

Excerpts by Tox Review Section Table

Initiative: Trichloroethylene Draft IRIS

Date Report Created: 3/31/2010

Comment Classification Included: major, other, testimony

Commenter Types Included: private citizen, local/state government, federal government, tribal, industry/business, public interest/ environmental, other

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
2.1	303	EPA-HQ-ORD-2009-0791-0007.1	Natural Resources Defense Council (NRDC) and Supoprters	A very recent study titled, "Association between Residential Proximity to PERC [PCE] Dry Cleaning Establishments and Kidney Cancer in New York City" reports on an exposure-dependent increase of 10 to 27% in kidney cancers (based on hospital discharges for kidney or renal cancer) associated with proximity to dry cleaners, as determined by NYC zip code after accounting for population density, socioeconomic strata and other variables. ⁶ Despite some limitations in the study design (an ecological study looking at large groups of people, not individuals) the authors report highly significant 'p-values' indicating that the results were very unlikely to occur by chance. ⁷ These data are highly relevant because PCE (perchloroethylene) dry cleaning fluid and TCE are both related chlorinated solvents and are often co-contaminants in soil and water. PCE and TCE are chemically very similar and are both metabolized to the same cancer-causing metabolite, trichloroacetic acid (TCA). ⁸	<p>-</p> <p>6 Ma J, Lessner L, Carpenter D, Schreiber J. 2010. Association between Residential Proximity to PERC Dry Cleaning Establishments and Kidney Cancer in New York City. Journal of Environmental and Public Health, Volume 2009 (2009), Article ID 183920, 7 pages. Available at http://www.hindawi.com/journals/jep/2009/183920.abs.html</p> <p>7 Ma et al, 2009. The rate of kidney cancer hospital discharges is positively associated with increasing exposure levels 2, 4, and 5, with rate ratios (RR) of 1.14, 1.17, and 1.15, respectively, and with P-values of .01, .006, and .03, respectively.</p> <p>8 Agency for Toxic Substances and Disease Registry (ATSDR). 1997. Toxicological profile for Trichloroethylene (TCE). Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. Complete profile available at http://www.atsdr.cdc.gov/toxprofiles/tp19.html</p>
2.3.1	176	EPA-HQ-ORD-2009-0791-0015.1	Center for Public Environmental Oversight	<p>I would like to stress the significance of the ambient air data presented in the Draft Toxicological Review for Trichloroethylene, found in Table 2-6.</p> <p>Often, when officials explain exposure standards to impacted communities, they tell us that the standards are conservative because they are based upon constant lifetime exposures, suggesting that very few people are exposed continuously. Furthermore, non-residential exposure scenarios allow greater exposure concentrations because people are assumed to return to pristine environments after part-time exposures in the workplace.</p> <p>The data, however, demonstrates that in many parts of the U.S. people are exposed to unacceptable or barely acceptable TCE levels in the air they breathe around the clock. With a baseline of exposure within or near the risk range requiring protection, any higher inhalation exposures—from vapor intrusion, industrial releases, or showers with contaminated water— elevate risk to even more unacceptable levels.</p> <p>Therefore, inhalation exposure standards, for both residential and non-residential environments, should take into account the fact that a large share of the U.S. population— probably most people in urban or other industrial areas—start with a default background exposure level or .25 µg/m3 or higher.</p>	<p>-</p> <p>-</p>
2.3.4	51	EPA-HQ-ORD-2009-0791-0007.1	Natural Resources Defense Council (NRDC) and Supoprters	<p>Here we present the dose response estimates that are provided in this draft assessment, with some attempt to translate them to plain language. A reference dose (RfD, oral exposure) or a reference concentration (RfC, inhalation exposure) are estimates (with uncertainty spanning perhaps an order of magnitude) of a continuous exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious non-cancer effects during a lifetime. For this TCE assessment the RfC/RfD are based on observed effects on the kidney, the adult immune system, the developing fetal heart, and the developing immune system.</p> <ul style="list-style-type: none"> • Non-cancer inhalation RfC is 0.001 ppm (5 µg/m3) • Non-cancer oral RfD is 0.0004 mg/kg/day (0.4 µg/kg/day) <p>The cancer risk estimate is an estimate of the excess cancer cases that would result from a lifetime of continuous</p>	<p>-</p> <p>4 Region 5 Superfund site report, Anoka County, Fridley Commons Park Well Field. Updated in 2006. Available at http://www.epa.gov/R5Super/npl/minnesota/MND985701309.htm</p> <p>5 International Agency for Research on Cancer (IARC) . Available at http://monographs.iarc.fr/ENG/Classification/ListagentsCASnos.pdf</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>exposure. 2 The cancer risk estimates for this TCE assessment are based on kidney cancer, NHL, and liver cancer. They are as follows;</p> <ul style="list-style-type: none"> • Cancer inhalation unit risk is 2x10per ppm (slope=4x10per µg/m); this means 20 excess cancer cases per 1,000 people exposed to 1 ppm TCE, or 4 excess cases per 1 million people exposed to 1µg/m3over a lifetime. • Cancer oral unit risk is 5x10-2 per mg/kg/day; this means 50 excess cancer cases per 1,000 people exposed to 1 mg/kg/day over a lifetime. • The estimated cancer risks at RfC/RfD = 2x10-5; this means 20 excess cancer cases per 1 million people exposed over a lifetime to the RfC/RfD..... <p>.....In water, TCE is found as a co-contaminant with its toxic degradate products, including vinyl chloride (VC),4 which are known to cause cancer in humans.5</p>	
2.4.2.1	110	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	Page 2-22: Line 36, the exposures in the cardboard workers in Germany likely were much higher, with peaks well above 1,000 ppm and prolonged exposures above the former occupational standard (> 200 ppm TWA).	AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany -
2.4.3	49	EPA-HQ-ORD-2009-0791-0007.1	Natural Resources Defense Council (NRDC) and Supoprters	Overall, we are pleased with the work that EPA staff have done, and support their efforts to finalize this assessment in a timely manner, so it can be used to guide health-protective clean up standards and exposure limits. The TCE assessment is long overdue. It was first released as an external draft in 2001, and since then has been stalled, re-shelved, re-reviewed, and re-re-reviewed. Meanwhile, people across the country continue to be exposed to TCE at unsafe levels.	- -
3.1.2	111	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	Page 3-6: The major toxicity of TCE after acute high dose exposure is narcosis. Kidney and liver damage are usually not observed (MAK, 1996).	AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany -
3.2	112	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	Page 3-13: Table 3-6, if the data in the table are not considered reliable why are they presented?	AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany -
3.2	113	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	Page 3-15: Line 27, TCA reversibly binds to proteins and the reversible protein binding is much more relevant for toxicokinetics of TCE as compared to covalent binding. It should also be noted that the 14C-TCE used in many of the early studies contained a number of reactive impurities.	AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany -
3.3	53	EPA-HQ-ORD-2009-0791-0007.1	Natural Resources Defense Council (NRDC) and Supoprters	In the body, TCE is metabolized into several toxic products, including dichloroacetic acid (DCA), trichloroacetic acid (TCA), chloral hydrate, and 2-chloroacetaldehyde. The CDC ATSDR says that “these products have been shown to be toxic to animals and are probably toxic to humans.” 3	- 3 ATSDR Public Health Statement for trichloroethylene. Updated in 2008. Available at http://www.atsdr.cdc.gov/toxprofiles/phs19.html
3.3	96	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>* Kinetic studies on acetylation, and β-lyase-mediated metabolism of DCVC support a low flux through β-lyase activation since the relative flux through the N-acetylation pathway (detoxication) is one to two orders of magnitude higher than through β-lyase activation (Green et al., 1997a). In addition, a low flux through β-lyase is indicated by the recovery of most of a low intravenous dose of DCVC isomers in urine as mercapturic acids in rats (Birner et al., 1997), the weak nephrotoxicity of DCVC (Green et al., 1997a) and observations with PERC, which is also metabolized by glutathione S-conjugate formation and β-lyase. The PERC metabolite S-(1,2,2-trichlorovinyl)-L-cysteine is cleaved by β-lyase to dichloroacetic acid (DCA) which, when formed in the kidney, is excreted with urine. While DCA is a metabolite of PERC in rats, this compound is not excreted as a PERC metabolite in humans (Völkel et al., 1998). In addition, dichloroacetylated proteins were detected both in rat kidney proteins and rat blood proteins after PERC inhalation. Such protein modifications were not detected in blood proteins from humans after identical exposures (Pähler et al., 1999). These observations indicate that flux through β-lyase in humans is even lower than in rodents.</p> <p>* Chloroacetic acid is formed by β-lyase from DCVC (Dekant et al., 1988). In rodents, chloroacetic acid and its</p>	<p>AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany</p> <p>Green, T., Dow, J., Ellis, M. K., Foster, J. R., and Odum, J. (1997a). The role of glutathione conjugation in the development of kidney tumours in rats exposed to trichloroethylene. <i>Chemico-Biological Interactions</i> 105, 99-117.</p> <p>Birner, G., Bernauer, U., Werner, M., and Dekant, W. (1997). Biotransformation, excretion and nephrotoxicity of haloalkene-derived cysteine S-conjugates. <i>Arch Toxicol</i> 72, 1-8.</p> <p>Völkel, W., Friedewald, M., Lederer, E., Pähler, A., Parker, J., and Dekant, W. (1998). Biotransformation of perchloroethene: dose-dependent excretion of trichloroacetic acid, dichloroacetic acid and N-acetyl-S-(trichlorovinyl)-L-cysteine in rats and humans after inhalation. <i>Toxicology and Applied Pharmacology</i> 153, 20-27.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				metabolites (Green and Hathway, 1975; Green and Hathway, 1977) are not significant metabolites of TCE (< 0.1 % of radioactivity in urine) (Dekant et al., 1984; Dekant et al., 1986a). If the β -lyase pathway is more relevant, such metabolites should be present in urine in higher concentrations. Other metabolites indicative of alternative processing of DCVC have also not been detected in humans exposed to TCE (Bloemen et al., 2001).	<p>Dekant, W., Berthold, K., Vamvakas, S., Henschler, D., and Anders, M. W. (1988). Thioacylating intermediates as metabolites of S-(1,2-dichlorovinyl)-L-cysteine and S-(1,2,2-trichlorovinyl)-L-cysteine formed by cysteine conjugate β-lyase. <i>Chemical Research in Toxicology</i> 1, 175-178.</p> <p>Green, T., and Hathway, D. E. (1975). The biological fate in rats of vinyl chloride in relation to its oncogenicity. <i>Chem Biol Interact</i> 11, 545-562.</p> <p>Green, T., and Hathway, D. E. (1977). The chemistry and biogenesis of the S-containing metabolites of vinyl chloride in rats. <i>Chem Biol Interact</i> 17, 137-150.</p> <p>Dekant, W., Metzler, M., and Henschler, D. (1984). Novel metabolites of trichloroethylene through dechlorination reactions in rats, mice and humans. <i>Biochem. Pharmacol.</i> 33, 2021-2027.</p> <p>Dekant, W., Schulz, A., Metzler, M., and Henschler, D. (1986a). Absorption, elimination and metabolism of trichloroethylene: a quantitative comparison between rats and mice. <i>Xenobiotica</i> 16, 143-152.</p> <p>Bloemen, L. J., Monster, A. C., Kezic, S., Commandeur, J. N., Veulemans, H., Vermeulen, N. P., and Wilmer, J. W. (2001). Study on the cytochrome P-450- and glutathione-dependent biotransformation of trichloroethylene in humans. <i>Int Arch Occup Environ Health</i> 74, 102-108.</p>
3.3.2	114	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	Page 3-23: Regarding saturation of TCE metabolism in humans, none of the human studies used dose-ranges where saturation of metabolism was seen in rats. Therefore, this conclusion should be removed.	AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany -
3.3.3.1	115	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	Page 3-24: Lines 9 to 14, the text is not logical. TCE oxide may rearrange to dichloroacetyl chloride and the TCE P450 intermediate may rearrange to give chloral (Miller and Guengerich, 1982; Liebler and Guengerich, 1983; Cai and Guengerich, 2001).	<p>AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany</p> <p>Miller, R. E., and Guengerich, F. P. (1982). Oxidation of trichloroethylene by liver microsomal cytochrome P-450: evidence for chlorine migration in a transition state not involving trichloroethylene oxide. <i>Biochemistry</i> 21, 1090-1097.</p> <p>Liebler, D. C., and Guengerich, F. P. (1983). Olefin oxidation by cytochrome P-450: evidence for group migration in catalytic intermediates formed with vinylidene chloride and trans-1-phenyl-1-butene. <i>Biochemistry</i> 22, 5482-5489.</p> <p>Cai, H., and Guengerich, F. P. (2001). Reaction of trichloroethylene and trichloroethylene oxide with cytochrome P450 enzymes: inactivation and sites of modification. <i>Chem Res Toxicol</i> 14, 451-458.</p>
3.3.3.1	116	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	Page 3-25: Lines 20 to 23, TCE oxide does not rearrange to chloral. Therefore, the text is confusing.	AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany -
3.3.3.1	117	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	Page 3-27, Lines 19 to 25, chloral hydrate has been identified as a circulating TCE metabolite and is also formed as the major product in the microsomal oxidation of TCE (Byington and Leibman, 1965; Cole et al., 1975).	<p>AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany</p> <p>Byington, K. H., and Leibman, K. C. (1965). Metabolism of trichloroethylene in liver microsomes. II. Identification of the reaction product as chloral hydrate. <i>Mol Pharmacol</i> 1, 247-254.</p> <p>Cole, W. J., Mitchell, R. G., and Salamonsen, R. F. (1975). Isolation, characterization and quantitation of chloral hydrate as a transient metabolite of trichloroethylene in man using electron capture gas chromatography and mass fragmentography. <i>J Pharm Pharmacol</i> 27, 167-171.</p>
3.3.3.1	118	EPA-HQ-ORD-2009-0791-	Halogenated Solvents Industry	Page 3-35: Metabolite recovery data in male and female human beings are available. In addition, metabolite excretion in humans and rats exposed to TCE by inhalation under identical conditions are available (Bernauer et al., 1996).	<p>AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany</p> <p>Bernauer, U., Birner, G., Dekant, W., and Henschler, D. (1996). Biotransformation of trichloroethene:</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
		0018.1	Alliance, Inc.		dose-dependent excretion of 2,2,2-trichloro-metabolites and mercapturic acids in rats and humans after inhalation. Arch Toxicol 70, 338-346.
3.3.3.2	120	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	Page 3-44: Table 3-23 should include additional data on GSH-conjugation of TCE (Dekant et al., 1990; Green et al., 1997a).	AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany Dekant, W., Koob, M., and Henschler, D. (1990). Metabolism of trichloroethene - in vivo and in vitro evidence for activation by glutathione conjugation. Chemico-Biological Interactions 73, 89-101. Green, T., Dow, J., Ellis, M. K., Foster, J. R., and Odum, J. (1997a). The role of glutathione conjugation in the development of kidney tumours in rats exposed to trichloroethylene. Chemico-Biological Interactions 105, 99-117.
3.3.3.2	122	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	Page 3-46: Information on β -lyase catalyzed metabolism of DCVC is available (Green et al., 1997a).	AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany Green, T., Dow, J., Ellis, M. K., Foster, J. R., and Odum, J. (1997a). The role of glutathione conjugation in the development of kidney tumours in rats exposed to trichloroethylene. Chemico-Biological Interactions 105, 99-117.
3.3.3.2	124	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	Page 3-47: DCVC-sulfoxide; it should be mentioned that sulfoxides and down-stream metabolites have never been identified in rodents after administration of TCE (or PERC) and therefore are, at best, formed in small traces.	AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany -
3.5	133	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	There is considerable uncertainty in the proposed RfC of 0.001 ppm for TCE, particularly related to potential uncertainty in the Physiologically Based Pharmacokinetic (PBPK) modeling of the DCVC dose metric in humans, and the relationship of that dose metric with increased kidney weight.	AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp. -
3.5	135	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>The allowance for inter-human PK variability double counts and misconstrues the nature of the dose-response curve.</p> <p>There are two questions about the allowance for human variability in metabolic activation. The first, addressed elsewhere in these comments, is whether the extent of variability has been reliably estimated. The second, addressed here, is how allowance for variability has been entered in to the RfD/C calculations. It would appear that allowance for human variability has been double-counted because inter-individual variability is built in to the tolerance distribution-based dose-response curve.</p> <p>The method employed in the document is to set a point of departure (PoD) on the animal-based dose-response curve, using central estimates of "standard rat" internal doses as the dose measure. That is, inter-individual PK variation among rats, even though it exists, was not estimated and not considered in the dose-response curve estimation. For non-cancer endpoints, the dose-response curve is interpreted as a tolerance distribution – as the cumulative distribution of individual sensitivity variation. The reason that some animals respond at a given (externally applied) dose and others do not is that some have their individual tolerances exceeded while others do not, and higher doses exceed the individual tolerances of a greater fraction of the variable population, thereby yielding higher disease incidences.</p> <p>Some of this variation is in PK, and so to some extent, the rats that respond do so because they are more vulnerable owing to their individual PK variation that makes them have a higher proportionality of internal to external dose. The contribution of this effect is captured in the fitted dose-response curve, which also reflects variation in sensitivity for other, non-PK reasons, but the contributions of PK variation are already incorporated, and are not readily split out without some attempt to characterize PK variation among individual rats.</p> <p>The rat dose-response curve is then used to determine a PoD by finding a dose that yields a low predicted response, say 1%. Because the dose scale is measured in average internal dose among the rats, the dose associated with a 1% response level is the average internal dose for rats such that 1% of them are expected to have their individual tolerances exceeded. For the sake of argument, if we hypothetically say that there is</p>	AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp. -

