The Department of Defense Comments on the IAR Draft USEPA TCE Risk Assessment, June 2009		
Comments submitted by: The Chemical Material Risk Management Directorate	Organization: Department of Defense	Date Submitted: Sept 1 2009

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1	3.5	General	Clearly, the Agency has devoted a great deal of effort to developing and applying PBPK models in the TCE risk assessment. The comprehensive effort to use Bayesian analysis to integrate a large number of kinetic studies of TCE and its key metabolites, conducted in three species, extends the earlier work of Hack et al. (2006) and is a very impressive accomplishment. The selection of toxicologically relevant internal doses for use as inputs to dose-response analysis was articulated well. The use of the PBPK models to characterize internal doses in many toxicity studies allowed EPA to extensively evaluate the dose-response relationships, to conduct route-to-route extrapolations of points of departure, to account for the contributions of pharmacokinetics to inter- and intra-species uncertainty and variability, and to develop harmonized inhalation and oral toxicity reference value assessments. As the precedents for use of these approaches to PBPK model development and application in risk assessment are limited, it is important that key assumptions and criteria for use in risk assessment be clearly articulated so that the scientific community can evaluate the modeling of TCE and how it was applied.	The key assumptions and criteria used in modeling and in the risk assessment need to be clearly presented.	S
2	3.5.4.2	p. 135; Lines 28-30	EPA did not include oxidative metabolism in the kidney in the model because of differences in P450 content. Considering that the metabolism of TCE in the liver is blood flow	The decision to not include TCE metabolism in the kidney as part of the model structure should be reconsidered.	S

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			limited rather than being limited by the level of enzyme activity (Lipscomb et al., 2003), this rationale is not persuasive. Lipscomb et al. (2003) found that the total metabolism of TCE did not differ greatly for a range of liver Vmax values reflecting inter-individual variation in enzyme expression. Sufficient amounts of metabolism in the kidney could effectively double the metabolic clearance of TCE in rats and humans and increase it by 50% in mice (based on liver and kidney blood flow rates).	**References:** Lipscomb JC, Teuschler LK, Swartout J, Popken D, Cox T, Kedderis GL. The impact of cytochrome P450 2E1-dependent metabolic variance on a risk-relevant pharmacokinetic outcome in humans. Risk Anal. 2003; 23(6):1221-38.	
3	3.5.5.1	p. 141; Line 9	There is no discussion of whether it is appropriate to pool the pharmacokinetic data for males and females and to pool the data across strains for rats and mice rather than develop strain- and/or gender-specific parameter distributions. While this could be considered applicable to all the model parameters (physiological, distribution, absorption, and metabolism), the greatest intraspecies differences would be anticipated to in the metabolic parameters.	The assumption that it is appropriate to pool kinetic data across strains and genders should be discussed and justified in the text.	S
4	3.5.5.1	p. 141; Line 10	The text notes that the least amount of data were available for mice. Additional data are now available, though we acknowledge one of the suggested references was likely published during preparation of this draft.	EPA should consider updating the mouse model based on the data of Kim et al. (2009) (in vivo data, including DCVG and DCVC levels) and Newman et al. (2007) (in vitro data on NacDCVC deacetylation). EPA should also consider the additional mouse TCA kinetic data collected by Green (2003) and Mahle et al.	S

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				(2001), as reported by Sweeney et al. (2009). **References:** 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. Newman D, Abuladze N, Scholz K, Dekant W, Tsuprun V, Ryazantsev S, Bondar G, Sassani P, Kurtz I, Pushkin A. Specificity of aminoacylase III-mediated deacetylation of mercapturic acids. Drug Metab Dispos. 2007; 35(1):43-50. 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.	
5	Table 3.5.4	p. 143	It is not clear why the Birner et al. (1997) studies with IV administration of DCVC to rats not used to develop kNat estimates. Additional low-dose TCE gavage data are also available for rats in a recent publication. We acknowledge this paper was only recently available. (Liu et al., 2009).	EPA should check their model for consistency with these data sets, and consider updating the rat model. **References:** Birner G, Bernauer U, Werner M, Dekant W. Biotransformation, excretion and	S

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				nephrotoxicity of haloalkene-derived cysteine S-conjugates. Arch Toxicol. 1997;72 (1):1-8. Liu Y, Bartlett MG, White CA, Muralidhara S, Bruckner JV. Presystemic elimination of trichloroethylene in rats following environmentally-relevant oral exposures. Drug Metab Dispos. 2009 Jul 6. Epub ahead of print..	
6	Table 3.5.8	p. 158	Literature data do not generally support extensive inter-individual variability in partition coefficients. For example, when the blood:air partition coefficient of 1,3-butadiene was measured in vitro for 24 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. 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 0.25 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. 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	In future Bayesian analyses, consideration should be given to not "updating" the partition coefficient distributions or limiting the implied variability/uncertainty. **References:** 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.	S

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			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 appear more narrowly distributed than they would in the absence of high partition coefficient variability.		
7	Table 3.5.9	p. 159	The incredibly broad posterior distributions of the mouse GSH pathway parameters (e.g., 2.5% and 97.5% values of 0.11 and 3,700,000 mg/L for the Km for hepatic TCE GSH conjugation) 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) do not seem plausible. Since no mouse or rat DCVG data were available 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.	As noted below (comment about p. 178-179), mouse blood DCVG and DCVC levels (Kim et al., 2009) should be considered in a recalibration of the mouse model. The GSH pathway predictions in the current model should not be used for interspecies extrapolation or for possible slope factors developed based on rodent data.	S
8	3.5.6.3	p. 161; Lines 9-12	Considering the extensive amount of detail provided about some aspects of the Bayesian process, surprisingly little detail is provided on evaluating the quality of fit/degree of concordance between data and models that resulted from the process.	Greater detail on what the “residual error” means should be provided.	S

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9	Table 3.5.13	p. 165	The descriptions of the quality of fit (e.g. "good") are vague.	The existing descriptions should be supplemented with quantitative information regarding of the residual error.	S
10	3.5.6.4	p. 174; Line 1	Sensitivity analyses of the updated TCE PBPK model are not provided. 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 two aspects of model evaluation: (1) parameter identifiability and (2) identification of key parameter values with respect to dose metric prediction in test species and humans. 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 that parameter's value. Specifically, it is unclear that the data used in model development allow for unambiguous determination of parameter values for the GSH	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. **Reference**: 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.	S

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			pathway in mice and rats. With respect to (2), 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 which drive the derivation of the toxicity reference values.	Available from: National Technical Information Service, Springfield, VA, and online at http://epa.gov/ncea.	
11	Figures 3.5.5 and 3.5.6 and captions	p. 178-9	GSH conjugation pathway and derivation of the cRfCs and cRfDs for kidney effects: The PBPK modeling of the GSH pathway in rodents, as described in EPA (2009), does not appear to be sufficiently robust for use in risk assessment. The use of PBPK model-derived estimates of GSH metabolism as a metric (rather than applied dose) had a 300- to 400-fold impact on the cRfC and RfD (p. 1076), after taking into account dose-response and interspecies differences. Although there is not necessarily an inherent problem with dose metrics that differ markedly from applied dose measures, use of GSH metabolism as the dose metric for the kidney resulted in kidney effects being identified as one of the key noncancer effects. The uncertainty in the dose metric is thus a key contributor to the overall uncertainty in the RfC and RfD derivation. Specifically, for the analyses of rat kidney effects, the analyses considered DCVC bioactivation, while the analyses for mouse kidney effects relied on the dose metric of total GSH produced, due to lack	Recommend that the models be updated using additional data, to see if the uncertainty can be reduced. If EPA opts not to undertake that effort, or the effort does not yield a sufficient reduction in uncertainty, a more reliably estimated dose metric such as total metabolized should be considered. To determine the potential value to updating the models, an initial comparison of the existing model to the following data sets with data relevant to the GSH pathway in rodents should be made: Kim et al. (2009) provide blood DCVG and DCVC time course data for mice dosed with 2000 mg TCE/kg BW (corn oil gavage) that could be used to refine the parameters related to this pathway for mice, which in turn serves as a starting point for the rat analyses. We acknowledge Kim et al. is a recent publication but believe the study would be very useful. Birner et al. (1997) administered DCVC (40 umol/kg) via iv to rats and provided time course information on excretion of DCVC and	S, M

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			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. 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. The uncertainty in the dose metrics is a product of the uncertainty in the parameter values (see our comments on page 159, provided below). Given this substantial uncertainty regarding these metrics in rodents, these metrics are not suitable for interspecies extrapolation. The concerns regarding the GSH-related metrics pertain primarily to rodents. The modeling of these dose metrics in humans appears to be better informed by the available kinetic data, so there is less concern regarding the use of these metrics for human route-to-route extrapolation, as found in the current kidney cancer assessment.	mercapturic acids. **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. 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.	
12	Figure 3.5.8 and	p. 181	The uncertainty of the estimate of "other" liver oxidation is also quite substantial (95%	We recommend that EPA retain its present approach, wherein it does not use this pathway	S

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	caption		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.	as a surrogate for DCA in any dose-response analyses.	
13	3.5.7.2.2	p. 191; Line 28	The statement on this page that the predictions related to GSH conjugation for rats and mice "remain more uncertain" than the human predictions is an understatement. The predictions for rats and mice are too uncertain as to be considered reliable for risk assessment.	Add a statement that the uncertainty is too great for use in risk assessment, and use other dose metrics or applied dose for toxicity reference value development (or update the model).	S
14	3.5.7.3	p. 195; Line 22	The 95% confidence limits on DCVC bioactivation span a range of nearly 2 orders of magnitude. The statement that GSH metabolism dose metrics were fairly well-characterized in rats is not founded.	We recommend that EPA use other dose metrics, use applied dose or further refine the model for toxicity reference value development. We believe the data to support such efforts exists in the literature.	S
15	4.0	p.206; Lines 1-9	The statement that OR is "considered an unbiased estimate of the hazard ratio" should be qualified.	That statement should be qualified as this is conditional based upon the following assumptions: 1) Controls are representative of the target population; 2) Cases are representative of all cases relative to severity and diagnostic criteria used; 3) Frequency of disease in the population is small.	S
16	4.0	p.206-208;	Several references appeared to missing from the reference list.	Add to all references to the reference list	E
17	4.0	p.207; 208	Hardell et al., 1994	Should be 1984; add to reference list	E

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18	Tables 4.0.1, 4.02, 4.03	pp.209-217	These Tables do include the key findings of the studies. For the sake of clarity and transparency a column with them should be inserted.	Add key findings	S
19	Table 4.0.4	pp.233-234	Generic evaluation criteria are included in the table.	Add specific criteria used for inclusion/exclusion of studies.	S
20	4.1.5 and 4.1.6	pgs. 281 and 283	In lines 31 and 32 it is reported that DCVC failed to produce any detectable DNA damage in rat proximal tubule. It is not clear why these data are not considered later on when talking about the "preponderance of data supporting genotoxicity" as the MOA. A study of Malley et al. (2006) indicates another example of a negative study on potential TCE- and/or DCVC-induced mutations.	The text should address these negative data regarding genotoxicity when considering the preponderance of data supporting genotoxity.	S, M
21	4.3	p. 391	The assumption that all negative studies are affected by non-differential misclassification is a default assumption that is not supported by data. They could also be affected by differential misclassification, no validation studies or empirical data are presented to support either assumption.	Suggest that the discussion include data that support EPA's assumptions.	S
22	4.3	p. 391	Clapp and Hoffman is a PMR study, it did not include complete cohort and did not have person-time available to accurately estimate risk.	PMR studies should not be referred to as cohort studies.	S
23	4.3	p. 392, Global	The text states that Zhao et al. study offered	Conduct more complete and balanced review	S

