TCE Meeting Presentation Supporting Material for L. Sweeney
Paul Dugard
to:
Marc Rigas
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Please respond to Paul Dugard
Show Details

Please find attached material that L. Sweeney will use as the basis for her presentation on May 10. This material is similar to the comments filed as part of the Aerospace Industries Alliance comments submitted during public review of the IRIS draft. However, as noted, significant changes have been made.

Thank you.

Paul Dugard

Comments on EPA's Toxicological Review of Tricholoroethylene (CAS No. 79-01-6), (Public Draft, October 2009).

CORRECTED AND REVISED MAY 3, 2010 for the Science Advisory Board

Key corrections and additions:

(1) Addition of a section on the implications of deviations between group/individual parameter distributions and the population distribution for a given parameter (page 4).

(2) Correction of wording regarding the EPA analysis of Kim et al. (2009) mouse blood DCVG and expanded recommendations and discussion of the implications of the EPA analysis for toxicity reference value derivation (page 5).

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Toxicology Excellence for Risk Assessment

SUMMARY

The extensive use of complex modeling in the trichloroethylene (TCE) assessment presents a formidable challenge to scientific peer review. EPA should facilitate peer review by providing an analysis of the most influential assumptions (commonly referred to as a "sensitivity analysis"). Such an analysis would not have to be complex itself, or delay the review of the draft excessively. However, a sensitivity analysis is necessary to provide a sufficient review of this document.

Some key assumptions in the physiologically based pharmacokinetic (PBPK) and dose response modeling in the assessment provide an example of why such an analysis is needed. For example, the assumption of GSH conjugation rate differences between humans and rodents apparently has a several hundred fold effect on the derived values for the inhalation reference concentrations. This assumption appears to be only weakly supported by the weight of the evidence, and EPA's own statistical analysis of the related dose metrics also casts doubt on its validity. EPA should use other data in the literature to improve this parameter estimate; its own analyses indicate that the estimates of GSH-related dose metrics (and therefore, candidate RfCs and RfDs) in mice may change by ~3x if recently-published data are incorporated into the parameter estimations.

Other examples that show the value of a sensitivity analysis are presented. Please consider the value of providing such an analysis to the Scientific Advisory Board reviewers and provide them with the information they need to conduct a full and scientifically robust peer review of this document.

INTRODUCTION

TERA appreciates the opportunity to provide comments on the public draft of EPA's Toxicological Review of Trichloroethylene. The comments provided below focus on physiologically based pharmacokinetic (PBPK) modeling, its role in the Agency's assessment of TCE, and the uncertainty regarding the model. Clearly, the Agency has devoted a great deal of effort to developing and applying PBPK models in the TCE risk assessment. The use of Bayesian analysis to integrate a large number of kinetic studies of TCE and its key metabolites, conducted in three species, is a very impressive accomplishment. As the precedents for use of these approaches for PBPK model development and application in risk assessment are limited, it is important that key assumptions and criteria for use in the risk assessment be clearly articulated so that the scientific community can evaluate the modeling of TCE and how it was applied. To that end, we identify the need for sensitivity analyses to identify these key assumptions such that they may be subjected to proper scrutiny.

WHY IS SCRUTINY OF THE TCE PBPK MODEL IMPORTANT?

The use of PBPK model-derived estimates of GSH metabolism as a metric (rather than applied dose) for kidney toxicity had a 300- to 400-fold impact on the cRfC and RfD (p. 5-51), after taking into account dose-response and interspecies differences. The use of internal dose metrics is generally preferred over applied dose when the data are sufficient, support the choice of dose metric, and tie the dose metric to the endpoint of interest, because such internal dose metrics are more predictive of the observed toxicity. Although there is not necessarily an inherent problem with dose metrics that differ markedly from applied dose measures, such large differences call for greater scrutiny of the reasons for the differences, and increase the importance of the consideration of the implications of uncertainties. The use of GSH metabolism (calculated using the PBPK model) as the dose metric for the kidney resulted in kidney effects being identified as one of the key noncancer effects. Intuitively, the 300 to 400-fold difference in the calculated cRfC and cRfD must somehow be related to the values of the parameters in the PBPK model, most likely those pertaining to GSH metabolism, but it is not necessarily clear which parameters are the key drivers, and whether large interspecies differences in these parameters are supportable based on the available data.