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>absolutely no inter-rat variation in PK, then all the rats in a hypothetical experiment at the 1% response dose will have the same internal dose, and which rats respond and which do not will be ruled entirely by variation in pharmacodynamic (PD) sensitivity to this fixed internal dose. But, if one instead hypothesizes that variation in sensitivity is entirely ruled by PK variation (with no contribution of PD variability) then the 1% of rats responding are that same 1% that are most sensitive owing to their PK variation – that is, they are the 99th percentile of the internal dose distribution.</p> <p>The reality is somewhere in between, with both PK and PD variability contributing to variation in ability to tolerate the dose. But without characterization of PK variation among individual rats, we have no way to split the components out (though there is the conventional split between PK and PD that we apply to Uncertainty Factors).</p> <p>Staying with the hypothetical case that sensitivity variation is all in PK, then the only reason to make further allowance for human PK variation is if variation in PK among humans is greater than variation among rats, and even then the correction should only be for the degree to which it is greater – that is, the ratio of the 99th percentile in humans versus the 99th percentile in rats rather than the ratio of the 99th to the 50th percentile in humans.</p> <p>The hypothetical case of pure PK dependence of sensitivity variation is made to clarify the argument, but in the real case of contributions from both PK and PD, the principle illustrated still applies. There is some mix of influence of PK- and PD-based sensitivity among the responding rats, and the effect of this is captured in the fitted dose-response curve, for which the dose variable is the average internal dose. That internal dose is likely higher on average among the 1% of rats responding, because of the contribution of PK to their sensitivity; but, since this is unmeasured, all the analysis can say is that when a group of rats is dosed at a given external level, the average internal dose among them has some level estimated by the rat PBPK model. In view of the (unknown) contribution of PK to sensitivity and the (unknown) degree to which PK varies among rats, there is some (unknown) degree to which some rats have higher-than-average internal doses and thereby have an increased response probability (which is dictated by PD sensitivity to internal dose levels).</p> <p>When the rat PoD is extrapolated to a human PoD based on average PK in the two species, it implicitly assumes that the mix of PK and PD, and the extent of inter-individual variation in PK, are the same in humans as in the rats. If one then makes a correction for the difference between the 50th percentile of PK in humans and the 99th percentile (as the draft reassessment does) it essentially implicitly assumes that all of the variation in sensitivity reflected in the dose-response curve is attributable to PK alone.</p> <p>If one assumes that the mix of PK and PD influence is similar across species, then the correct correction is the ratio of 99th percentiles across species, but since the 99th percentile in rats is not estimated, this cannot be calculated. If one cannot assume that the mix of PK and PD is the same, then it is doubly impossible to calculate a correction.</p> <p>The method that has been employed in the draft reassessment seems to implicitly assume that all of the dose-response in rats is attributable to PD (and this drives the PoD down as far as possible in internal-dose terms) and that all of the dose-response in humans is attributable to PK (and this drives the sensitive human allowance down as far as possible). The net result is to yield an RfC that is overcorrected for human inter-individual variation to a degree that is not possible to know with the analyses available.</p>	
3.5	139	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>Transparency means more than just showing all the calculations in large appendices; there is a critical need for effective communication about the impact of choices and judgments that are made, about the basis for those judgments, and about the impacts of those judgments vis-à-vis possible alternatives on the final outcome.</p> <p>For example, it should be made clear that the chief impact on changing the RfD/C from what they would be under default procedures (and from how they were previously characterized) is the invocation of much greater flux through the conjugative metabolic pathway in humans than had previously been estimated. As discussed further elsewhere in these comments, this result is the chief reason that an internal-dose basis for an RfC based on kidney toxicity comes out much lower than if the RfC were based on other endpoints or on applied dose,</p>	AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp. -

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>though this conclusion is not obvious without deep reading of the document and detailed tracing of the calculations. There are reasons to question whether this finding of high human flux through the conjugative pathway is correct (as discussed elsewhere), but any discussion of that question and any documentation of the basis for that conclusion is far removed from its application in a later chapter. The discussion of what pathway, and what measure of that pathway's activity, is best used as an internal dose metric for kidney toxicity is in yet another place, and these conclusions can also be questioned. But again, that discussion (to the extent it exists anywhere) is far removed from its place of application.</p>	
3.5	142	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>It is not clear that DCVC constitutes an appropriate basis for an internal dose metric for kidney non-cancer toxicity.</p> <p>The kidney is seen as a sensitive target, and low RfC values drive the consideration of an overall RfC. The incorporation of internal doses makes the calculated RfC much lower than it would be if based on administered doses. It is therefore critically important that the internal-dose basis of kidney toxicity characterization be correct and reliable. The changes in non-cancer toxicity standards implied by the analyses in the Draft Reassessment hinge largely on assumptions about the PK of internal doses in kidney in rats and humans; and, if these assumptions are wrong, the basis for lowering the RfC is lost.</p> <p>This being said, there are many questions about the PK assumptions that have been employed. First is the choice of DCVC as the basis for the dose metric. Just because DCVC is used for kidney cancer evaluation does not mean that the same dose measure is appropriate for non-cancer toxicity. Indeed, Lash et al. (2000) describe formic acid as a potential mode of action (MOA) for kidney damage for TCE, distinguishing the case of cancer and non-cancer kidney effects, stating, "Hence, although formic acid formation may contribute to TCE-induced renal damage, this is not likely to be a significant MOA in TCE-induced kidney carcinogenesis" (emphasis added). While the beta-lyase pathway may play a predominant role in kidney carcinogenesis, the possible roles of other chemical actors (formic acid and trichloroethanol) are not adequately addressed. The PBPK modeling effort focuses solely on the products of the beta-lyase pathway and apparently ignores these other possibilities. The conclusions are accordingly dependent on this being the correct dose metric. If alternative pathways could be addressed via the model, this could either provide some support for US EPA's position that they are not relevant or it could show that a different dose metric is warranted. The current argument, i.e., that there are differences in kidney histopathology between TCE- and trichloroethanol-treated rats, and that this indicates a different MOA, is not particularly compelling.</p>	AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp.
3.5	146	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>The document's conclusion that humans have high flux through the conjugative pathway is at odds with previous assessments, and is not well supported by evidence; yet, this assumption markedly lowers RfC/D values compared to those using traditional applied-dose approaches.</p> <p>The consensus of scientific opinion had been that humans have low flux through the conjugative pathway, which would lead to low internal doses to the kidney. It was also the consensus that it is difficult to pin down the extent of flux through this pathway for experimental reasons. The draft reassessment document indicates that the human flux through the conjugation pathway can be concluded to be much greater than in rats. In view of the importance of this judgment to the eventual RfD/C, it must be clearly explained why this altered conclusion is warranted.</p> <p>As stated on page 3-128, the PBPK model reports one to two orders of magnitude more glutathione (GSH) conjugation and DCVC bioactivation in humans relative to rats. US EPA acknowledges that the 95% confidence intervals of the predicted population means for the two species overlap but there is little discussion of how this result is inconsistent with much of the previous data on TCE metabolism and TCE health effects in both humans and animals. For example, Lash et al. (2000) state that metabolic studies of PCE and Compound A indicate greater flux through the beta-lyase pathway in rats compared to humans (i.e., several fold higher in rodents). It would be unusual if TCE were somehow different from these structurally similar compounds such that the flux in humans was many times higher than in rats. Along similar lines, Lash et al. (2007) state that the flux of tetrachloroethylene (PCE) through the GSH pathway is approximately fivefold faster in rodents than that of TCE. They also indicate that the reactive intermediates derived via the beta-lyase pathway from PCE are more reactive than those derived from TCE. This would suggest that PCE should be a much stronger kidney toxicant than TCE in the rat; yet, to our knowledge, neither chemical could be regarded as a very potent nephrotoxicant.</p>	<p>AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp.</p> <p>Lash, LH; Parker, JC; Scott, CS. 2000. "Modes of action of trichloroethylene for kidney tumorigenesis." Environ. Health Perspect. 108(Suppl. 2):225-240.</p> <p>National Toxicology Program (NTP). 1990. "Carcinogenesis studies of trichloroethylene (without epichlorohydrin) (CAS No. 79-01-6) in F344/N rats and B6C3F1 mice (gavage studies)." Research Triangle Park, NC. National Institutes of Health. NTP TR 243; NIH Publication No. 90-1779. 174p., May.</p> <p>National Institute of Health (NIH). 1977. "Bioassay of tetrachloroethylene for possible carcinogenicity." Bethesda, MD. National Technical Information Service (NTIS), Springfield, VA. NCI-CG-TR-13; NIH 77-813.</p> <p>Lash, LH; Putt, DA; Huang, P; Hueni, SE; Parker, JC. 2007. "Modulation of hepatic and renal metabolism and toxicity of trichloroethylene and perchloroethylene by alterations in status of cytochrome P450 and glutathione." Toxicology 235(1-2):11-26.</p> <p>Henschler, D; Vamvakas, S; Lammert, M; Dekant, W; Kraus, B; Thomas, B; Ulm, K. 1995. "Increased incidence of renal cell tumors in a cohort of cardboard workers exposed to trichloroethene." Arch. Toxicol. 69(5):291-299.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>For example, in the National Toxicology Program (NTP) and National Institute of Health (NIH) oral bioassays (NTP, 1990; NIH, 1977) toxic nephrosis was observed in rats treated with either chemical and at similar doses. In human studies, neither chemical is consistently shown to be a potent nephrotoxicant (if anything, studies such as that by Henschler et al. (1995) would suggest TCE is more potent). This line of reasoning argues against the primary role of the beta-lyase pathway in PCE/TCE nephrotoxicity, and should be discussed in the document.</p> <p>The basis for finding such large human flux through the conjugative pathway is also questionable. The result comes from the hierarchical Bayesian analysis of the PBPK model. The US EPA PBPK model yields good fits to the rat and human urinary DCVC excretion data and also to S-dichlorovinyl glutathione (DCVG) measured in human blood. We would suggest caution, however, in assuming that just because the model, as formulated and parameterized, fits the available DCVC/DCVG data, that highly quantitative predictions can then be made concerning the mean and variation of the various model parameters. This is particularly of concern given the huge changes resulting from the Bayesian updating of the DCVC bioactivation constants (i.e., from 0.14 to 0.0087 in the rat and from 0.0021 to 0.023 in the human). The basis for the prior is not clear, but what is evident is that something other than direct experimental characterization is driving the updated DCVC bioactivation result, and some direct confirmation that such large flux actually occurs would seem critical to using this result in so influential a manner.</p> <p>Given the disparity between the model results and prior general scientific opinion about rat vs. human differences in GSH conjugation towards TCE, it would be valuable to use the model to predict what possible DCVC target organ doses would be for some of the key epidemiology studies. The reported prevalence of kidney damage could then be compared across studies for logical consistency with estimated DCVC concentrations. This would serve as a useful "reality check" for a model that is making novel claims regarding chemical toxicity. In any case, a clear and convincing case must be made as to why the previous scientific consensus about human DCVC activation and its estimation is being overturned.</p>	
3.5	149	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>Reliable estimates of the extent of variability among humans in DCVC activation have not been established, yet this factor is very influential in lowering the RfC/D.</p> <p>It is not only the high estimate of the average amount of human DCVC activation via flux through the conjugative pathway that results in markedly lowered reference values, it is also the calculation of the impact of estimated variability among humans in this rate. Elsewhere in these comments it is argued that the method for considering the impact of inter-human variability is flawed; but, in addition, there is the question of how reliably its extent has been estimated. In the previous comment it was noted that the soundness of the basis for estimating a much-changed average DCVC activation is unclear in view of widely acknowledged experimental difficulties and the evident influence of the Bayesian updating procedure. This concern applies even more to the characterization of variation among individuals, and great care must be taken to avoid attributing to genuine inter-individual variability differences that are really just due to experimental error, which can have marked effects for measurements on single individuals.</p> <p>US EPA notes that the variability in the renal GSH conjugation and bioactivation of DCVC is substantial due to the data set of Lash et al. (1999, as cited in the assessment). The Lash et al. data set, consisting of eight males and eight females in the 100-ppm dose group and five individuals (three males, two females) in the 50-ppm dose group is indeed very limited for characterizing such an important parameter in the model. The stability of any variance estimate drawn from such a small sample size (when developing a model meant to characterize the whole human population) should be viewed as tentative. This has fairly important implications when attempting to use the PBPK model for RfC calculations in ways meant to protect large fractions (i.e., 99%) of the human population. It would also be helpful to show the model predictions as compared to Lash et al.'s results for the 50-ppm dose group (Figure 3-10 only shows the 100-ppm group) to get a better sense of the model's predictive ability at lower exposure concentrations.</p>	<p>AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp.</p> <p>-</p>
3.5	155	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>There is uncertainty in the PBPK model reflecting a higher DCVC bioactivation in humans than in rodents.</p> <p>In addition, the one p-cRfC that was based on an inhalation study (Woolhiser et al., 2006) was 400-fold lower than the cRfC derived from the applied dose default methodology from the same study. US EPA discusses how this difference is due to a 30- to 100-fold difference between rats and humans in DCVC bioactivation that is</p>	<p>AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp.</p> <p>-</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				reflected in the PBPK modeling, with humans having a higher level of DCVC bioactivation in the model. As discussed above, there is uncertainty in this difference that needs careful consideration before placing such emphasis on this model as the basis of an inhalation RfC. Given that the Woolhiser et al. (2006) study is the only inhalation study in this narrow lower end of the range, this study inherently provides more weight to the proposed RfC than the other four oral studies, and is discussed in more detail below.	
3.5	160	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	Although derivation and consideration of a range of RfCs is a sound approach to deriving an RfC, choosing the lowest range of RfCs (without a sufficient weight-of-evidence evaluation of the RfCs in that range), reflected by only one inhalation study for which the effect of increased kidney weight is questionable, is not strongly supported by the scientific evidence for TCE non-cancer effects. This is based on: (1) the fact that the significance of the observed effect in the Woolhiser study was weak and based on a small sample size; (2) uncertainty in the oral to inhalation route-to-route extrapolation for the five other RfCs in the range; (3) uncertainty in the PBPK model reflecting a higher DCVC bioactivation in humans than in rodents that was used for three of these RfCs; (4) uncertainty in the relevance of increased kidney weight as a critical effect for non-cancer effects of TCE; and finally, (5) the fact that there is another narrow range of six RfCs (from 0.013 to 0.12 ppm) that are all based on inhalation studies and for which, had a level of confidence in those RfCs been presented, might in fact reflect a more robust set of RfCs, base on a weight-of-evidence analysis of those endpoints.	AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp. -
3.5	186	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	Lack of sensitivity analyses to identify key data sets and assumptions in models and numerical derivations. The key risk outcomes of the assessment are based on multiple assumptions and data sets. AIA agrees with DOD and NASA that sensitivity analyses are needed to test the effects of these assumptions and to enable evaluation of the most important assumptions.	AUTHOR: Lisa Goldberg -
3.5	214	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>Lisa M. Sweeney, Ph.D., DABT Toxicology Excellence for Risk Assessment</p> <p>The extensive use of complex modeling in the trichloroethylene (TCE) assessment presents a formidable challenge to scientific peer review. EPA should facilitate peer review by providing an analysis of the most influential assumptions (commonly referred to as a "sensitivity analysis"). Such an analysis would not have to be complex itself, or delay the review of tile draft excessively. However, a sensitivity analysis is necessary to provide a sufficient review of this document.</p> <p>Some key assumptions in the physiologically based pharmacokinetic (PBPK) and dose response modeling in the assessment provide an example of why such an analysis is needed. For example, the assumption of glutathione (GSH) conjugation rate differences between humans and rodents apparently has a several hundred fold effect on the derived values for the inhalation reference concentrations. This assumption appears to be only weakly supported by the weight of the evidence; EPA's own statistical analysis of the related dose metrics also casts doubt on its validity. EPA should use other data in the literature to improve this parameter estimate.</p> <p>Other examples that show tile value of a sensitivity analysis are presented. Please consider the value of providing such an analysis to the Scientific Advisory Board reviewers and provide them with the information they need to conduct a full and scientifically robust peer review of this document.</p>	AUTHOR: Lisa M. Sweeney, Ph.D., DABT -
3.5	217	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	The comments provided below focus on physiologically based pharmacokinetic (PBPK) modeling, its role in the Agency's assessment of TCE, and the uncertainty regarding the model. Clearly, the Agency has devoted a great deal of effort to developing and applying PBPK models in the TCE risk assessment. The use of Bayesian analysis to integrate a large number of kinetic studies of TCE and its key metabolites, conducted in three species, is a very impressive accomplishment. As the precedents for use of these approaches for PBPK model development and application in risk assessment are limited, it is important that key assumptions and criteria for use in the risk assessment be clearly articulated so that the scientific community can evaluate the modeling of TCE and how it was applied. To that end, we identify the need for sensitivity analyses to identify these key assumptions, such that they may be subjected to proper scrutiny.	AUTHOR: Lisa M. Sweeney, Ph.D., DABT -
3.5	219	EPA-HQ-ORD-2009-0791-	Aerospace Industries Association	<p>WHY IS SCRUTINY OF THE TCE PBPK MODEL IMPORTANT?</p> <p>The use of PBPK model-derived estimates of GSH metabolism as a metric (rather than applied dose) for kidney</p>	AUTHOR: Lisa M. Sweeney, Ph.D., DABT -