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			better exposure assessment than other studies. Semi qualitative exposure assignments do not reflect any improvement over exposure assessment methods used in several other cohort studies (e.g., Morgan et al. 19981; Boice 1999, 2006; Blair et al. 1998) among others.	of exposure assessment methods across different cohort studies. Consult Blake et al. 2008.	
24	4.3	p. 395	In the discussion of confounders and kidney cancer there is a statement: "because it is unlikely that exposure to trichloroethylene is associated with smoking." No justification is provided for this statement, and there is later there is later discussion that the Raaschou-Nielson study suggested higher smoking in the TCE exposed population. Also higher smoking rates are often reported in occupations often associated with TCE exposure.	Revise discussion on smoking as a confounding factor. Also see Leigh et al. 1996 and Bang et al. 2001 for information about smoking and occupation.	S
25	4.3	p. 399	Characterizing kidney cancer risks (from meta-analysis) as "robust" is not supported by the findings; heterogeneity, modest increase, exposure assessment limitations, and confounding factors are not fully addressed.	Suggest characterizing the kidney cancer risks as "suggestive, with limitations"; the findings do not support them being characterized as robust.	S
26	4.3.5.1	p. 433	The Maltoni studies indicate a great deal of negative results and positive results only for renal tumors in male rats exposed to the highest dose (600 ppm). There is also discussion of some negative data regarding VHL mutations.	Recommend including discussion of the negative results in the Maltoni studies. As currently written, it is not evident that there negative results.	S
27	4.3.3	Global	This subsection gives a thorough review of the literature, including a balanced discussion of	When evaluating MOA, the EPA should determine whether the mutations are an early	S

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			study limitations and inconsistencies. As noted in the context of Section 4.3.7, the association of an oncogene mutation with a tumor is not sufficient to show a causal connection with the chemical exposure, since the mutation may be a part of the tumor development process, without regard to chemical exposure. For an MOA evaluation, it is important to determine whether the mutations are an early step, and whether they are the mutations that would be expected from direct DNA interaction by the chemical or a metabolite.	step, and whether they are the mutations that would be expected from direct DNA interaction by the chemical or a metabolite.	
28	4.3.1.1	p. 386, last para.	This section notes a lack of statistical treatment and consideration of confounders, which lead to uncertainties. In the conclusions, however, such uncertainties seem to be ignored.	This uncertainty should be accounted for in the document and in the discussion.	S, M
29	4.3.1.1	p. 387, 2nd para	This section notes there was no adjustment for creatinine. This seems like an important omission for the study.	Recommend including further discussion of this uncertainty.	S
30	4.3.2.2	391	Section 4.3.2.2 discusses the Charbotel et al., 2006 study, which the U.S. EPA used to derive the inhalation unit risk. Page 391 states that "…*high cumulative TCE exposure (2.16, 95% CI: 1.02, 4.60) with a positive and statistically significant trend test, p=0.04* (Charbotel et al. 2006)." …*This study suggests an association between exposures to high levels of TCE and increased risk of RCC. Further epidemiological studies are necessary to analyze the effect of*	Explain why higher levels of TCE were more relevant in the assessment of TCE from epidemiological studies, rather than lower levels of exposure, which are relevant for environmental exposures.	S, M

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			lower levels of exposure.		
31	4.3.3	p. 423	In the he discussion on VHL mutation, no clear conclusions regarding TCE exposure and kidney cancer risk are presented. Mixed results are presented, but no final conclusions are provided. It may be that given the mixed results one cannot conclude either way, or the quality of positive and negative studies may vary leading to reliance on one set of studies. This section should provide a summary wrap-up.	Section should provide a summary/conclusion on the discussion.	S
32	4.3.5	Global	This section regarding kidney tumors needs to be modified to present a clear and balanced picture of the data regarding kidney cancer in laboratory animals, including the strengths and limitations of the studies. In the interpretation of the kidney tumor data, the text appears to rely primarily on reported rarity of kidney tumors in rats (reported as 0.4% in corn oil gavage controls in NTP studies). This is a critical aspect of the argument, since comparisons with concurrent controls are generally either negative or very marginal with regard to statistical significance. Because this is	If analysis of cancer risk by way of historical controls is desired, then the analysis needs to be done on a study-by-study basis, using appropriate historical control ranges, we believe the data exists, but if such data are not available, the rationale and appropriateness of other data needs to be addressed.	S, M

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			such a fundamental aspect of any argument for biological significance of the kidney tumors, additional information is needed to substantiate (or disprove) the reported rarity and characterize the variability in the background response. Specifically, we know that historical control values: • Vary with year of the bioassay • Vary with rodent • Are nearly always given in ranges • Often vary by sex within a given strain and species In light of these many factors contributing to the historical control range, it is important that all of this information be provided for all of the comparisons with each strain. (As an aside, the 0.4% number appears to come directly from the NTP, 1990 study and should be cited as such, not cited to Rhomberg. That study also provides some information about ranges, and additional information about ranges is available from the NTP website. Citing to the original study is also important because that is the most contemporaneous data on historical controls.) The document needs to provide information on the basis for any historical control data, include such information as strain, sex, year, and range among studies.		

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			No similar data are provided for the other strains for which tumor data are provided. As noted, in light of inter-strain and inter-sex variability, it is very important that comparisons with historical controls be based on contemporaneous information from the same strain and sex whenever possible. If such information is not available, the implications and associated uncertainties need to be discussed. Information on historical control response is often available from the animal suppliers.		
33	4.3.5	Global	Additional information and transparency is needed in the description of the NTP (1990) study. This study had numerous limitations that were not discussed in the context of the kidney cancer data. Some of these limitations were discussed in the context of the liver cancer data, but the data need to be presented in such a way (with cross-referencing if needed) so that the reader can understand the strengths and limitations of the data set in the context of the data, without assuming that the reader will see that information in other contexts. These uncertainties and limitations to the animal studies should also be addressed in Section 6. Uncertainties in the quantitative portion of the dose-response assessment are discussed in Section 6.2.2, but that section does not appear to address uncertainties in the qualitative	The document should clearly present the limitations of the NTP 1988 and, 1990 studies, and the implications of those limitations for the weight of evidence evaluation. This should be done both in the context of the study data and in the context of the risk characterization (Chapter 6). Furthermore, if EPA wishes to present the results of NTP (1988) study as showing any indication of a kidney tumor response, the discussion needs to reference the pooled analysis and associated limitations.	S, M

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			assessment. A key issue with the NTP (1990) study is that the male rat study was conducted at a very high dose that exceeded the MTD; only 17 animals survived until termination. In fact, as noted by EPA in the context of the liver data, NTP (1990) concluded that the study in male rats was equivocal or inadequate with regard to the ability to detect the presence or absence of a carcinogenic response, due to significantly reduced survival compared to vehicle controls and because of the high rate (e.g., 20% in the high-dose males) of deaths due to gavage error. NTP (1990) further stated that the high toxicity could mean that the "true" cancer response was higher or lower than what was observed. As stated in that report, the true response could be lower because the tumors were secondary to toxicity, or it could be higher because the high mortality decreased the response and ability to detect a response (due to rats dying before a tumor developed). None of these issues are apparent from the description of the study, and clearly presenting them is an important aspect of transparency and allowing the reader to independently evaluate all aspects of the data. Similarly, the report of the 4-strain study (NTP, 1988) described that series of studies as "inadequate studies of carcinogenic activity		

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			because of chemically-induced toxicity, reduced survival, and deficiencies in the conduct of the studies." The NTP report goes on to state that "for these reasons, these studies were considered inadequate to evaluate the presence or absence of carcinogenic potential of trichloroethylene." The NTP report also stated that rats could not always be unequivocally assigned to a high or low dose group; this issue casts considerable uncertainty on any attempt to evaluate the results of the 4-strain data and evaluate the presence of a dose-response relationship. Due to this uncertainty, NTP (1988) pooled the low- and high-dose responses for each sex/strain combination. Apparently based on this pooled analysis, NTP stated that "despite these limitations, tubular cell neoplasms of the kidney were observed in rats exposed to trichloroethylene and interstitial cell neoplasms of the testis were observed in Marshall rats exposed to trichloroethylene." The NTP study also included both untreated and vehicle controls; in the absence of contemporaneous historical control data in the same strain, having information on the untreated controls would help the reader have a better understanding of the background response and associated range. None of these issues and study limitations was evident in the description of the NTP (1988)		

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			study. A clear presentation of issues, uncertainties, and bases for conclusions is critical to transparency of EPA's conclusions and the credibility of the resulting assessment.		
34	4.3.5	Global	Integration of the kidney results from the various laboratory animal studies. This section needs much additional clarity and transparency for the logical reasoning used, including discussions of study limitations, issues and uncertainties. For example, Tables 4.3.5, 4.3.6, and 4.3.8 through 10, show one statistically significant response out of greater than 90 dosed/tumor groups in chronic studies (including male and female rats and mice). A frequency of 1 or even several statistically significant events is expected in such a large number of dosed/tumor groups, if a 0.05 p-value is used. Two of the three studies showing any evidence of an increase over background (NTP, 1988, 1990) had serious limitations and were considered by the study authors to be inadequate for evaluation of carcinogenicity. Specifically, the high toxicity in the one group with a statistically significant response and associated limitations were noted above. As noted above, there appear to have been several additional analyses that were part of the overall evaluation but were not presented (e.g., the pooled exposure group analysis of NTP 1988). In addition, several studies, which EPA cites, show	A more clear presentation of the strengths and limitations of the various laboratory animal studies are needed, including comparison with relevant historical controls. Either a stronger argument for an association between TCE exposure and kidney cancer needs to be presented, or the conclusions reconsidered. In particular, a simple comparison to concurrent controls among the unusually large number of studies does not suggest any cancer risk; this should be clearly stated. EPA should also clearly address the description by NTP that two of the key studies were inadequate for evaluation of carcinogenicity. In addition, several studies, which are cited in the document, show no increase in kidney tumors; these studies are not summarized in these tables and are not included in the 90 dosed/tumor groups. These need to be included in the Tables.	S,M

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			no increase in kidney tumors; these studies are not summarized in these tables and are not included in the 90 dosed/tumor groups. As presented, the data are not convincing that there is a clear pattern of increased kidney tumors exists. EPA needs to make this clearer or modify its conclusions.		
35	4.3.5.1	p. 433; Lines14 & 30	Text does not match the descriptions found in Tables 4.3.9 and 4.3.10. Specifically, Table 4.3.9 states that a 2-year exposure was associated with the high dose tumor response found in Table 4.3.9---not 8 weeks (line 14). (Additional information in general about the different components of the Maltoni et al. 1988 study would be useful, in light of the potentially confusing study design, with both 8-week and 2-year exposures and lifespan observation.) Similarly, an increase in benign adenomas is mentioned in the text (line 30), but not found in Table 4.3.10.	Insure that the text and the tables match.	S,E
36	4.3.5.2	p. 434; Lines 2-5	Text does not match what is found in Tables 4.3.6 to 4.3.8. No statistically significant tumor results are found in Tables 4.3.6 or 4.3.8. Table 4.3.7 does not show any tumors. The single statistically significant effect is found in Table 4.3.5.	Insure that the text and the Tables match.	S,E
37	4.3.5.2	p. 434; Lines 19-21	Text does not match what is found in Table 4.3.8. See major comments regarding conduct	Insure that the text and the Tables match.	S,E

