

# **A Regulatory Approach for Deriving Trichloroethylene Cancer Potency Estimates for use in the Development of Health Based Remediation Closure Levels**

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## **Introduction**

The Office of Land Quality (OLQ) of the Indiana Department of Environmental Management (IDEM) has derived cancer potency estimates, termed slope factors, for Trichloroethylene (TCE, CAS 79-01-6). The slope factors will be used in the development of protective health based exposure levels and made available to the various remedial programs to close or screen sites. Slope factors for TCE were initially determined using a hierarchy of sources (RISC, 2001).

In general, the toxicological information used to derive slope factors is continually updated as new information becomes available relative to the functional mechanisms of cancer and potency for a particular carcinogen. As a result, OLQ updates the cancer slope factors used to derive closure levels and uses the Risk Integrated System of Closure (RISC, 2001) hierarchy in the determination of the new slope factors. Prior to the 2003 OLQ cancer slope factor update, the EPA National Center for Environmental Assessment released a draft document titled, "Trichloroethylene Health Risk Assessment: Synthesis and Characterization" (NCEA, 2001). This document described a range of slope factors for TCE from 0.4 to 0.02 (mg/kg-day)<sup>-1</sup>. EPA Regions 3, 6 & 9 interpreted the NCEA document (2001) and determined for their policy use that the 0.4 (mg/kg-day)<sup>-1</sup> slope factor was appropriate. The 0.4 (mg/kg-day)<sup>-1</sup> was summarily adopted for use as inhalation and ingestion slope factors in the USEPA Regions 3, 6 and 9 Preliminary Remediation Goal tables (PRGs, 2005).

Normally, EPA Regions 3, 6 & 9 would use the Integrated Risk Information System (IRIS, 2005) as the source of cancer slope factors. However, because EPA withdrew its TCE slope factor from IRIS in the late 1980s, the Regions defaulted to the NCEA. In turn, OLQ following its own hierarchy, required the use of the EPA PRG tables as a source for slope factor data, and also adopted the 0.4 (mg/kg-day)<sup>-1</sup> slope factor. This changed the closure levels used in clean-ups, and some of the changes were significant. The regulated community expressed concerns over the use of the new slope factor for TCE. OLQ initially cited the use of the hierarchy, and some of the potency issues addressed in the NCEA report to support the use of the 0.4 (mg/kg-day)<sup>-1</sup> slope factor. However, given the concerns expressed by the regulated community, OLQ continued to investigate how the NCEA paper was used to derive the 0.4 (mg/kg-day)<sup>-1</sup> slope factor and the issues surrounding its use.

As a result of the continued investigation, OLQ has concluded that the oral and inhalation slope factor of 0.4 (mg/kg-day)<sup>-1</sup> may not be appropriate for use in the RISC Default Closure Levels and proposes the use of new oral and inhalation slope factors for residential and commercial applications. For commercial sites OLQ is proposing an oral

slope factor of  $0.034 \text{ (mg/kg-day)}^{-1}$  and an inhalation slope factor of  $0.018 \text{ (mg/kg-day)}^{-1}$ . For residential sites IDEM is proposing an oral slope factor of  $0.10 \text{ (mg/kg-day)}^{-1}$  and an inhalation slope factor of  $0.054 \text{ (mg/kg-day)}^{-1}$ . In general, these changes will increase the RISC default closure levels.

The slope factors are derived using the range presented in the NCEA (2001) draft Health Risk Assessment (HRA). Following the recommendations of the NCEA (2001) and the Science Advisory Board (SAB) review of the NCEA draft HRA (SAB, 2002, Section 11.2.1) adjustments to the slope factors are made for early life exposure, resulting in higher slope factors for residential applications.

OLQ recognizes that significant controversy surrounds the use of the NCEA (2001) report and that the National Academy of Sciences (NAS) has undertaken an analysis of the NCEA (2001) document and its ancillary issues (NAS, 2004). The NAS is expected to complete their evaluation sometime in 2006, at which time EPA must evaluate the findings, develop a new draft, solicit comments and finally, issue new guidance. This process may take years. In the interim, OLQ realizes that while certain offices at EPA are not using the NCEA guidance document, others are, and that a broader interpretation of the use of toxicity values from NCEA is necessary.

OLQ has selected the new slope factors based on the following criteria.

- Selected values should adequately protect health but should not be overly conservative
- Selected values should be based on the best current understanding of the state of the science concerning TCE toxicity
- EPA guidance should be followed wherever it is available

OLQ is aware that additional scientific studies have become available since the release of the NCEA document (see Lewandowski and Rhomberg, 2005). OLQ will not attempt to use this information to adjust or derive a new slope factor range, believing the NCEA document sets a suitable range of slope factor values as a starting point. However, as it has been appropriate, OLQ has used subsequent EPA and literature references and guidance on applications of the NCEA range, including adjustments for early life exposures. It is recognized that once the decision was made not to use the  $0.4 \text{ (mg/kg-day)}^{-1}$  slope factor, OLQ could have reverted to the previous (pre 2001), slope factors. OLQ believes this to be inappropriate given the significant body of new information presented in the NCEA and supporting documents. Finally, it should be noted that OLQ evaluated the middle of the NCEA range as a reasonable estimator for a single slope factor. The SAB in its review of the NCEA (2001) document made it clear (SAB, 2002, Section 7.2.1.3) that the range is not an interval estimate in the sense of a statistical confidence interval, and therefore it is inappropriate to calculate a central tendency value from the range of values presented by NCEA.

OLQ notes that while great controversy surrounds how to apply the NCEA document, there is widespread support for the use of a range of values (SAB, 2002; IRIS, 2005). Although the shift to a range approach has been occurring for some time, it has only become a significant issue with TCE. In the past, EPA used a single point estimate for a slope factor. Beginning with compounds such as PCBs, Benzene, and 1,2

Dibromomethane (IRIS, 2005) EPA began a shift to multiple slope factors, or a range of values. OLQ has not been able to find adequate guidance on how to apply a range (except for PCBs), nor does it believe this guidance is provided in the NCEA document or the SAB review. OLQ has investigated ways to use a range approach for default closure levels and site specific applications and for many reasons, discussed herein, finds it is not feasible without further guidance from EPA.

Consequently, OLQ has selected a single study or group of studies from within the NCEA range in an approach similar to the compelling example presented by Lewandowski and Rhomberg (2005). The OLQ approach differs from that of Lewandowski and Rhomberg (2005) in that OLQ has used a top down approach (as explained more fully below) and much of the evaluation of the studies in the range has been made based on how they have been used in the regulatory setting. The top down approach is warranted given the significant body of evidence indicating that TCE is a multiple species, multiple site carcinogen that appears to exhibit multiple modes of carcinogenic action. Using the top down approach, OLQ began with the study that yielded the largest, most conservative slope factor; evaluated the reasonableness of its use to derive a single point slope factor and then, if that study was unsatisfactory, moved sequentially down the potential hierarchy until OLQ found a study, or series of studies, considered adequate to derive a slope factor. This top down regulatory approach to support study selection seems reasonable to OLQ and is transparent, in that it gives details on the possible selection of all studies.

The NCEA document (2001, Preface) and new guidance on early life exposure (EPA, 2005), and other EPA documents (USEPA, 1997), reveal that the movement to a range is part of a shift to reconsider a host of policy issues surrounding potency. The significance of this direction should be noted, given that the National Academy of Sciences (2004) has agreed to undertake a thorough analysis of many of the issues surrounding the slope factor for TCE.

OLQ recognizes the confusion and disagreement on the use of the NCEA document within EPA and its "Draft" status. However, the use of the upper end of the slope factor range given in this document by Regions 3, 6 & 9 in their PRG tables clearly evidences EPA support for this document. In addition, the new science it presents simply cannot be ignored. NCEA (2001) has sorted through a large body of data and information on TCE and established a range of reasonable values that indicate the potency of TCE. OLQ, while disagreeing with the lack of guidance on many aspects concerning the range, does believe the range presents a reasonable starting point from which to derive a slope factor

The use of a range raises many issues that have not been addressed by EPA. Principal among these is how to use a range, as opposed to a single point estimator, for screening levels or for site-specific purposes applicable across all sites. Other issues are also significant. For instance,

- What qualifies a study for inclusion within the range
- Are there limitations that should be placed on some studies due to quality or content

- How should a regulatory body address disproportionate risk or co-exposure from other similar contaminants

These issues must also be addressed in the context of selecting a single point estimator.

### **Current Guidance on Use of a Range of Values to Derive Slope Factors**

OLQ has investigated how to use a range in the derivation of screening levels (termed Default Closure Levels). Screening level tables are generally used to address a wide range of applications within a given state and as such, are very conservative. As most states have screening level tables, it would seem at first, reasonable to use the high end of the range in setting screening level values. Indeed, this approach was taken by many states (Dourson *et al.*, 2004). Although, it remains to be determined if this approach was taken simply because many states rely on the use of the Regions 3, 6 & 9 PRG slope factor values, and all three regions adopted the high end of the range by default, or if states evaluated the NCEA document and then explicitly chose the high end of the range as the most appropriate value. Regardless, if the high end of the range is used to set screening levels then it follows that there must be some condition under which a deviation from the most conservative position is warranted.

It is difficult to determine how to select a single slope factor from within the range of slope factors provided by NCEA. Little guidance is given and what is presented seems confusing. NCEA (2001) in Section 1.4 identifies guidance on the use of the range stating “An assessment of maximum individual risk would use the upper end of the slope factor range, while an assessment of the number of cancer cases in the general population could use the midpoint of the range.” This is in contradiction to a statement made in Section 4.5.6.4 “Risk assessments involving the presence of risk factors such as diabetes or alcohol consumption, or high background exposure to TCE or its metabolites would more appropriately choose a higher slope factor.” It is rare to find a population that does not include diabetics, and/or does not consume alcohol. Diabetes is quite prevalent in the general population as is alcohol consumption. These statements drive a risk assessor to continually select the higher slope factor.

The EPA Science Advisory Board in its 2002 review of NCEA document, while in support of listing a range of slope factors, clearly indicated the EPA guidance did not present sufficient means for determining use of a given slope factor within the range (SAB, 2002). Quoting from Section 7 of the SAB report “... the draft risk assessment incorrectly suggests that the different slope factors apply to different characteristics of the exposed population (page 4-30, lines 1-6). The Panel advises that Section 4.5.6.4 of the draft assessment be revised to indicate more clearly how the various slope factors can be based on variability” and “The Panel suggests that it is important to provide both upper confidence limit estimates and the mean “expected value” estimate when developing risk ranges to give users confidence intervals. It (*the SAB*) notes that it will also be important for the Agency (*EPA*) to provide risk management guidance that might indicate when it is most appropriate to use mean values or when to use high end confidence intervals.” Finally in response to a discussion of the use of a range, while in general approving of

this approach, the SAB states, “Further investigation of this new approach for risk assessment is, however, warranted.”