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
		0009.1	(AIA)	<p>toxicity had a 300- to 400-fold impact on the cRfC and RID (p. 5-51), after taking into account dose-response and interspecies differences. The use of internal dose metrics is generally preferred over applied dose when the data are sufficient, support the choice of dose metric, and tie the dose metric to the endpoint of interest, because such internal dose metrics are more predictive of the observed toxicity. Although there is not necessarily an inherent problem with dose metrics that differ markedly from applied dose measures, such barge differences call for greater scrutiny of the reasons for the differences, and increase the importance of the consideration of the implications of uncertainties. The use of GSH metabolism (calculated using the PBPK model) as the dose metric for the kidney resulted in kidney effects being identified as one of the key noncancer effects. Intuitively, the 300 to 400-fold difference in the calculated cRfC and cRfD must somehow be related to the values of the parameters in the PBPK model, most likely those pertaining to GSH metabolism, but it is not necessarily clear which parameters are the key drivers, and whether large interspecies differences in these parameters are supportable based on the available data.</p>	
3.5	222	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>CONSIDERATION OF CONFIDENCE AND UNCERTAINTIES IN THE CURRENT PBPK MODEL PARAMETER ESTIMATES</p> <p>GSH conjugation pathway rate estimates</p> <p>The extremely broad posterior distributions of the mouse GSH pathway parameters resulting from the Bayesian model optimization (e.g. 2.5% and 97.5% values of 0.1 l and 3,700,000 mg/L, a range exceeding 7 orders of magnitude, for the Km for hepatic TCE GSH conjugation) (p. 3-93) indicate that the parameterization is highly uncertain. The extremely large differences in optimized, posterior estimates of Km for hepatic GSH conjugation in humans vs. rats or mice (approximately 1000-fold difference, based on median values) are contrary to the understanding that similar enzymes are involved in TCE conjugation across species. Since no mouse or rat S-dichlorovinyl glutathione (DCVG) data were used for model calibration and the differences between rodent and human Kms for DCVG production seem implausible, we conclude that the parameterization of the GSH pathway is highly suspect.</p>	<p>AUTHOR: Lisa M. Sweeney, Ph.D., DABT</p> <p>-</p>
3.5	224	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>Partition coefficients</p> <p>Data in the literature do not generally support extensive interindividual variability in partition coefficients. For example, when the blood:air partition coefficient of 1,3-butadiene was measured in vitro for 24 human subjects, the values ranged from 1.22 to 1.84, with a mean +/- standard deviation of 1.57 +/- 0.14 (Lin et al., 2002). In contrast, in some cases the posterior distributions of partition coefficients developed in EPA's analyses of TCE and its metabolites cover very wide ranges (p. 3-90). For example, the posterior estimate of the free trichloroacetic acid (TCA) body:blood partition coefficient in the rat had a median value of 0.77 with 2.5th percentile and 97.5 percentile estimates of 0.24 and 2.7, suggesting greater than 10-fold differences to cover 95% of the population. It is unlikely that this parameter is truly this variable, particularly in a standard rat colony, in light of the typically small variability in rats and in the more variable human population. If the posterior distributions of the partitioning parameters are allowed to be more variable than is realistic, it is likely that the optimization process shifted the variability away from other parameters (which could truly be more uncertain and/or variable) in order to create best-fit parameter distributions. As a result, these other parameters could appear more narrowly distributed than they would in the absence of high partition coefficient variability.</p>	<p>AUTHOR: Lisa M. Sweeney, Ph.D., DABT</p> <p>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.</p>
3.5	226	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>Oral Absorption Rates</p> <p>The distributions for absorption parameters for corn oil and water gavage (p. 3-92) were highly variable -the ratio of the 97.5% and 2.5% values frequently exceeds 100,000-fold. A likely contributor was inappropriately lumping absorption rate from both cam oil and water into a single distribution, rather than separate distributions.</p> <p>Uncertainty in Calculated Dose Metrics</p> <p>The uncertainty in the parameter values produces uncertainty in the calculated dose metrics. Specifically, the EPA analyses considered dichlorovinyl cysteine (DCVC) bioactivation as a metric for rat kidney effects, while</p>	<p>AUTHOR: Lisa M. Sweeney, Ph.D., DABT</p> <p>Chiu WA; Okino MS, Evans MV. Characterizing uncertainty and population variability in the toxicokinetics of trichloroethylene and metabolites in mice, rats, and humans using an updated database, physiologically based pharmacokinetic (PBPK) model, and Bayesian approach. Toxicol Appl Pharmacol. 2009; 241 (1):36-60.</p> <p>Evans MV, Chiu WA, Okino MS, Caldwell JC. Development of an updated PBPK model for trichloroethylene and metabolites in mice, and its application to discern the role of oxidative metabolism in TCE-induced hepatomegaly. Toxicol Appl Pharmacol. 2009; 236(3):329-40.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>the analyses for mouse kidney effects relied on the dose metric of total GSH produced, due to lack of data on DCVG and DCVC in the mouse. The 95% confidence limits for the population median estimates of the fraction of intake that is conjugated with GSH cover a very large range of values; spanning over 3 orders of magnitude at concentrations and doses of toxicological interest in mice, and spanning about 1.5 orders of magnitude in rats. As noted by EPA, this range reflects only uncertainty, not variability. The DCVC bioactivation estimates in rats are highly uncertain, with the 95% confidence limits on the median spanning a range of 2 orders of magnitude. EPA acknowledges that the predictions related to GSH conjugation for rats and mice "remain more uncertain" than the human predictions (p. 3-131), but then states that GSH metabolism dose metrics were fairly well- characterized in rats (p. 3-138, line 4.). This large uncertainty in the dose metric necessarily translates to uncertainty in the corresponding cRfC and cRfD.</p> <p>The uncertainty of the estimate of "other" liver oxidation is also quite substantial (95% confidence limits approaching a 100-fold range). This uncertainty does not have a substantial impact on the risk assessment because this metric was not used to derive any reference values or slope factors.</p> <p>MODEL PARAMETER ESTIMATES COULD (AND SHOULD) BE IMPROVED USING CURRENTLY AVAILABLE DATA</p> <p>Data that could potentially improve the estimation of PBPK model parameters, including some of the highly uncertain parameters, are currently available. Some of these data were clearly available to EPA at the time of model development; other data were more recently published, but should certainly be considered at this time to improve the models as described in the IRIS draft and published, peer-reviewed versions of the model (Chiu et al., 2009; Evans et al., 2009).</p> <p>EPA has compared the predictions of the models they used to the following recently published data sets for mice and reported their findings (Appendix A, Section A.6 and linked files).</p> <p>Kiln et al. (2009) provide blood DCVG and DCVC time course data for mice dosed with 2000 mg TCE/kg BW (corn oil gavage). The model (as used in the assessment) consistently underpredicted the blood DCVG data. (DCVC is not currently considered in the model structure.) Best fit parameters for the Kim et al. (2009) study were then developed. These new parameters were then used to estimate the fractional flux through the GSH pathway for mice continuously exposed to TCE via ingestion. It was found that the new, best-fit parameters resulted in a substantially lower fraction of ingested TCE being predicted to be metabolized by the GSH pathway in mice (three-fold lower). Hence, for any oral studies in mice, the potency of any GSH metabolite was likely overestimated by 3-fold, with corresponding underestimates in human cRfDs based on these dose metrics. While EPA may consider the parameters used in the assessment to be "reasonably consistent with the Kiln et al. (2009) data" (p. A-75, line 9); a potential three-fold change in candidate RfDs for a key endpoint deserves to be followed up.</p> <p>EPA also compares the model used in the assessment to additional mouse TCA kinetic data from Kim et al (2009) and data collected by Green (2003) and Mahle et al (2001) that were reported by Sweeney et al. (2009). Some large discrepancies were observed, especially at higher dosages and for females. EPA attributes these discrepancies in part to liver metabolism (assumed negligible in the Sweeney et al. (2009) model); but first pass metabolism does not explain the less-than linear increases in blood TCA observed for increasing drinking water concentration of TCA (Mahle et al., 2001). If anything, the impact of first pass metabolism should decrease with increasing drinking water concentration of TCA.</p> <p>Other model structures could be considered by EPA. The performance of the GSH-related metrics in the rodent models could potentially be improved by consideration of the Kim et al (2009) mouse DCVC blood data and the rat DCVC data of Birner et al. (1997).</p> <p>Another example of how it might be helpful to consider alternate model structures concerns the human data of Chiu et al. (2007). It is disconcerting that the greatest discrepancies between the model and the tested human database were for the Chiu et al. (2007) data. This data set is particularly important because the study involved volunteers exposed to 1 ppm TCE. In contrast, the bulk of the human calibration and validation data were for</p>	<p>Kim S, Kim D, Pollack GM, Colhns 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. <i>Toxicol Appl Pharmacol.</i> 2009; 238(1):90-9.</p> <p>Sweeney LM, Kirman CR, Gargas ML, Dugard PH. Contribution of trichloroacetic acid to liver tumors observed in perchloroethylene (pert)-exposed mice. <i>Toxicology.</i> 2009; 260(1-3):77-83.</p> <p>Birner G, Bernauer U, Werner M, Dekant W. Biotransformation, excretion and nephrotoxicity of haloalkene-derived cysteine S-conjugates. <i>Arch Toxicol.</i> 1997; 72(1): 1-8.</p> <p>Liao KH, Tan YM, Clewell HJ 3rd. Development of a screening approach to interpret human biomonitoring data on volatile organic compounds: reverse dosimetry of biomonitoring data for trichloroethylene. <i>Risk Anal.</i> 2007; 27(5):1223-36.</p> <p>U.S. Environmental Protection Agency (EPA). (2006) Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment. National Center for Environmental Assessment, Washington, DC; EPA/600/R-05/043F. Available from: National Technical Information Service, Springfield, VA, and online at http://epa.gov/ncea.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>much higher exposures (40 ppm- 160 ppm). Since the Chiu et al. (2007) exposures were at levels most relevant to current environmental or occupational exposures, it would be desirable for the model to fit the data, and the lack of fit is a concern. It is our assumption that the residual error statistics reported in Appendix A (e.g., Table A-14 on p. A-73 for humans) reflect the discrepancies between the data and the predictions generated from the group-specific distributions of parameters. As such, the group-specific parameter distributions reflect an interpretation of the fit between the data and the model that should provide the least discrepancy -a comparison between the data and the population-based parameters would yield a greater residual error. Clearly, based on a review of both the individual-specific and population-based predictions, the "fit" is worse when the population-based parameters are used instead of the individual-specific parameter values. Despite the ability to generate individual-specific parameter distributions, the discrepancies for the Chiu et al. (2007) data exceed 2.0 (a cut-off value used by EPA to indicate a concern -p. 3-99) for 3 out of 7 measures (highest value was 2.9 for CVen). Chiu et al. (2007) is the only group that had residual error >2 for any measurement. For 5 out of 7 measures, the Chiu et al. (2007) study had the highest residual error. There does not appear to be any reason to exclude the Chiu et al. (2007) data; rather, as previously noted, fit to this study is of particular interest, since it is the only study with measurements in the low-exposure range of interest for environmental and occupational exposures. EPA has also not tested the model against biomonitoring data, which would also test the model at low doses/concentrations.</p> <p>We recommend that EPA explore the possibility of different model structures that might improve the fit to the Chiu et al. (2007) data without necessarily compromising the fit to the other data. While it does not seem likely that the volunteers in the Chiu et al. (2007) study would be physiologically dramatically different from those in the other 6 groups, some generalizations can be made from the individual specific parameters found in the linked human file for A.5.1. Compared to other individuals/groups, the individuals in the Chiu et al. (2007) study had lower optimized ventilation/perfusion ratios, low blood:air partition coefficients, and low blood flow to slowly perfused tissue but high blood flow to fat and widely scattered values for the slowly perfused tissues: blood partition coefficient. With respect to the biomonitoring data, EPA should consider how the updated model performs with respect to predictions of blood TCE (NHANES data) for the population, given what is known about general populations' exposure to TCE. The approach used could be similar to that used by Liao et al. (2007).</p> <p>MODEL SENSITIVITY ANALYSES THAT COULD (AND SHOULD) BE PERFORMED ON THE EPA TCE PBPK MODEL</p> <p>EPA has not provided any sensitivity analyses of the updated TCE PBPK model. As noted in EPA (2006), "it is important to carry out sensitivity analyses under conditions reflecting the studies providing data for model calibration (i.e., pharmacokinetic studies), under conditions appropriate for estimating dose metrics in critical studies, and finally under conditions appropriate to the risk assessment." To paraphrase, sensitivity analyses are particularly helpful for the following aspects of model evaluation: (1) parameter identifiability, (2) identification of key parameter values with respect to dose metric prediction in test species and (3) identification of key parameter values with respect to dose metric prediction in humans at the toxicity reference value. With respect to (1), parameter identifiability, sensitivity analyses for predictions of experimentally determined dose measures in pharmacokinetic studies indicate whether the available data were in fact useful for "identifying" a parameter value. That is, if no experimentally determined dose measure is sufficiently sensitive to a parameter's value, the data cannot then be said to have contributed to the identification of that parameter's value. Specifically; it is unclear whether the data used in model development allow for unambiguous determination of parameter values for the GSH pathway in mice and rats, in light of the wide confidence limits of the posterior distributions noted above. With respect to (2) and (3), sensitivity analyses of dose metrics used as internal points of departure (iPODs) in rodents and the same metrics in humans help to focus the critical evaluation of the reliability of key parameter estimates that drive the derivation of the toxicity reference values. These analyses are inter-related. The analyses for the iPODs 2 and 3 above can identify which parameters are key in determining the risk values. These risk values are the major conclusions of the report, and understanding the key determinants of uncertainty in the risk values (and the degree of uncertainty in those key determinants) is critical to the credibility and transparency of the calculated risk values. Given the large number of parameters in the model, it is impractical for reviewers to be able to scrutinize all of the parameters or to intuitively know which are "key". Once these "key" parameters are enumerated, the subsequent task is to evaluate whether one is confident that the numerical values of these parameters are reasonably well identified. While the general literature may be consulted for</p>	