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			and analysis of data from this study.		
38	4.3.6.3	p. 446, lines 6-8	We agree with the paragraph stating "*although TCOH and possibly TCA may contribute to TCE-induced nephrotoxicity, their contribution is likely to be small compared to that of DCVC,*" as the role of TCOH and TCA in TCE-induced nephrotoxicity is indeed quite small.	It should be stated that the data does not support any significant role.	S, M
39	4.3.7	Global	Evaluation of mode of action**:** EPA did a nice job at the initial level of laying out lines of evidence according to the modified Hill criteria, but we believe that transparency of the process would be enhanced by following commissioned work by ILSI and IPCS as well as elements of the EPA Cancer Guidelines (2005). This is particularly true with respect to characterization of the data regarding the hypothesized mutagenic mode of action. The analysis needs to lay out a hypothesized *pathway* for primary and alternative MOAs, including the *sequence* of key events and evaluation of potential rate- and dose-limiting key events. Laying out the data for all the key events in a pathway in a sequential fashion in tables that show dose-response and temporal relationships is recommended as a transparent way to organize the data and help the author clarify an analysis of a hypothesized MOA. Note in particular that the evaluation of dose-response and temporality does not ask merely whether a dose response	We recommend that the document clearly lay out the sequence of key events for the hypothesized MOAs and evaluate these MOAs according to the MOA/human relevance framework, arraying the data on key events with respect to dose and time to see whether the expected progressions exist. The genotoxicity data (particularly the *in vivo* data) need to be assimilated and then evaluated with regard to the expected results of direct DNA damage according to the hypothesized MOA. Unless a consistent line of evidence supporting direct DNA damage as the MOA can be shown (note that direct DNA reactivity is a consideration for applying the ADAF, not simply genotoxicity), the ADAF should not be applied.	S M

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			(for example) is seen for a hypothesized key event, but whether that analysis shows that the key event is happening *before* the tumor (or, better yet, before a tumor precursor, such as a preneoplastic lesion), both with regard to dose and time . Thus, if, for example, a dose-response is seen for in vivo genotoxicity, but increases are seen only at (ideally, internal) doses well above the tumor dose, this argues against the genotoxicity endpoint being a precursor to the tumor, although it may enhance the tumor response. Positive results in *in vitro* (or even selected *in vivo*) genotoxicity assays is not sufficient on its own to show a mutagenic MOA. Showing a mutagenic MOA is, of course, is different from choosing linear extrapolation as a default in the absence of sufficient data to identify the MOA. For example, Section 4.1.1.4.1 gives a nice initial discussion of the results of a 12-day study of transgenic *lacZ* animals exposed via inhalation to TCE that was negative in all tissues evaluated, including lung, liver, bone marrow, and kidney. Further evaluation of these data is needed to interpret the results with respect to the proposed MOA. EPA notes in the context of the DCA assay (Leavitt et al. 1997) that the small and late increase in mutations means that it is unlikely that DCA would have reached a sufficient tissue concentration. A		

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			similar depth of analysis is needed for other aspects of the in vivo genotoxicity data. For example, while the text appropriately notes that the *lacZ* assay will not detect small deletions, EPA needs to evaluate whether small deletions would be expected based on the proposed MOA, with a discussion of how direct DNA interaction by TCE or a metabolite would result in a small deletion. This gap would not be a concern if the proposed MOA would result in point mutations. Furthermore, the data regarding the *VHL* mutation in renal cell carcinomas needs to be further evaluated to determine whether that mutation can be shown as a TCE-related mutation, or whether the mutation is simply a common step in the development of RCCs, but not an early step that is part of the MOA definition. EPA is proposing that GSH conjugation metabolites directly interact with DNA to cause mutations. The proposed MOA then should then lay out what sort of mutations would result from those interactions, and evaluate the data with regard to that hypothesis. , This evaluation should assimilate the genotoxicity data by type of endpoint (e.g., gene mutation vs. chromosome aberration) for an integrated picture of a chemical's action. EPA describes TCE as being positive in the micronucleus assay but not in *in vitro* or *in vivo* chromosome		

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			aberration assays, and suggests that such findings are consistent with micronuclei induction due to spindle damage. This hypothesis should be further investigated to determine whether the database on in vivo chromosomal changes supports a DNA reactive or other mechanism of genotoxicity. Similar evaluations should be considered for other in vivo endpoints, with particular attention to the reasons for differences in results (e.g., interspecies or route-specific differences in toxicokinetics and delivered tissue dose). The document provides a nice analysis with regard to the VHL mutation data, including a thorough discussion of study limitations and inconsistencies. However, it is also important to distinguish mutations that are part of the development of a tumor regardless of MOA, from mutations that play an early and rate-limiting role in the tumor development. An increase in oncogene mutations in a tumor may simply reflect the process needed for tumor development. The text notes a hotspot in VHL mutations associated with renal cell carcinoma in TCE-exposed patients in some studies; is this mutation one that would be expected based on direct interaction of DCVC or other metabolites in the hypothesized MOA with DNA? The text correctly notes that VHL gene inactivation can result from many mechanisms in addition to		

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			point mutations, including hypermethylation and loss of heterozygosity; of course, these other mechanisms would not be indicative of a direct DNA interactive mechanism for TCE-induced kidney tumors. This comment also applies to Section 4.3.3. Based on this evaluation, the document does not use the existing body of data to show a burden of proof for showing a mutagenic MOA, and the data as presented are not sufficient to apply an ADAF. This, of course, is separate from using a linear extrapolation as a default. Finally, based on the proposed pathway (or alternative pathways) EPA should also use the framework to explicitly test alternative (non-DNA reactive) MOAs for kidney tumorigenicity. This is especially true since kidney toxicity is seen both in a time and dose related manner prior to the occasional, and perhaps random, tumor development.		

The Department of Defense Comments on the IAR Draft USEPA TCE Risk Assessment, June 2009		
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40	4.3.7.1	p. 447, lines 11-13	This paragraph states "*DCVG, DCVC, and NAcDCVC have been demonstrated to be genotoxic in the most available* in vitro *assays. In particular, DCVC was mutagen in the Ames test...*" It appears that classifying DCVC as a genotoxin is an overstatement, because while there exist a fair amount of data supporting genotoxic effects of DCVC, the data that are positive also show that DCVC is ***very*** weak in comparison to what are considered "classic" genotoxic agents (e.g., benzidine, mitomycin C, dimethylnitrosamine). Martha Moore and Karen Harrington-Brock, in their state-of-the-science paper that was part of the April, 2000 supplement to *Environmental Health Perspectives* [EHP 108 (Suppl. 2), 215-224 (2000)], clearly made the conclusion that while DCVC can act as a mutagen, this likely only plays a modest role. This apparent shift in position is not clear.	Please explain why this evidence has not been considered in the IAR Review Draft regarding DCVC mutagenicity.	S, M
41	4.3.7.3	p. 451, lines 19-20	The paragraph states "*Along with metabolites derived from GSH conjugation of TCE, oxidative metabolites are also present and could induce toxicity in the kidney.*" As indicated in the title of this section this hypothesized mode of action has limited evidence or inadequate experimental support. We question the importance of oxidative metabolites in kidney toxicity, because there are really no good data to support TCOH or TCA as being nephrotoxic,	The document should explain why in the absence of good data to support TCOH or TCA as nephrotoxic, and weak evidence that oxidative metabolites affect the kidney after TCE exposure, this mode of action is being considered.	S , M

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			certainly not at any reasonable dose.		
42	4.3.7.3.4	p. 453, lines 3-9	This paragraph states, "***Is the hypothesized mode of action sufficiently supported in the test animals?*** **Mutagenicity:** *The predominance of positive genotoxicity data in the database of available studies of TCE metabolites derived from GSH conjugation (in particular the evidence of kidney-specific genotoxicity following in vivo exposure to TCE or DCVC), coupled with the toxicokinetic data consistent with the in situ formation of these GSH-conjugation metabolites of TCE in the kidney, supports the conclusion that a mutagenic MOA is operative in TCE-induced kidney tumors.*" The descriptor "predominance" seems to be overemphasized, and the critical issue of dose relevance, overlooked.	Dose relevance should be considered relative to kidney carcinogenicity.	S, M
45	4.3.8	p. 455; Lines 32-34	Note the major comments in this section regarding statements that a small increase is evident. The statement that the results are based on limited studies is questionable. One view is that many of these studies individually have difficulties, but the breadth of the experimental animal work, including inhalation and oral dosing, multiple strains and species, and numerous doses, all points to the conclusion that TCE does not cause kidney tumors. An alternative view is that there is very weak support for the conclusion that TCE causes		S

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			kidney tumors in male rats, but the conclusions are limited by testing at very toxic doses and problems with study conduct in the key studies.		
43	4.4	p. 480	The document states that Morgan and Cassidy, 2002 study is suggestive of excess liver cancer. These data are not supportive of this claim. [RR=1.29 (0.74-2.05)] A review of geographic studies also does not mention the limitation that these studies can be influenced by migration patterns i.e., many who move out will not be characterized, and recent immigrants to community carry their health risks from their previous locations.	Further discussion of limitations of community "geographic" studies is warranted.	S
44	4.4	p. 482, 493	Overall meta-RR is in the range of 1.3 and is statistically significant. However, the lack of higher effects in "high" exposed summary led to conclusion of a less robust effect (i.e., lack of dose-response). This is a reasonable interpretation, but given the similar levels of effect for kidney and lymphoma, this questions the *robust* interpretation of that literature, given similar magnitude of effect and same sets of studies with same type of limitations. There are differences in these sets of findings, however it is not clear whether they lead to different conclusions given the large overlap in the studies relied upon.	Consistent criteria for interpreting meta-analysis results should be described and utilized in this section.	S
45	4.4.5	p. 516 - 517	EPA provided a useful 2+ pages of description of negative or inconclusive studies on the	EPA has written this section in a more balanced fashion than some other tumor	S, M

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			carcinogenicity of TCE in the liver (pages 516 to 518), but it is disappointing that EPA did not show these data in this section. EPA also stated in several place that these data were limited in their ability to demonstrate an effect. For example, the document states that NTP (1990) is limited in its ability "to demonstrate a dose-response for hepatocarcinogenicity" (page 517, lines 24 and 25), presumably to show that these data cannot be used as a strong negative finding. However, modified incidences for kidney cancer from these same studies are shown in Table 4.3.5 for NTP (1990) and discussed in the section on kidney cancer, as a way of showing positive findings, despite the mortality at high dose. Of course, limitations to NTP (1990) are applicable for the evaluation of either kidney or liver cancer. However, EPA's approach to the NTP (1990) study should not depend on the tumor endpoint being evaluated. Similarly, the 2+ pages of description of positive studies on the carcinogenicity of TCE in the liver (pages 518 to 520) were useful, but if these data are not shown anywhere in this section, there can be no independent evaluation of these conclusions. Statements of statistical significance of positive results were also not given, but implied in the summary on page 521. This lends to a lack of clarity and transparency	sections of the document. However, the overall text is not convincing that TCE is a liver tumorigen because no specific data from the studies are shown. One or more tables are needed showing tumor response with doses and statements of statistically significance by the referenced authors, or the EPA authors.	