OLQ attempted to derive a method to use the range on a site specific basis; first by evaluating the guidance on the use of the range in the NCEA document, and then by attempting to define conditions of exposure or potency that could serve as some means to use a different slope factor from within the range. These attempts were unsuccessful. In part, this was because the use of a given slope factor from within a range is dependent upon the criteria used to select the studies that quantify the range. Issues such as degree of confidence and potential confounding issues, all impact how to use a given study.

Until EPA issues new guidance, OLQ has elected to stay with a single point policy. The decision to stay with a single point policy has necessitated developing procedures on how to select a single point from within the range that go beyond simply taking the best study. It requires a host of considerations. Principal among these is disproportionate risk to children, the nature and extent of cancer types and species response, and potential advantages of combining information from similar studies. Each of these major issues will be addressed below.

### **Derivation of a Single Slope Factor Value**

An integral part of using all available science is consideration of the weight of evidence for potency. Recent publications were discussed in the NCEA (2001) document that provided overarching consideration. Table 1 below lists a series of factors that describe TCE carcinogenic potency.

**Table 1**  
**Initial TCE Potency Considerations**

1. Evidence for multiple modes of carcinogenic action
2. Cancer response at multiple sites and in multiple species (including the association between animal and human cancer development sites)
3. Increased response with concurrent exposure to compounds metabolized by the same pathways where there is common significant indirect cumulative exposure
4. A significant degree of uncertainty in the data-base for assessing cancer response
5. Non-definitive conclusions regarding genotoxicity
6. The potential for disproportionate response in certain subpopulations

OLQ notes that many of the studies used to validate the NCEA range have also been used by states, regulatory agencies and others, to derive slope factors or supplement their derivation (SAB, 2002; Cal-EPA, 1999; Lewandowski and Rhomberg, 2005;

USEPA OAQPS, 2005c; Ontario Ministry of the Environment, 2005). The NCEA range (2001) is supportable and OLQ will use the range as a starting point. There is a large body of regulatory data and information on TCE that can also be used, including justifications for numerous slope factors by states, regulatory agencies and countries. Suitable criteria to evaluate the regulatory applicability of a study or group of studies for a “single point slope factor” include the following.

- Is the study currently used to quantitatively establish a slope factor used by a state, regulatory agency or country?
- Is the study well received in the professional and regulatory community for quantitatively determining a slope factor?
- Is the study used to support the derivation of a slope factor?
- How widespread is the use of the study in development of a slope factor?

## **Oral Slope Factor Evaluation**

### ***Cohn et al 1994 Study***

The Cohn *et al.* (1994) study was used by NCEA (2001) to set the high end of the range at  $0.4 \text{ (mg/kg-day)}^{-1}$ . It yields the most conservative slope factor and will be evaluated for use in the derivation of an oral slope factor. This study examined the association between TCE levels in drinking water and cancer response. The Cohn *et al.* (1994) study was an ecological study. Individual levels of exposure were not known but attributed to TCE levels in the water supply. Lewandowski and Rhomberg (2005) make the point that, “ecological studies are generally not considered analytical studies because they deal with broad groups rather than individuals (individuals with disease in case control studies or individual members in cohort studies).” Lewandowski and Rhomberg (2005) further state that “Ecological studies are primarily used for hypothesis generation and are generally not used for demonstrating causation or quantitative risk analysis.”

A similar conclusion is drawn by Wartenberg *et al.* (2000) who states that the community based studies (which include the 1994 Cohn *et al.* study) have a number of limitations: “Exposure is assessed at the community level rather than the individual. Contemporaneous or retrospective assessment of disease relative to exposure compromises interpretability.” Although Wartenberg *et al.* (2000) believe that solvent exposure causes cancer they do not believe the body of current work is sufficient to specify the particular agents nor to estimate the magnitude of that risk. Both Wartenberg *et al.* (2000) and Lewandowski and Rhomberg (2005) make the point that the Cohn *et al.* (1994) study was not able to assess the contribution of confounders such as age, ethnicity, or diet. Further support is provided by Rodricks (1998) defining the general principles and uses of ecological studies and indicating that because these types of studies do not consider the exposure or disease status of individuals they cannot demonstrate causality. Their primary value is in hypothesis generation or weight of evidence.

Since the Cohn *et al.* (1994) study was used by the NCEA (2001) to calculate a slope factor that sets the upper boundary of the range; it is reasonable to examine the exposure levels used in that calculation. Lewandowski and Rhomberg (2005) indicate that the

Cohn *et al.* (1994) study uses water data primarily from the 1980s but not the preceding exposure period. Since the time of residence is not known, exposure estimates are uncertain. Given that the latency period for cancer is equal to or greater than 20 years, the data Cohn *et al.* (1994) collected may not accurately reflect TCE levels in drinking water at the critical time of exposure. Both Wartenberg *et al.* (2000) and Lewandowski and Rhomberg (2005) also make the point that there were other solvents present in the drinking water making it difficult, if not impossible, to quantify the contribution of TCE to the health effects experienced.

Another similar issue concerns additional exposure to TCE via inhalation that results from household uses of drinking water other than direct ingestion. Absorption by the inhalation route was not factored into the Cohn *et al.* (1994) slope factor calculations presented in the NCEA document (NCEA, 2001). Such additional exposures result from food preparation, showering, bathing and washing dishes and laundry. Both Rhomberg (2000) and Wartenberg *et al.* (2000) note that TCE could have volatilized, and inhalation may have played a role in the magnitude of the cancer response. It is clear from RISC (2001) and US EPA (1991) that inhalation intake from volatile compounds can be as much as 4.8 times oral intake if one assumes that inhalation is a viable pathway. Assuming that the entire carcinogenic response is due to oral intake alone underestimates the dosage that gave rise to the response and therefore overestimates the potency. A comparable slope factor considering intake from both oral and inhalation (using US EPA, 1991) and assuming oral and inhalation slope factors are equal, indicates the oral slope factor would be adjusted downward by at least a factor of 4.8, or from  $0.4 \text{ (mg/kg-day)}^{-1}$  to  $0.084 \text{ (mg/kg-day)}^{-1}$ .

Similarly, if one assumes all intake is from the ingestion route and calculates a slope factor which is then directly route extrapolated from the oral to inhalation, the original error is significantly compounded. Cal-EPA (1999), in its derivation of a Public Health goal for TCE in drinking water, draws a similar conclusion when calculating a slope factor for drinking water and TCE and uses a factor that addresses the inhalation and dermal components of exposure.

Further support for not using the NCEA slope factor from the Cohn *et al.* study is presented by those that have derived a slope factor subsequent to the release of the 1994 Cohn study. The California Environmental Protection Agency (Cal-EPA), in deriving its Public Health Goal for Trichloroethylene in Drinking Water (Cal-EPA, 1999), uses the liver tumors from the National Cancer Institute (NCI, 1976) data, the lung and liver tumor data from Maltoni *et al.* (1986) and lung tumor data from Fukuda *et al.* (1983) to derive a slope factor, using the human study of Henschler *et al.* (1995) to validate the oral slope factor. No mention is made in the California work of an approach using the Cohn *et al.* (1994) study even though the Cal-EPA oral slope factor was derived in 1999, five years after the Cohn *et al.* (1994) study.

An examination of results from Dourson *et al.* (2004) indicate that the Netherlands National Institute of Public Health and Environmental Protection (RIVM) made cancer potency decisions in 2001 that do not seem to be similar to NCEA potency estimates. In fact, when extrapolating the threshold approach that was taken by RIVM with TCE to a comparable cancer slope factor, the result is somewhere between 100 and 1000 times smaller than that given by the EPA NCEA range. It seems unlikely that the Cohn *et al.*

(1994) study was given much weight in deriving the RIVM (Baars, et al., 2001) cancer potency value.

The USEPA Office of Air Quality Planning and Standards (US EPA OAQPS, 2005) lists the requirement to use a value of  $0.007 \text{ (mg/kg-day)}^{-1}$  as an inhalation slope factor in all risk assessments. NCEA (2001) using the Cohn *et al.* (1994) study derives a slope factor of  $0.4 \text{ (mg/kg-day)}^{-1}$ . The EPA OAQPS value of  $0.007 \text{ (mg/kg-day)}^{-1}$  is 57 times smaller. If the Cohn *et al.* (1994) study is a realistic quantitative estimate of the upper end of the range then EPA OAQPS would not require the use of a slope factor 57 times less. Finally, the World Health Organization (2000) in deriving their inhalation protective value, states that quantitative risk estimates from human data could not be made due to the confounding issues present in the studies. The Ontario Ministry of the Environment (2005) supports the use of the WHO value.

Since the Cohn *et al.* (1994) study is used to set the top of the NCEA range at  $0.4 \text{ (mg/kg-day)}^{-1}$ , and given that this change can result in a 70 fold difference in clean up values, the level of confidence in this study should be very high and its use well supported. However, the Cohn *et al.* (1994) study is not suitable for use as a quantitative measure of cancer potency. As Wartenberg *et al.* (2000) points out in reference to the many human studies evaluated “We recommend further study to better specify the specific agents that confer this risk and to estimate the magnitude of that risk.” If the Cohn *et al.* (1994) study is eliminated then what follows next in the top down approach is a group of mouse bioassays (NCEA 2001, Section 4.5.6.1).

### ***1976 NCI and the 1990 NTP Mouse Studies***

Unlike the Cohn *et al.* (1994) study, the 1976 NCI and the 1990 NTP mouse studies have considerable support outside the NCEA document. California had enough confidence in the 1976 study to use it, in conjunction with other studies, to derive an oral slope factor for use in its drinking water standard (Cal-EPA, 1999). Support for the 1976 NCI study also comes from its use by the International Agency for Research on Cancer in 1979 to determine that there was limited evidence TCE is carcinogenic in animals (Cal-EPA, 1999). The NTP peer review of the NTP (1990) study categorized the mouse results as “clear and unequivocal” (Lewandowski and Rhomberg, 2005). EPA found the 1976 study (and another study) to be suitable for deriving the 1985 TCE slope factor (EPA, 1985).

Lewandowski and Rhomberg (2005) state that the 1976 NCI study has findings that are of “uncertain validity.” Lewandowski and Rhomberg (2005) point to a change in the dosing regimen and the presence of the stabilizer epichlorohydrin, a known carcinogen, as reasons for making this determination. Lewandowski and Rhomberg do not question the validity of the NTP (1990) study as much, but still cite a decrease in survival rate and body weight as complicating issues. However, Lewandowski and Rhomberg (2003) do indicate that the 1976 NCI study data “appeared to be in accord with data from the well conducted mouse portion of the 1990 NTP study.” As concerns epichlorohydrin, Cal-EPA (1999) found that the epichlorohydrin doses were small compared to the doses that elicited cancer response and that epichlorohydrin appears to initiate tumors at sites by localized tumorigenic action where it is in direct contact with tissue (such as nasal or forestomach). Cal-EPA (2005) drew the conclusion that the epichlorohydrin was not the

cause of the cancer response in the 1976 NCI study. Rhomberg also states that epichlorohydrin causes site of contact tumors (Rhomberg, 2000). Despite a change in dosing regimen in the NCI (1976) study the results have been widely used in the development of regulatory standards (Cal-EPA, 1999; USEPA, 1985). The mouse results from the NTP (1990) were assessed by a peer review group as “clear and unequivocal” (Lewandowski and Rhomberg, 2005). It should also be noted that both studies have been widely used to derive potency estimates using various pharmacokinetic models (Bois, 2000; Rhomberg, 2000).

