concentration)
Risk Value (mg/m^3)	NA	NA	2 E-1	6 E-1	4 E-2
Year	1997	1992	1999	1999	2001
Uncertainty Factor	NA	NA	1000	?	1000
Critical Organ or Effect	NA	NA	Liver, kidney, CNS	Eyes, CNS	CNS, liver, endrocrine system
Species	NA	NA	multiple	human	Human, rat, mouse

[a] TCA is provisional because toxicity via the inhalation route is limited even though the database is larger than the oral database.
[b] – US EPA, 2001

Table 5. Summary of Cancer Oral Risk Values for Trichloroethylene (adapted from *ITER*, 2004)

	ATSDR	HEALTH CANADA	RIVM	CALEPA	US EPA
Risk Value Name	NA	TD_{05} [a]	TDI (Tolerable Daily Intake)	OSF (Oral Slope Factor)	OSF (Oral Slope Factor)
Risk Value $(mg/kg\text{-}day)^{-1}$	NA	2E+2 [a]	NA [b]	1.3 E-2	2 E-2 to 4 E-1 (range)
Year	1997	1992	1999	1999	2001 [c]
Classification	NA	II	NA	NA	highly likely to produce cancer in humans
Critical Organ or Effect	NA	Testes	NA	Liver	liver
Species	NA	Rat	NA	mouse	Human, rat, mouse

[a] The mg/kg-day dose associated with an increased tumor risk of 5%.
[b] RIVM determined that TCE is gentoxic and carcinogenic. For the type of genotoxicity (numerical chromosome aberration in vivo), a threshold of action is assumed to exist. Therefore, RIVM concluded it is justified to use a threshold extrapolation method for limit value derivation.
[c] – US EPA, 2001

Table 6. Summary of Cancer Inhalation Risk Values for Trichloroethylene (adapted from *ITER*, 2004)

	ATSDR	HEALTH CANADA	RIVM	CALEPA	US EPA
Risk Value Name	NA	TC_{05} [a]	TCA (Tolerable Concentration in Air)	Inhalation Slope Factor	Inhalation Slope Factor
Risk Value $(mg/kg\text{-}day)^{-1}$	NA	8.2 E+1 [a]	NA [b]	7 E-3	2 E-2 to 4 E-1 (range)
Year	1997	1992	1999	1999	2001 [c]
Classification	NA	NA	II	NA	highly likely to produce cancer in humans
Critical Organ or Effect	NA	NA	Testes, lungs	Liver	liver
Species	NA	NA	Rat	mouse	Human, rat, mouse

[a] The mg/m³ concentration associated with an increased tumor risk of 5%.

[b] RIVM determined that TCE is genotoxic and carcinogenic. For the type of genotoxicity (numerical chromosome aberration in vivo), a threshold of action is assumed to exist. Therefore, RIVM concluded it is justified to use a threshold extrapolation method for limit value derivation.
[c] – US EPA, 2001

APPENDIX A
BACKGROUND INFORMATION

Many of the issues in TCE risk assessment are related to the different risk assessment methods that organizations use to derive risk values. The following organizations have all developed risk values for TCE: California Environmental Protection Agency (CalEPA), Health Canada, the International Programme on Chemical Safety (IPCS), the Netherlands National Institute of Public Health and Environmental Protection (RIVM), and the U.S. Environmental Protection Agency (EPA). This Appendix describes how the different organizations define the concepts of risk assessment.

California Environmental Protection Agency (CalEPA)

CalEPA (2000) uses a slightly different noncancer risk assessment method and terminology than other groups. The term public health goal (PHG) is used for oral drinking water values and reference exposure level (REL) for inhalation values. A public health goal (PHG) is determined by applying an uncertainty factor (UF) and default body weight and water consumption (70kg/2L) to the NOAEL (or if appropriate, a benchmark dose) and multiplying by the relative source contribution (RSC).[2] CalEPA incorporates PBPK analyses and mechanism of action in many of their risk assessments, and in such cases, considers a PBPK cross-species extrapolation to represent half of the cross-species differences (toxicokinetics and toxicodynamics) (Howd, 2004). A reference exposure level (REL) is derived by the application of an UF to the NOAEL (or if appropriate, a benchmark dose).

The uncertainty factors applied are determined on a case-by-case basis. CalEPA (2000) uncertainty factors range from 1 to 10 in various categories. Uncertainty factors are applied for subchronic to chronic variability, extrapolation of a LOAEL to a NOAEL, extrapolation from animal studies to humans (interspecies variability), and human variability (intraspecies variability), they do not automatically add a 10-fold UF for children's sensitivity. An additional conversion factor of 3,500 µg/m3 per mg/kg-day is applied for route-to-route extrapolation when using non-inhalation data for the determination of a REL (CalEPA, 2000).