CONSIDERATION OF CONFIDENCE AND UNCERTAINTIES IN THE CURRENT PBPK MODEL PARAMETER ESTIMATES

GSH conjugation pathway rate estimates

The extremely broad posterior distributions of the mouse GSH pathway parameters resulting from the Bayesian model optimization (e.g. 2.5% and 97.5% values of 0.11 and 3,700,000 mg/L, a range exceeding 7 orders of magnitude, for the Km for hepatic TCE GSH conjugation) (p. 3-93) indicate that the parameterization is highly uncertain. The extremely large differences in optimized, posterior estimates of Km for hepatic GSH conjugation in humans vs. rats or mice

(approximately 1000-fold difference, based on median values) are contrary to the understanding that similar enzymes are involved in TCE conjugation across species. Since no mouse or rat DCVG data were used for model calibration and the differences between rodent and human Kms for DCVG production seem implausible, we conclude that the parameterization of the GSH pathway is highly suspect.

Partition coefficients

Literature data do not generally support extensive interindividual variability in partition coefficients. For example, when the blood:air partition coefficient of 1,3-butadiene was measured in vitro for 24 human subjects, the values ranged from 1.22 to 1.84, with a mean ± standard deviation of 1.57 ± 0.14 (Lin et al., 2002). In contrast, in some cases the posterior distributions of partition coefficients developed in EPA's analyses of TCE and its metabolites cover very wide ranges (p. 3-90). For example, the posterior estimate of the free TCA body:blood partition coefficient in the rat had a median value of 0.77 with 2.5th percentile and 97.5 percentile estimates of 0.24 and 2.7, suggesting greater than 10-fold differences to cover 95% of the population. It is unlikely that this parameter is truly this variable, particularly in a standard rat colony, in light of the typically small variability in rats and in the more variable human population. If the posterior distributions of the partitioning parameters are allowed to be more variable than is realistic, it is likely that the optimization process shifted the variability away from other parameters (which could truly be more uncertain and/or variable) in order to create best-fit parameter distributions. As a result, these other parameters could appear more narrowly distributed than they would in the absence of high partition coefficient variability.

Oral Absorption Rates

The distributions for absorption parameters for corn oil and water gavage (p. 3-92) were highly variable--the ratio of the 97.5% and 2.5% values frequently exceeds 100,000-fold. A likely contributor was inappropriately lumping absorption rate from both corn oil and water into a single distribution, rather than separate distributions.

Uncertainty in Calculated Dose Metrics

The uncertainty in the parameter values produces uncertainty in the calculated dose metrics. Specifically, the EPA analyses considered DCVC bioactivation as a metric for rat kidney effects, while the analyses for mouse kidney effects relied on the dose metric of total GSH produced, due to lack of data on DCVG and DCVC in the mouse. The 95% confidence limits for the population median estimates of the fraction of intake that is conjugated with GSH cover a very large range of values, spanning over 3 orders of magnitude at concentrations and doses of toxicological interest in mice, and spanning about 1.5 orders of magnitude in rats. As noted by EPA, this range reflects only uncertainty, not variability. The DCVC bioactivation estimates in rats are highly uncertain, with the 95% confidence limits on the median spanning a range of 2 orders of magnitude. EPA acknowledges that the predictions related to GSH conjugation for rats

and mice “remain more uncertain” than the human predictions (p. 3-131), but then states that GSH metabolism dose metrics were fairly well-characterized in rats (p. 3-138, line 4.). This large uncertainty in the dose metric necessarily translates to uncertainty in the corresponding cRfC and cRfD.

The uncertainty of the estimate of “other” liver oxidation is also quite substantial (95% confidence limits approaching a 100-fold range). This uncertainty does not have a substantial impact on the risk assessment because this metric was not used to derive any reference values or slope factors.