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			regarding the TCE's liver tumorgencity.		
46	4.4.4.7	p. 516, line 6	This section states: *"Available data also suggests that TCE is does not induce..."* There seems to be a number of sentences where editing was not completed.	Ex. of necessary edit: "Available data also suggests that TCE ~~is~~ does not induce."	E
47	4.4.5	p. 517; Line 11	This section misstates the implications of the absence of response in controls, stating that this makes the test animal less sensitive to the results of TCE exposure. The opposite is true.	Correct the implication of the absence of response in controls.	S
48	4.4.6.2.1	p. 526; Lines 16-19	We agree with EPA that if the mode of action is related to TCA, there should be dose-response concordance for liver weight increase as a function of TCA produced by metabolism of TCE, and liver weight increases for TCA from oral dosing. However, we question why EPA would stop at the level of total TCA production from TCE metabolism, rather than use TCA liver concentration as the dose metric in the dose response analyses. A similar analysis was conducted by Sweeney et al. (2009) to evaluate the contribution of TCA to the liver tumorigenicity of perchloroethylene (perc) in B6C3F1 mice. In their analysis, Sweeney et al. (2009) used the TCA submodel from the Hack et al. (2006) version of the TCE model, and identified decreased apparent systemic bioavailability of TCA with increasing dose. Sweeney et al. demonstrated a concordance between the dose response-relationships for	We recommend that EPA do a reanalysis of the hepatomegaly endpoint (liver weight increases) using liver TCA dosimetry rather than TCA produced (from TCE exposures) or administered. The below references may be useful, we do however acknowledge they may not have been yet published during preparation of the Toxicological Review. **References:** 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. Evans MV, Chiu WA, Okino MS, Caldwell JC. Development of an updated PBPK model for	S

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			liver TCA and liver tumors in mice inhaling perc or ingesting TCA that was not apparent in EPA's analyses based on administered TCA and TCA produced from perc metabolism (EPA, 2008), similar to the analyses presented in EPA's draft TCE assessment and Evans et al. (2009).	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.	
49	4.4.7	Global	Considerable effort was put into the presentation of extensive data and alternative lines of evidence regarding the MOA for liver carcinogenicity. As noted for Section 4.3.7, use of the mode of action/human relevance framework to organize the data would be tremendously helpful in helping the reader assimilate the data. In particular, tables evaluating the various pathways and sequences of key events for dose-response and temporality *with regard to the tumor endpoint* are highly recommended. The three questions regarding human relevance are addressed in 4.4.7.4, and information relevant to the modified Hill criteria is presented throughout this section, but organizing the data systematically and in tables, showing the progression (or lack thereof) of key events with regard to dose response and temporality, through preneoplastic and neoplastic lesions, is desirable. Additional care is also needed in evaluating some MOAs and laying out lines of evidence	EPA needs to use its MOA/human relevance/framework presented in the *Guidelines for Carcinogen Risk Assessment* EPA 2005) and tables evaluating dose-response and temporal concordance of the sequence of key events, through the development of tumors, in order to organize and evaluate the MOA data.	S, M

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			with regard to MOA. For example, an argument raised against PPARα agonism as a MOA is that PPARα agonism and associated key events are not sufficient for carcinogenesis for a prototype chemical. However, the definition of a key event is that it is a *necessary* event for cancer; in teaching and explanations of the cancer guidelines, this is always coupled with the notation that a key event is *not necessarily sufficient* for carcinogenesis. In addition, a biological process may be a key event on the tumor pathway, even if tumors are reported after the key event has been knocked out. In such cases, the relevant question is whether preneoplastic lesions occur before or after the key event (in the non-knockout situation), and how the timing of preneoplastic lesions changes in the presence of the knockout. If the preneoplastic lesions occur much later in the knockout, this is an indication that the hypothesized key event is important in the development of the preneoplastic lesions (and the tumor), although other processes may also contribute.		

The Department of Defense Comments on the IAR Draft USEPA TCE Risk Assessment, June 2009		
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50	4.4.7.4.2	p. 584; Lines 3-4	The comment above on page 526, lines 16-19 provides the rationale for our assertion that the role of TCA in hepatomegaly should have been evaluated differently. Therefore until the relationship between TCA and hepatomegaly is properly analyzed, it is premature to conclude that TCA is insufficient to account for the rodent liver tumors. Such an analysis would lend support to a liver cancer mode of action for TCE which is not relevant to humans, or for which a nonlinear low dose extrapolation is appropriate.	We recommend that EPA do a reanalysis of the hepatomegaly (liver weight increases) using liver TCA dosimetry rather than TCA produced (from TCE exposures) or administered. We believe study data do exist to perform this analysis.	S
51	4.5	p. 626, Global	All cancer sites: Seven cohort studies are characterized as including "detailed job exposure matrices". In fact the Raaschou-Nielson study, the largest study to date used in the meta analysis did not have a job exposure matrix. Rather any "TCE facility" with less than 200 employees was considered as TCE exposed regardless of the job titles. Many different types of jobs are likely to have been included in TCE exposed group.	Review Raaschou-Nielson exposure procedures and revise characterization of these methods. Consult Raaschou-Nielson et al 2002, particularly Figure 2.	S
52	4.5	p. 628	The Hardell case-control study of non-Hodgkin's Lymphoma is labeled as a "high quality" study. Several features of that study such as: hospital based case-control study, self-report of TCE exposure may be biased (they did not incorporate industrial hygiene assessment or a JEM to better characterize exposure), plus the	Recommend that a more in-depth summary of this study be provided, rather than a sole descriptor as a "high quality" study. Most epidemiologic reviews would not characterize the study as "high quality"	S

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			fact that observed OR is so much higher than all other studies suggests that this study likely applied biased methods.		
53	4.5	p. 628	Four case control studies designated as "high quality" are listed: Siemiatycki, 1991; Nordstrom, 1998, Persson and Fredrikson 1999 and Wang 2009. The exposure assessment methods all basically involved self report, which could be subject to reporting/recall and would act to positively bias risk estimates. All of these studies were not statistically significant and had generally low observed relative risk estimates (three were 1.2 or less).	These four studies warrant better characterization of methods to justify classification as "high quality". It should be noted that none of the findings were statistically significant.	S
54	4.5	p. 628	The discussion regarding Blair et al 1998 findings on page 628 is incomplete. Incidence findings, which show no association, should also be discussed (see page 631 Table 4.5-3). The Radican extended follow-up mortality study should be emphasized more since it represents more complete analysis of this cohort.	Suggest revision of the meta-analysis to include Radican findings instead of Blair 1998. Recommend using Blair incidence results instead of mortality results.	S
55	4.5	p. 634, Global	Table 4.5-4 Reference to View Master Employees, (ATSDR, 2004). It should be noted that this PMR analysis was conducted only among a subset of the deaths in this cohort and does not represent any representation of the mortality experience of the complete cohort. This would apply for presenting findings for any of the cancer outcomes. Also this cohort had a very high turnover and a large percentage of workers who had less than one year work	Describe limitations of these PMR analyses. Consider dropping them from table as they do not meet minimal threshold of an epidemiologic study and are subject to severe bias.	S

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			experience.		
56	4.5	p. 635	Table 4.5-4 Morgan et al study was among workers in Arizona not California	Suggest editorial revision	E
57	4.5	p. 651	It would be more appropriate for the discussion present here to focus on NHL only. Although this is not ideal, it represents a more homogeneous group of cancers than to include studies with leukemias (i.e., Nordstrom). Many leukemia studies likely include Hairy leukemias, this was not addressed missed in the summary.	Leukemia findings should be consulted. See Alexander et al. 2006 meta-analysis.	S
58	4.5	p. 652, Global	References to meta-analyses of Mandel et al. 2006 and Alexander et al 2006 are inappropriate. NRC did not find weakness in these two studies, in fact on careful review of these studies it is apparent that they addressed all of the specific issues identified by NRC as necessary for a meta-analysis of TCE. NRC was referring to limited information provided in a presentation at one of their meetings by Kelsh et al. NRC did not review the published meta-analysis studies. Thus comments directed at the presentations should not be applied to the published meta-analysis studies. The presentation format did not allow for complete summary of data and methods.	EPA should consult published meta-analysis of Mandel et al. 2006, Alexander et al. 2006, 2007. These studies provide complete meta-analysis approach as recommended by NRC.	S
59	4.5	p. 634, Global	Table 4.5-4 Reference to View Master Employees (ATSDR, 2004). It should be noted that this PMR analysis was conducted only among a subset of the deaths in this cohort and	Describe limitations of the PMRs. Consider dropping from table as they do not meet minimal threshold of an epidemiologic study	S

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			does not represent any representation of the mortality experience of the complete cohort. This would apply for presenting findings for any of the cancer outcomes. Also this cohort had a very high turnover and a large percentage of workers who had less than one year work experience.	and are subject to severe bias.	
60	4.5	p. 635	Table 4.5-4 Morgan et al study was among workers in Arizona not California	Suggest editorial revision	E
61	4.5	p. 650, middle paragraph and associated Appendix	Boice is preferred over Zhao et al for substitution because it assessed a larger cohort, had more follow-up time and exposure assessment was more precise.	Reconsider use of Zhao findings over Boice et al. and suggest reviewing exposure assessment procedures in the two studies. The Zhao study may involve more misclassification. The Boice research team may have had better access to exposure information.	S
62	4.5	p. 651	Text regarding classification of lymphomas. It would be more appropriate to focus on NHL only. Although not ideal, it represents a more homogeneous group of cancers than to include studies with leukemias (i.e., Nordstrom). Many leukemia studies likely include Hairy leukemias.	Recommend that the leukemia findings be consulted. See Alexander et al. 2006 meta-analysis	S
63	4.5	p. 652, Global	References to meta-analyses of Mandel et al. 2006 and Alexander et al 2006 are inappropriate. NRC did not find weakness in these two studies, in fact on careful review of these studies it is apparent that they addressed all of the specific issues identified by NRC as necessary for a meta-analysis of TCE. NRC was referring to limited	EPA should consult published meta-analysis of Mandel et al 2006, Alexander et al. 2006, 2007. These studies provide complete meta-analysis approach as recommended by NRC.	S

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			information provided in a presentation at one of their meetings by Kelsh et al. To our knowledge the published meta-analysis studies were not addressed as part of the NRC review. Thus comments directed at the presentations should not be applied to the published meta-analysis studies. The presentation format did not allow for complete summary of data and methods.		
64	4.6.2.2	Global	EPA provided a useful description of positive and negative or inconclusive experimental animals studies on the carcinogenicity of TCE in the lung (pages 723 and 724), and showed data for these studies in Table 4.6.4 (pages 741-2) and Figure 4.6.1 (page 743). We agree with EPA that the overall effect of TCE is negative in rats and hamsters, but do not agree that the "overall results are consistent with TCE causing mild increases in pulmonary tumor incidence in mice", since the results to us look equivocal that is, only 1 statistically significant finding in one study where epichlorohydrin was a known contaminant (e.g., see Table 4.6.4 and Figure 4.6.1). In contrast, as summarized in Table 4.6.3, the non-cancer toxicity of TCE to the lungs appears quickly and is apparently dose/concentration related. It would be helpful if these latter data were shown in the document. We are not sure that an exhaustive description of the potential MOA for this tumor endpoint is warranted in this document, due to the	EPA should reconsider its statement that the experimental animal data suggest that TCE causes mild increases in pulmonary tumor incidence in mice in light of the apparently equivocal data.	S, M

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			equivocal nature of the tumor in one experimental animal species and EPA's conclusion that the human studies are neither positive nor negative, but appreciate that the document did give this some attention.		
65	4.7.3.1.2 4.7.3.3.5	814 869	These pages state that a follow-up study of the Camp Lejeune cohort for birth defects and childhood cancers was initiated in 1999 and expected to be completed soon (GAO, 2007a, b)	This information should be updated and include information regarding the recent NAS Camp Lejeune 2009 report: "Contaminated Water Supplies at Camp Lejeune: Assessing Potential Health Effects." http://www.nap.edu/catalog/12618.html	E
66	4.9.1	p. 918	The text below is unclear: *"Early and later lifestages differ greatly from adulthood in body composition, organ function, and many."* It is not clear how late life stages differ from adults.	Clarify meaning of later lifestages.	E
64	4.9.1.1.1	p. 919	Text is unclear *"Children exposed to soil vapor levels ranged from 0.18-140 mg/m3 in indoor air."*	This text needs clarification. Soil vapor concentrations are not equivalent to indoor air concentrations. Clarify whether soil vapor concentrations were converted to indoor air concentrations using a model (e.g., Johnson Ettinger or a default attenuation factor).	S
65	4.9.1.1.2	p. 920	*"..and children have increased ventilation rates per kilogram of body weight compared to adults, with an increased alveolar surface area per kilogram body weight for the first two years*	More recent USEPA documents should be referenced in this section including: the Child-Specific Exposures Factors Handbook (2008) http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm	E