There is further support for the use of these studies. The SAB concluded that the epidemiology studies suggest the strongest support for liver cancer (2002, page 11). Lewandowski and Rhomberg (2003) support this position by noting that the mouse liver tumor data appear to be the best source for assessing oral exposure to TCE, and that the liver endpoint seen in both mice and humans lends support to the idea that cross-species extrapolation is valid. Lewandowski and Rhomberg (2003) also state that none of the data from the human studies is significantly better than the mouse liver data as a basis for deriving a slope factor. Lewandowski and Rhomberg (2003) support the position of selecting  $0.03 \text{ (mg/kg-day)}^{-1}$  as a suitable slope factor by comparing it to the Anttila *et al.* (1995) study using a route to route conversion and obtaining slope factor results lower than  $0.03 \text{ (mg/kg-day)}^{-1}$ .

Based on this evidence, OLQ believes the NTP (1990) and NCI (1976) mouse bioassay data are suitable for the derivation of an oral slope factor. OLQ contracted Toxicology Excellence for Risk Assessment (TERA) of Cincinnati, Ohio to develop slope factors using the NCI (1976) and the NTP (1990) data in conjunction with PBPK modeling. TERA used the new harmonized PBPK model.<sup>1</sup>

The results of the TERA modeling work (2005) were statistically combined based on recommendations from Ecology and the Environment (E&E), as attached. The geometric mean slope factor was selected based on the conclusion drawn by E&E that the human equivalent LED10s (the 95% lower confidence limit of the dose of a chemical needed to produce an adverse effect in 10 percent of those exposed to the chemical, relative to control) from the four mouse study results (2 studies, 2 sexes) were lognormally distributed. This approach is similar to Cal-EPA (1999) and EPA (1985). The slope factor was derived by taking the geometric mean of the combined male and female LED10s from both the NCI (1976) and the NTP (1990) mouse gavage studies. The new oral slope factor is  $0.034 \text{ (mg/kg-day)}^{-1}$ . This slope factor compares well with others that have been derived as indicated in Table 2 below.

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<sup>1</sup> TERA in cooperation with the United States Air Force (USAF) and the United States Environmental Protection Agency (EPA) facilitated and provided support to a USAF-EPA workgroup to develop a harmonized physiologically-based pharmacokinetic (PBPK) model for trichloroethylene (TCE) and its metabolites (TERA, 2004). The model incorporates the latest science from a distinguished panel including those responsible for initial model development (notably, Clewell (2000) and Fisher (1998).

**Table 2**  
**Recent Trichloroethylene Oral Slope Factor Comparisons**

<b>Study/Modeling Result</b>	<b>Description</b>	<b>Slope Factor calculation from the geometric mean of the LED10s (mg/kg-day)<sup>-1</sup></b>	<b>Slope Factor calculation from the harmonic mean of the LED10s (mg/kg-day)<sup>-1</sup></b>	<b>Study Derived Slope Factor (mg/kg-day)<sup>-1</sup></b>
TERA, 2005	NCI (1976) and NTP (1990) Oral gavage studies. PBPK modeling using TERA (2004). PoD determined using average of 6 best fitting models (P-value >0.9). Four LED10s and slope factors calculated	0.034	0.039	
Rhomberg, 2000 Bois-Fisher TCA	Using NCI (1976) and NTP (1990) Oral gavage studies. PBPK TCA modeling using Bois (2000a), PoD determined using Multi stage Weibull or Global86. Four slope factors calculated	0.022	0.032	
Rhomberg, 2000 Bois-Clewell TCA	Using NCI (1976) and NTP (1990) Oral gavage studies. PBPK TCA modeling using Bois (2000b), PoD determined using Multi stage Weibull or Global86. Four slope factors calculated	0.13	0.20	
Rhomberg, 2000 Bois-Clewell DCA	Using NCI (1976) and NTP (1990) Oral gavage studies. PBPK DCA modeling using Bois (2000b), PoD determined using Multi stage Weibull or Global86. Four slope factors calculated	0.026	0.040	
Rhomberg 2000 averaging all B-F and C-F TCA and DCA modeling results		0.043	0.091	
Cal-EPA, 1999	Citing the use of NCI (1976) oral gavage, Maltoni et al (1986) inhalation Abbas and Fisher (1997) PBPK modeling. Four slope factors used, gavage studies male & female, and inhalation study male & female	0.013*	0.026	
Health Canada (1996)	Slope factor calculated using 5,000 safety factor for TD <sub>05</sub> value of 200 mg/kg-day after			0.00025***

	Health Canada (1996) using safety factor that represents 0.00001 risk and backcalculating SF using standard risk assessment methods			
USEPA, 1985	Using NCI 1976 and NTP 1982 Mouse gavage studies, geometric mean of all dose groups	0.011**		

\* Geometric mean of the slope factors, similar to geometric mean of LED10s

\*\* Geometric mean of  $q^*$ , (95% upper limit of slope in the multistage model)

\*\*\* EPA (NCEA, 2001) derived slope factor from same data and found, using appropriate EPA scaling factors, a slope of  $0.004 \text{ (mg/kg-day)}^{-1}$

### Inhalation Slope Factor Evaluation

USEPA Regions 3, 6 and 9 in their PRG tables (PRG, 2005) have selected slope factors at the top of the NCEA (2001) range ( $0.4 \text{ (mg/kg-day)}^{-1}$ ) for both the inhalation and the oral ingestion routes. Support for this approach is provided by the fact that only a single slope factor range was developed by NCEA (2001) for both inhalation and ingestion. This was considered reasonable because the toxic effects are systemic and independent of the route of entry (Personal communication Weihsueh Chiu, 2005).

While OLQ would agree that TCE causes liver cancer by both inhalation and ingestion (NCEA, 2001), there is little evidence to indicate that the numerical slope factors are quantitatively the same by both oral and ingestion routes. Table 3 below lists inhalation slope factors derived by various methods to support this conclusion.

Given that an oral slope factor and an inhalation slope factor are quantitatively different, OLQ finds multiple lines of evidence to support an inhalation slope close to the lower end of the NCEA (2001) range (USEPA OAQPS, 1995; Cal-EPA, 1999; NCEA, 2001). OLQ will derive an inhalation slope factor using the results of the TERA (2005) PBPK modeling of the NCI (1976) and NTP (1990) oral gavage data. OLQ will use the geometric mean of the inhalation slope factors citing the E&E conclusion (2005, attached) for a lognormal distribution of the data. Although the mouse studies are gavage, the use of the harmonized PBPK model accounts for the difference with inhalation exposures. Inhalation data converted to oral equivalents is well established (Cal-EPA, 1999; NCEA, 2001) and the reverse, the use of oral doses converted to inhalation doses has also been well established (EPA, 1985; Ontario Ministry of the Environment, 2005 citing Massachusetts).

**Table 3**

## Recent Trichloroethylene Inhalation Slope Factor Comparisons

Study/Modeling Result	Description	Slope Factors calc'd from the geometric mean of the LED10s (mg/kg-day) <sup>-1</sup>	Slope Factors calc'd from the harmonic mean of the LED10s (mg/kg-day) <sup>-1</sup>	Study Derived Slope Factor (mg/kg-day) <sup>-1</sup>
TERA, 2005 (attached)	NCI (1976) and NTP (1990) Oral gavage studies. PBPK modeling using TERA, 2004. PoD determined using average of 6 best fitting models (P-value >0.9)	0.018	0.021	
Cal-EPA	Citing geometric mean from Bell et al., 1978 (unpublished); Henschler et al., 1980; Fakuda et al., 1983; Maltoni et al., 1986. Inhalation studies 95% UCL q <sub>i</sub> * range 0.006-0.098 (mg/kg-day) <sup>-1</sup>	0.007*		
Lewandowski and Rhomberg, 2005	Using Anttila et al., (1995) inhalation, dermal cohort study. Liver cancer endpoint used to derive slope factor (quantitative estimate derived by EPA NCEA, 2001 section 4.5.1.1 liver cancer response)			0.0032
Health Canada (1996)	Slope factor calculated using 5,000 safety factor for TC <sub>05</sub> value of 82 mg/m <sup>3</sup> after Health Canada (1996) citing safety factor that represents 0.00001 risk and backcalculating SF using standard risk assessment methods.			0.004
RIVM, Netherlands (Baars, et al, 2001 as cited in Dourson et al., 2004)	RIVM classified TCE as a threshold compound, derived a TDI (RFD) protective of cancer. A comparable slope factor was derived using the TDI as a risk based conc and working backwards through standard risk assessment equations			0.0033
USEPA Office of Air Programs (USEPA OAQPS, 2005)	After Cal-EPA using hierarchy listed at Office of Air Planning and Standards 2005			0.007
US EPA, 1985	Using NCI (1976) and NTP (1988) Mouse gavage studies extrapolated to inhalation dose	0.0046**		
US EPA, 1987	Using Maltoni et al (1986) and Fudaka et al (1983)	0.006		
WHO, 2000	Using Leydig Cell Tumors, Rat;			0.002

	Maltoni et al., 1986.			
New, York (Ontario, 2005)	Emission Standard not necessarily used for an ambient air standard, Massachusetts similar SF (Ontario, 2005)			0.008

\* Geometric mean calculated from unit risks derived from four studies (CAL-EPA, 2005)

\*\* Calculated from the oral slope factor (oral slope derived using a geometric mean) using dose conversion (EPA, 1985)

The geometric mean of  $0.018 \text{ (mg/kg-day)}^{-1}$  is slightly below the bottom of the NCEA (2001)  $0.02\text{-}0.4 \text{ (mg/kg-day)}^{-1}$  range. It compares well with the value used by the Office of Air Quality Planning and Standards at  $0.007 \text{ (mg/kg-day)}^{-1}$  (USEPA OAQPS, 2005). It also is well supported by a human study Henschler *et al.* (1995), from which Cal-EPA (1999) derived a slope factor of  $0.019 \text{ (mg/kg-day)}^{-1}$ , and NCEA (2001) derived a slope factor of  $0.018 \text{ (mg/kg-day)}^{-1}$ .