DEVIATION BETWEEN POPULATION AND GROUP OR INDIVIDUAL POSTERIOR ESTIMATES OF PARAMETER VALUES

EPA provides summary tables containing statistical summaries of the posterior distributions of the approximately 60 sampled parameters (Appendix A.5.1). EPA acknowledges that the posterior parameter distributions are “difficult to interpret” (Page 3-87) and provide no guidance as to how to interpret these individual or group posterior estimates. In reviewing these summaries, for each parameter, we deemed a deviation between a group (or individual) parameter estimate and the population estimate of that parameter to be of potential interest if the population median parameter value did not fall within the 95 percent confidence interval for the respective group or individual. We believe it is notable that the deviations do not appear to be randomly distributed, but are generally concentrated within a limited number of groups/individuals. For the mouse, out of 15 deviations of interest in 10 groups, Groups 1 and 3 each accounted for 5 deviations, Group 7 accounted for 3 deviations, and Group 2 had 2, while the other 5 groups had no deviations. For the human data sets, (44 individuals or groups), there were a total of 101 deviations (~2.5 per individual or group, on average), of which one individual accounted for 13 and another individual accounted for 8 deviations. Both of those individuals were in the group of 9 males in the Fisher et al. (1998) study; each of these nine individuals exhibited at least one deviation, with a total of 36 deviations for the group (~4 per person). Similarly, the six individuals in the Chiu et al. (2007) group accounted for 23 deviations (almost 4 per person) and the Bernauer et al. (1996) group accounted for 6 deviations (could not be assessed as individuals). For the 19 rat groups, the 15 deviations (less than 1 per group), were concentrated into two groups which each had 5 deviations, while the other groups had 0 or 1. We can postulate at least two different interpretations for the concentration of discrepancies, and these two theories have widely different consequences. Theory 1: These studies are problematic or reflect genuinely different subpopulations, and therefore the deviations from the population distributions are of no concern. Theory 2: The designs of the studies with the greater number of discrepancies are distinctive and allow the “true” values of the parameter(s) of interest to be captured (i.e., measured variables are sensitive to the sampled parameters) while other studies are generally insensitive to these parameters, so if enough iterations were conducted (perhaps 100s of thousands of iterations, rather than 10s of thousands of iterations), eventually the populations

posteriors would converge around these currently "outlying" distributions. EPA should address this concern and provide discussion of these group and individual posteriors.

MODEL PARAMETER ESTIMATES COULD (AND SHOULD) BE IMPROVED USING CURRENTLY AVAILABLE DATA

Data that could potentially improve the estimation of PBPK model parameters, including some of the highly uncertain parameters, are currently available. Some of these data were clearly available to EPA at the time of model development; other data were more recently published, but should certainly be considered at this time to improve the models as described in the IRIS draft and published, peer-reviewed versions of the model (Chiu et al., 2009; Evans et al., 2009).

EPA has compared the predictions of the models they used to the following recently published data sets for mice and reported their findings (Appendix A, Section A.6 and linked files). However, EPA did not provide the posteriors that resulted from these recalibrations.

Kim et al. (2009) provide blood DCVG and DCVC time course data for mice dosed with 2000 mg TCE/kg BW (corn oil gavage). The model (as used in the assessment) consistently underpredicted the blood DCVG data. (DCVC is not currently considered in the model structure.) Best fit parameters for the Kim et al. (2009) study were then developed. These new parameters were then used to estimate the fractional flux through the GSH pathway for mice continuously exposed to TCE via ingestion. It was found that the new, best-fit parameters resulted in a substantially higher fraction of ingested TCE being predicted to be metabolized by the GSH pathway in mice (three-fold higher). Hence, for any oral studies in mice, the potency of any GSH metabolite was likely overestimated by 3-fold (due to the 3-fold underestimate in dose), with corresponding underestimates in human cRfDs based on these dose metrics. Because the GSH pathway is a relatively minor contributor to the overall clearance of TCE, it is highly plausible that the updated posteriors based on this data set (not provided) would show that only the GSH-related parameters changed substantially. Thus, if the population parameters were updated by including the Kim et al. (2009) study, there might only be changes in the population estimates of the GSH-related parameters, which presumably would be "driven" by the new data. While EPA may consider the parameters used in the assessment (the values derived without consideration of the Kim et al. data) to be "reasonably consistent with the Kim et al. (2009) data" (p. A-75, line 9), a potential three-fold change in candidate RfDs for a key endpoint deserves to be followed up. At a minimum, all mouse GSH-related dose metrics should be recalculated using the Kim et al. (2009) posterior. It would follow that the human-equivalent values (cRfCs and cRfDs) would then need to be recomputed based on new mouse internal points of departure (iPODs).

EPA also compares the model used in the assessment to additional mouse TCA kinetic data from Kim et al. (2009) and data collected by Green (2003) and Mahle et al. (2001) that were reported by Sweeney et al. (2009). Some large discrepancies were observed, especially at higher dosages

and for females. EPA attributes these discrepancies in part to liver metabolism of TCA (assumed negligible in the Sweeney et al. (2009) model, but first pass metabolism does not explain the less-than linear increases in blood TCA observed for increasing drinking water concentration of TCA (Mahle et al., 2001), since, if anything, the impact of first pass metabolism should decrease with increasing drinking water concentration of TCA.