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			(NRC, 1993)."	?deid=199243	
66	4.10.2	p. 979	A review of the available epidemiologic evidence and related meta-analyses, and the experimental animal data as presented in the document indicate "suggestive evidence of carcinogenic potential" of TCE based on the EPA cancer guidelines. The overall database may indicate that TCE is at the low end of "likely human carcinogen," but the document as written does not currently make that case. Description of TCE as a known human carcinogen is precluded by: • Methodological and analytical inconsistencies in the epidemiology literature, such as weak summary associations, differences in results by sub-groups, lack of evidence of dose-response relationships or insufficient data to fully evaluate exposure trends, and the potential influence of confounding by lifestyle or occupational factors. The description of TCE as a likely carcinogen based on the presented material is currently precluded by: • Conflicting experimental animal data for kidney and immune tumors, the lack of presentation of data for mouse liver tumors, and the equivocal nature of the mouse lung tumors, and incomplete presentation in the document of the analysis and reasoning	Recommend reevaluating the assigned cancer weight of evidence description.	S, M

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			supporting the conclusions for each tumor type.		
67	5.1	p. 1030; Lines 5-6	Reading the text it seems that there was an assumption that the PBPK model for a given species was suitable for estimating internal doses for all studies conducted in that species, irrespective of differences in the strain, gender, and age of the animals used in model development vs. the animals used in the toxicity studies.	The document should discuss the limitations and uncertainties related to applying the PBPK models in this manner.	S
68	5.1.1	p. 1032; Lines 8-10	The assessment does not consider non-numerical data ("e.g., data presented in line or bar graphs rather than in tabular form"). This adds limitations to the analysis that could have otherwise been overcome.	EPA should either use available software to convert figures to numerical data, or ask authors to provide original data in tabular form.	S
69	5.1.3.1	p. 1063; Lines 35-36	The text states that tissue-specific dose metrics used in dose-response analyses were "limited to dose metrics that could be adequately estimated by the PBPK model." While we agree with the use of this criterion, we do not agree that the dose metrics related to the GSH pathway are adequately estimated by the PBPK model.	We recommend that the PBPK model be updated to improve the characterization of the GSH pathway in rodents. We believe data exist to perform such an update.	S
70	5.1.3.2	p. 1073; Line 9 and footnote	EPA used the 99th percentile of the population distribution as the "sensitive" individual, based on toxicokinetic variability. EPA defends the choice of not using a higher percentile based on statistical grounds (in the footnote), but provides	The text should provide a better rationale for the definition of "sensitive" and provide information on how the choice of the 99th percentile, rather than other well-supported values, such as 95%, affected the outcome of	S

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			no rationale for not using a lower percentile.	the analysis.	
71	5.1.3.3	p. 1077; Line 3	Characterization of the confidence in the PBPK model as "high" is not currently justified for GSH-related dose metrics.	Consider updating the PBPK model based on additional data related to the GSH pathway, and then reassess the confidence in the predictions of these metrics.	S
72	5.1.3.3	p. 1077	Only for the endpoint of hepatomegaly was an an evaluation of the dose-response relationship for a TCE metabolite (via direct dosing) considered. This was 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. This approach would provide a more scientifically-supported analysis.	The dose-response analyses for key effects should be augmented by considering the dose-response relationships for TCE metabolites, such as TCA, when such data were available	S
73	Table 5.1.23	p. 1106	A BMR of 1% (rather than 5%) was used for fetal heart malformations "some of which could have been fatal." It is unclear why this should be necessary, since if lethal fetal heart malformations from TCE were an important effect, the outcome would have had an impact on reproductive success in two generation studies. Thus it does not seem to be necessary to employ a lower BMR for this study.	Suggest using a BMR of 5% for this endpoint.	S
74	5.2.2	Global	In the use of the human data to evaluate the cancer dose-response, it is important to distinguish between the use of linear extrapolation as a default and the determination that the shape of the dose-response curve is	Recommend distinguishing between the use of the linear extrapolation as a default and the determination that the shape of the curve is linear. As part of educating the risk assessment	S

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			really linear. It is not clear how EPA reached the determination that the epidemiology data are linear in the range of observation. It would not be unexpected to see nonlinearities (e.g., increased slope) at the higher doses in the epidemiology studies. However, it is recognized that such a finding is different from the determination as a default to use linear extrapolation to low doses.	community, it should be clear that the shape of the dose-response curve (either in the range of the data or the range of extrapolation) is different from the question of MOA, and biology data, not curve shape, should be used to evaluate MOA.	
75	5.2.2, 5.2.2.1, 5.2.2.1.1, 5.2.2.1.3 Table 5.2.12 Appendix B	p. 1153-1155; 1158 p..13	Charbotel et al. (2006, 2009) are listed as assigning subject exposures using job-exposure matrix approaches in Appendix B. An interviewer in Charbotel et al. (2006) used a questionnaire to separate the cases into low, medium, and high exposure groups. The Arve Valley France is devoted to screw cutting and machining of metals, so that there must also have been metal accumulation in the kidney of the study subjects. It is well known that metals tend to accumulate in the kidney over an individual's lifetime, regardless of exposure. Charbotel (2006, page 8) states that "cases (RCC) tended more often to have been working in the screw-cutting industry and metal-product manufacturing than control, but these differences were not significant". The EPA should confirm whether sufficient effort was made to eliminate bias in the study. These sections of the TCE Toxicological	Ensure that the uncertainties associated with the Charbotel et al. (2006) study are adequately addressed stated elsewhere in the document are addressed in Sections 4.3 and 5.2.	S

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			Review does cite several uncertainties with Charbotel et al. as indicated in the following quotes: Page 1158: "*An important source of uncertainty in the underlying Charbotel et al. (2006) study is the retrospective estimates of TCE exposures in the study subjects*." Page 16 : *Charbotel et al. (2006, 2009) furthermore presents analyses for data they considered as better quality, including higher confidence exposure information and excluding proxy respondents, in addition to analyses using both living and proxy respondents*. Appendix B further states that "*Without quantitative measures, however, it is not possible to quantify exposure difference between groupings nor is it possible to compare similarly named categories across studies. Exposure misclassification potential is likely and would downward bias resulting risk estimates.*" We believe that exposure misclassifications may also result in upward bias impacting risk estimates, based on the recall of the workers, their personal potential misperceptions concerning their actual exposures (which may also be influenced by the age and gender of the workers) and the difficulty of separating out potential effects when numerous other		

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			coexposures are involved.		
76	5.2.2.2	p. 1160-1163	Trichloroethylene Issue Paper 4: Issues in Trichloroethylene Cancer Epidemiology; EPA/600/R-05/025, February 2005 quotes Raaschou-Nielsen et al. (2003) as one of the studies used to adjust the IUR. It notes *"the present results and those of previous studies suggest that occupational exposure to TCE to past higher levels may be associated with elevated risk for NHL."* This indicates that this was a high exposure study.	We recommend that the Toxicological Review point out that NHL may not be relevant to humans in environmental exposures to TCE which are much lower and that this is an important area of future research needs.	S, M
77	5.2.2.2 Appendix C.4.3., C.6. 5.2.2	1160-1163 Pages C-29, lines 19-21, 23-28., C-32, lines 16-18. p.1153	We agree with USEPA's conclusions from page C-32 that "*The meta-analyses of the overall effect of TCE exposure on liver (and gall bladder/biliary passages) cancer also suggest a small, statistically significant increase in risk, but the study database is more limited*." Page C-29 states, *Thus, while there is a suggestion of an increased risk for liver cancer associated with TCE exposure, the statistical significance of the pooled estimates is dependent on one study, which provides the majority of the weight in the meta-analyses…Furthermore, meta-analyses results for the highest-exposure groups yielded lower RRp estimates than for an overall effect…At present, there is only modest support for such an effect* [that is, liver cancer in humans related to TCE exposure]. USEPA used an adjustment factor of 4 based on	We recommend that liver not be included in the factor.	S, M

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			3 tumor types to account for potential multiple cancer sites in humans (kidney, NHL, liver) using data from Raaschou-Nielsen (2003) and other epidemiological studies. Page 1153 states that of the epidemiological studies of TCE and cancer, only one had sufficient exposure-response information for dose-response analysis. This was the Charbotel et al. (2006) case-control study of TCE and kidney cancer incidence. Thus it appears that epidemiological data for liver cancer were inadequate. Other epidemiological studies were referenced in Section 5.2.2.2, which provides information for a comparison of RR estimates across cancer types. "*These epidemiologic data were used to derive an adjusted inhalation unit risk estimate for the combined risk of developing kidney cancer, NHL [non-Hodgkins Lymphoma], or liver cancer. The human PBPK [physiologically-based pharmacokinetic] model was then used to perform route-to-route extrapolation to derive an oral unit risk estimate for the combined risk of kidney cancer, NHL, or liver cancer…*" It is also stated that if liver cancer was not factored in the resulting final cancer estimate based only on kidney cancer and NHL would be 25% lower than when including liver cancer.		

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			Although EPA felt that this difference was not significant, we believe that this is a significant increase that is not supported by the paucity of liver cancer data of relevance to humans environmentally exposed to low concentrations of TCE.		
78	5.2.2.1.1	p.1153	Section 5.2.2.1.1 (on page 1153) states that *The exposure categories were constructed as tertiles based on the cumulative exposure levels in the exposed control subjects*. This statement is also supported by Charbotel et al., 2006. The fact that these tertiles were based on the exposed control subjects and not the case subjects may not be clear to the reader.	Recommend that additional information be provided to explain why the tertiles were based on the controls rather than the estimated exposure levels of the cases in Charbotel (2006) if this was the study design.	E
79	5.2.2.1.3; Appendix B; Sections 4-7 and 9.4	Page 1158; p. 13-17 and 30-32	Page 1158 states that *An important source of uncertainty in the underlying Charbotel et al. (2006) study is the retrospective estimates of TCE exposures in the study subjects*. Charbotel et al. (2006, 2009) are listed as assigning subject exposures using job-exposure matrix approaches in Appendix B. Page 16 states *Charbotel et al. (2006, 2009) furthermore presents analyses for data they considered as better quality, including higher confidence exposure information and excluding proxy respondents, in addition to analyses using both living and proxy respondents*. According to Charbotel et al., 2006, "*in the*	We recommend that the main section of the report as well as the appropriate sections of the various Appendices where Charbotel et al. (2006) is discussed should include statements made by the Charbotel et al. (2006) authors that the relative risk was no longer statistically significant after accounting for the potential confounding from co-exposures to cutting oil and other petroleum-based oils. It should also be reported that when exposure to cutting fluids and to other petroleum oils were added to the conditional logistic regression model, the OR for RCC in the highest class of cumulative TCE exposure was reduced to 1.96 (0.71-5.37). We also recommend that the text include a	S

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			present study the OR between RCC and TCE exposure was 1.6 and did not reach statistical significance. A statistically significantly increased RCC risk was only observed in the high TCE dose category. …After adjustment for exposure to cutting fluids and other petroleum oils, the increased risk of RCC linked with the highest cumulative dose was still high but not longer statistically significant. Indeed, many patients had been exposed to TCE in screw-cutting workshops, where cutting fluids are widely used, making it difficult to distinguish between cutting oil and TCE effects…A link between RCC and exposure to cutting oils has already been identified in a case-control study (Bruning et al., 2003), with an OR of 4.92 (1.70-14.27). However, the analyses of this study did not take into account exposure to TCE." *"…A significantly increased risk of RCC was identified for the highest cumulative dose: the adjusted OR was 2.16. A significant trend was also identified between cumulative dose and RCC risk (P=0.04)…However, only for high cumulative dose plus peaks was a significant increase in adjusted OR observed [OR=2.73 (1.06-7.07), compared with the non-exposed group] (Table 6)…When exposure to cutting fluids and to other petroleum oils were added to the conditional logistic regression model, the*	discussion of the fact that 75.6 % of the Charbotel et al. (2006) cases were included via local urologists and that there may be an increased incidence of RCC detection in kidney patients that have CT scans, as applicable.	