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>evaluation of anatomical/physiological parameter values, chemical-specific pharmacokinetic parameters are typically inferred from model fit. Hence, the ability to uniquely and conclusively "identify" these parameter values (#1 above) based on the studies available for fitting is necessary for overall confidence in the risk values identified using the models.</p> <p>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.</p> <p>Regarding 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, RID, and a chosen cancer risk level (e.g., 1 in 10⁵) under conditions of continuous exposure. We recommend that these analyses be conducted for the key endpoints (i.e., those from which the risk values were derived) and the candidate RfCs and RIDs that are within approximately 3-fold of the final RfC and RID.</p> <p>Without conducting the sensitivity analyses, it is difficult to fully anticipate what the results would be, and how that would change the risk assessment. We can speculate, however, that GSH-pathway-related metrics will likely be sensitive to the V_{max} and K_m for this particular pathway; and may also be sensitive to the rates for competing pathways. If it is found that none of the metrics in the experimental studies (e.g.; chamber TCE concentration, blood TCA concentration) are sensitive to the values used for the GSH pathway, it must then be concluded that the parameters for the GSH pathway are not well identified in rodents, so no reliable estimates of these metrics can be used for the derivation of human equivalent concentrations or human equivalent doses. If that is the case, other risk-relevant internal doses or a default approach should be used.</p>	
3.5	234	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>An important consideration, especially when PBPK modeling is to be used, is the choice of dose metric. Assumptions/beliefs about the mode of action are embedded within the choice of dose metric used for dose-response analyses and route-to-route or interspecies extrapolations. Considerations include the use of parent compound vs. total metabolites generated vs. concentrations of specific metabolites, and opting to use peak values, time-weighted average (TWA) values; or cumulative values. For example, why did EPA use TCA produced rather than TWA liver TCA concentration to evaluate the potential dose-response relationship between TCE administration and liver weight increases in mice (Section 4.5)? Until the relationship between TCA and hepatomegaly is properly analyzed, it is premature to assert that TCA is insufficient to account for the rodent liver tumors.</p>	AUTHOR: Lisa M. Sweeney, Ph.D., DABT -
3.5	246	EPA-HQ-ORD-2009-0791-0012.1	McKenna, Long & Aldrige, LLP	<p>New policy: EPA is... *Using PbPk modeling so extensively has the effect of new policy by the sheer magnitude of its influence in the assessment.</p>	- -
3.5	256	EPA-HQ-ORD-2009-0791-0012.1	McKenna, Long & Aldrige, LLP	<p>Main messages: Non-cancer findings The new inhalation reference concentrations depend too heavily on assumptions in the PbPk and dose-response modeling</p>	- -
3.5	259	EPA-HQ-ORD-2009-0791-0012.1	McKenna, Long & Aldrige, LLP	<p>Main messages: Non-cancer findings Assuming higher human production of DCVC is a critical part of the complicated analysis of RfC, RfD, and cancer dose response – It is disputed science and EPA’s analysis appears to show that it does not fit the modeling well</p>	- -
3.5	266	EPA-HQ-ORD-2009-0791-	McKenna, Long & Aldrige, LLP	<p>EPA needs to show the effect of their assumptions and modeling choices - The inter-related PbPk and dose-response modeling for multiple endpoints and dose metrics is so complex that</p>	- -

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
		0012.1		<p>even experts have trouble sifting through it.</p> <p>- Even a simple narrative of the most influential assumptions and data sets (and their support) would be helpful.</p> <p>- The narrative does not have to be exhaustive and time consuming.</p> <p>- Scientists at EPA may already know the most sensitive parameters.</p>	
4	305	EPA-HQ-ORD-2009-0791-0014.1	Exponent Health Services	<p>Specific Comments to EPA Meta-Analysis of Epidemiologic Studies</p> <p>A meta-analysis is a systematic methodological and statistical technique for combining results data across individual studies to produce a more precise “weighted” estimate of relative risk. An equally important function of a meta-analysis is in evaluating potential heterogeneity. Heterogeneity reflects unexplained variation between study results, and a meta-analysis that has significant heterogeneity may not be a valid quantitative summarization of studies (Greenland). Heterogeneity may be the result of differences in study design, measurement techniques, patterns of associations by exposure level or occupational group, underlying differences in health susceptibility in the study populations, or other characteristics. A single meta-analysis model will not indicate the exact source of heterogeneity; rather, it is necessary to conduct a variety of sensitivity analyses by important factors such as intensity or duration of exposure, where applicable. Moreover, even if statistical heterogeneity is not indicated by p-value testing, between-study variability may be present. Thus, relying upon a p-value for heterogeneity in a meta-analysis may provide a false sense of consistency across the literature. To prevent this, sub-group analyses by similar exposure characteristics or other factors should be examined.</p> <p>A meta-analysis cannot answer all facets of causality between an exposure and disease, nor is it intended to do so, but it can clarify or augment the existing literature on any potential associations between an exposure and outcome. As such, a meta-analysis can be considered a type of weight-of-evidence approach to evaluate a body of literature (Weed 2005). A metaanalysis of epidemiologic observational data is subject to the inherent biases and methodological limitations from the original studies that gave rise to the summary associations observed in metaanalyses.</p> <p>Therefore, interpretation of meta-analysis findings should be done in consideration of the strengths and weakness of the underlying studies.</p>	- -
4.1	3	EPA-HQ-ORD-2009-0791-0010.1	ARCADIS on behalf of Deltrex Corporation	<p>The U.S. EPA has stated ...”TCE is characterized as “Carcinogenic to 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 U.S. EPA further states that “the evidence is ‘compelling’ for lymphoma and limited for liver and biliary tract cancers.” This conclusion overstates the results of the meta-analysis. Meta-analysis can be used in a systematic review of epidemiologic data regarding exposure and potential harm. Elements of this analysis should include a clearly stated purpose, careful literature searches, explicit inclusion and exclusion criteria, assessments of study validity and thus bias, and well-articulated definitions and rules of inference for selected causal criteria. The U.S. EPA has made a good attempt to follow these guidelines (Weed 2000; Blair et al. 1995) for the meta-analysis contained in their document, but the discussion in Appendix B is not clear about the U.S. EPA’s criteria for choosing the specific literature. It is equally important for the U.S. EPA to explain the hypothesis under investigation in the meta-analysis. In other words, what is the specific scientific study question to be answered? The U.S. EPA provides a sizable body of literature that may be complete, but the document lacks clarity. Choice of literature must support the basic study question, and criteria to use or exclude specific studies can have a profound effect on the results of the risk assessment. This may be a contributing factor in the U.S. EPA’s overreaching interpretation of the data and conclusions.</p>	- -
4.1	91	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>Toxicological Review of Trichloroethylene In Support of the IRIS Database (Draft of October 2009)</p> <p>Comments of Prof. W. Dekant</p> <p>I have been asked to comment on the IRIS Document on trichloroethylene (TCE) by the Halogenated Solvents Industry Alliance. My laboratory has published extensively on the biotransformation of TCE and was among the</p>	AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany -

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>first to report formation of glutathione-S-conjugates from TCE. My area of expertise is biotransformation of xenobiotics, mechanisms of toxicity, and genotoxicity testing and I have published more than 180 manuscripts in these areas. Moreover, I am, or have been, a member of several advisory panels charged with health risk assessment of chemicals including the European Union Scientific advisory committee on Health and Environment (SCHER). As a member of this committee, I was the lead author of the review of the European Chemicals Bureau risks assessment report on TCE. I also have followed the many controversies in the risk assessment of TCE over the last 30 years.</p> <p>General Comments</p> <p>The toxicity database on TCE is very large, with a number of controversial areas relevant to health risk assessment. EPA has generated a large document and attempted to comprehensively cover the available toxicology information on TCE and its metabolites. Most of the available studies are covered by the assessment. However, the document fails to provide a detailed evaluation of the strengths and weaknesses of the individual studies and a selection of key studies based on a weight of evidence approach. In several places in the document, study results are just reiterated and some of the conclusions relevant for deriving RfDs and RfCs have apparently been taken from reviews. EPA should develop comprehensive detailed justifications based on evaluation of the individual studies and consideration of data not supporting conclusions by EPA. Identical criteria should be applied to the level of evidence required to support or discount a mode of action (MoA).</p>	
4.2.1.2	125	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	Page 4-34: Line 1, conclusion on bacterial mutagenicity. A more detailed weight-of-evidence evaluation of the contradictory database is needed here.	AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany -
4.2.5	126	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	Table 4-18: Robbiano study, the study did not apply DCVG or DCVC and thus should not be included in the table.	AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany -
4.2.7	127	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	Page 4-83: Line 28, DCVC is not a "direct-acting" mutagen since bacteria express β -lyase (Dekant et al., 1986b). Thus, this is a difference when compared to S-(2-chlorethyl)-L-cysteine, which does not require enzymatic transformation.	AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany Dekant, W., Vamvakas, S., Berthold, K., Schmidt, S., Wild, D., and Henschler, D. (1986b). Bacterial β -lyase mediated cleavage and mutagenicity of cysteine conjugates derived from the nephrocarcinogenic alkenes trichloroethylene, tetrachloroethylene and hexachlorobutadiene. <i>Chemico-Biological Interactions</i> 60, 31-45.
4.4	67	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>1. Kidney Toxicity and Carcinogenicity</p> <p>1.1 General: EPA has followed a recommendation of the NRC in the review of the 2001 IRIS draft released in 2006 to accord greater weight to kidney toxicity and tumorigenesis than to liver responses in the mouse. In general, we support the change in emphasis recommended by the NRC but EPA has now applied unbalanced and incorrect interpretations to the data from epidemiological and toxicity studies to generate unfounded concerns about exposure to TCE and effects on the kidney.</p>	AUTHOR: Paul H. Dugard, Halogenated Solvents Industry Alliance, Inc. -
4.4	132	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	* It is not clear that DCVC constitutes an appropriate basis for an internal dose metric for kidney non-cancer toxicity.	AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp. -
4.4	144	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>It is not clear that DCVC constitutes an appropriate basis for an internal dose metric for kidney non-cancer toxicity.</p> <p>The kidney is seen as a sensitive target, and low RfC values drive the consideration of an overall RfC. The incorporation of internal doses makes the calculated RfC much lower than it would be if based on administered doses. It is therefore critically important that the internal-dose basis of kidney toxicity characterization be correct and reliable. The changes in non-cancer toxicity standards implied by the analyses in the Draft Reassessment hinge largely on assumptions about the PK of internal doses in kidney in rats and humans; and, if these assumptions are wrong, the basis for lowering the RfC is lost.</p>	AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp. Lash, LH; Parker, JC; Scott, CS. 2000. "Modes of action of trichloroethylene for kidney tumorigenesis." <i>Environ. Health Perspect.</i> 108(Suppl. 2):225-240.

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>This being said, there are many questions about the PK assumptions that have been employed. First is the choice of DCVC as the basis for the dose metric. Just because DCVC is used for kidney cancer evaluation does not mean that the same dose measure is appropriate for non-cancer toxicity. Indeed, Lash et al. (2000) describe formic acid as a potential mode of action (MOA) for kidney damage for TCE, distinguishing the case of cancer and non-cancer kidney effects, stating, "Hence, although formic acid formation may contribute to TCE-induced renal damage, this is not likely to be a significant MOA in TCE-induced kidney carcinogenesis" (emphasis added). While the beta-lyase pathway may play a predominant role in kidney carcinogenesis, the possible roles of other chemical actors (formic acid and trichloroethanol) are not adequately addressed. The PBPK modeling effort focuses solely on the products of the beta-lyase pathway and apparently ignores these other possibilities. The conclusions are accordingly dependent on this being the correct dose metric. If alternative pathways could be addressed via the model, this could either provide some support for US EPA's position that they are not relevant or it could show that a different dose metric is warranted. The current argument, i.e., that there are differences in kidney histopathology between TCE- and trichloroethanol-treated rats, and that this indicates a different MOA, is not particularly compelling.</p>	
4.4	153	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>Additional uncertainties should be noted in a weight-of-evidence evaluation of kidney toxicity. As described above, there is uncertainty in extrapolation from rodents to humans in the DCVC bioactivation portion of the PBPK model that is the basis of the proposed RfC for kidney effects. There is additional uncertainty regarding whether the kidney effect endpoint from the Woolhiser et al. (2006) rat inhalation study (increased kidney weight) is in fact related to DCVC bioactivation. If an associated level of confidence, based on the weight of evidence, had been derived and presented for the RfC based on the Woolhiser et al. (2006) study (and for each proposed RfC and RfD), the reader, and risk managers and decision makers could evaluate the level of confidence in the proposed toxicity values against other potential RfCs/RfDs that may reflect what appear to be less sensitive endpoints, but perhaps with a higher associated level of confidence based on the weight of evidence.</p>	AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp. -
4.4	157	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>There are limitations, and lack of transparency, in using the Woolhiser et al. (2006) as the basis of one of the candidate RfCs.</p> <p>The Woolhiser et al. (2006) study is an unpublished rat inhalation study that was designed to examine immunotoxicity of TCE, but also contained information on kidney weights. Therefore, there is no way for the reader to easily review the results of this study. As discussed in the Draft TCE Reassessment, rats were exposed to 0, 100, 300, and 1,000 ppm TCE for 6 hours/day, 5 days/week, for four weeks. The authors observed significantly elevated kidney weights at 1,000 ppm TCE exposure. But the Draft TCE Reassessment notes that the "small number of animals and the variation in initial animal weight limit the ability of this study to determine statistically significant increases." Therefore, this study provides weak evidence that inhalation of TCE results in increased kidney weight.</p>	AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp. -
4.4	158	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>There is uncertainty in the relevance of increased kidney weight as a critical effect for non-cancer effects of TCE.</p> <p>The observed effect from the Woolhiser et al. (2006) study was increased kidney weight relative to body weight. One other rodent inhalation study (Kjellstrand et al., 1983) discussed in the Draft TCE Reassessment also observed increased kidney weight from TCE inhalation, and another (Maltoni et al., 1988) observed meganucleocytosis. It is not clear that increased kidney weight or meganucleocytosis is directly related to kidney toxicity. Although some older studies seem to suggest that kidney weight increase is related to kidney toxicity (Feron et al., 1973), more recent studies (Bailey et al., 2004) suggest that the kidney weight to body weight ratio is uncertain, and other methods should be used to confirm weight increases. Barton and Clewell (2000) note that "Although short exposures produced increased kidney weight, it is unclear if this represents a reliable indicator of chronic toxicity (53,54)." As discussed by Hayes (2008), organ weight to body weight changes are typically secondary effects and not necessarily adverse. In addition, there does not appear to be any evidence to suggest that DCVC bioactivation is related to increased kidney weight, at least this is not discussed in the Draft Reassessment.</p>	AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp. -
4.4.2.5	6	EPA-HQ-ORD-2009-0791-0010.1	ARCADIS on behalf of Deltrex Corporation	<p>"The following provides a brief review of the meta-analysis for kidney, lymphoma, and liver cancers as shown in Appendix C, Tables C-1 through C-11."</p> <p>"Kidney Cancer: For overall TCE exposures, four of the 14 studies (Anttila et al. 1995; Boice et al. 1999; Greenland et al. 1994; and Siemiatycki 1991) used in the kidney meta-analysis had individual study relative risks</p>	- Anttila, A., E. Pukkala, M. Sallmen et al. 1995. Cancer incidence among Finnish workers exposed to halogenated hydrocarbons. J Occup Environ Med 37:797-806. Boice, J.D., D.E. Marano, J.P Fryzek et al. 1999. Mortality among aircraft manufacturing workers.