CalEPA has separate guidelines for carcinogen assessment depending on whether the chemical falls under Proposition 65 regulations (Prop 65). If the chemical is not listed on Prop 65 CalEPA follows the U.S. EPA guidelines for cancer assessment, applying one of three methods: 1) linear, 2) nonlinear using a margin of exposure (MOE) analysis, or 3) both linear and nonlinear (MOE) analyses (Howd, 2004). However, safe harbor levels are developed if the chemical falls under Prop 65, no significant risk levels

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[2] California EPA's PHG can be used to derive an equivalent RfD by removing the RSC, water consumption, and body weight values. Removing these values for TCE would result in an RfD equivalent of 0.5 mg/kg-day.

(NSRLs) for carcinogens and maximum allowable daily levels (MADLs) for reproductive toxicants (CalEPA, 2001). The NSRL is the daily intake level calculated to result in one excess case of cancer in an exposed population of 100,000, assuming lifetime exposure at the level in question (CalEPA, 2001). The MADL is the highest level at which the chemical would have no observable adverse reproductive effect assuming exposure at 1,000 times that level (CalEPA, 2001). Prop 65 aids interested parties in determining whether warnings are required, thus assuring the public of the exposures and discharges that are of concern or prohibited.

Health Canada

Meek et al. (1994) described Health Canada's methods for determining human health risk for cancer and noncancer toxicity. For noncancer toxicity, a Tolerable Daily Intake (TDI) or Tolerable Concentration (TC) is derived from the application of an uncertainty factor to the NOAEL or LOAEL (or if appropriate, a benchmark dose). Health Canada derives uncertainty factors on a case-by-case basis, depending principally on the quality of the data base. A factor of 1 to 10 is used to account for intra- and interspecies variation with toxicokinetic and toxicodynamic data used to adjust this UF whenever appropriate. An additional factor of 1 to 100 is used to account for inadequacies of the data base which include, but are not limited to, lack of adequate data on developmental, chronic, or reproductive toxicity, the use of a LOAEL when a NOAEL is unavailable, and inadequacies of the critical study. An additional UF between 1 and 5 may be incorporated where sufficient information exists to indicate a potential for interaction with other chemical substances.

If the chemical is essential or beneficial for human health, a dietary requirement is considered in the derivation of the TDI or TC. In exceptional cases, an additional UF is applied in deriving a TDI or TC for severe, irreversible effects such as teratogenicity. Notwithstanding all of these individual factors, a total UF in excess of 10,000 is not applied, due to the judgment that a data base warranting such high UF is insufficient to develop a meaningful TDI or TC.

For cancer toxicology, a tumorigenic dose 05 (TD_{05}) is used for oral exposure and a tumorgenic concentration 05 (TC_{05}) is used for inhalation exposure and it is considered that some probability of harm to human health at any level of exposure exists. The TD_{05} is the total intake (expressed as mg/kg-day) associated with a 5% increase in tumor incidence or mortality due to tumors, scaled to reflect interspecies variation, where appropriate. The TC_{05} is the concentration in air (expressed in mg/m^3) associated with a 5% increase in tumor incidence or mortality due to tumors, scaled in the same manner as the TD_{05} (Health Canada, 1996). Since TD_{05}s and TC_{05}s were computed from the curve within or close to the experimental region, division by an additional factor of 2 would equate to the lower 95% confidence limit and afford similar protection as the low dose risk estimates generally considered to be "essentially negligible" by other agencies (i.e., 10^{-5} to 10^{-6}) (Health Canada, 1996).

International Programme on Chemical Safety (IPCS) and the International Agency for Research on Cancer (IARC)

Groups within the auspices of the World Health Organization (WHO) conduct noncancer risk assessments similarly. However, the terminology and choice of uncertainty factors are slightly different. For example, WHO and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) uses the terms safety factor and Acceptable Daily Intake (ADI). The International Programme on Chemical Safety (IPCS) uses uncertainty factor and Tolerable Intake (TI). We briefly describe the IPCS method here.

Similar to other groups, IPCS (1994) derives a TI from the application of an uncertainty factor to the NOAEL or LOAEL of the critical effect (or if appropriate a benchmark dose). Uncertainty factors are judged on a case-by-case basis, depending principally on the quality of the data base. As with several other schemes, IPCS's factors for inter-individual variability and interspecies extrapolation consist of uncertainties in both toxicokinetics and toxicodynamics. However, unlike any other UF scheme, IPCS uses default values for both toxicokinetics and toxicodynamics within each of these areas of uncertainty, based, in part, on the scheme of Renwick (1993). IPCS's default values are 3.16 for both inter-individual toxicokinetics and toxicodynamics, and 2.5 and 4 for interspecies toxicokinetics and toxicodynamics, respectively. These default values multiply to 10 within each overall uncertainty factor, but more importantly are to be replaced with Chemical Specific Adjustment Factors (CSAF) factors whenever possible.

IPCS also allows for a UF for adequacy of the pivotal study, for example, when a LOAEL to NOAEL extrapolation is needed. The value of this factor can be other than 10-fold depending on the nature of the effects and dose-response relationship. IPCS also recommends a UF for adequacy of the overall data base with a factor of 1 to 100, the higher value being used where major deficiencies in the data exist with respect to quality, quantity, or omission. IPCS also allows for a UF based on nature of toxicity. An additional UF is applied in deriving a TI for severe, irreversible effects such as teratogenicity. A recent text is available that guides the user in the estimation of Chemical Specific Adjustment Factors (CSAF).