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			OR for RCC in the highest class of cumulative TCE exposure was reduced to 1.96 (0.71-5.37). When considering the combined effect of cumulative and peak, the OR for the high-exposure group with peaks was 2.63 (0.79-8.83) after adjusting for smoking, BMI and exposure to cutting fluids and other petroleum oils. This result was similar to the RCC risk observed for this class in the model presented in Table 6. Exposures to cutting fluids and other petroleum oils were significantly different at the 10% level (P=0.10) between cases and controls and were, therefore, included as potential confounders in the multivariate analysis." "*Exposure to TCE was strongly associated with exposure to cutting fluids and petroleum oils. About 90.3% of subjects exposed to cutting oils were also exposed to TCE, and 57.9% of those exposed to TCE were exposed to cutting oils. For other petroleum oils, 83.6% of subjects exposed to other oils were also exposed to TCE, and, conversely, 31.7% of those exposed to TCE were also exposed to other oils (Charbotel et al., 2006)."* Charbotel et al., 2006 further states that "*…Indeed, some misclassification bias may have occurred due to (i) inclusion of deceased patients (proxy interviews for these cases and*		

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			their controls), (ii) elderly patients (over 80 years of age), (iii) low confidence of exposure assessment and (iv) difference in the quality and validation of the TCE exposure when using the specific screw-cutting questionnaire or the general occupational questionnaire. To assess the impact of these points, a specific analysis was performed including only alive patients <80 years of age and only job periods described with the screw-cutting questionnaire and having a high level of confidence with respect to TCE exposure." There is not acknowledgement in the text that the authors state in Charbotel et al. (2006) that the relative risk was no longer statistically significant for RCC after accounting for the potential confounding from co-exposures to cutting oil and other petroleum-based oils.		
80	5.2.2.3	p. 1164	Page 1164 states that "*When one sums the oral slope factor estimates based on the primary (preferred) dose metrics for the 3 individual tumor types shown in Table 5.2.1.6, the resulting total cancer oral unit risk (slope factor) estimate is $4.63x10^{-2}$ per mg/kg/day*." Page 1166 states "*The preferred estimate of the inhalation unit risk for TCE is $2.20x10^{-2}$ per ppm ($2x10^{-2}$ per ppm [$4x10^{-6}$ per ug/m^3] rounded to 1 significant figure), based on*	Discuss the advantages of properly controlled animal studies and newer technologies that may help address the problems encountered with the current epidemiological database.	S

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			human kidney cancer risks reported by Charbotel et al. (2006) and adjusted for potential risk for tumors at multiple sites. This estimate is based on good-quality human data, thus avoiding the uncertainties inherent in interspecies extrapolation. This value is supported by inhalation unit risk estimates from multiple rodent bioassays, the most sensitive of which range from $1x10^{-2}$ to $2x10^{-1}$ per ppm [$2x10^{-6}$ to $3x10^{-5}$ per ug/m^3].” Although we agree with the USEPA that human data are preferred, we believe that it is worth noting that properly designed animals studies (e.g., with proper adherence to good laboratory practice “GPL”), where exposure concentrations are known and other experimental conditions are controlled may result in more accurate results and potential bias from exposure misclassification, co-exposures, etc. than the Charbotel et al. (2006) data combined with the uncertainties in the modeling (BMD, PBPK), etc. USEPA performed.		
81	References	1175	The NRC TCE (2006) review stated that “*species differences in susceptibility and phenotypic differences in tumors derived from TCE and its metabolites suggest that there are mechanistic differences in the way these chemicals (peroxisome proliferators) cause tumors that cannot be fully explained by*	We acknowledge that the referenced paper was published after preparation of the draft assessment; however if time permits, the EPA authors may wish to consider: M.V. Evans, W. Chiu, et al., (2009) , *Development of an updated PBPK model for trichloroethylene and metabolites in mice, and its application to*	S

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			peroxisome proliferation. A recently published scientific paper by M.V. Evans, Chiu, et al., (2009) may provide additional relevant information.	*discern the role of oxidative metabolism in TCE-induced hepatomegaly*, Toxicology and Applied Pharmacology 236 (2009) 329-340.	
82	6.0	Global	The EPA Review Draft (pp. 855-857) notes that potential limitations of the cardiac malformation data base have been raised. The conclusion is that the animal data provide "strong, but not unequivocal evidence" of TCE-induced cardiac malformations; and the final evaluation is that there is sufficient concern regarding the potential for TCE to lead to cardiac defects (p. 861). Emphasis is placed on the Johnson et al. (2003) and Dawson et al. (1993) studies and it is noted that Johnson "has provided individual litter incidence data to the USEPA for independent statistical analysis" (P. Johnson, personal communication, 2008) (see Section 6, dose-response)" (US EPA, 2009, p. 857). It is unclear why Section 6, dose-response is referenced as no description of these data or how they were used is included in this Section. Analysis performed on the data is not clear and it is also unclear how it has been incorporated into EPA's risk assessment. Much emphasis was placed on one set of studies that show a putative positive response to low-exposure levels of TCE, without considering the	Describe how Johnson 2003 data from individual litter incidence were used and analyzed in the risk assessment. a) Present maternal and offspring data from the Johnson et al 2003 study, including historical control data using their novel cardiac dissection method. b) Present the calculations used to determine the dosages in these studies and compare dosages to other studies. By way of comparison and as a quick example, the high dose animals in the Johnson study received 1100 ppm in drinking water (equivalent to 1.1 mg/mL). If the rats drank 50 mL/day and they weighed 300 g, their daily dose would be ~184 mg/kg/day, absorbed &distributed with water throughout the day. This is about 35% of the dose received in the Fisher study. In a drinking water exposure, intake is spread over a long period of time and blood levels are expected to be lower than those of a gavage study (Fisher et al provided gavage doses of 500 mg/kg/day as a bolus dose). EPA should critically analyze	S, M

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			overall data base and the limitations of the focus studies. The Johnson et al. (2003) and Dawson et al. (1993) studies have significant limitations regarding the reporting of standard maternal and fetal parameters. Without evaluating all of the maternal and fetal parameters, it is not possible to get a clear idea of how the animals are responding to treatment and whether the endpoint values are within historical ranges. Studies where major components of the results are not reported or the missing data has not been evaluated by the risk assessors may be useful in supporting other, more complete, data sets, but are of questionable value as a primary study in establishing an exposure standard.	differences in dosing regimens; how a bolus dose that would result in a higher maternal peak blood concentration given on the critical day of gestation for cardiac development was negative yet the Johnson study that used lower doses distributed over non/less critical days of gestation yielded positive results. c) Provide the rationale for not discussing the double blind Fisher study which used the Johnson dissection technique (Johnson was a co-author of that study). d) Present the mean litter incidence data that is claimed to have been provided by personal communication from Johnson and show how these were used and analyzed in the risk assessment. Maternal toxicity data (since the critical dose is initially to the dam) should also have been requested; if they are available they should also be presented and analyzed.	
83	6.1.2 Appendix C Appendix B	p.1187 p C-31, lines 17-19; lines 26-29. p. C-29, lines 30-32.	NAS NRC 2006 states *"Trichloroethylene and some of its metabolites in the glutathione-conjugation pathway have been shown to be both toxic and carcinogenic to the kidneys. There is concordance between animal and human studies, which supports the conclusion that trichloroethylene is a potential kidney carcinogen. Studies with experimental animals and human tissues indicate a genotoxic mode of*	Discuss the discrepancies noted regarding human predictions and implications regarding TCE mode of action in humans and the incidence of kidney cancer in humans based on the modeling results. EPA should clearly identify the largest sources of uncertainty and variability.	S, M

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			action. The metabolite S-dichlorovinyl-L-cysteine has been linked with the development of kidney cancer, but there are no studies of the carcinogenic potential of this metabolite. The magnitude of exposure needed to produce kidney damage is not clear. Thus, it is not possible to predict whether humans are more or less susceptible than other animals to trichloroethylene induced kidney cancer." The NRC also concluded that there was no evidence of peroxisome proliferation in the human kidney. An important question to address is whether humans metabolize TCE more like rats or mice. Historical data reported by Lash et al., 2000 and others, as discussed in the text, have shown that the rate of TCE conjugation to glutathione and kidney tumor formation in rodents following chronic high dose exposure is species specific (e.g., mice do not form kidney tumors but rats do) (Lash et al., 2000). Apparently, all three species produce the same metabolites, just in different amounts. Cummings et al. (2000) states "it is the first study to characterize P450-dependent metabolism of TCE in the rat kidney and provides evidence that CYP2E1 primarily, and		

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			CYP2C11 secondarily, are responsible for metabolism of TCE to chloral hydrate (CH) in the rat kidney. Applicability of these findings to humans is complicated by the fact that the human kidney apparently does not express CYP2E1 (Amet et al., 1997; Cummings et al., 2000b), and metabolism of TCE to chloral hydrate (CH) in isolated human PT cells was either barely detectable or completely undetectable (Cummings and Lash, 2000; Cummings et al., 2000a)." These considerations suggest that the modulating effect of renal P450 activity on renal toxicity of TCE, which is mediated by metabolism via the GSH conjugation pathway, will be less significant in humans than in rats. Evans, W. Chiu et al. (2009) states that *key conclusions from the PBPK model predictions include: (1) as expected, TCE is substantially metabolized, primarily by oxidation at doses below saturation; (2) GSH conjugation and subsequent bioactivation in humans appears to be 10- to 100-fold greater than previously estimated [from toxicokinetic and PBPK modeling]; and (3) mice had the greatest rate of respiratory tract oxidative metabolism as compared to rats and humans.* The text states that *the extent of total recovery in human studies (60-70%), as reviewed in*		

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			Chiu et al. (2007) is substantially less than in rodent studies (upwards of 90%), consistent with a greater role for GSH conjugation in humans. In addition, it has been suggested that "saturation" of the oxidative pathway for volatiles may lead to marked increases in flux through the GSH conjugation pathway…but the PBPK model predicts only a modest, at most [about] 2-fold, change in flux, because there is evidence that both pathways can be saturated for this substrate at similar exposures. Therefore, the hypothesis that metabolic saturation of the oxidative pathway would lead to substantially non-linear toxicity is not supported for TCE. The text is not convincing that experimental data show that humans are 10 to 100 more times sensitive to kidney cancer than animals. If this were true, there would be more human data available in existing literature to corroborate this finding.		
84	6.1.3.2	p. 1189	In section 6.1.3.2, there is no discussion of dose relevance for humans.	Please include a discussion of dose relevance to humans.	S, M
85	6.1.3.7 4.7.3, 4.10.1.7.	1193-1194	Some epidemiological studies have reported associations between parental exposure to TCE and spontaneous abortion or perinatal death, and decreased birth weight or small for gestational age, although other studies reported mixed or null findings. While comprising both	Discuss how biomonitoring data and current on-going children's studies (such as, The "Children's Chemical Evaluation Program") may help in more accurately determining the potential developmental effects of exposure to low environmental concentrations of TCE and	S