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>(RRs) less than 1.0, and the other 10 studies had individual RRs between 1.0 and 2.47. The pooled relative risk (RRp) estimates for overall TCE exposure was 1.25 (95% Confidence Intervals [CI]: 1.11, 1.41). Further, for the highest TCE exposed groups within the 12 studies pooled for RRp estimates, three of the studies (Boice et al., 1999; Radican et al., 2008; and Siemiatycki 1991) had individual study RRs lower than for the overall TCE exposure. The pooled RRp estimate for the highest TCE exposure group was 1.53 (95% CI: 1.23, 1.91).” ” Therefore, it can be agreed that the liver cancer meta-analysis is limited and conclusions by the U.S. EPA that the human epidemiology evidence of TCE exposure is “convincing” for kidney cancer and “compelling” for lymphoma are overreaching.” ” The meta-analysis human epidemiology database for each of the three types of cancer (14 studies for kidney, 16 studies for lymphoma, and 9 studies for liver) is relatively small compared to the volumes of data reviewed for other chemicals such as arsenic, asbestos, dioxin, perchlorate, ethylene oxide, etc. The U.S. EPA should perform an internal quality review of its own practices or standards of care for the use of human epidemiology data for developing toxicity values.”</p>	<p>Occup Environ Med 56:581–597. Greenland, S., A. Salvan, D.H. Wegman et al. 1994. A case-control study of cancer mortality at the transformer-assembly facility. Int Arch Occup Environ Health 66:49–54. Siemiatycki, J. 1991. Risk factors for cancer in the workplace. Boca Raton: CRC Press.</p>
4.4.2.5	23	EPA-HQ-ORD-2009-0791-0010.1	ARCADIS on behalf of Deltrex Corporation	<p>The majority of RR estimates for the individual studies are at or below 2.0 for the overall TCE exposure and the highest TCE exposure group. In addition, the meta-analysis for each of the cancer types showed RRp estimates below 2.0. Risk measurements in epidemiology studies infer causality, but the strength of that association provides the public health significance of the inference. The basic rule is the higher the observed increase in risk, “the less likely that other factors explain the excess, unless the other factors are themselves likely to produce a similar high risk.” Cole (1980) points out that a relative risk of less than 2.0 may be readily explicable by some unperceived bias or confounding factor, while those above 5.0 are less likely to be so explained. While it is not impossible for an agent to pose a low risk and be the causal agent, conclusions that an association is causal when relative risks are low at high exposure may be in error. Further, an RR of 2 or less whether it is from a quantitative meta-analysis or qualitative application of Hill’s criteria still remains on the borderline of what is typically called a “weak” association. Even the authors of the individual studies acknowledge this in their study discussions/conclusions. For example, Charbotel (2006) states: “The results of the present study do not agree with the negative results obtained by a number of large cohort studies... Although this study shows a possible link between high levels of exposure to TCE and increased risk of RCC, further epidemiological studies are necessary to assess the effect of lower levels of exposure.” Further, the highest exposure groups’ meta-analysis RRs, while slightly higher, also still remain in the weak association category. Even if this were to be considered significant, the U.S. EPA needs to further explain why possible high-dose industrial/workplace inhalation exposures are of public health significance for extrapolation to low dose environmental exposures through other environmental media (water, soil, etc.)</p>	<p>- Cole, P. 1980. Introduction In: Breslow NE and Day NE (Ed. W. Davis) Statistical Methods in Cancer Research. International Agency for Research on Cancer (IARC) Science Publication No. 32. IARC Lyon, France, pp 14-39. Charbotel, B., J. Fevotte, M. Hours et al. (2006) Case-control study on renal cell cancer and occupational exposure to trichloroethylene. Part II: Epidemiological aspects. Ann Occup Hyg 50(8):777–787.</p>
4.4.2.5	56	EPA-HQ-ORD-2009-0791-0007.1	Natural Resources Defense Council (NRDC) and Supoprters	<p>It is especially significant that a meta-analysis of 14 high-quality studies found a statistically significant pooled relative risk estimate for kidney cancer of 1.25 (95%CI 1.11, 1.41). Importantly, the association was dose-dependent, with the highest exposed group having a relative risk of 1.53 (95% CI 1.23, 1.91). This means that the risk of getting kidney cancer from TCE exposure is on average 53% higher than background (without TCE exposure) in the highest exposed group, and possibly as high as 91%. Epidemiology studies are usually biased towards the null, meaning that they tend to err on the side of not finding a true causal relationship between an exposure and an outcome, rather than finding a causal relationship where none exists. This design bias makes it harder to detect a true causal relationship between an exposure and an outcome when one exists. This often happens because of a common error called exposure misclassification that occurs when exposed individuals accidentally end up in the control groups (no or low exposure) and unexposed individuals accidentally get put into the “exposed” or “high exposed” groups. This misclassification error results in exposed individuals with the measured outcome (kidney cancer in this case) in the control groups, and unexposed individuals without the measured outcome in the exposure groups, ultimately falsely reducing the risk differences between the two groups. Thus, the meta-analysis of 14 robust studies that finds a statistically significant causal relationship, reported by EPA in this TCE assessment, is a powerful scientific statement supporting a causal relationship between TCE exposure and kidney cancer.</p>	<p>- -</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
4.4.2.5	196	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	When examining the data for TCE and non-Hodgkin lymphoma, kidney cancer, and liver cancer, associations were inconsistent across occupational groups (summary results differed between aerospace/aircraft worker cohorts compared with workers from other industries), study design, location of the study, quality of exposure assessment (e.g., evaluating studies that relied upon biomonitoring to estimate exposure vs. semi-quantitative estimates vs. self-report, etc.), and by incidence vs. mortality endpoints. Although EPA examined high dose categories, it did not evaluate any potential dose-response relationships across the epidemiologic studies (except for the Charbotel et al. 2006 study). In our reviews of the epidemiologic data reported in various studies for different exposure levels (e.g. cumulative exposure and duration of exposure metrics): we did not find consistent dose-response associations between TCE and the three cancer sites under review (Mandel et al., 2006; Alexander et al., 2007; Kelsh et al., 2010) Ail established dose-response trend is one of the more important factors when making assessments of causation in epidemiologic literature. These issues are addressed in greater detail in the accompanying comments by Michael Kelsh and Dominic Alexander.	AUTHORS: Michael Dourson, Ph.D., DABT and Lynne Haber, Ph.D., DABT from Toxicology Excellence for Risk Assessment and Michael Kelsh, Ph.D., MPH and Dominik Alexander, Ph.D., MPH from Exponent, Health Sciences Charbotel B, Fevotte J, Hours M, martin J, Beregeret A. Case-Control Study on Renal Cell Cancer and Occupational Exposure to Trichloroethylene. Part 11: Epidemiological Aspects. Ann.Occup.Hyg. 2006. Mandel JH, Kelsb MA, Mink PJ, Alexander D, Kalmes RM, Weingart M, Yost L Goodman M. Occupational trichloroethylene exposure and non-Hodgkins lymphoma: A meta-analysis and review. Occup Environ Med 2006; 63(9):597-607. Alexander DD, Kelsh MA, Mink PJ, Mandel JH. Basu R, Weingart W. A meta-analysis of occupational trichloroethylene exposure and liver cancer. Int Arch Occup Environ Health 2007; 81(2):127-143. Kelsh MA, Alexander DD, Mink PJ, Mandel JH. Occupational trichloroethylene exposure and kidney cancer: a meta-analysis. Epidemiology. 2010 Jan;21(1):95-102.
4.4.2.5	239	EPA-HQ-ORD-2009-0791-0019.1	Patton Boggs LLP	NAS/EPA Interpretations Completely Inconsistent * EPA: "Carcinogenic to humans," based on "convincing evidence of a causal association between TCE exposure in humans and kidney cancer" * NAS: Several TCE cohort studies reported increased risk of kidney cancer... Results often based on a relatively small number of exposed persons and varied quality of exposure data... The Committee concludes that "there is limited/suggestive evidence of an association between chronic exposure to TCE or PCE and kidney cancer."	- -
4.4.2.5	273	EPA-HQ-ORD-2009-0791-0014.1	Exponent Health Services	EPA's Toxicological Review of Trichloroethylene (TCE) External Review Draft: Comments Regarding Meta-Analysis of Epidemiologic Studies and Use of the Charbotel et al. 2006 Study in Quantitative Risk Assessment EPA concluded that the epidemiologic data were robust and consistent, and, in some cases, strongly supportive of providing evidence of trichloroethylene (TCE) carcinogenicity. Other reviews and meta-analyses have not reached these same conclusions, noting heterogeneity of findings (i.e. lack of consistent findings), lack of consistent exposure response evidence, and other methodological problems of the epidemiologic studies. With respect to the case-control studies of Charbotel et al. 2006, EPA considered this sufficient data for quantitative doseresponse modeling. Although Charbotel et al. 2006 have provided individual level TCE exposure estimates, limitations in the exposure assessment and study design features of this study do not permit use of Charbotel et al. 2006 data in more quantitative dose response or cancer slope factor modeling. Selection bias, where renal cell cancers among screw-cutting industry workers are more likely to be enrolled in the case control study than other renal cell cancers, is a concern, the fact that forty percent of exposure assignments of renal cancer case are based on qualitative TCE exposure assessment procedures, and the reliance on self-reported work history are important limitations that do not permit use of Charbotel et al 2006 data in quantitative risk analysis.	- Charbotel, B; Fevotte, J; Hours, M; et al. (2006) Case-control study on renal cell cancer and occupational exposure to trichloroethylene. Part II: Epidemiological aspects. Ann Occup Hyg 50(8):777-787.
4.4.2.5	294	EPA-HQ-ORD-2009-0791-0014.1	Exponent Health Services	In EPA's External Draft Report, it was stated that the meta-analysis of TCE and kidney cancer produced a small and statistically significant increase in risk, with a stronger effect observed in the highest exposure analysis. The association between TCE and kidney cancer was judged as robust, which does not reflect the inconsistencies in these data. For example, the summary association for all studies is 1.25, and for cohort studies is 1.16, and for case-control studies is 1.41. Thus, the summary findings appear sensitive to the study design being used. The findings are also sensitive to the type of sub-group or exposure classification being analyzed. As mentioned above, in the case of kidney cancer, biomonitoring studies showed different results (no association, with summary relative risk very close to 1.0 (Kelsh et al., 2010) than case control studies base on selfreported information. In summary, there are too many inconsistencies between the data and exposure differences across studies to conclude that the findings are robust.	- Kelsh MA, Alexander DD, Mink PJ, Mandel JH. Occupational trichloroethylene exposure and kidney cancer: a meta-analysis. Epidemiology. 2010 Jan;21(1):95-102.
4.4.6	73	EPA-HQ-ORD-2009-	Halogenated Solvents	1.2 Metabolism of TCE Relevant to Kidney Toxicity and Carcinogenicity (see the comments of Prof. Dekant for full technical detail): Under the assumed mode of action (MoA) for TCE (see critique below), products of the	AUTHOR: Paul H. Dugard, Halogenated Solvents Industry Alliance, Inc. -