### Early Life Exposure and Other Considerations

OLQ has investigated disproportionate response in children and will agree with the Science Advisory Board's recommendation (2002) that some adjustment should be made to account for an increased TCE response in children. The SAB (2002) states in Section 11.2.1 "Based on the TCE database, children appear to be at greater risk than adults from TCE, due to possible differences in exposure, metabolism, and clearance" and "... the panel raises concerns about childhood leukemia and lymphomas associated with drinking water contamination (New Jersey Drinking Water Study). It should be noted that this is the only data set used by EPA to address children's cancer risk differently from adults. Thus, if EPA were to decide not to include that study in its determination of cancer risk, then an adjustment of the cancer slope factor would be needed to address the children's risk issue." The SAB (2002, Section 11.2.2) states that it is generally accepted knowledge that children are at greater risk than adults from TCE. There is literature support for this conclusion with instances of high cancer response rates in children with potential solvent exposure (Lagakos *et al.*, 1986; Stienmaus *et al.*, 2004). Costas *et al.* (2002) presents support for a chemical agents' potential to affect fetal growth, and evaluates exposure to contaminated wells in Woburn, Massachusetts, citing an increased risk of childhood leukemia in children whose mothers consumed solvent (including TCE) contaminated well water.

Given the recommendation of the SAB (2002) attempts were made to quantitatively estimate the degree of increased response. An approach was taken using the EPA "Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens" (2005b) which uses slope factor weighting corresponding to differing age groups in early life exposure.

If TCE were to be classified as a mutagen, then early life exposure could be treated exactly as outlined by EPA (2005b) where: the slope factor is adjusted by a factor of 10 from 0-2 years of age, a factor of 3 for 2-16 years of age and a factor of 1 for ages greater than 16 years. A simple comparison of the magnitude of the cumulative calculated risk for the age periods of 0-2, 2-16 and 16-30 years, using EPA (2005b) recommended slope

factor adjustments and standard risk equations, can be made to the standard risk using the Indiana RISC (2001) default closure level equations for 0-30 years exposure with an unadjusted slope factor. In other words, the total risk from the combined early life slope adjusted equations could be compared with the risk from the unadjusted 0-30 equation and the relative magnitude of the risk estimates determined. The magnitude of the difference is an indicator of the overall increased potency estimate that results from childhood adjustments to the slope factor. Although the magnitude of the risk for the air, soil and water adjustments differ somewhat, the risk from early life adjusted exposure calculations are all somewhere between 2.8 and 5.2 times greater than the unadjusted equations. At issue is whether or not TCE is a mutagen. Moore and Brock (2000) consider it unlikely TCE is a mutagen, Cal-EPA (1999) and NCEA (2001) indicate its genotoxicity cannot be ruled out while the WHO (2000) states it is genotoxic. RIVM considers TCE to be mutagenic, but that the available mutagenicity data suggest a threshold response (Baars, et al., 2001). OLQ will take the position that a genotoxic mechanism of action cannot be ruled out and allow for possible mutagenicity.

The 2.8-5.2 slope factor adjusted range compares well with a range derived from an analysis of the Cohn *et al.* (1994) study where a disproportionate response was seen in children. While Cohn *et al.* (1994) has been assessed as inappropriate for use as a single best estimator of a slope factor, it has clearly been established as an indicator of disproportionate response (SAB, 2002). In the Cohn *et al.* (1994) study, for females age 0-20 the rate ratio or the relative risk (RR) for Acute Lymphocytic Leukemia (ALL) was 3.26, while that for all leukemia in females was 1.43. Following the general approach given by NCEA (2001) OLQ contracted with E & E to derive slope factors for comparison. Two sets of slope factors were derived using appropriate weight and intake factors, after NCEA (2001). Each set of slope factors was used to determine the magnitude of difference in overall cancer response between child and adult. The first set was for ALL in females 0-20 years of age compared to ALL in all females, and the second, ALL in females 0-20 years of age compared to all leukemia in females. The ratios of the RR were 5.3 and 1.3 respectively. These results agree well with the range derived using the EPA (2005b) early life procedure of 5.2 to 2.8.

While there is no direct comparison implied or stated with these two dissimilar methods, and considerable extrapolation must be assumed to compare these two approaches, the results of the Cohn *et al.* (1994) study may give some broad indication of greater sensitivity of young children to the carcinogenic effects of solvents. It should be noted that the reservations about using the Cohn *et al.* (1994) study to develop quantitative estimates of the carcinogenic potency of TCE focus mainly on the uncertainties about the degree of exposure (TCE dose) received by the members and whether the entire carcinogenic response should be attributed to TCE (in lieu of co-exposure to other chemicals). The relative risks for the cancers investigated are not in question.

As there is little guidance on how to adjust slope factors for disproportionate response in early life exposure, and a disproportionate response is indicated (SAB, 2002), OLQ will use the low end of 2.8- 5.2 OLQ derived range using EPA (2005b) guidance, rounded to 3, to adjust the human equivalent slope factors derived from the NCI 1976 and NTP 1990 mouse studies. It should be noted that many animal studies commence after the animals

have reached sexual maturity, therefore the results of these studies generally do not reflect any exposure during early life stages.

The human equivalent slope factors TERA (2005) derived from the NCI (1976) and the NTP (1990) studies will be used without adjustment for adult only (worker) exposure scenarios in which exposure of children is not expected. For residential and other exposure scenarios involving the general population, which include children, the slope factors derived from the NCI and NTP mouse studies will be multiplied by the childhood adjustment factor of 3. This approach creates an adult only exposure slope factor and a child inclusive slope factor.

Adult only exposures are limited to “commercial or non-residential” applications while child exposures are common to recreational or residential exposures. OLQ is proposing the following slope factors be used for residential and commercial applications.

**Table 4**  
**Residential and Industrial Slope Factors**

Land Use	Oral Slope Factor (mg/kg-day) <sup>-1</sup>	Inhalations slope factor (mg/kg-day) <sup>-1</sup>
Residential	0.10	0.054
Industrial	0.034	0.018

It is worth noting that if a slope factor was derived from the Cohn study using an exposure estimate based on the total potential household exposure from TCE in drinking water, as was done by Cal-EPA (1999) in deriving its Public Health Goal for TCE in drinking water, rather than drinking water ingestion only, the human population based slope factor would approximate a value of 0.1 (mg/kg-day)<sup>-1</sup>, the proposed OLQ value obtained from the NCI and NTP studies after application of the childhood adjustment factor (i.e., exposure to the TCE in 7.1 rather than 2.0 liters of water per day and a slope factor of 0.368 mg/kg-day<sup>-1</sup> rounded to 0.4, would be  $0.4 * 2.0 / 7.1 = 0.1$ ).

**Sensitive Subpopulations and Cumulative exposure**

The NCEA (2001) document raises issues about selecting a more conservative slope factor based on sensitive subpopulations, co-contaminant exposure and/or cumulative risk. The NCEA approach uses risk factors such as diabetes, alcohol consumption or co-exposure to other chemicals in conjunction with TCE or its metabolites as reasons for selecting a higher slope factor (NCEA, 2001; section 4.5.6.4). This raises questions regarding how these parameters should be addressed in selection of a single slope factor.

As discussed, the SAB (2002) took a clear position on the approach used by NCEA (2001) indicating that different slope factors should not be applied to different characteristics of the exposed population. Until there is clear guidance that these issues are relevant to the selection of a slope factor OLQ will not adjust or select a slope factor based on specific considerations of these criteria.

It is clear from the NCEA document and EPA (1997) in general, including the SAB (2002) that risk assessment is evolving from a focus on one toxic effect of one pollutant in one environmental media toward integrated assessments covering multiple effects in multiple media, including the cumulative effects of multiple pollutants in multiple media. OLQ believes there is merit to a broader consideration of the data and issues. While OLQ agrees that cumulative exposure to additional contaminants may increase the toxic response it makes little sense to assume this phenomena is limited to TCE. OLQ addressed, in general, the issue of increased response from co-contaminant exposure when the RISC document was released in 2001.

OLQ believes that cumulative issues were also addressed when the original 2001 RISC document was released. Unless adequate evidence can be supplied that indicates TCE is different in regard to cumulative exposure, no adjustment of the slope factor will be made above that considered when RISC was released in 2001.

### **Summary and Conclusions**

OLQ has investigated the significant issues surrounding the application of a range of slope factors provided by NCEA (2001). Because clear guidance on how to apply the range is not presented in the NCEA (2001) document, a single slope factor for each of the inhalation and ingestion routes has been derived for use in calculating screening level values. OLQ supports the use of the NCEA (2001) range as an appropriate data set from which to select a single point estimate for the slope factor.

The approach OLQ has taken attempts to limit excess conservatism, while utilizing the current science understanding of TCE. The oral and inhalation slope factors for use in screening level tables for commercial or non-residential sites have been derived at  $0.034 \text{ (mg/kg-day)}^{-1}$  and  $0.018 \text{ (mg/kg-day)}^{-1}$ , respectively. These slope factors compare well with recently developed slope factors from many different countries and/or regulatory agencies. The studies used to derive the slope factors have also been widely used in a similar manner, deriving similar values.

There is sufficient evidence to support an adjustment to the commercial slope factors to account for a disproportionate response in children in a residential exposure setting. Human studies have indicated the potential for a disproportionate child response. Comparison of an EPA procedure for disproportionate response in children from mutagens to the standard risk assessment approaches used by OLQ indicates (for mutagens) the difference is between 2.8 and 5.2. While the science community has mixed opinion on the mutagenicity of TCE, the EPA Science Advisory Board has indicated the need to consider disproportionate response in children when selecting slope factors.

Based on these results an adjustment using a factor of “3” was made to the commercial slope factors and should be applied where children are typically exposed, such as in residential exposure. Using this adjustment, the residential/recreational oral and inhalation slope factors are  $0.1 \text{ (mg/kg-day)}^{-1}$  and  $0.054 \text{ (mg/kg-day)}^{-1}$  respectively. No other adjustments or changes were deemed necessary.

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# **Human Trichloroethylene Cancer Slope Factor Estimation**

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September 30, 2005

## **Introduction**

Until recently, the state of the science for modeling the kinetics of TCE was two PBPK models which resulted in significantly different cancer slope factors. The PBPK models for TCE were recently harmonized in an effort organized by *TERA* and jointly supported by the EPA and DoD (USAF-EPA, 2004). Bayesian analysis was performed to recalibrate the harmonized model, resulting in updated posterior parameter distributions based on a more complete database of kinetic information for mice and humans.

The harmonized model was used to compute updated cancer slope factor estimates based on the NCI (1976) and NTP (1990) bioassays of mouse liver tumors. The mouse PBPK model was used to estimate the internal dose metric, the area under the trichloroacetic acid concentration in liver curve (TCA AUC), corresponding to the doses administered in the bioassays. Then benchmark dose-response modeling was conducted to estimate a lower bound on the effective dose for a 10% extra risk of liver carcinogenesis ( $LED_{10}$ ). Next, the human PBPK model was run to estimate the inhaled concentration and orally ingested dose of TCE corresponding to the  $LED_{10}$ . Finally, the human cancer slope factor was calculated using linear extrapolation from the risk at the  $LED_{10}$  to 0. This slope factor estimate represents the most current, state of the science estimate of the risk of liver carcinogenesis in humans from TCE exposure.