Other model structures could be considered by EPA. The performance of the GSH-related metrics in the rodent models could potentially be improved by consideration of the Kim et al. (2009) mouse DCVC blood data and the rat DCVC data of Birner et al. (1997).

Another example of how it might be helpful to consider alternate model structures concerns the human data of Chiu et al. (2007). It is disconcerting that the greatest discrepancies between the model and the tested human database were for the Chiu et al. (2007) data. This data set is particularly important because the study involved volunteers exposed to 1 ppm TCE. In contrast, the bulk of the human calibration and validation data were for much higher exposures (40 ppm-160 ppm). Since the Chiu et al. (2007) exposures were at levels most relevant to current environmental or occupational exposures, it would be desirable for the model to fit the data, and the lack of fit is a concern. It is our assumption that the residual error statistics reported in Appendix A (e.g., Table A-14 on p. A-73 for humans) reflect the discrepancies between the data and the predictions generated from the group-specific distributions of parameters. As such, the group-specific parameter distributions reflect an interpretation of the fit between the data and the model that should provide the least discrepancy—a comparison between the data and the population-based parameters would yield a greater residual error. Clearly, based on a review of both the individual-specific and population-based predictions, the "fit" is worse when the population-based parameters are used instead of the individual-specific parameter values. Despite the ability to generate individual-specific parameter distributions, the discrepancies for the Chiu et al. (2007) data exceed 2.0 (a cut-off value used by EPA to indicate a concern—p. 3-99) for 3 out of 7 measures (highest value was 2.9 for CVen). Chiu et al. (2007) is the only group that had residual error >2 for any measurement. For 5 out of 7 measures, the Chiu et al. (2007) study had the highest residual error. There does not appear to be any reason to exclude the Chiu et al. (2007) data; rather, as previously noted, fit to this study is of particular interest, since it is the only study with measurements in the low-exposure range of interest for environmental and occupational exposures. EPA has also not tested the model against biomonitoring data, which would also test the model at low doses/concentrations.

We recommend that EPA explore the possibility of different model structure that might improve the fit to the Chiu et al. (2007) data without necessarily compromising the fit to the other data. While it does not seem likely that the volunteers in the Chiu et al. (2007) study would be physiologically dramatically different from those in the other 6 groups, some generalizations can be made from the individual specific parameters found in the linked human file for A.5.1. Compared to other individuals/groups, the individuals in the Chiu et al. (2007) study had lower optimized ventilation/perfusion ratios, low blood:air partition coefficients, and low blood flow to

slowly perfused tissue but high blood flow to fat and widely scattered values for the slowly perfused tissues:blood partition coefficient. With respect to the biomonitoring data, EPA should consider how the updated model performs with respect to predictions of blood TCE (NHANES data) for the population, given what is known about general populations' exposure to TCE. The approach used could be similar to that used by Liao et al. (2007).

MODEL SENSITIVITY ANALYSES THAT COULD (AND SHOULD) BE PERFORMED ON THE EPA TCE PBPK MODEL

EPA has not provided any sensitivity analyses of the updated TCE PBPK model. As noted in EPA (2006), "it is important to carry out sensitivity analyses under conditions reflecting the studies providing data for model calibration (i.e., pharmacokinetic studies), under conditions appropriate for estimating dose metrics in critical studies, and finally under conditions appropriate to the risk assessment." To paraphrase, sensitivity analyses are particularly helpful for the following aspects of model evaluation: (1) parameter identifiability, (2) identification of key parameter values with respect to dose metric prediction in test species and (3) identification of key parameter values with respect to dose metric prediction in humans at the toxicity reference value. With respect to (1), parameter identifiability, sensitivity analyses for predictions of experimentally determined dose measures in pharmacokinetic studies indicate whether the available data were in fact useful for "identifying" a parameter value. That is, if no experimentally determined dose measure is sufficiently sensitive to a parameter's value, the data cannot then be said to have contributed to the identification of that parameter's value. Specifically, it is unclear whether the data used in model development allow for unambiguous determination of parameter values for the GSH pathway in mice and rats, in light of the wide confidence limits of the posterior distributions noted above. With respect to (2) and (3) , sensitivity analyses of dose metrics used as internal points of departure (iPODs) in rodents and the same metrics in humans help to focus the critical evaluation of the reliability of key parameter estimates that drive the derivation of the toxicity reference values. These analyses are inter-related. The analyses for the iPODs (#2 and #3 above) can identify which parameters are key in determining the risk values. These risk values are the major conclusions of the report, and understanding the key determinants of uncertainty in the risk values (and the degree of uncertainty in those key determinants) is critical to the credibility and transparency of the calculated risk values. Given the large number of parameters in the model, it is impractical for reviewers to be able to scrutinize all of the parameters or to intuitively know which are "key". Once these "key" parameters are enumerated, the subsequent task is to evaluate whether one is confident that the numerical values of these parameters are reasonably well identified. While the general literature may be consulted for evaluation of anatomical/physiological parameter values, chemical-specific pharmacokinetic parameters are typically inferred from model fit. Hence, the ability to uniquely and conclusively "identify" these parameter values (#1 above) based on the studies available for fitting is necessary for overall confidence in the risk values identified using the models.