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
		0791-0018.1	Industry Alliance, Inc.	<p>glutathione conjugation pathway are deemed to be responsible for kidney toxicity and carcinogenicity. In this hypothesis, the initial product in this path, DCVG, is converted to DCVC which, in turn, may be activated in the kidney or detoxified and excreted following acetylation. In a number of places in the IRIS document, EPA states that “Glutathione conjugation and subsequent bioactivation in humans appears to be 10- to 100-fold greater than previously thought.” This notion of a high proportion of TCE being metabolized via the glutathione conjugation pathway is based upon the work of Lash and co-workers which depended upon a questionable analytical technique. If EPA had employed a critical evaluation of the evidence, the substantial and credible information from three other laboratories (Dekant, Green and Kim/Rusyn and co-workers) that indicate a very low level of metabolism of TCE via the glutathione conjugation pathway would have been preferred. The extent of metabolism of TCE via the glutathione conjugation pathway (and DCVC activation) in humans is lower than the already low levels in rodents.</p> <p>The incorrect assumption of high rate of formation of DCVG in humans leads to false interpretations of rodent kidney toxicity and carcinogenicity, both qualitative and quantitative. Man would be presumed much more sensitive to kidney effects than rodents for a given external dose. For example, the admission that “the inclusion of PBPK reduces RfC and RfD by 300- to 400-fold” when kidney toxicity is the basis, is almost certainly the result of the erroneous estimates – if anything, the use of PBPK should lead to higher RfC and RfD values than those based on external dose.</p> <p>It is essential that EPA reevaluates the extent of metabolism of TCE via the glutathione conjugation pathway in rodents and man.</p>	
4.4.6	93	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>1. Extent of glutathione S-conjugate formation from TCE</p> <p>EPA concludes that the extent of formation of S-(1,2-dichlorovinyl)glutathione (DCVG) from TCE in humans is much higher than in rodents. Since this conclusion has a major impact on the derivation of RfCs and RfDs for TCE, it should be fully justified and based on consideration of all available data. Apparently, EPA supports this conclusion based on high blood concentrations of DCVG reported in humans after inhalation of TCE (Lash et al., 1999b). This observation is in contrast to the very low concentrations of the isomers of N-acetyl-S-(1,2-dichlorovinyl)-L-cysteine (N-acetyl-DCVC) in urine. If the overall wealth of information is disregarded, it is possible to conclude that urinary metabolite content cannot be used as a quantitative marker for metabolic flux through the glutathione conjugation pathway (Lash et al., 2000) and that most of the DCVG may undergo bioactivation by β-lyase and the products retained in the kidney. However, a number of observations refute these conclusions:</p> <p>- In the human study with TCE inhalation, high concentrations of DCVG in blood were indicated using a complex analytical procedure, often called the “Reed-Method” (Reed et al., 1980). This method was developed to determine low concentrations of glutathione and glutathione disulfide and may be used to quantify DCVG formation in biological samples. The method involves reaction of the thiol with iodoacetamide and the amino group with chlorodinitrobenzene, followed by ion exchange chromatography and UV-detection of the dinitrophenyl chromophore. Due to the ion-exchange chromatography with a high salt concentration in the eluate, retention time shifts are common due to column deterioration (Lash et al., 1999b). Since the method is not selective for DCVG and analysis of biological samples produces many peaks, retention time shifts may create problems for locating the DCVG peak.</p> <p>A number of inconsistent datasets questions the reliability of the “Reed-method” to determine DCVG and DCVC:</p> <p>- In a study assessing DCVG and DCVC formation in rodents after high oral doses of TCE, DCVG-concentrations reported in blood were high, but did not show dose or time-dependence (Lash et al., 2006). In addition, the study reports high concentrations of DCVC excreted in urine. EPA calls the results of this study “aberrant”, but apparently did not further assess reliability. Others have reported a very low rate of DCVC-formation in vivo (Dekant et al., 1990; Kim et al., 2009) and DCVC has not been reported as urinary metabolite of TCE using either mass spectrometry or HPLC which radiochemical detection after administration of ¹⁴C-TCE (Dekant et al., 1986a).</p>	<p>AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany</p> <p>Lash, L. H., Putt, D. A., Brashear, W. T., Abbas, R., Parker, J. C., and Fisher, J. W. (1999b). Identification of S-(1,2-dichlorovinyl)glutathione in the blood of human volunteers exposed to trichloroethylene. <i>J Toxicol Environ Health A</i> 56, 1-21.</p> <p>Lash, L. H., Parker, J. C., and Scott, C. S. (2000). Modes of action of trichloroethylene for kidney tumorigenesis. <i>Environ Health Perspect</i> 108 Suppl 2.</p> <p>Lash, L. H., Putt, D. A., and Parker, J. C. (2006). Metabolism and tissue distribution of orally administered trichloroethylene in male and female rats: identification of glutathione- and cytochrome P-450-derived metabolites in liver, kidney, blood, and urine. <i>J Toxicol Environ Health A</i> 69, 1285-1309.</p> <p>Lash, L. H., Qian, W., Putt, D. A., Desai, K., Elfarra, A. A., Sicuri, A. R., and Parker, J. C. (1998). Glutathione conjugation of perchloroethylene in rats and mice in vitro: sex-, species-, and tissue-dependent differences. <i>Toxicol Appl Pharmacol</i> 150, 49-57.</p> <p>Dekant, W., Schulz, A., Metzler, M., and Henschler, D. (1986a). Absorption, elimination and metabolism of trichloroethylene: a quantitative comparison between rats and mice. <i>Xenobiotica</i> 16, 143-152.</p> <p>Hissink, E. M., Bogaards, J. J. P., Freidig, A. P., Commandeur, J. N. M., Vermeulen, N. P. E., and van Bladeren, P. J. (2002). The use of in vitro metabolic parameters and physiologically based pharmacokinetic (PBPK) modeling to explore the risk assessment of trichloroethylene. <i>Environmental Toxicology and Pharmacology</i> 11, 259-271.</p> <p>Dekant, W., Koob, M., and Henschler, D. (1990). Metabolism of trichloroethene - in vivo and in vitro evidence for activation by glutathione conjugation. <i>Chemico-Biological Interactions</i> 73, 89-101.</p> <p>Reed, D. J., Babson, J. R., Beatty, P. W., Brodie, A. E., Ellis, W. W., and Potter, D. W. (1980). High-performance liquid chromatography analysis of nanomole levels of glutathione, glutathione disulfide, and related thiols and disulfides. <i>Anal Biochem</i> 106, 55-62.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>- The "Reed-method" has also been used to determine DCVG-formation from TCE in subcellular fractions from liver and kidney of rats, mice, and humans. Again, high rates of formation of DCVG were reported (table 1). In contrast, using C-TCE and radioactivity detection, much lower reaction rates were observed in other studies (table 1). In addition, isolated glutathione, S-transferases also have a very low capacity to metabolize TCE to DCVG (Hissink et al., 2002) and the application of the "Reed-method" to study formation of S-(1,2,2-trichlorovinyl)glutathione (TCVG) from perchloroethylene (PERC) in subcellular fractions also gave much higher rates of formation (Lash et al., 1998) when compared with methods using 14C-perchloroethylene and HPLC with radioactivity detection (Dekant et al., 1987; Green et al., 1990; Dekant et al., 1998).</p> <p>Therefore, DCVG concentrations determined by the "Reed-method" may be greatly overestimated. The more reliable and consistent data support a very low extent of DCVG formation in rodents:</p> <p>- Very low rates of formation of DCVG in rodent liver subcellular fractions are consistent with very low blood levels of DCVG in mice (Kim et al., 2009) and a very low biliary elimination of DCVG in rats after oral administration of doses > 2 000 mg TCE/kg bw (Dekant et al., 1990). In mice, DCVG concentrations were several thousand-fold lower than those of the oxidative metabolite trichloroacetic acid (TCA) (Kim et al., 2009). In rats, biliary elimination of DCVG within seven hours after oral administration was 2 microg and therefore accounted for << 0.01 % of administered dose (Dekant et al., 1990). Due to its molecular weight (> 350 D) and the presence of effective transport systems for glutathione S-conjugates in the canalicular membrane, most of the DCVG formed in rat liver is expected to be excreted in bile. Therefore, the low concentrations of DCVG in blood of mice and the low recovery of DCVG in bile of rats after TCE-administration well support very low rates of DCVG formation.</p> <p>- Even when considering the high rates of DCVG formation reported in subcellular fractions and the only 3-fold difference in reaction rates between mouse, rat and humans (table 1), it is difficult to explain why DCVG-blood levels in mice after a very high oral dose are orders of magnitude lower than those reported in humans after inhalation exposures giving a much lower internal TCE-dose.</p> <p>- High blood concentrations of DCVG and a high flux through β-lyase bioactivation are not consistent with the human toxicity data on TCE. Despite high occupational exposures to TCE between the 1950s and 1970s (occupational exposure limits for TCE were 200 ppm in Germany and were often exceeded for prolonged times), overt nephrotoxicity was rarely observed even after many years of exposures (MAK, 1996). Using the blood concentrations reported and extrapolating to a daily exposure to 200 ppm TCE for 8 h, daily doses of DCVC of approx. 5-7 mg/kg bw should have been received by workers. A significant flux through β-lyase bioactivation should have resulted in renal effects considering the alleged potency of DCVC.</p> <p>- Kinetic studies on acetylation, and β-lyase-mediated metabolism of DCVC support a low flux through β-lyase activation since the relative flux through the N-acetylation pathway (detoxication) is one to two orders of magnitude higher than through β-lyase activation (Green et al., 1997a). In addition, a low flux through β-lyase is indicated by the recovery of most of a low intravenous dose of DCVC isomers in urine as mercapturic acids in rats (Birner et al., 1997), the weak nephrotoxicity of DCVC (Green et al., 1997a) and observations with PERC, which is also metabolized by glutathione S-conjugate formation and β-lyase. The PERC metabolite S-(1,2,2-trichlorovinyl)-L-cysteine is cleaved by β-lyase to dichloroacetic acid (DCA) which, when formed in the kidney, is excreted with urine. While DCA is a metabolite of PERC in rats, this compound is not excreted as a PERC metabolite in humans (Völkel et al., 1998). In addition, dichloroacetylated proteins were detected both in rat kidney proteins and rat blood proteins after PERC inhalation. Such protein modifications were not detected in blood proteins from humans after identical exposures (Pähler et al., 1999). These observations indicate that flux through β-lyase in humans is even lower than in rodents.</p> <p>- Chloroacetic acid is formed by β-lyase from DCVC (Dekant et al., 1988). In rodents, chloroacetic acid and its metabolites (Green and Hathway, 1975; Green and Hathway, 1977) are not significant metabolites of TCE (< 0.1 % of radioactivity in urine) (Dekant et al., 1984; Dekant et al., 1986a). If the β-lyase pathway is more relevant, such metabolites should be present in urine in higher concentrations. Other metabolites indicative of alternative processing of DCVC have also not been detected in humans exposed to TCE (Bloemen et al., 2001).</p>	<p>Kim, S., Kim, D., Pollack, G. M., Collins, L. B., and Rusyn, I. (2009). 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. <i>Toxicol Appl Pharmacol</i> 238, 90-99.</p> <p>Dekant, W., Martens, G., Vamvakas, S., Metzler, M., and Henschler, D. (1987). Bioactivation of tetrachloroethylene. Role of glutathione S-transferase-catalyzed conjugation versus cytochrome P-450-dependent phospholipid alkylation. <i>Drug Metab Dispos</i> 15, 702-709.</p> <p>Dekant, W., Birner, G., Werner, M., and Parker, J. (1998). Glutathione conjugation of perchloroethene in subcellular fractions from rodent and human liver and kidney. <i>Chem Biol Interact</i> 116, 31-43.</p> <p>Green, T., Odum, J., Nash, J. A., and Foster, J. R. (1990). Perchloroethylene-induced rat kidney tumors: an investigation of the mechanisms involved and their relevance to humans. <i>Toxicol. Appl. Pharmacol.</i> 103, 77-89.</p> <p>Green, T., Dow, J., Ellis, M. K., Foster, J. R., and Odum, J. (1997a). The role of glutathione conjugation in the development of kidney tumours in rats exposed to trichloroethylene. <i>Chemico-Biological Interactions</i> 105, 99-117.</p> <p>Völkel, W., Friedewald, M., Lederer, E., Pähler, A., Parker, J., and Dekant, W. (1998). Biotransformation of perchloroethene: dose-dependent excretion of trichloroacetic acid, dichloroacetic acid and N-acetyl-S-(trichlorovinyl)-L-cysteine in rats and humans after inhalation. <i>Toxicology and Applied Pharmacology</i> 153, 20-27.</p> <p>MAK (1996). Trichlorethylene. In <i>Occupational Toxicants - Critical data evaluation for MAK values and classification of carcinogens by the commission for the investigation of health hazards of chemical compounds in the work area</i> (H. Greim, Ed.), pp. 201-244. Wiley-VCH, München.</p> <p>Birner, G., Bernauer, U., Werner, M., and Dekant, W. (1997). Biotransformation, excretion and nephrotoxicity of haloalkene-derived cysteine S-conjugates. <i>Arch Toxicol</i> 72, 1-8.</p> <p>Dekant, W., Berthold, K., Vamvakas, S., Henschler, D., and Anders, M. W. (1988). Thioacylating intermediates as metabolites of S-(1,2-dichlorovinyl)-L-cysteine and S-(1,2,2-trichlorovinyl)-L-cysteine formed by cysteine conjugate β-lyase. <i>Chemical Research in Toxicology</i> 1, 175-178.</p> <p>Green, T., and Hathway, D. E. (1975). The biological fate in rats of vinyl chloride in relation to its oncogenicity. <i>Chem Biol Interact</i> 11, 545-562.</p> <p>Green, T., and Hathway, D. E. (1977). The chemistry and biogenesis of the S-containing metabolites of vinyl chloride in rats. <i>Chem Biol Interact</i> 17, 137-150.</p> <p>Dekant, W., Metzler, M., and Henschler, D. (1984). Novel metabolites of trichloroethylene through dechlorination reactions in rats, mice and humans. <i>Biochem. Pharmacol.</i> 33, 2021-2027.</p> <p>Bloemen, L. J., Monster, A. C., Kezic, S., Commandeur, J. N., Veulemans, H., Vermeulen, N. P., and Wilmer, J. W. (2001). Study on the cytochrome P-450- and glutathione-dependent biotransformation of trichloroethylene in humans. <i>Int Arch Occup Environ Health</i> 74, 102-108.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics																																																																																																				
4.4.6	99	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>Table 1: [SEE FOLLOWING PAGE] Reported rates of formation of DCVC from Trichloroethene (TCE) in rat, mouse and human subcellular fractions. The concentration of TCE in the incubation is based on the amount added. N.d. = not determined</p> <p>In summary, the evidence does not support EPA's conclusions that DCVG is released to the blood from TCE at a high rate in rodents and humans or that the rate is greater in humans than it is in rats and mice. The evidence indicates that the glutathione conjugation pathway is less active in humans than in rodents.</p>	<table border="1"> <thead> <tr> <th>Tissue</th> <th>Species</th> <th>TCE Conc (mM)</th> <th>Rate of DCVC formation (pmol/minxmg)</th> <th>Analytical method to determine DCVG</th> <th>Reference</th> </tr> </thead> <tbody> <tr> <td rowspan="3">Liver cytosol</td> <td>Rat</td> <td>1.4 (¹⁴C)</td> <td>0.54 (non-enzymatic reaction rates subtracted)</td> <td rowspan="10">HPLC with radiochemical detection, peak identity confirmed by LC/MS</td> <td rowspan="10">(Green <i>et al.</i>, 1997b)</td> </tr> <tr> <td>Mouse</td> <td>1.9 (¹⁴C)</td> <td>0.35</td> </tr> <tr> <td>Human</td> <td>1.9 – 2.5 (¹⁴C)</td> <td>0.012 – 0.055</td> </tr> <tr> <td rowspan="3">Liver microsomes</td> <td>Rat</td> <td>1.4 (¹⁴C)</td> <td>Not different from non-enzymatic reaction</td> </tr> <tr> <td>Mouse</td> <td>1.9 (¹⁴C)</td> <td>n.d.</td> </tr> <tr> <td>Human</td> <td>1.9 – 2.5 (¹⁴C)</td> <td>n.d.</td> </tr> <tr> <td rowspan="3">Kidney cytosol</td> <td>Rat</td> <td>1.4 (¹⁴C)</td> <td>Not different from non-enzymatic reaction</td> </tr> <tr> <td>Mouse</td> <td>n.d.</td> <td></td> </tr> <tr> <td>Human</td> <td>n.d.</td> <td></td> </tr> <tr> <td rowspan="3">Kidney microsomes</td> <td>Rat</td> <td>1.4 (¹⁴C)</td> <td>Not different from non-enzymatic reaction</td> </tr> <tr> <td>Mouse</td> <td>n.d.</td> <td></td> </tr> <tr> <td>Human</td> <td>n.d.</td> <td></td> </tr> <tr> <td>Liver cytosol</td> <td>Rat</td> <td>4 (¹⁴C)</td> <td>< 2</td> <td rowspan="2">HPLC with radioactivity detection, peak identity confirmed by GC/MS after hydrolysis</td> <td rowspan="2">(Dekant <i>et al.</i>, 1990)</td> </tr> <tr> <td>Liver microsomes</td> <td>Rat</td> <td>4 (¹⁴C)</td> <td>2</td> </tr> <tr> <td rowspan="3">Liver cytosol</td> <td>Rat</td> <td>2</td> <td>121 (males) 81 (females)</td> <td rowspan="10">Derivatisation and ion exchange HPLC ("Reed-method")</td> <td rowspan="10">(Lash <i>et al.</i>, 1999a)</td> </tr> <tr> <td>Mouse</td> <td>2</td> <td>408 (males) 361 (females)</td> </tr> <tr> <td>Human</td> <td>1</td> <td>1 700 – 4 180</td> </tr> <tr> <td rowspan="3">Liver microsomes</td> <td>Rat</td> <td>2</td> <td>171 (males) 120 (females)</td> </tr> <tr> <td>Mouse</td> <td>2</td> <td>666 (males) 426 (females)</td> </tr> <tr> <td>Human</td> <td>1</td> <td>495 – 3 245</td> </tr> <tr> <td rowspan="3">Kidney cytosol</td> <td>Rat</td> <td>2</td> <td>7.5 (males) 5.3 (females)</td> </tr> <tr> <td>Mouse</td> <td>2</td> <td>93 (males) 61 (females)</td> </tr> <tr> <td>Human</td> <td>na</td> <td>810 (vmax)</td> </tr> <tr> <td rowspan="3">Kidney microsomes</td> <td>Rat</td> <td>2</td> <td>Nd (males) 1.0 (females)</td> </tr> <tr> <td>Mouse</td> <td>2</td> <td>91 (males) 278 (females)</td> </tr> <tr> <td>Human</td> <td>na</td> <td>6 290 (vmax)</td> </tr> </tbody> </table> <p>AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany</p>	Tissue	Species	TCE Conc (mM)	Rate of DCVC formation (pmol/minxmg)	Analytical method to determine DCVG	Reference	Liver cytosol	Rat	1.4 (¹⁴ C)	0.54 (non-enzymatic reaction rates subtracted)	HPLC with radiochemical detection, peak identity confirmed by LC/MS	(Green <i>et al.</i> , 1997b)	Mouse	1.9 (¹⁴ C)	0.35	Human	1.9 – 2.5 (¹⁴ C)	0.012 – 0.055	Liver microsomes	Rat	1.4 (¹⁴ C)	Not different from non-enzymatic reaction	Mouse	1.9 (¹⁴ C)	n.d.	Human	1.9 – 2.5 (¹⁴ C)	n.d.	Kidney cytosol	Rat	1.4 (¹⁴ C)	Not different from non-enzymatic reaction	Mouse	n.d.		Human	n.d.		Kidney microsomes	Rat	1.4 (¹⁴ C)	Not different from non-enzymatic reaction	Mouse	n.d.		Human	n.d.		Liver cytosol	Rat	4 (¹⁴ C)	< 2	HPLC with radioactivity detection, peak identity confirmed by GC/MS after hydrolysis	(Dekant <i>et al.</i> , 1990)	Liver microsomes	Rat	4 (¹⁴ C)	2	Liver cytosol	Rat	2	121 (males) 81 (females)	Derivatisation and ion exchange HPLC ("Reed-method")	(Lash <i>et al.</i> , 1999a)	Mouse	2	408 (males) 361 (females)	Human	1	1 700 – 4 180	Liver microsomes	Rat	2	171 (males) 120 (females)	Mouse	2	666 (males) 426 (females)	Human	1	495 – 3 245	Kidney cytosol	Rat	2	7.5 (males) 5.3 (females)	Mouse	2	93 (males) 61 (females)	Human	na	810 (vmax)	Kidney microsomes	Rat	2	Nd (males) 1.0 (females)	Mouse	2	91 (males) 278 (females)	Human	na	6 290 (vmax)
Tissue	Species	TCE Conc (mM)	Rate of DCVC formation (pmol/minxmg)	Analytical method to determine DCVG	Reference																																																																																																				
Liver cytosol	Rat	1.4 (¹⁴ C)	0.54 (non-enzymatic reaction rates subtracted)	HPLC with radiochemical detection, peak identity confirmed by LC/MS	(Green <i>et al.</i> , 1997b)																																																																																																				
	Mouse	1.9 (¹⁴ C)	0.35																																																																																																						
	Human	1.9 – 2.5 (¹⁴ C)	0.012 – 0.055																																																																																																						
Liver microsomes	Rat	1.4 (¹⁴ C)	Not different from non-enzymatic reaction																																																																																																						
	Mouse	1.9 (¹⁴ C)	n.d.																																																																																																						
	Human	1.9 – 2.5 (¹⁴ C)	n.d.																																																																																																						
Kidney cytosol	Rat	1.4 (¹⁴ C)	Not different from non-enzymatic reaction																																																																																																						
	Mouse	n.d.																																																																																																							
	Human	n.d.																																																																																																							
Kidney microsomes	Rat	1.4 (¹⁴ C)	Not different from non-enzymatic reaction																																																																																																						
	Mouse	n.d.																																																																																																							
	Human	n.d.																																																																																																							
Liver cytosol	Rat	4 (¹⁴ C)	< 2	HPLC with radioactivity detection, peak identity confirmed by GC/MS after hydrolysis	(Dekant <i>et al.</i> , 1990)																																																																																																				
Liver microsomes	Rat	4 (¹⁴ C)	2																																																																																																						
Liver cytosol	Rat	2	121 (males) 81 (females)	Derivatisation and ion exchange HPLC ("Reed-method")	(Lash <i>et al.</i> , 1999a)																																																																																																				
	Mouse	2	408 (males) 361 (females)																																																																																																						
	Human	1	1 700 – 4 180																																																																																																						
Liver microsomes	Rat	2	171 (males) 120 (females)																																																																																																						
	Mouse	2	666 (males) 426 (females)																																																																																																						
	Human	1	495 – 3 245																																																																																																						
Kidney cytosol	Rat	2	7.5 (males) 5.3 (females)																																																																																																						
	Mouse	2	93 (males) 61 (females)																																																																																																						
	Human	na	810 (vmax)																																																																																																						
Kidney microsomes	Rat	2	Nd (males) 1.0 (females)																																																																																																						
	Mouse	2	91 (males) 278 (females)																																																																																																						
	Human	na	6 290 (vmax)																																																																																																						
4.4.6	102	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>2. The role of glutathione S-conjugates in nephrotoxicity and renal tumor formation by TCE</p> <p>Since S-conjugates of TCE are nephrotoxic in rodents and genotoxic in vitro, it is appealing to conclude that S-conjugate formation is involved in nephrotoxicity of TCE and that the MoA for kidney tumor formation is genotoxicity. However, a number of contradictory findings are not adequately considered in the IRIS-document:</p>	<p>AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany</p> <p>Green, T., Dow, J., Ellis, M. K., Foster, J. R., and Odum, J. (1997a). The role of glutathione conjugation in the development of kidney tumours in rats exposed to trichloroethylene. <i>Chemico-Biological Interactions</i> 105, 99-117.</p>																																																																																																				