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			occupational and environmental exposures, these studies are overall not highly informative due to the small numbers of cases and limited exposure characterization or to the fact that exposures were to a mixture of solvents. As the EPA used ADAF factors to help address the potential for increased health risk from early life exposures, this appears to be an important area for new research. In addition, further investigation of the actual increases in RCC and/or other cancers in populations exposed environmentally to TCE using more sophisticated biomonitoring data and Cancer Registry/mortality data, quantititative CDC's NHANES data, etc.	its metabolites.	
86	6.1.4	Global	This section does a thorough evaluation of some aspects of uncertainty, but other aspects (such as limitations to the animal cancer studies) are not mentioned at all.	The various issues noted elsewhere in these comments should be discussed, along with the implications of those uncertainties to the final conclusions. These include, but are not limited to: Limitations in the key animal cancer studies. Difficulties in evaluating the significance of a weak increase in tumors that are rare, but not so rare as to reliably have a zero background. Limitations in the rodent kidney dosimetry.	S
87	6.1.4	p. 1195, lines 11-16	This paragraph states, "*Following U.S. EPA (2005a) Guidelines for Carcinogen Risk Assessment, based on the available data as of*	Please explain why cytotoxicity and proliferation are not being well considered as MOAs.	S, M

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			2009, TCE is characterized as carcinogenic in humans by all routes of exposure. This conclusion is based on ***convincing evidence*** *of a causal association between TCE exposure in humans and kidney cancer. The* ***strong consistency*** *of the epidemiologic data on TCE and kidney cancer argues against chance, bias, and confounding as explanations for the elevated kidney cancer risks.*" The data are not supportive of that a strong conclusion can be made about TCE acting as a human carcinogen. We believe that there is no "convincing evidence" and "strong consistency" as they are not supported by actual data. The document emphasizes genotoxicity as the absolute MOA, however the supporting evidence is fairly weak. The alternative MOA, involving cytotoxicity and proliferation, seems to be dismissed. The conclusions here depart from consensus reached in other forums in 2000 and 2006. The data discussed in the Interagency Review Draft does not quite justify such a change.		
88	6.1.4	p. 1195, lines 27-29	The paragraph states, "*Given the modest relative risk estimates and the relative rarity of the cancers observed, and therefore the limited statistical power of individual studies, the consistency of the database is compelling.*" This sentence sounds contradictory. On one hand, it is stated that there is "modest relative	The text needs to better explain and justify the relevance of the consistency of the database given the earlier statement that cancers are rare and the associated studies had limited statistical power.	S,M

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			risk," a "relative rarity of cancers," and "limited statistical power."and then the conclusion is that "the consistency of the database is compelling."		
89	6.1.4	p. 1196 - 1197, lines 35-36 and 1-8	This section discusses renal tumors in rats and mice, but does not state that tumors are only observed at very high doses.	Please include in this paragraph information stating that the renal tumors are only observed at very high dose.	S, M
90	6.1.4	p. 1198-1199, lines 33-36 and 1	This paragraph states, "*Human studies have reported markers for nephrotoxicity at current occupational exposures, although data are lacking at lower exposures. Nephrotoxicity alone appears to be insufficient, or at least not rate-limiting, for rodent renal carcinogenesis, since, although very high incidences of toxicity are observed in both mice and rats, kidney tumors are only observed at low incidences in rats.*" As a rationalization for the reported lack of site concordance for tumor incidence across species, this logic is inconsistent.	We recommend that conclusions be presented in a more balanced and transparent manner.	S, M
	6.1.5	p 1200, lines 12-17	The paragraph states, "*Because the weight of evidence supports a mutagenic MOA for TCE carcinogenicity in the kidney(see Sect. 4.3.7), and there is an absence of chemical-specific data to evaluate differences in carcinogenic susceptibility, early-life susceptibility should be assumed and the age-dependent adjustment factors (ADAFs) should be applied, in accordance with the Supplemental Guidance (see summary below in Sect.6.2.2.5).*" This statement about "*weight of evidence supports a*		

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	6.2.1.3.2 6.2.1.3.2	p. 1207, lines 29-31 p. 1208, lines 10-12	*mutagenic MOA…in kidney"* is another unjustifiable overstatement and overuse of unsuitable descriptors to influence an outcome that can be perceived as predetermined. The paragraph states, "*In addition, as discussed in Sections 3.3 and 3.5, pharmacokinetic data indicate substantially more production of GSH-conjugates thought to mediate TCE kidney effects in humans relative to rats and mice.*" The conclusion about "*pharmacokinetic data indicate* ***substantially*** *more production of GSH conjugates…*" The data do no support the statement relative to substantial production of GSH conjugates.. The paragraph states, "*As discussed above and in Chapter 3, this is due to the available data supporting not only substantially more GSH conjugation in humans than in rodents but also substantial inter-individual toxicokinetic variability.*" The statement ***"evidence for substantial inter-individual toxicokinetics variability…"*** is not supported by the data. While we agree that there is pharmacokinetic variability (e.g., variations in CYPs, GSTs), there is little evidence to support that these may be associated with specific toxic effects.		
91	6.2.2.5	p. 1225, line 5	The summary of the example calculations evaluating the potential impact of ADAFs is unclear and does not seem necessary.	Consider removing the ADAF example text, or better describe the intent for placing it in the	E

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				document.	
92	6.2.2.5	p. 1225, line 15	Current text states: *"Additionally, the ADAFs are general default factors, and it is uncertain to what extent they reflect increased early-life susceptibility for exposure to TCE, if increased early-life susceptibility occurs."*	Modify the text to explicitly state whether the default ADAFs are appropriate for TCE. Suggest also indentifying whether TCE-specific ADAFs can be developed based on the TCE scientific literature. Should refer reader to section 4.9.2 where this is discussed in detail. The way it is currently written implies that default guidance is being followed, when actually, the available data were reviewed and found to be inconclusive.	S
93	Appendix A; A.3	p. A-38; Lines 7-9	EPA notes that closed chamber uptake (metabolism) of TCE by mice appeared to be faster than could be achieved by blood-flow limited hepatic metabolism, so they added respiratory tract metabolism. EPA does not discuss whether alternative locations for extrahepatic TCE metabolism (e.g., kidney) were tested, as suggested in the conclusions from the evaluation of Hack et al. (2006) (p. 133).	EPA should add discussion of other tested model structure(s) (if any), justify the location of extrahepatic TCE metabolism, and/or note that uncertainty regarding the location of extrahepatic metabolism is a limitation of the model.	S
94	Table A.9	p. A-69	It is not clear in the appendix tables that the posterior population means are not the parameter means, but rather the ratio of the final value to the baseline value. This distinction was made in the main text p. 154, but not the appendix, where it should be restated. Readers of this document are more likely to be interested	Reiterate that the final "scaled" values are found in the main text.	E

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			in what the final parameters were than how good EPA's estimate was when they set the baseline value in the prior distributions.		
95	Tables A.9, A.11, and A.13	pp. A-69, A-71, A-74	Since the group-specific (individual-specific, for the human model) parameter distributions were not provided, it is difficult for the reviewers to assess whether any groups appear to be "outliers" with respect to the parameter distributions.	Group-specific parameter distributions should be provided.	S
96	Table 1.10	p. A-70	Residual error information for mouse simulations was not broken out by "group", as with rat and human data.	Residual error information by "group" for the mouse should be provided.	S
97	Table A.14	p. A-76	Deviation between the model and data at lower levels of human exposure**.** It is of concern that the greatest discrepancies between the model and the tested human database were for the Chiu et al. (2007) data (p. A-76). This data set is particularly important because the study involved volunteers exposed to 1 ppm TCE, while the bulk of the human calibration and validation data were for exposures an order of magnitude or more higher (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-76 for humans) reflects the discrepancies	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. One possibility would be to describe oxidative metabolism of TCE using two saturable terms (with differing Kms) rather than a single Vmax and Km. 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). **References:**	S

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			between the data and the predictions generated from the group-specific distributions of parameters. As such, this reflects an interpretation of the fit between the data and the model which 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 populations based predictions, the "fit" is worse when the population-based parameters are used. Since the parameter distributions for each group were not provided, it is not possible to assess the extent to which the parameter distributions for one particular individual (group) deviate from the overall "population" represented by all the studies. It does not seem likely that the volunteers in the Chiu et al. (2007) study would be dramatically different from those in the other 6 groups. 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. 163) 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)	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.	

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			data. EPA has also not tested the model against biomonitoring data, which would also test the model at low doses/concentrations.		
98	Appendix B	Global	The methods for conducting the systematic review, and selecting articles for relevance to the review study question are not described in the Appendix text. The current systematic review provides a comprehensive full-text summary of several articles.	Methods for performing the systematic review should be included; such methods usually include the protocol used (Cochrane or other adapted protocol), make-up of the review team, statement of the article eligibility criteria (written in English, published in a peer-review journal, primary study, measured TCE exposure and all-cause/cause specific mortality, etc). Systematic review team members usually screen titles and abstracts to quickly identify and exclude non-relevant articles. Full-text screening of articles usually precedes quality assessment and rank/scoring of articles.	S
99	Appendix B	Global	Data summary and extraction should only be completed on those studies with adequate validity to answer the systematic review question.	After assigning clear quality scores to the articles, present data extraction summaries of only those articles which answer the systematic review question.	S
100	Appendix B	Global	There is no mention of any 'sensitivity analysis'of the systematic review.	Suggest that the following sensitivity analysis questions be considered: 1) How do the results change if the inclusion/exclusion criteria are changed?; 2) What if the 'quality' rankings were higher or lower?; 3) What happens if we include lower methodological quality studies?	S
101	Appendix	Global	The information in Appendix B provides a very	Recommend that systematic review be revised	S

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	B		thorough and detailed review of the epidemiology literature related to cancer and tricholoroethelyne. A comprehensive literature review should not be confused with a systematic review. A systematic review should provide a concrete overview of primary studies related to a clearly defined objective research question using clearly defined and reproducible protocol/method.	to include a concrete overview of primary studies related to a clearly defined objective research question using clearly defined and reproducible protocol/method. Two references that may be useful in modifying the systematic review approach are: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 [updated September 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org. Slavin, R. E. (1995). Best evidence synthesis: An intelligent alternative to meta-analysis. Journal of Clinical Epidemiology, 48(1), 9-18.	
102	Appendix B, Section I	p. B-1; Paragraph 1	There is a lack of a clear and precise study question to be addressed by the systematic review. For all systematic reviews, the criteria used to determine which articles will be included and/or excluded is based on the study question.	The study question needs to be restated as an objective.	S
103	Appendix B, Section II	pp. 2-6; Categories A-H	The authors identify both the criteria used and the 'ideal' to assess the quality of each article, but do not provide any ranking or objective scoring scheme to rate each article.	The criteria used to assess the quality and ranking of potential articles should be decided 'a priori' and each potential article independently reviewed/scored by at least two team members required to reach consensus. At a minimum, each study should be evaluated	S