To aid with the demonstration of parameter identifiability, we recommend that EPA conduct sensitivity analyses for those sets of experimentally determined dose measures that they believe helped to identify the parameters with the greatest uncertainty. For example, the closed chamber TCE gas uptake and oral dosing studies are most constrained by mass balance, and are thus more likely to be sensitive to minor pathways such as GSH conjugation and extrahepatic metabolism.

Regarding the key dose metrics, we recommend that EPA conduct sensitivity analyses for rodents for the dose metrics of interest under the relevant dosing regimens corresponding to the iPODs and for humans at the recommended RfC, RfD, and a chosen cancer risk level (e.g., 1 in 10^5) under conditions of continuous exposure. We recommend that these analyses be conducted for the key endpoints (i.e., those from which the risk values were derived) and the candidate RfCs and RfDs that are within approximately 3-10x of the final RfC and RfD.

Without conducting the sensitivity analyses, it is difficult to fully anticipate what the results would be, and how that would change the risk assessment. We can speculate, however, that GSH-pathway-related metrics will likely be sensitive to the Vmax and Km for this particular pathway, and may also be sensitive to the rates for competing pathways. If it is found that none of the metrics in the experimental studies (e.g., chamber TCE concentration, blood TCA concentration) are sensitive to the values used for the GSH pathway, it must then be concluded that the parameters for the GSH pathway are not well identified in rodents, so no reliable estimates of these metrics can be used for the derivation of human equivalent concentrations or human equivalent doses. If that is the case, other risk-relevant internal doses or a default approach should be used.

OTHER KEY CHOICES IN THE RISK ASSESSMENT NOT RELATED TO PBPK MODEL PARAMETER VALUES.

One of the many parameters to be considered in a sensitivity analysis is the dose or exposure concentration. Clearly, the value of the iPOD will be related to the dose, especially at doses below saturating levels. Many risk assessment choices feed into identifying the point of departure for the RfCs/RfDs and slope factors, some of which will be discussed below.

First, the study considered for use as the basis for the potential risk value needs to be evaluated to determine if it is suitable for risk assessment. Considerations include the use of suitable test species, numbers of animals, appropriate test material (e.g., acceptable purity, or a standardized mixture), adequate documentation, and ethical conduct of the study. Even if a single study is inadequate by itself, it may be possible to combine studies to yield adequate information, or use the study to support findings from another study. Toxicity studies of key metabolites should also be considered. For the endpoint of hepatomegaly EPA does appear to have considered evaluating the dose-response relationship for a TCE metabolite (in this case, TCA) via direct dosing and the effect of interest, in order to compare that relationship to the relationship between

the same metabolite and the effect of interest when that compound is produced from TCE metabolism. Evaluation of the dose-response from direct-dosing studies of key metabolites and demonstration of consistency with the dose response seen from dosing with TCE would provide a more scientifically-supported analysis.

Second, suitable endpoints within the study need to be selected. Endpoints should be reproducible adverse effects relevant to humans. EPA's decision to not consider non-numerical data ("e.g., data presented in line or bar graphs rather than in tabular form", page 5-4, line 4) for Benchmark Dose analyses seems arbitrary and inappropriately limiting. Current technology makes it quite feasible to digitally quantify graphical results (e.g., using Plot Digitizer) and include them in the assessment.

Next, an appropriate response level needs to be chosen. The response level could be qualitative (e.g., mild irritation) or quantitative (percent affected). In some cases, the choice of response level should be further explained or reconsidered. For example, EPA did not adequately explain the use a BMR of 1% for heart defects, when higher BMRs were used for other endpoints. An appropriate dose-response model (or models) also needs to be selected (e.g., linearized multi-stage model or others in BMDS).