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>* Formation rates for DCVC in subcellular fractions from mice and rats are similar (or even higher in mice) suggesting similar doses of DCVC to the kidney in both species (Green et al., 1997a; Kim et al., 2009). Moreover, activation of TCE by the β-lyase pathway is higher in mice (Eyre et al., 1995), DCVC is more nephrotoxic in mice, and causes higher rates of cell replication and covalent binding in mice as compared to rats (Eyre et al., 1995; Green et al., 1997a). Yet, mice are not sensitive to TCE induced renal tumor formation.</p> <p>* Based on the nephrotoxicity of DCVC and the low rates of formation of DCVC both in rats and mice in vivo, it is questionable if the very low concentrations of DCVG formed in rodents can explain nephrotoxicity and tumor formation. Extrapolating the DCVG blood concentrations observed after single doses to the doses applied in the carcinogenicity studies with TCE in rats, daily DCVC-doses in the two year studies were less than 0.03 mg/kg bw. This is orders of magnitude below the doses of DCVC required to induce nephrotoxicity during chronic administration (Terracini and Parker, 1965) and further questions an involvement of this pathway in nephrotoxicity of TCE.</p> <p>* EPA concludes that trichloroethanol and formic acid formation may not be involved in the toxicity of TCE to the kidney due to differences in pathology observed between TCE and trichloroethanol treated rats. In my opinion, such comparisons are difficult since differences in the kinetic profiles of a compound formed as a metabolite or administered per se are likely major confounders. The mode of action for TCE-induced renal tumors due to effects of increased formic acid excretion due to disturbances in intermediary metabolism by trichloroethanol is supported by renal toxicity of trichloroethanol, insufficient rates of DCVC/DCVC-formation to account for renal toxicity and the absence of genotoxic effects of TCE on rat kidney in vivo.</p> <p>* EPA states that data on VHL gene mutations support a mutagenic MoA in TCE-induced kidney tumors. This is based on studies (Bruning et al., 1997; Brauch et al., 2004) reporting VHL mutations in renal tumors of TCE-exposed individuals. It is concluded that comparison of TCE-exposed and non-exposed patients (Brauch et al., 2004) revealed clear differences with respect to (1) frequency of somatic VHL mutations, (2) incidence of C454T transition, and (3) incidence of multiple mutations. As discussed in Brauch et al. (2004), the mutation frequency in the non-exposed patients (10%) was considerably lower than that commonly observed in sporadic renal tumors, e.g. 82% (Nickerson et al., 2008) or 71% (Banks et al., 2006), and technical problems using archived tissue samples may be one of the causes. Given that exon 3, which harbors the multiple mutations seen in TCE exposed patients, did not amplify in most of the controls, there is only limited evidence for a difference in the incidence of multiple mutations and frequency of somatic VHL mutations, although the C454T transition appears to be characteristic of tumors in TCE exposed patients. However, the presence of mutations in human tumors does not lead to the conclusion that VHL mutations occur early during carcinogenesis. Hence, they are not evidence for a direct genotoxicity of TCE in the kidney. In contrast, experimental data in rats show that neither TCE nor its active metabolite DCVC induce VHL mutations (Mally et al., 2006), suggesting that VHL mutations in humans may be acquired at later stages of tumor development. While the document argues that the VHL gene may not be a target gene in rodent models of renal carcinogenesis, only few studies have looked at VHL in rats and there is no support for the hypothesis that the role of VHL is different in rats and humans.</p> <p>* The Eker rat may be a useful rodent model for renal cell carcinoma (RCC), but the molecular basis for chemically induced tumor formation in rats and RCC in humans may be widely different from spontaneous tumor formation in this rat strain, as high-grade RCCs can develop in the absence of mutations in the Tsc2 gene in rats (Toyokuni et al., 1998). Development of high-grade renal cell carcinomas in rats independently of somatic mutations in the Tsc2 and VHL tumor suppressor genes (Toyokuni et al., 1998) demonstrates that mutational inactivation of TSC2 or VHL is not a prerequisite for renal carcinogenesis. The similar pathway activation in Eker rat RCC as that seen in humans with VHL mutations reported (Liu et al., 2003) involves deregulation of HIFα and VEGF expression which frequently occur in various cancers and provide little evidence to suggest that Tsc-2 inactivation in rats is "analogous" to inactivation of VHL in human RCC.</p> <p>* Epidemiological data may support an association between specific VHL mutations and TCE exposure, this does not indicate an early event in RCC and – in the absence of experimental support - should not be taken as support for a mutational MoA.</p> <p>* EPA uses micronucleus and comet assay data in rat kidney after TCE-administration as support for a genotoxic</p>	<p>Kim, S., Kim, D., Pollack, G. M., Collins, L. B., and Rusyn, I. (2009). 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. <i>Toxicol Appl Pharmacol</i> 238, 90-99.</p> <p>Eyre, R. J., Stevens, D. K., Parker, J. C., and Bull, R. J. (1995). Acid-labile adducts to protein can be used as indicators of the cysteine S-conjugate pathway of trichloroethene metabolism. <i>J Toxicol Environ Health</i> 46, 443-464.</p> <p>Terracini, B., and Parker, V. H. (1965). A Pathological Study on the Toxicity of S-Dichlorovinyl-L-Cysteine. <i>Food Cosmet Toxicol</i> 3, 67-74.</p> <p>Bruning, T., Weirich, G., Hornauer, M. A., Hofler, H., and Brauch, H. (1997). Renal cell carcinomas in trichloroethene (TRI) exposed persons are associated with somatic mutations in the von Hippel-Lindau (VHL) tumour suppressor gene. <i>Arch Toxicol</i> 71, 332-335.</p> <p>Brauch, H., Weirich, G., Klein, B., Rabstein, S., Bolt, H. M., and Bruning, T. (2004). VHL mutations in renal cell cancer: does occupational exposure to trichloroethylene make a difference? <i>Toxicol Lett</i> 151, 301-310.</p> <p>Nickerson, M. L., Jaeger, E., Shi, Y., Durocher, J. A., Mahurkar, S., Zaridze, D., Matveev, V., Janout, V., Kollarova, H., Bencko, V., Navratilova, M., Szeszenia-Dabrowska, N., Mates, D., Mukeria, A., Holcatova, I., Schmidt, L. S., Toro, J. R., Karami, S., Hung, R., Gerard, G. F., Linehan, W. M., Merino, M., Zbar, B., Boffetta, P., Brennan, P., Rothman, N., Chow, W. H., Waldman, F. M., and Moore, L. E. (2008). Improved identification of von Hippel-Lindau gene alterations in clear cell renal tumors. <i>Clin Cancer Res</i> 14, 4726-4734.</p> <p>Banks, R. E., Tirukonda, P., Taylor, C., Hornigold, N., Astuti, D., Cohen, D., Maher, E. R., Stanley, A. J., Harnden, P., Joyce, A., Knowles, M., and Selby, P. J. (2006). Genetic and epigenetic analysis of von Hippel-Lindau (VHL) gene alterations and relationship with clinical variables in sporadic renal cancer. <i>Cancer Res</i> 66, 2000-2011.</p> <p>Mally, A., Walker, C. L., Everitt, J. I., Dekant, W., and Vamvakas, S. (2006). Analysis of renal cell transformation following exposure to trichloroethene in vivo and its metabolite S-(dichlorovinyl)-L-cysteine in vitro. <i>Toxicology</i> 224, 108-118.</p> <p>Toyokuni, S., Okada, K., Kondo, S., Nishioka, H., Tanaka, T., Nishiyama, Y., Hino, O., and Hiai, H. (1998). Development of high-grade renal cell carcinomas in rats independently of somatic mutations in the Tsc2 and VHL tumor suppressor genes. <i>Jpn J Cancer Res</i> 89, 814-820.</p> <p>Liu, M. Y., Poellinger, L., and Walker, C. L. (2003). Up-regulation of hypoxia-inducible factor 2α in renal cell carcinoma associated with loss of Tsc-2 tumor suppressor gene. <i>Cancer Res</i> 63, 2675-2680.</p> <p>Robbiano, L., Baroni, D., Carrozzino, R., Mereto, E., and Brambilla, G. (2004). DNA damage and micronuclei induced in rat and human kidney cells by six chemicals carcinogenic to the rat kidney. <i>Toxicology</i> 204, 187-195.</p> <p>Clay, P. (2008). Assessment of the genotoxicity of trichloroethylene and its metabolite, S-(1,2-dichlorovinyl)-L-cysteine (DCVC), in the comet assay in rat kidney. <i>Mutagenesis</i> 23, 27-33.</p> <p>Swenberg, J. A., and Lehman-McKeeman, L. D. (1999). a2u-Globulin associated nephropathy as a mechanism of renal tubular cell carcinogenesis in male rats. In <i>IARC-Scientific Publications: Species differences in thyroid, kidney and urinary bladder carcinogenesis</i> (C. C. Capen, E. Dybing, J. M. Rice, and J. D. Wilbourn, Eds.), pp. 95-118. International Agency on Cancer Research, Lyon.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>MoA. However, the positive micronucleus (Robbiano et al., 2004) assay applied a very high dose and used an inappropriate route of administration (ip injection of ½ of the LD50). Due to the high dose applied and the route of administration, the results may be confounded by inflammatory responses and should not be used for conclusions. A comet assay in the kidney using repeated inhalation exposures to TCE was negative (Clay, 2008). The decision to not use this study in the assessment is insufficiently justified. The inhalation study used a higher number of animals (5/group) as compared to the ip study, which states n > 3 with an apparent maximum of 5. The comet assay also shows that administered DCVC is no more than weakly active in the kidney.</p> <p>* EPA argues that there is no link between nephrotoxicity and renal tumor formation. However, there are a number of compounds that cause renal tumors in rats without being genotoxic. For example, cytotoxicity and regenerative cell proliferation (Swenberg and Lehman-McKeeman, 1999) is accepted as MoA for ALPHA2U-globulin binding agents (TCE does not bind to ALPHA2u-globulin, but is most likely to cause renal tumors through nephrotoxicity).</p> <p>In summary, the data do not support a genotoxic mode of action for kidney carcinogenicity via S-conjugates of TCE. The decision of EPA to employ S-conjugate-mediated genotoxicity in support of a linear dose response relationship for renal cell carcinoma should be revised to reflect the balance of the data. A non-linear dose response relationship is well supported by the available evidence.</p>	
4.4.6	260	EPA-HQ-ORD-2009-0791-0012.1	McKenna, Long & Aldrige, LLP	<p>Main messages: Non-cancer findings Assuming higher human production of DCVC is a critical part of the complicated analysis of RfC, RfD, and cancer dose response – It is disputed science and EPA’s analysis appears to show that it does not fit the modeling well</p>	- -
4.4.6	261	EPA-HQ-ORD-2009-0791-0012.1	McKenna, Long & Aldrige, LLP	<p>Main messages: Non-cancer findings Assuming higher human production of DCVC is a critical part of the complicated analysis of RfC, RfD, and cancer dose response – It is disputed science and EPA’s analysis appears to show that it does not fit the modeling well</p>	- -
4.4.7	71	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>1.2 Metabolism of TCE Relevant to Kidney Toxicity and Carcinogenicity (see the comments of Prof. Dekant for full technical detail): Under the assumed mode of action (MoA) for TCE (see critique below), products of the glutathione conjugation pathway are deemed to be responsible for kidney toxicity and carcinogenicity. In this hypothesis, the initial product in this path, DCVG, is converted to DCVC which, in turn, may be activated in the kidney or detoxified and excreted following acetylation. In a number of places in the IRIS document, EPA states that “Glutathione conjugation and subsequent bioactivation in humans appears to be 10- to 100-fold greater than previously thought.” This notion of a high proportion of TCE being metabolized via the glutathione conjugation pathway is based upon the work of Lash and co-workers which depended upon a questionable analytical technique. If EPA had employed a critical evaluation of the evidence, the substantial and credible information from three other laboratories (Dekant, Green and Kim/Rusyn and co-workers) that indicate a very low level of metabolism of TCE via the glutathione conjugation pathway would have been preferred. The extent of metabolism of TCE via the glutathione conjugation pathway (and DCVC activation) in humans is lower than the already low levels in rodents.</p> <p>The incorrect assumption of high rate of formation of DCVG in humans leads to false interpretations of rodent kidney toxicity and carcinogenicity, both qualitative and quantitative. Man would be presumed much more sensitive to kidney effects than rodents for a given external dose. For example, the admission that “the inclusion of PBPK reduces RfC and RfD by 300- to 400-fold” when kidney toxicity is the basis, is almost certainly the result of the erroneous estimates – if anything, the use of PBPK should lead to higher RfC and RfD values than those based on external dose.</p> <p>It is essential that EPA reevaluates the extent of metabolism of TCE via the glutathione conjugation pathway in rodents and man.</p>	AUTHOR: Paul H. Dugard, Halogenated Solvents Industry Alliance, Inc. -
4.4.7.1	75	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>1.3 Mode of Action for Kidney Toxicity and Carcinogenicity (for additional technical detail see the comments of Prof. Dekant): EPA considers that the formation of DCVC from TCE and its activation in kidneys of rats, mice and humans to be the cause of toxicity and, through genotoxicity, tumor formation. A balanced evaluation of the evidence simply does not support these opinions. The summary of Prof. Dekant’s review is as follows:</p>	AUTHOR: Paul H. Dugard, Halogenated Solvents Industry Alliance, Inc. Terracini, B., and Parker, V. H. (1965). A Pathological Study on the Toxicity of S-Dichlorovinyl-L-Cysteine. Food Cosmet Toxicol 3, 67-74.