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				regarding methodology, precision of measurements, bias/adjustment and external validity.	
104	Appendix B, Section II	p. B-1; Paragraph 1	In the first sentence, "…studies considered…assess the relationship between **TCE** and **?** are identified…"	Correct the grammar of the first sentence.	E
105	Appendix B, Section II	p. B-1; Paragraph 1	It is not plausible to complete a thorough search of the literature using only one bibliographic database (PubMed) using six search terms. Additionally, bibliographic review of primary TCE studies is only one additional search method. There is no mention of other medical bibliographic databases, foreign language literature or "Grey Literature".	Consider expanding search terms to include at a minimum, derivations of trichloroethelyne and related chemical compounds and epidemiology related study design search terms. Consider developing a literature search strategy using the following bibliographic databases; Academic Search Complete (EBSCO Publishing) (http://www.ebscohost.com/) TOXLINE (National Library of Medicine) (http://toxnet.nlm.nih.gov) Cumulative Index to Nursing and Allied Health Literature (CINAHL) (http://www.ebscohost.com/cinahl/)	S
106	Appendix C	Global	When making conclusions regarding body of epidemiologic research, it is unclear what specific *apriori* criteria were utilized, such as strength of association, dose-response, etc. to characterize weight of evidence from qualitative review and meta-analyses. It is stated that for each of the three malignancies (lymphoma, kidney, liver), a "small" association was observed. Strength of association is important because weak associations (e.g., RRs < 1.50) can be influenced by bias or confounding.	Suggest development of more explicit specific criteria for summarizing weight of evidence. Preferably this would include factors such as strength of association, consistency of findings, potential biases that could affect conclusions, exposure assessment.	S

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107	Appendix C	Global	P-values for heterogeneity are referred to as "significant" only if they are <0.05. However, it is common in assessments of heterogeneity to consider p-values up to 0.10 (or even higher) as "significant" in meta-analyses.	To be more transparent in meta-analysis process the exact P values for heterogeneity should be provided for reviewers to decide the extent of heterogeneity. Using a lower p-value threshold may provide a false sense of consistency across meta-analysis models.	S
108	Appendix C	Global	In the meta-analysis results summary tables, when the fixed effects result equals the random effects result, this is labeled as no observable heterogeneity. Heterogeneity reflects differences in effect sizes between studies not necessarily differences between summary associations by type of model (i.e., fixed vs. random).	For transparency reasons, the specific p-values for heterogeneity should be reported. Also it is important to note that the statistical testing for heterogeneity is generally a low powered and relatively insensitive method to identify between study variability. Recommend that this be addressed throughout the analytical sections of the document.	S
109	Appendix C	Global	It was stated (page C-7 for example) that approaches to investigate sources of heterogeneity, such as qualitative tiering based on quality of exposure information was *rejected* because it was *difficult to judge the quality of information*. In fact numerous assertions are made about the quality of studies throughout the document. Despite the claimed difficulty in evaluating the quality of information, relatively strong conclusions are made regarding risks of lymphoma, kidney, and liver cancer and TCE exposure.	Before judgments are made on the epidemiologic studies, the quality of information should be examined thoroughly. For example, data from studies that utilized biomonitoring for TCE exposure were essentially null for kidney cancer. It could be argued that the quality of information for the biomonitoring studies may be superior, although studies are smaller.	S
110	Appendix C	Global	Incidence data from Zhao 2005 should be used as the primary selection rather than mortality data. Mortality data were relied upon because more cases were observed on one instance	Recommend that the sensitivity analyses include incidence from this study; however, incidence data should be used in the primary models and mortality data in the sensitivity	S

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			(lymphoma), thereby increasing statistical power. However, statistical power should not be a concern in a meta-analysis because data across numerous studies are analyzed. Furthermore, it is stated that the "incidence estimates are generally preferred" (pg. C-9) when the Blair 1998 study was discussed. Thus, the methodology used was inconsistent. Data extraction methodology should be conceptualized *a priori*, rather than selecting data at the analytical phase. Note: this should be applied to all three cancers (lymphoma, kidney, liver).	analyses.	
111	Appendix C	Global	Publication bias is stated as a potential issue in the assessment of lymphoma. However, it is concluded that the epidemiologic data lend "substantial support" to the conclusion that TCE increases the risk of NHL. This is somewhat contradictory. Using Duval and Tweedie's trim-and-fill method, four studies to the left of the summary association were imputed, resulting in a marked attenuation of the overall association, including a lack of statistical significance.	The strength of judgment for lymphoma should be re-considered due to the likely influence of publication bias.	S
112	Appendix C	Global	Sensitivity analyses should be conducted by removing all studies that relied upon self-reported exposure.	Recommend re-analyzing by creating sub-groups for which studies did not rely upon self-reported exposure estimates.	S
113	Appendix C	Global	For the three cancer sites, statistical differences between cohort and case-control studies are mentioned briefly with regards to explaining	Meta-regression techniques should be relied upon when discussing characteristics that "explain" heterogeneity. Clarify whether such	S

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			some of the heterogeneity. It is unclear how this conclusion was reached. If this was based on meta-regression techniques it needs to be discussed.	techniques were utilized.	
114	Appendix C	Global	Data from the study by Nordstrom et al. 1998 should not be included in the meta-analyses of lymphoma. It is acknowledged that the non-Hodgkin lymphoma's have had recent diagnostic classification changes, thus certain malignancies like CLL and HCL may be included with NHL. However, most studies (prior to this classification change) included these malignancies with a broad category of leukemia. Including HCL with NHL for example, may result in a reporting bias.	Suggest removal of Nordstrom et al. 1998 from the primary meta-analyses of lymphoma, and include it in the sensitivity analyses only.	S
115	Appendix C	pp. C-13 - C-14	In the evaluations of "kidney" cancer, renal cell carcinoma (RCC) was preferably selected because RCC and other kidney cancers were stated as being "very different cancer types." One could make a valid point that the lymphomas are even more heterogeneous malignancies, yet several lymphoma sub-types were combined, including hairy cell leukemia. Thus, the data inclusion methodology is inconsistent by cancer type.	A uniform method of data extraction and analysis should be incorporated for all types of cancer.	S
116	Appendix C	Global, p. C-15	Data extraction from the Zhao 2005 study is inconsistent between cancer sites. For example, data that were not adjusted for other exposures were extracted for lymphoma but data that were adjusted for other exposures were extracted for	The analyses should be revised with uniform data extraction and analytical methodologies.	S

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			kidney cancer. This is not consistent. Furthermore, mortality data were extracted for lymphoma but incidence data were extracted for kidney cancer because the number of incidence cases equaled the number of mortality cases. The selection of data in a meta-analysis should be based on the most appropriate data in a *consistent* fashion rather than the number of cases in an individual study.		
117	Appendix C	p. C-20	For kidney cancer, no sub-group analyses were conducted for the highest exposure analyses. In order to sufficiently understand any potential exposure-disease associations, sub-groups analyses should be conducted	Recommend adding sub-groups analyses for studies that utilized biomonitoring for TCE exposure, for specific exposure metrics, and for study design.	S
118	Appendix C	p. C-23, 398	It is stated that "Heterogeneity was not observed in any of the analyses." The p-value for heterogeneity was reported infrequently. There is heterogeneity across the studies of TCE and kidney cancer, as evident in the forthcoming meta-analysis by Kelsh et al. 2009 (Epidemiology).	P-values should be reported throughout.	S
119	Appendix C	pp. C-28 -C-29	The summary association in the highest exposure analysis is lower than that for the overall analysis. This is referred to as an "anomalous finding." It seems that this is an anomalous finding only if there is an assumption of a TCE-Liver cancer association.	Consider adding discussion that starts with no assumptions regarding potential association and describes empirical data and what they mean.	S
120	Appendix	p. C-31	The results are referred to as "robust," thus,	Suggest analyses by specific exposure metrics,	S, M

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	C		"supporting a conclusion that TCE exposure increases the risk of kidney cancer." The robustness appears to be based solely upon the sensitivity analyses. Moreover, in the overall analysis, the summary association across the cohort studies was not statistically significant (refer to C-55). The results should be recharacterized as something other than robust.	study quality, study design, and method of exposure estimate before conclusions can be formulated.	
121	Appendix C	p. C-29	In paragraph C-4, "kidney cancer" should actually be stated as "liver cancer."	Revision suggested.	E
122	Appendix C	p. C-58	In the highest exposure analysis for kidney cancer, an OR of 3.34 was extracted from Charbotel that reflected cumulative exposure. However, in the text of Charbotel, a more adjusted OR (adj for cutting fluids) was reported (, OR = 1.96, 95% CI: 0.71-5.37). This result should have been used.	Suggest re-analyzing with the more adjusted data from Charbotel et al. 2006. At the very least, these data should be included in a sensitivity analysis.	S
123	Appendix C	p. C-66	In the analysis of liver cancer, an RR of 3.7 was used for Axelson 1994. The RR was 0.0 at the highest level of exposure (no observed cases although a CI was reported). This RR should have been used in the analysis. Instead, data for the second category of exposure was combined with the highest category of exposure producing the RR of 3.7.	We suggest that reevaluation be performed using the appropriate risk estimate, which is 0.0.	S
124	Appendix E	E-1 to E-388	Appendix E, entitled Analysis of Liver and Coexposure Issues for the TCE Toxicological Review" focuses on liver toxicity, as the title	We recommend that co-exposures to petroleum oils/cutting oils and kidney toxicity/cancer be included, as applicable.	S, M

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			indicates, and co-exposures to TCE and other chemicals, such as other solvents, alcohol, etc. It does not appear to discuss co-exposures to petroleum oils/cutting oils, exposure to metals in machine work and kidney toxicity/cancer.		
125		Global	In such a large document, it can be a challenge to provide all needed data yet succinctly summarize the data. In particular, because the document was organized by study endpoint, several key aspects in describing studies were either not included in the document, or needed to be mentioned more than once.	It would be very useful if the key animal and maybe epidemiology studies were described in one central location that included standard descriptions of study methods and study limitations. This could be followed by the target-specific discussions, as in the current document, but it would allow the reader to go to one place to understand the strengths and limitations of the key studies, without needing to repeat those considerations for each target endpoint.	E
126	Table of Contents	Pages iv-xxi	Although we appreciate the fact that the various Appendices have their own Table of Contents, we believe that it would be helpful if the IAR Review Draft included a list of the titles of the various Appendices in the Table of Contents, and a brief summary of their contents in the Guide to Readers of This Document. The authors may also wish to add an acronym list.	Consider adding these edit items to the main report.	E
127		Global	The majority of the renal cell carcinoma cases in the Charbotel (2006) study were male, in keeping with the high incidence of male RCC in	None	O

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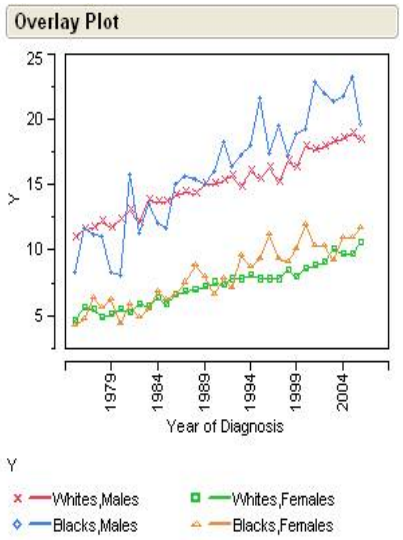
			non-exposed males. The SEER cancer database was examined and the following figure was developed, showing the incidence of RCC in the U.S. over time. There is an increasing trend (especially for males) of RCC that is unlikely to be explained by exposure to TCE. While this IRIS TCE document provides a scientific argument for protecting from "theoretical cancers", the underlying basis for the annual increase in kidney cancers should also be addressed by other Federal programs. 		

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