## **The Data**

### National Cancer Institute Bioassay (1976)

The National Cancer Institute (NCI) conducted a bioassay using 50 B6C3F1 mice of each sex per group at 2 doses, with 20 of each sex as matched controls (NCI, 1976). The mice were exposed by oral gavage 5 consecutive days per week for 78 weeks, and sacrificed at 90 weeks.

Dosing began at approximately 6 weeks of age. The initial doses were 1000 and 2000 mg/kg for male mice and 700 and 1040 mg/kg for female mice. There were no apparent signs of toxicity, so the doses were increased so that the time weighted average (TWA) doses were 1169 and 2339 mg/kg for male mice and 869 and 1739 for female mice. Male mice were treated with 1000 and 2000 mg/kg for 12 weeks, then the dose was changed to 1200 and 2400 mg/kg for the remaining 66 weeks. Female mice were dosed at 700 and 1400 mg/kg for 12 weeks, then at 900 and 1800 mg/kg for the remaining 66 weeks.

The average body weight of the mice in each dose group was reported every week for the first 10 weeks, and every fourth week thereafter. The reported body weights were used to compute TWA body weights for the mice. For both sexes in all dose and control groups, the TWA body weight was much less than the default values of 37.3 g for male B6C3F1 mice and 35.3 g for female B6C3F1 mice in chronic studies (EPA, 1988). The TWA body weight for male mice is 32 g for both dose groups. The TWA body weight for female mice is 26 and 25 g in the low and high dose groups, respectively.

### National Toxicology Program Bioassay (1990)

The National Toxicology Program (NTP) conducted a bioassay where groups of 50 B6C3F1 mice of each sex were administered 1000 mg/kg TCE via oral gavage (NTP, 1990). The dose was given 5 days per week for 103 weeks. The mice were 8 weeks old when dosing began, and were sacrificed at 112 to 115 weeks of age.

The average body weight of the mice was reported at weeks 0, 1, 20, 39, 60, 80, and 99. The reported body weights were used to compute TWA body weights for the mice. For both sexes in the dosed groups, the TWA body weight was very similar to the default values of 37.3 g for male B6C3F1 mice and 35.3 g for female B6C3F1 mice in chronic studies. The TWA body weights were 37.3 and 32.6 g for male and female mice, respectively.

## **Mouse PBPK Model Simulations**

The harmonized PBPK model used best estimates for parameter values, the expected values of posterior distributions of the population means. Equations were added to compute the TCA AUC. The dosing schedule was simulated as 5 consecutive doses given 24 hours apart, followed by two 24-hour periods of no dosing before the cycle was started again. The model was run until periodicity was achieved (i.e., the daily peak and minimum TCA concentrations in the liver did not change from week to week).

The effect of modeling the dose as the lifetime average daily dose (LADD) reported by Rhomberg (2000) was also investigated. Using the LADD, the daily TCA AUC was somewhat larger than that obtained using the discrete, 5-day on, 2-day off dosing schedule. This is likely due to saturation of the oxidative pathway leading to TCA production at the high peaks resulting from the gavage doses, allowing more TCE to be metabolized via the glutathione pathway, which does not produce TCA. A greater fraction of the lower-level, constant input at the LADD can be metabolized via the oxidative pathway, leading to a higher TCA AUC. Therefore, for cancer slope factor calculations, the LADD was not used.

## **Dose-Response and Testing for Differences in Tumor Response Between the NCI and NTP Studies**

Multiple regression was used to test for differences in the dose-response between the NCI and NTP studies. The regression was performed separately for male and female mice. A Probit model was used to regress the tumor response on the internal dose, stratified by study (coded as 0 for the NCI study and 1 for the NTP study). The stratified model was fit to the data, and the study coefficients were used to determine whether there is a difference between the studies by testing whether the coefficients were significantly different from 0. The stratified multiple regression is useful for performing a simple meta-analysis of the two studies. It allows the studies to borrow some power from each other that would not be available if the studies were analyzed alone. Furthermore, a probit model would have as many model parameters as there are observations in the NTP study, if the NTP data were modeled alone, leaving no degrees of freedom for the calculation of goodness of fit p-values for model evaluation.

The studies were also modeled separately using the EPA's BMDS software for the NCI study, and a custom calculation for the NTP study. A custom calculation was used for the NTP study because there were only 2 dose groups and a simple linear fit was desired, but BMDS does not include a linear dichotomous model. The linear dose-response model was programmed in Excel by *TERA*.

## Human PBPK Model Simulations

The harmonized human TCE PBPK model was run to estimate the administered oral dose or inhalation concentration corresponding the LED<sub>10</sub> computed using the mouse liver tumor data. The best estimates for parameter values were used, which were the expected values of posterior distributions of the population means. The inhalation scenario was modeled as continuous inhalation of a constant concentration of TCE in ppm. The oral exposure scenario was modeled as a constant oral ingestion rate of TCE in mg TCE per kg body weight per day. The harmonized model facilitates easy conversion of a discontinuous mouse dosing pattern to the expected pattern of exposure in humans, as shown here.

## Results

Table 1 shows the TCA AUC dose metrics corresponding to the bioassay gavage doses computed using the harmonized mouse PBPK model. The estimated internal doses are very similar for both sexes, and do not explain the apparent increased sensitivity of the male mice. These data were used as input to the tests for differences between studies and benchmark dose modeling.

Table 1  
Internal Dose Metrics, TCA AUC from Mouse Studies

Study	Sex	Gavage dose mg/kg/day	Internal dose mg*day/L	Malignant tumors
NCI	Male	0	0	1/20
		1169	1190	26/50
		2339	1420	31/48
	Female	0	0	0/20
		869	1070	4/50
		1739	1300	11/47
NTP	Male	0	0	8/48
		1000	1160	31/50
	Female	0	0	2/48
		1000	1140	13/49

The multiple regression did not reveal a statistically significant difference in the intercept or slope of the dose-response curve between the two studies of male mice (P-value > 0.14). However, inspection of the graph of the data suggests that the responses are different between the two studies. This difference was likely not detected due to a small sample size and limited statistical power, and so study-specific modeling of the tumor data was performed. A statistically significant difference was found for the responses of

the female mice, and study-specific modeling of the female mouse data was performed as well.

The results of the study-specific modeling performed using BMDS and the linear regression are summarized in Tables 2 through 4. Several of the models provide very good fits to the NCI data (P-value  $\geq 0.90$ ). However, inspection of figure 1 shows that there are no data points near the estimated ED<sub>10</sub> for the male mice, leading to a wide range of values for the LED<sub>10</sub>, as shown in Table 2. The LED<sub>10</sub>s range from 133 to 413 mg-hr/L for the best-fitting models, with an average LED<sub>10</sub> of 293 mg-hr/L. The results for the female mice in Table 3 are much more consistent, with an average of 842 mg-hr/L for the best-fitting models, and figure 2 shows that the ED<sub>10</sub> is estimated near the middle data point.

A linear model was used to model the NTP data. P-values could not be computed for the model of the NTP data because there are two model parameters (i.e., slope and intercept) and only two dose groups. The figures of the linear model fits are shown in figures 3 and 4. The maximum likelihood estimate (MLE) and upper bound (UB) lines cross because the dose that results in a 10% extra risk is minimized, which is not the same as finding the upper bound for the regression line. The smallest dose that gives 10% extra risk (subject to the 95% confidence restraints) is consistent with an intercept that is smaller than the MLE estimate, and a slope that is larger. This is because the 10% extra risk target changes when the intercept changes, accounting for the background response. The full output of the BMDS modeling is presented in Appendices 1 and 2. Additional output from the linear modeling of the NTP data are presented in Appendices 3 and 4.

Table 2  
Dose-response Modeling of the NCI Data for Male Mice Using BMDS

<b>Model</b>	<b>P-value</b>	<b>AIC</b>	<b>Residual</b>	<b>ED<sub>10</sub></b> <b>mg-hr/L</b>	<b>LED<sub>10</sub></b> <b>mg-hr/L</b>
Probit	0.99	144	0.008984	410	300
Multistage 2	0.96	144	-0.011	470	130
Quantal Quadratic	0.96	144	-0.03738	470	410
Logistic	0.90	144	0.08838	460	320
Multistage 1	0.51	144	-0.134	170	130
Quantal Linear	0.51	144	-0.4704	170	130
Gamma	NA	146	5.90E-05	550	130
Log-Logistic	NA	146	1.52E-13	590	82
Log-probit	NA	146	5.34E-13	610	250
Weibull	NA	146	-1.20E-06	490	130
<b>Average*</b>				<b>450</b>	<b>290</b>

\* The average is computed over the 4 best-fitting models (P-value  $\geq 0.90$ )

Table 3  
Dose-response Modeling of the NCI Data for Male Mice Using BMDS

Model	P-value	AIC	Residual	ED <sub>10</sub>	LED <sub>10</sub>
				mg-hr/L	mg-hr/L
Gamma	1.00	83	-4.94E-06	1100	800
Log-Logistic	1.00	83	8.24E-13	1100	800
Log-probit	1.00	83	1.04E-13	1100	820
Weibull	1.00	83	5.40E-05	1100	790
Probit	0.99	83	0.000344	1100	900
Logistic	0.94	83	0.01407	1100	930
Multistage 3	0.60	82	-0.349	1000	600
Multistage 2	0.40	83	-0.434	940	540
Quantal Quadratic	0.40	83	-1.027	940	770
Multistage 1	0.23	84	-0.507	740	500
Quantal Linear	0.23	84	-1.251	740	500
Average*				<b>1100</b>	<b>840</b>

\* The average is computed over the 6 best-fitting models (P-value  $\geq$  0.90)

Table 4

Linear Dose-response Model for Mouse Liver Tumors in the NTP Bioassay

	Male	Female
P-value	NA	NA
ED <sub>10</sub> (mg-hr/L)	210	740
LED <sub>10</sub> (mg-hr/L)	170	410

### Harmonized Human PBPK Model Simulations

Tables 5 shows the air concentrations, ingestion rates, and slope factors corresponding to the LED<sub>10</sub>s from the mouse studies. The slope factors are significantly lower (i.e., less conservative) when computed based on the female mice, as expected from the lesser sensitivity of the female as compared with male mouse. This is possibly due to toxicodynamic differences between the sexes.