An important consideration, especially when PBPK modeling is to be used, is the choice of dose metric. Assumptions/beliefs about the mode of action are embedded within the choice of dose metric used for dose-response analyses and route-to-route or interspecies extrapolations. Possible alternatives include the use of parent compound, total metabolites generated, or concentrations of specific metabolites, and opting to use peak values, time-weighted average (TWA) values, or cumulative values. These choices were also not fully explained. For example, why did EPA use TCA produced rather than TWA liver TCA concentration to evaluate the potential dose-response relationship between TCE administration and liver weight increases in mice (Section 4.5)? Since TCA is a stable metabolite, its effect in tissues would be anticipated to be related to its concentration rather than its rate of production (in contrast to reactive metabolites which are expected to be limited to the tissue in which they are generated, and for which production rate normalized to tissue volume is an appropriate dose metric). Until the relationship between TCA and hepatomegaly is properly analyzed, it is premature to assert that TCA is insufficient to account for the rodent liver tumors.

Uncertainty factors obviously have an impact on the RfC/RfD. In cases where the relationship between external dose and internal dose is nonlinear, RfC values may differ depending on whether one first applies UFs to the test species point of departure and then completes the interspecies extrapolation or if one reverses the sequence, first extrapolating to human external dose, they dividing by the UFs. As a replacement for the use of default values of the pharmacokinetic variability component of UF_H, EPA used the 99th percentile of the population distribution as the "sensitive" individual, based on toxicokinetic variability. EPA defends the choice of the 99th percentile rather than the 95th percentile based on the inclusion of both

uncertainty and variability in the distribution, but does not explain why the inclusion of variability suggests the need to use a higher percentile value from the distribution or how the agency concluded that the 99th percentile was the appropriate value. EPA should provide information on how the choice of the 99th percentile, rather than other well-supported values, such as the 95th percentile, affected the outcome of the analysis. While the choice of the percentile to use to characterize human variability is a scientific policy choice, uncertainty in the distribution is larger at the tails, and therefore has a much larger impact on the 99th percentile than on the 95th percentile.

REFERENCES

Birner G, Bernauer U, Werner M, Dekant W. Biotransformation, excretion and nephrotoxicity of haloalkene-derived cysteine S-conjugates. Arch Toxicol. 1997; 72(1):1-8.

Chiu WA, Okino MS, Evans MV. Characterizing uncertainty and population variability in the toxicokinetics of trichloroethylene and metabolites in mice, rats, and humans using an updated database, physiologically based pharmacokinetic (PBPK) model, and Bayesian approach. Toxicol Appl Pharmacol. 2009; 241(1):36-60.

Evans MV, Chiu WA, Okino MS, Caldwell JC. Development of an updated PBPK model for trichloroethylene and metabolites in mice, and its application to discern the role of oxidative metabolism in TCE-induced hepatomegaly. Toxicol Appl Pharmacol. 2009; 236(3):329-40.

Kim S, Kim D, Pollack GM, Collins LB, Rusyn I. Pharmacokinetic analysis of trichloroethylene metabolism in male B6C3F1 mice: Formation and disposition of trichloroacetic acid, dichloroacetic acid, S-(1,2-dichlorovinyl)glutathione and S-(1,2-dichlorovinyl)-L-cysteine. Toxicol Appl Pharmacol. 2009; 238(1):90-9.

Liao KH, Tan YM, Clewell HJ 3rd. Development of a screening approach to interpret human biomonitoring data on volatile organic compounds: reverse dosimetry on biomonitoring data for trichloroethylene. Risk Anal. 2007; 27(5):1223-36.

Lin YS, Smith TJ, Wypij D, Kelsey KT, Sacks FM. Association of the blood/air partition coefficient of 1,3-butadiene with blood lipids and albumin. Environ Health Perspect. 2002; 110(2):165-8.

Sweeney LM, Kirman CR, Gargas ML, Dugard PH. Contribution of trichloroacetic acid to liver tumors observed in perchloroethylene (perc)-exposed mice. Toxicology. 2009; 260(1-3):77-83.

U.S. Environmental Protection Agency (EPA). (2006) Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment. National Center for Environmental Assessment, Washington, DC; EPA/600/R-05/043F. Available from: National Technical Information Service, Springfield, VA, and online at http://epa.gov/ncea.