The International Agency for Research on Cancer (IARC, 1999) publishes monographs of substances to critically review the available data in order to evaluate the carcinogenic risk to humans. IARC, international working groups, and chemical carcinogenesis experts assess the exposure situations and identify additional research needed in addition to evaluating the carcinogenic risks to humans in each monograph. However, IARC does not derive cancer risk values.

Netherlands National Institute of Public Health and Environmental Protection (RIVM)

Rademaker and Linders (1994) described RIVM's methods for determining human health risk. For noncancer toxicity, the critical effect is selected and the lowest (sub)chronic NOAEL/LOAEL on this effect is used with uncertainty factors to determine an Estimated-Concentration-of-No-Concern (ECNC).

RIVM's factors for interspecies variability and intraspecies variability are default values of 10-fold where necessary. RIVM also uses default values of 10-fold for duration of the study and LOAEL to NOAEL extrapolation. However, depending on the available information for an individual compound, these default UF values can be adjusted for the type of effect (nature, severity, and biological significance), duration of the study, and the extent of the data set. RIVM also notes that higher composite uncertainty factors will often be applied for chemicals with limited data sets when compared to chemicals with larger data sets.

For cancer assessment RIVM derives maximum permissible risk (MPRs) levels, which consist of a tolerable daily intake (TDI) for oral exposure and a tolerable concentration in air (TCA) for inhalation exposure. When evaluating carcinogenic risk a distinction is made between two fundamentally different approaches (Baars et al., 2001). Genotoxic carcinogens are assumed to exert their activity at the smallest dose, thus a threshold for genotoxic activity does not exist resulting in an excess lifetime cancer risk. The risk estimate is based on known tumor incidence and assumes a linear approach between dose and cancer incidence, implying that cancer incidence from a particular genotoxic chemical is zero only if the dose is zero. The MPR for genotoxic chemicals has been defined as an excess lifetime cancer risk of 10^{-4} (Baars et al., 2001).

For chemicals that are not genotoxic, a certain threshold needs to be exceeded before a toxic effect will occur, assuming the effect is due to receptor interaction. When the threshold approach is applied a TDI or TCA is derived, representing the estimated amount of a chemical that can be ingested or inhaled daily during one's entire lifetime without appreciable risks (Baars et al., 2001). An uncertainty factor is applied to extrapolate from the NOAEL to the MPR, which is different from the linear approach for genotoxic chemicals. A 10-fold UF can be applied for interspecies variation, intraspecies variation, and limited data sets as needed (Baars et al., 2001).

U.S. Environmental Protection Agency (EPA)

Groups within the U.S. federal government conduct noncancer risk assessments similarly. However, the terminology and choice of uncertainty factors are slightly different. For example, U.S. ATSDR uses the terms uncertainty factor and Minimal Risk Level (MRL). U.S. FDA uses the terms safety factor and Acceptable Daily Intake (ADI). U.S. EPA uses the terms uncertainty factor and Reference Dose (RfD) or Reference Concentration (RfC). We describe U.S. EPA's methods here.

Similar to other groups, EPA derives RfDs and RfCs (Barnes and Dourson, 1988; Dourson, 1994; Jarabek, 1994, 1995; US EPA, 1994, 2002) from the application of uncertainty factors to the NOAEL or LOAEL of the critical effect (or if appropriate a benchmark dose). Uncertainty factors are judged on a case-by-case basis. EPA's factor for interhuman variability (designated as H) is intended for the differences in sensitivity among the members of the human population, primarily toxicokinetics and toxicodynamics. Experimental animal to human variability (designated as A) is intended to account for the uncertainty in extrapolating animal data to humans, and is also primarily toxicokinetics and toxicodynamics. Subchronic to chronic variability (designated as S) is intended to account for the uncertainty in extrapolating from less than chronic NOAELs (or LOAELs) to chronic levels. LOAEL to NOAEL variability (designated as L) accounts for the uncertainty in extrapolating from LOAELs to NOAELs. Data base completeness (designated as D) accounts for the inability of any single study to adequately address all possible adverse outcomes. EPA previously used an additional modifying factor, as an occasional, adjustment in the estimation of an RfD or RfC to account for areas of uncertainty not explicitly addressed by its other factors. The value of the MF was greater than zero and ≤ 10, with the default value being 1.

EPA cancer assessment is viewed as a two-step process. First the mode of action and dose-response for each tumor type is determined. Second is an analysis of the data for all tumor types that are increased in incidence by the chemical. The overall synthesis results in a consideration of the number of sites, their consistency across sexes, strains and species, the strength of the mode of action information for each tumor type, the anticipated relevance of each tumor type to humans, and the consistency of the means of estimating risks across tumor types (US EPA, 1999). Depending upon the tumor data and analysis one of the following dose response extrapolations may be used: 1) linear, 2) nonlinear using a margin of exposure (MOE) analysis, or 3) both linear and nonlinear (MOE) analyses. In rare cases, detailed mode of action information may be available which allow the formulation of a biologically based model (US EPA, 1999).