Table 5

Human Equivalent Concentration/Ingestion Rate and Slope

Sex	Study	LED <sub>10</sub> (mg-hr/L)	Inhalation (ppm)	Oral Ingestion (mg/kg/day)	Inhalation Slope (ppm) <sup>-1</sup>	Oral Slope (mg/kg/day) <sup>-1</sup>
Male	NCI	290	3.0	2.4	0.033	0.042
	NTP	170	1.7	1.4	0.059	0.071
Female	NCI	840	8.6	6.9	0.012	0.014
	NTP	410	4.1	3.3	0.024	0.030

### Additional Results from the Stratified Regression

In addition to testing for differences between the two studies, the stratified regression can also be used to conduct a simple meta-analysis and estimate ED<sub>10</sub>s and LED<sub>10</sub>s for the two studies. This approach has advantages over modeling the different studies alone, particularly for the NTP study with only 2 dose groups, in that it allows the studies to borrow power from each other. Table 6 and figures 5 and 6 shows the results of the multiple regression models. The male mice appear to be about 3 times as sensitive as the female mice. The ED<sub>10</sub> and LED<sub>10</sub> values computed for the NCI study are similar to those developed by Rhomberg using the Clewell et al. (2000) TCE model. However, the results of the NTP study are substantially higher than those computed by Rhomberg using the Clewell et al. (2000) TCE model. This is likely due to the differences in dose-response modeling approaches used. Rhomberg used a time-to-tumor model that takes advantage of the time of death as well as the dosing information. This approach may be more appropriate than the summary dose group data approach employed for this project.

Statistical analysis of the stratified regression coefficients did not reject the hypothesis that the dose-response in the two studies were the same. Thus, in addition to the separate study-specific and stratified modeling approaches, the male mouse data were also pooled for LED<sub>10</sub> estimation. The results of the pooled modeling are shown in Table 7. As expected, the ED<sub>10</sub> and LED<sub>10</sub> of the pooled data analysis falls between the results for the NCI and NTP studies shown in Table 6. Although this approach is supported by the statistical tests of the regression coefficients, any difference was likely not detected due to a small sample size and limited statistical power, and so the study-specific or stratified modeling of the tumor data is preferred over the pooled modeling.

Table 6  
Stratified Regression Modeling of Mouse Liver Tumors

Study	Gender	ED10 mg-hr/L	LED10 mg-hr/L	Goodness of Fit P-value
NCI	Male	410	300	0.99
	Female	1100	900	0.99
NTP	Male	270	210	0.99
	Female	820	540	0.99

Table 7  
Regression Modeling of Pooled Male Mouse Liver Tumor Data

P-value	ED10 mg-hr/L	LED10 mg-hr/L
0.34	310	270

Slope factors may also be computed from the stratified and pooled regression results, as shown in Table 8. The results are similar for all modeling approaches, with the results of the stratified and pooled regression yielding slightly smaller slope factors.

Table 8  
Human Equivalent Concentration/Ingestion Rate and Slope Factor Based on Stratified Regression Models

Sex	Study	LED <sub>10</sub> (mg-hr/L)	Inhalation (ppm)	Oral Ingestion (mg/kg/day)	Inhalation Slope (ppm) <sup>-1</sup>	Oral Slope (mg/kg/day) <sup>-1</sup>
Male	NCI	300	3	2.4	0.033	0.042
	NTP	210	2.1	1.7	0.048	0.059
	Pooled	270	2.7	2.2	0.037	0.045
Female	NCI	900	9.2	7.4	0.011	0.014
	NTP	540	5.5	4.4	0.018	0.023

## Discussion

The slope factors computed in this report are based on the state of the science PBPK model for performing animal to human dosimetry adjustments. The harmonized PBPK model was developed through multiple partner collaboration with authors of earlier TCE PBPK models, and Bayesian analysis was conducted using several mouse and human data sets, resulting a comprehensive characterization of parameter distributions.

Benchmark dose-response modeling was conducted following EPA practice where possible (i.e., analysis of the NCI data set), but custom approaches were developed to utilize data not amenable to modeling with BMDS. The NTP bioassay was conducted using only 2 dose groups, and this is not enough data to properly model using BMDS. Two approaches were used to incorporate the information in the NTP study. First, since only 2 data points were available, a simple, straight-line model that is not available in BMDS was fit to the tumor response data. This approach is conservative because it does not have the S-shaped curve characteristic of the dichotomous BMDS models. Secondly, a stratified regression approach was used to analyze the data from both studies simultaneously. This simple meta-analysis approach allows the studies to borrow information from each other, increasing the statistical power and performance of the dose-response curve-fitting for the individual studies. A probit model was used for the stratified regression, and other models (e.g., logistic, multistage, or Weibull) should also be used and model dependency evaluated.

A third way to enhance the dose-response modeling is to use time-to-tumor modeling as in Rhomberg (2000). Time-to-tumor models take advantage of the time of death as well as the dosing information. This approach may be more appropriate to the summary dose group data approach employed for this report. Time-to-tumor modeling was not

conducted in this analysis due to time and budget constraints, but is highly recommended to enhance the assessment.

The PBPK modeling was conducted using the means of the posterior parameter distributions. This represents the best estimate of the kinetics in mice and humans, but a probabilistic approach to the PBPK modeling could be taken utilizing the posterior parameter distributions to examine the uncertainty and variability associated with the dose metric estimates. This analysis requires considerable additional effort, and it was not conducted for this report. However, such an investigation would be very valuable in understanding the level of confidence in the slope factor estimate.

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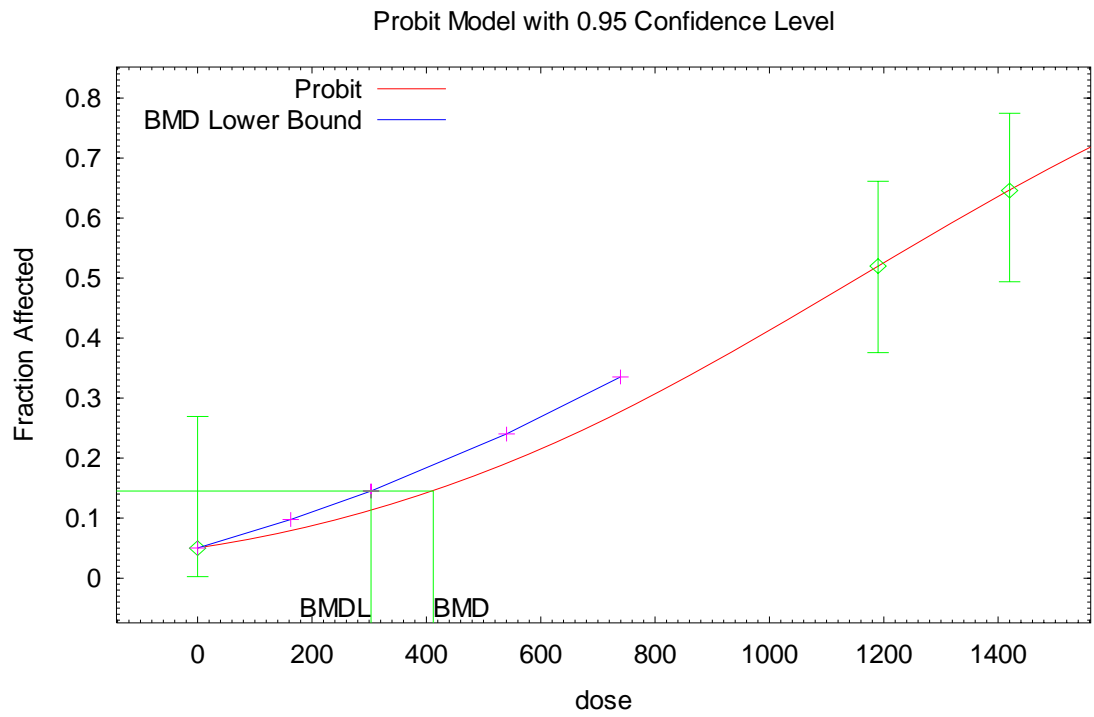
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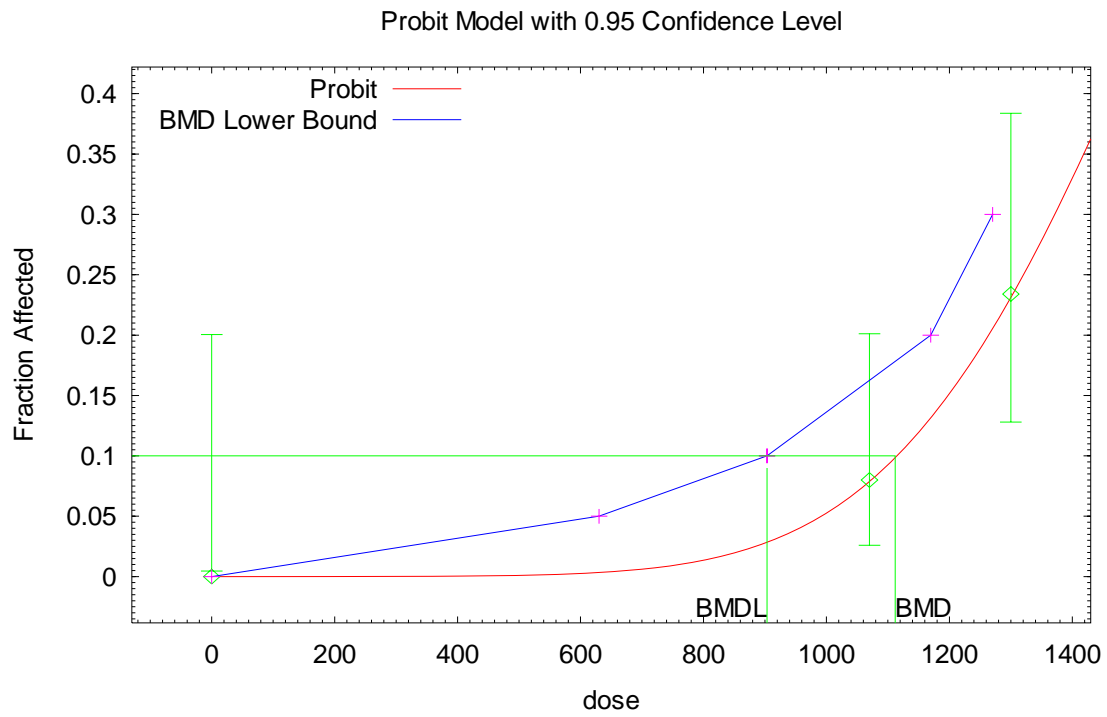
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Figure 1  
BMD5 Probit Model for Liver Tumors in Male Mice from the NCI Bioassay



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Figure 2  
BMD5 Probit Model for Liver Tumors in Male Mice from the NCI Bioassay



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Figure 3  
Linear Model for Liver Tumors in Male Mice from the NTP Bioassay

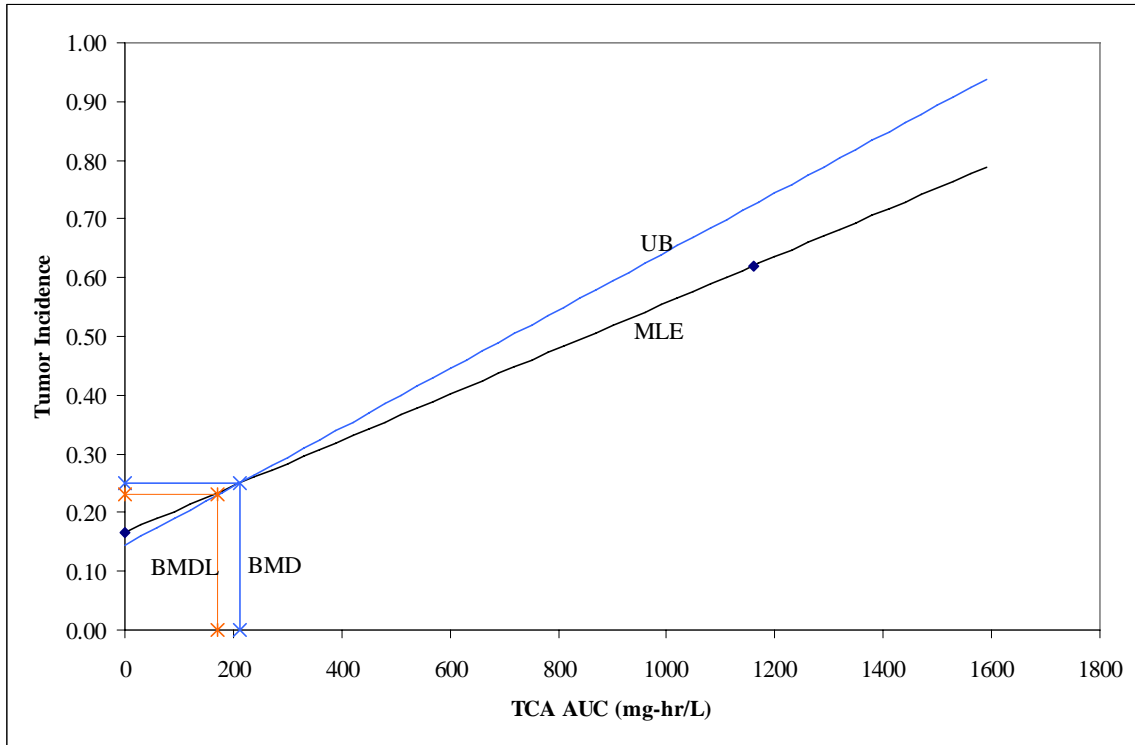


Figure 4  
Linear Model for Liver Tumors in Male Mice from the NTP Bioassay

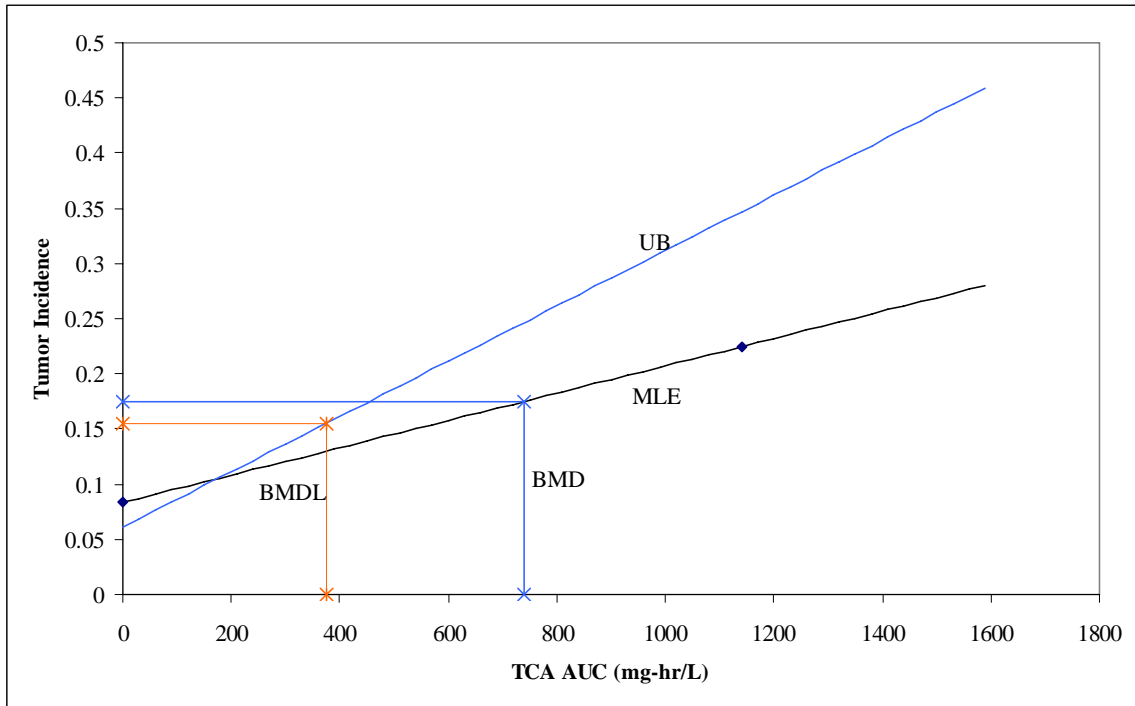


Figure 5  
Stratified Dose-response Model for Liver Tumors in Male Mice

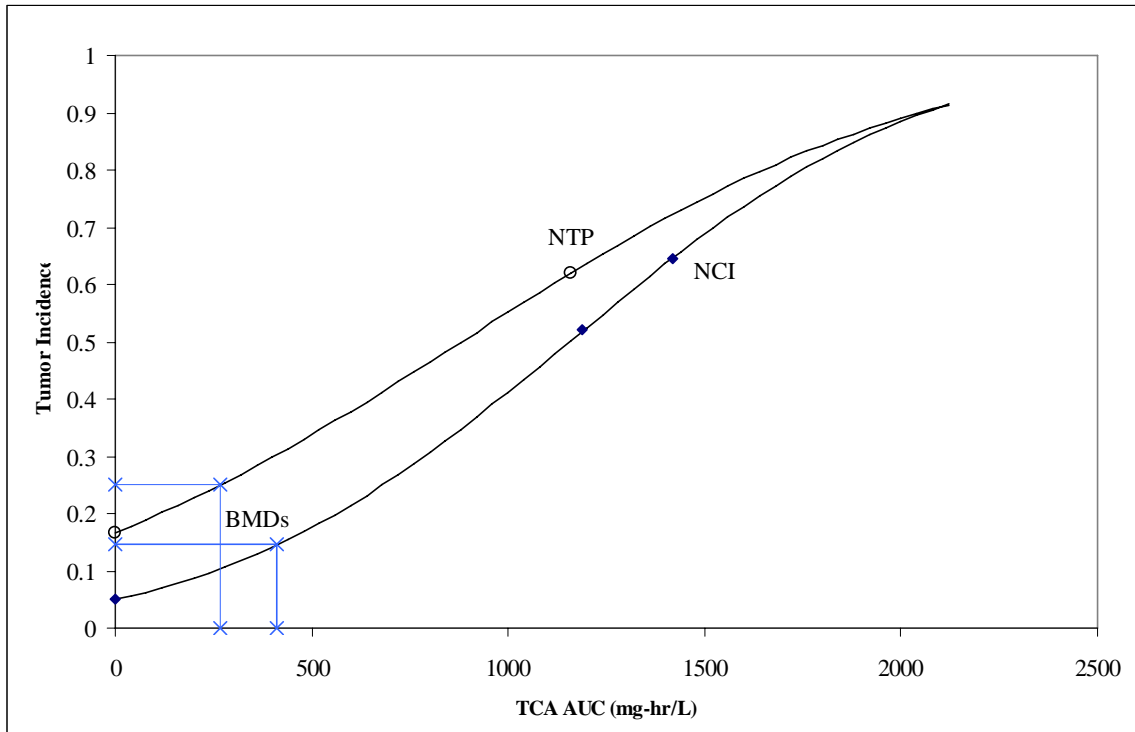


Figure 6  
Stratified Dose-response Model for Liver Tumors in Female Mice

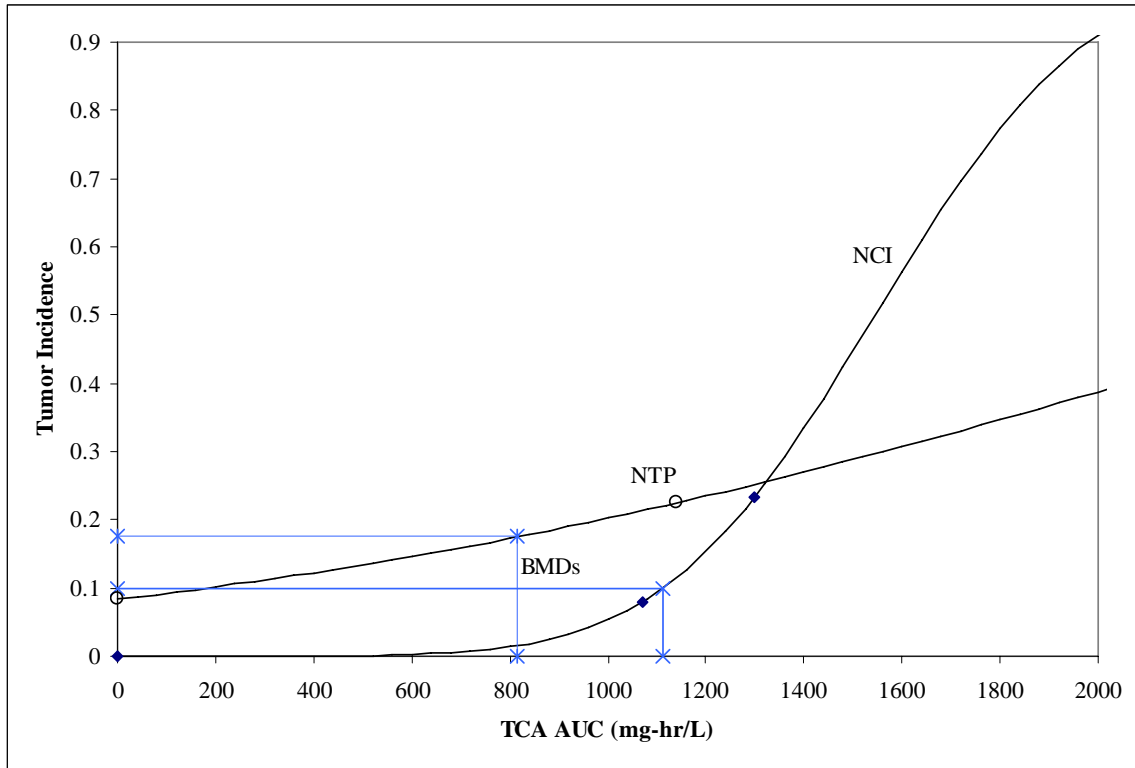
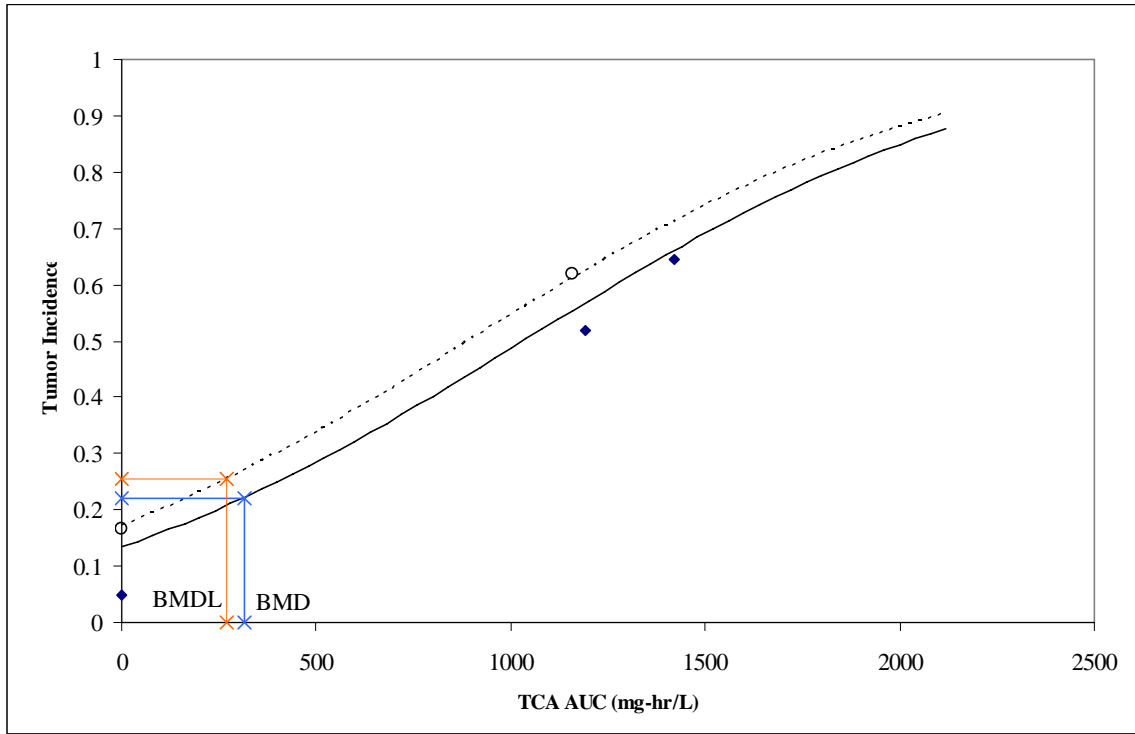


Figure 7  
Pooled Dose-response Model for Liver Tumors in Male Mice



## Report from E & E Regarding Methodology Used to Combine Data Sets Completed by Carl Stineman for IDEM November 2005

### Combining Data Sets

When multiple studies or data sets are available that are suitable for deriving quantitative dose-response estimates, USEPA's final Guidelines for Carcinogen Risk Assessment (USEPA 2005) recommends that all data sets be considered and that data sets that are comparable and compatible be combined as circumstances permit. Combining information from multiple studies increases the confidence and decreases the uncertainty of the final dose response estimate. Meta-analysis is suggested for combining multiple human epidemiological studies and a variety of techniques are suggested for combining dose response extrapolations from animal studies. One option, if the data sets are biologically and statistically compatible, is to combine the datasets in a joint analysis. Another is to combine responses that operate through a common mode of action.

IDEM has determined that the animal studies most appropriate for use in deriving slope factors for TCE are the 1976 NCI (NCI 1976) and the 1990 NTP (NTP 1990) studies of the carcinogenicity of TCE in mice. The carcinogenicity of TCE was evaluated, and positive results were obtained, in both sexes of mice in each of these studies. It was further determined that the best way to extrapolate the mouse bioassay results to cancer slope factors for humans was through the use of PBPK modeling. IDEM contracted with TERA to perform the modeling and derive human equivalent slope factors based on these mouse studies. The modeling and the results obtained are described in a TERA report entitled Human Trichloroethylene Cancer Slope Factor Estimation (TERA 2005).

TERA examined the four datasets available (2 sexes by 2 studies) and determined that the dose-response patterns observed were sufficiently different from one another, based on a combination of statistical and graphical evaluations, that the datasets could not or should not be combined for derivation of a single slope factor in a joint analysis. Therefore TERA derived four separate slope factors independently from the four data sets available. IDEM then tasked E & E, Inc. to recommend the most appropriate method for combining these four independent slope factors into a single value that best represents the carcinogenic potency of TCE in humans.

The task comes down to determining the most appropriate mathematical method for combining the estimates. In the past, USEPA and other environmental regulatory agencies have combined multiple independent slope factors using either geometric (USEPA 1994 and CalEPA 1999) or harmonic (USEPA 2001 and Rhomberg 2000) means. The equation for the geometric mean is:

$$GM = \sqrt[n]{x_1 x_2 \dots x_n}$$

A geometric mean is generally appropriate if the values to be combined are lognormally distributed. The equation for the harmonic mean is:

$$\frac{1}{H_n} = \frac{1}{n} \sum \frac{1}{x_i}$$

A harmonic mean is generally appropriate when the values to be combined are rates. A common example of the use of a harmonic mean is for calculating the average speed for a trip consisting of multiple segments completed at different speeds.

TERA and others have determined that the most appropriate dose metric for estimating the dose-response relationship for the induction of liver tumors in mice by TCE is the area under the concentration/time curve (AUC) for trichloroacetic acid (TCA) in the liver. TCA is a metabolite of TCE believed to be one of the compounds responsible for its carcinogenic effect in the liver. Therefore the dose response relationship was initially estimated in terms of the internal dose of TCA to the liver (TCA AUC in the liver – mg\*day/L). The internal dose-response relationship was fitted using various models appropriate for the data sets using EPA’s Benchmark Dose Software (BMDS). The lower 95% confidence limits on the effective dose for 10% of the sample population – the LED<sub>10s</sub> were estimated in this way. This internal dose metric was then converted to external oral and inhalation doses to the mouse, and human equivalent doses using the harmonized PBPK models developed and implemented by TERA. Slope factors were calculated by linear extrapolation from the human equivalent LED<sub>10s</sub> to the origin.

The human equivalent external inhalation and oral doses derived from the PBPK model for the four data sets were tested for their goodness of fit to normal, lognormal and gamma distributions using the goodness of fit tests included in USEPA’s ProUCL software package. As shown in Table 1, the data adequately fit all of these distributions, probably because of the small number of data points. However the correlations obtained with the lognormal and gamma distributions are greater than with the normal distribution.

**Table 1 Goodness of Fit Test Results for the Human Equivalent External Inhalation and Oral LED<sub>10</sub> Doses**

Route / LED <sub>10</sub> Dose	Assumed Distribution	Correlation R	Goodness of Fit Test	Statistic	Critical value (p<0.05)	Data Fit Assumed Distribution?
Inhalation (ppm)	Normal	0.9754	Shapiro-Wilk	0.957	0.748	Yes
	Lognormal	0.9956	Shapiro-Wilk	0.997	0.748	Yes
	Gamma	0.996	Kolmogorov-Smirnov	0.172	0.396	Yes
Oral (mg/kg-day)	Normal	0.985	Shapiro-Wilk	0.975	0.748	Yes
	Lognormal	0.9922	Shapiro-Wilk	0.989	0.748	Yes
	Gamma	0.993	Kolmogorov-Smirnov	0.169	0.396	Yes

Since the data better fit a lognormal distribution, the geometric mean would appear to be an appropriate statistic to characterize the central tendency of the four dose response relationships.

Gold, et al (1989) advocate the use of the harmonic mean as a summary cancer potency statistic when more than one positive carcinogenicity study is available. The main argument in favor of using the harmonic mean as the summary statistic for the effective dose is that it is closer to the lowest effective dose estimate than the geometric or arithmetic means. Tables 2 and 3 compare the results obtained using the geometric and harmonic means of the LED<sub>10</sub> values as summary statistics. Table 2 is derived from Table 3-1 from the TERA report which provides the results of independent analyses of the 4 mouse data sets. The TERA report also provides, in Table 3-2, the LED<sub>10</sub> and SF results obtained using a stratified regression model analysis of the 4 data sets. Table 3 below provides the geometric and harmonic mean results for the stratified regression model analysis presented in Table 3-2 of the TERA report.

**Table 2 Geometric and Harmonic Mean estimates of LED<sub>10</sub>s and SFs from Table 3-1 of the TERA report – independent analyses.**

Sex	Study	Internal Dose LED <sub>10</sub> (mg-hr/L)	External Human Equiv LED <sub>10</sub> Inhalation (ppm)	External Human Equiv LED <sub>10</sub> Oral Ingestion (mg/kg-day)	Inhalation Slope Factor (ppm) <sup>-1</sup>	Oral Slope Factor (mg/kg day) <sup>-1</sup>
Male	NCI	290	3	2.4	0.033	0.042
	NTP	170	1.7	1.4	0.059	0.071
Female	NCI	840	8.6	6.9	0.012	0.014
	NTP	410	4.1	3.3	0.024	0.03
Summary Statistic						
Geometric Mean LED <sub>10</sub> / SF*		361	3.66	2.96	0.027	0.034
Harmonic Mean LED <sub>10</sub> / SF*		388	3.12	2.53	0.032	0.039

\* SF = 0.1/LED<sub>10</sub>

**Table 3 Geometric and Harmonic Mean estimates of LED<sub>10</sub>s and SFs from Table 3-2 of the TERA report – stratified regression model analyses.**

Sex	Study	Internal Dose LED <sub>10</sub> (mg-hr/L)	External Human Equiv LED <sub>10</sub> Inhalation (ppm)	External Human Equiv LED <sub>10</sub> Oral Ingestion (mg/kg-day)	Inhalation Slope Factor (ppm) <sup>-1</sup>	Oral Slope Factor (mg/kg day) <sup>-1</sup>
Male	NCI	300	3	2.4	0.033	0.042
	NTP	210	2.1	1.7	0.048	0.059
Female	NCI	900	9.2	7.4	0.011	0.014
	NTP	540	5.5	4.4	0.018	0.023
Summary Statistic						
Geometric Mean LED <sub>10</sub> / SF*		418	4.23	3.39	0.024	0.029
Harmonic Mean LED <sub>10</sub> / SF*		467	3.64	2.93	0.028	0.034

\* SF = 0.1/LED<sub>10</sub>

The slope factors derived using the geometric and harmonic means as summary statistics for the LED<sub>10</sub>s are within about 15% of one another, with the harmonic mean approach yielding slightly greater cancer potency estimates. Both approaches appear to yield valid and very similar summary cancer potency estimates thus either approach could be used to derive a consensus cancer potency estimate from the 4 mouse liver tumor bioassay results.

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