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>From the known potency of DCVC administered directly to rats, the toxicity of TCE in chronic or long term experiments in rats cannot be explained solely on the extent of DCVC production and activation. The generation of a flood of formic acid through the kidney of rats exposed to TCE (by a mechanism fully understood) does lead to recognizable kidney damage. Although EPA dismisses formic acid because histopathological damage appears to be different between that seen for trichloroethanol (generates formic acid only – no DCVC component) and TCE, it appears highly likely that a combination of DCVC and formic acid damage underlies kidney toxicity in the rat. In mice, less formic acid is released following TCE administration and DCVC activation is greater in mouse kidney which suggests that DCVC may play a greater role in mouse kidney toxicity. Since DCVC is not a highly potent kidney toxicant, the very low levels generated in man are unlikely to cause kidney toxicity. Human experience supports this: Despite historical occupational exposures greater than 100 ppm on an 8 hour time-weighted-average with peak exposures reaching many thousand ppm, kidney disease has not been associated with TCE. Those studies in which markers of kidney damage have been studied have not provided clear evidence of an effect of TCE in man. The conclusion must be that kidney damage is highly unlikely to occur at current occupational exposure levels (ACGIH TLV is 10 ppm, 8 hour TWA) and of no concern for the general population.</p> <p>EPA considers that kidney tumors in rats result from the genotoxicity following DCVC activation. The reasons to consider this to be improbable are 1) That DCVC, although positive in in vitro bacterial mutagenicity tests (following activation by endogenous bacterial enzymes or enhanced by exogenous rat kidney preparations), has not been found, in credible studies, to be anything more than weakly genotoxic in vivo. 2) Combining the weak genotoxicity with the low levels generated in rats does not indicate a primary role for generation of tumors by a genotoxic mechanism. 3) The single long term experiment involving direct administration of DCVC to rats did not generate tumors in a protocol which would have been expected to show induction of tumors by a genotoxic mechanism (Terracini and Parker, 1965). This study cannot be used to “prove the negative” (i.e. DCVC is not a kidney carcinogen) but, despite its age, was well designed and conducted. 4) DCVC activation in the mouse kidney is greater than in rat kidney but kidney tumors have not been induced by TCE in any study. A genotoxic mode of action might have been expected to induce tumors in mice.</p> <p>On balance, rat kidney tumors are unlikely to have arisen via a genotoxic mechanism following TCE administration. Since tumors have only been induced at dose levels of TCE that cause frank kidney toxicity, and male rats have a recognized tendency to develop kidney tumors under circumstances of repeated damage-repair cycles, this seems to be the most plausible mode of action.</p> <p>Whether the incidence of rat kidney tumors should be used to calculate human cancer risk is debatable, but if such calculations are employed, a non-linear MoA should be assumed.</p>	
4.4.7.1	103	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>2. The role of glutathione S-conjugates in nephrotoxicity and renal tumor formation by TCE</p> <p>Since S-conjugates of TCE are nephrotoxic in rodents and genotoxic in vitro, it is appealing to conclude that S-conjugate formation is involved in nephrotoxicity of TCE and that the MoA for kidney tumor formation is genotoxicity. However, a number of contradictory findings are not adequately considered in the IRIS-document:</p> <p>* Formation rates for DCVC in subcellular fractions from mice and rats are similar (or even higher in mice) suggesting similar doses of DCVC to the kidney in both species (Green et al., 1997a; Kim et al., 2009). Moreover, activation of TCE by the β-lyase pathway is higher in mice (Eyre et al., 1995), DCVC is more nephrotoxic in mice, and causes higher rates of cell replication and covalent binding in mice as compared to rats (Eyre et al., 1995; Green et al., 1997a). Yet, mice are not sensitive to TCE induced renal tumor formation.</p> <p>* Based on the nephrotoxicity of DCVC and the low rates of formation of DCVC both in rats and mice in vivo, it is questionable if the very low concentrations of DCVG formed in rodents can explain nephrotoxicity and tumor formation. Extrapolating the DCVG blood concentrations observed after single doses to the doses applied in the carcinogenicity studies with TCE in rats, daily DCVC-doses in the two year studies were less than 0.03 mg/kg bw. This is orders of magnitude below the doses of DCVC required to induce nephrotoxicity during chronic administration (Terracini and Parker, 1965) and further questions an involvement of this pathway in nephrotoxicity of TCE.</p>	<p>AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany</p> <p>Green, T., Dow, J., Ellis, M. K., Foster, J. R., and Odum, J. (1997a). The role of glutathione conjugation in the development of kidney tumours in rats exposed to trichloroethylene. <i>Chemico-Biological Interactions</i> 105, 99-117.</p> <p>Kim, S., Kim, D., Pollack, G. M., Collins, L. B., and Rusyn, I. (2009). 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. <i>Toxicol Appl Pharmacol</i> 238, 90-99.</p> <p>Eyre, R. J., Stevens, D. K., Parker, J. C., and Bull, R. J. (1995). Acid-labile adducts to protein can be used as indicators of the cysteine S-conjugate pathway of trichloroethene metabolism. <i>J Toxicol Environ Health</i> 46, 443-464.</p> <p>Terracini, B., and Parker, V. H. (1965). A Pathological Study on the Toxicity of S-Dichlorovinyl-L-Cysteine. <i>Food Cosmet Toxicol</i> 3, 67-74.</p> <p>Bruning, T., Weirich, G., Hornauer, M. A., Hofler, H., and Brauch, H. (1997). Renal cell carcinomas in</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>* EPA concludes that trichloroethanol and formic acid formation may not be involved in the toxicity of TCE to the kidney due to differences in pathology observed between TCE and trichloroethanol treated rats. In my opinion, such comparisons are difficult since differences in the kinetic profiles of a compound formed as a metabolite or administered per se are likely major confounders. The mode of action for TCE-induced renal tumors due to effects of increased formic acid excretion due to disturbances in intermediary metabolism by trichloroethanol is supported by renal toxicity of trichloroethanol, insufficient rates of DCVC/DCVC-formation to account for renal toxicity and the absence of genotoxic effects of TCE on rat kidney in vivo.</p> <p>* EPA states that data on VHL gene mutations support a mutagenic MoA in TCE-induced kidney tumors. This is based on studies (Bruning et al., 1997; Brauch et al., 2004) reporting VHL mutations in renal tumors of TCE-exposed individuals. It is concluded that comparison of TCE-exposed and non-exposed patients (Brauch et al., 2004) revealed clear differences with respect to (1) frequency of somatic VHL mutations, (2) incidence of C454T transition, and (3) incidence of multiple mutations. As discussed in Brauch et al. (2004), the mutation frequency in the non-exposed patients (10%) was considerably lower than that commonly observed in sporadic renal tumors, e.g. 82% (Nickerson et al., 2008) or 71% (Banks et al., 2006), and technical problems using archived tissue samples may be one of the causes. Given that exon 3, which harbors the multiple mutations seen in TCE exposed patients, did not amplify in most of the controls, there is only limited evidence for a difference in the incidence of multiple mutations and frequency of somatic VHL mutations, although the C454T transition appears to be characteristic of tumors in TCE exposed patients. However, the presence of mutations in human tumors does not lead to the conclusion that VHL mutations occur early during carcinogenesis. Hence, they are not evidence for a direct genotoxicity of TCE in the kidney. In contrast, experimental data in rats show that neither TCE nor its active metabolite DCVC induce VHL mutations (Mally et al., 2006), suggesting that VHL mutations in humans may be acquired at later stages of tumor development. While the document argues that the VHL gene may not be a target gene in rodent models of renal carcinogenesis, only few studies have looked at VHL in rats and there is no support for the hypothesis that the role of VHL is different in rats and humans.</p> <p>* The Eker rat may be a useful rodent model for renal cell carcinoma (RCC), but the molecular basis for chemically induced tumor formation in rats and RCC in humans may be widely different from spontaneous tumor formation in this rat strain, as high-grade RCCs can develop in the absence of mutations in the Tsc2 gene in rats (Toyokuni et al., 1998). Development of high-grade renal cell carcinomas in rats independently of somatic mutations in the Tsc2 and VHL tumor suppressor genes (Toyokuni et al., 1998) demonstrates that mutational inactivation of TSC2 or VHL is not a prerequisite for renal carcinogenesis. The similar pathway activation in Eker rat RCC as that seen in humans with VHL mutations reported (Liu et al., 2003) involves deregulation of HIFα and VEGF expression which frequently occur in various cancers and provide little evidence to suggest that Tsc-2 inactivation in rats is "analogous" to inactivation of VHL in human RCC.</p> <p>* Epidemiological data may support an association between specific VHL mutations and TCE exposure, this does not indicate an early event in RCC and – in the absence of experimental support - should not be taken as support for a mutational MoA.</p> <p>* EPA uses micronucleus and comet assay data in rat kidney after TCE-administration as support for a genotoxic MoA. However, the positive micronucleus (Robbiano et al., 2004) assay applied a very high dose and used an inappropriate route of administration (ip injection of 1/2 of the LD50). Due to the high dose applied and the route of administration, the results may be confounded by inflammatory responses and should not be used for conclusions. A comet assay in the kidney using repeated inhalation exposures to TCE was negative (Clay, 2008). The decision to not use this study in the assessment is insufficiently justified. The inhalation study used a higher number of animals (5/group) as compared to the ip study, which states n > 3 with an apparent maximum of 5. The comet assay also shows that administered DCVC is no more than weakly active in the kidney.</p> <p>* EPA argues that there is no link between nephrotoxicity and renal tumor formation. However, there are a number of compounds that cause renal tumors in rats without being genotoxic. For example, cytotoxicity and regenerative cell proliferation (Swenberg and Lehman-McKeeman, 1999) is accepted as MoA for ALPHA2U-globulin binding agents (TCE does not bind to ALPHA2u-globulin, but is most likely to cause renal tumors through nephrotoxicity).</p>	<p>trichloroethene (TRI) exposed persons are associated with somatic mutations in the von Hippel-Lindau (VHL) tumour suppressor gene. Arch Toxicol 71, 332-335.</p> <p>Brauch, H., Weirich, G., Klein, B., Rabstein, S., Bolt, H. M., and Bruning, T. (2004). VHL mutations in renal cell cancer: does occupational exposure to trichloroethylene make a difference? Toxicol Lett 151, 301-310.</p> <p>Nickerson, M. L., Jaeger, E., Shi, Y., Durocher, J. A., Mahurkar, S., Zaridze, D., Matveev, V., Janout, V., Kollarova, H., Bencko, V., Navratilova, M., Szeszenia-Dabrowska, N., Mates, D., Mukeria, A., Holcatova, I., Schmidt, L. S., Toro, J. R., Karami, S., Hung, R., Gerard, G. F., Linehan, W. M., Merino, M., Zbar, B., Boffetta, P., Brennan, P., Rothman, N., Chow, W. H., Waldman, F. M., and Moore, L. E. (2008). Improved identification of von Hippel-Lindau gene alterations in clear cell renal tumors. Clin Cancer Res 14, 4726-4734.</p> <p>Banks, R. E., Tirukonda, P., Taylor, C., Hornigold, N., Astuti, D., Cohen, D., Maher, E. R., Stanley, A. J., Harnden, P., Joyce, A., Knowles, M., and Selby, P. J. (2006). Genetic and epigenetic analysis of von Hippel-Lindau (VHL) gene alterations and relationship with clinical variables in sporadic renal cancer. Cancer Res 66, 2000-2011.</p> <p>Mally, A., Walker, C. L., Everitt, J. I., Dekant, W., and Vamvakas, S. (2006). Analysis of renal cell transformation following exposure to trichloroethene in vivo and its metabolite S-(dichlorovinyl)-L-cysteine in vitro. Toxicology 224, 108-118.</p> <p>Toyokuni, S., Okada, K., Kondo, S., Nishioka, H., Tanaka, T., Nishiyama, Y., Hino, O., and Hiai, H. (1998). Development of high-grade renal cell carcinomas in rats independently of somatic mutations in the Tsc2 and VHL tumor suppressor genes. Jpn J Cancer Res 89, 814-820.</p> <p>Liu, M. Y., Poellinger, L., and Walker, C. L. (2003). Up-regulation of hypoxia-inducible factor 2alpha in renal cell carcinoma associated with loss of Tsc-2 tumor suppressor gene. Cancer Res 63, 2675-2680.</p> <p>Robbiano, L., Baroni, D., Carrozzino, R., Mereto, E., and Brambilla, G. (2004). DNA damage and micronuclei induced in rat and human kidney cells by six chemicals carcinogenic to the rat kidney. Toxicology 204, 187-195.</p> <p>Clay, P. (2008). Assessment of the genotoxicity of trichloroethylene and its metabolite, S-(1,2-dichlorovinyl)-L-cysteine (DCVC), in the comet assay in rat kidney. Mutagenesis 23, 27-33.</p> <p>Swenberg, J. A., and Lehman-McKeeman, L. D. (1999). a2u-Globulin associated nephropathy as a mechanism of renal tubular cell carcinogenesis in male rats. In IARC-Scientific Publications: Species differences in thyroid, kidney and urinary bladder carcinogenesis (C. C. Capen, E. Dybing, J. M. Rice, and J. D. Wilbourn, Eds.), pp. 95-118. International Agency on Cancer Research, Lyon.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>In summary, the data do not support a genotoxic mode of action for kidney carcinogenicity via S-conjugates of TCE. The decision of EPA to employ S-conjugate-mediated genotoxicity in support of a linear dose response relationship for renal cell carcinoma should be revised to reflect the balance of the data. A non-linear dose response relationship is well supported by the available evidence.</p>	
4.5	232	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>OTHER KEY CHOICES IN THE RISK ASSESSMENT NOT RELATED TO PBPK MODEL PARAMETER VALUES.</p> <p>One of the many parameters to be considered in a sensitivity analysis is the dose or exposure concentration. Clearly, the value of the iPOD will be related to the dose, especially at doses below saturating levels. Many risk assessment choices feed into identifying the point of departure for the RfCs/RfDs and slope factors, some of which will be discussed below.</p> <p>First, the study considered for use as the basis for the potential risk value needs to be evaluated to determine if it is suitable for risk assessment. Considerations include the use of suitable test species, numbers of animals, appropriate test material (e.g., acceptable purity or a standardized mixture), adequate documentation, and ethical conduct of the study. Even if a single study is inadequate by itself, it may be possible to combine studies to yield adequate information, or use the study to support findings from mother study. Toxicity studies of key metabolites should also be considered. For the endpoint of hepatomegaly EPA appears to have considered evaluating the dose-response relationship for a TCE metabolite (in this case, TCA) via direct dosing and the effect of interest, in order to compare that relationship to the relationship between the same metabolite and the effect of interest when that compound is produced from TCE metabolism. Evaluation of the dose-response from direct-dosing studies of key metabolites and demonstration of consistency with the dose response seen from dosing with TCE would provide a more scientifically-supported analysis.</p>	AUTHOR: Lisa M. Sweeney, Ph.D., DABT -
4.5	236	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>An important consideration, especially when PBPK modeling is to be used, is the choice of dose metric. Assumptions/beliefs about the mode of action are embedded within the choice of dose metric used for dose-response analyses and route-to-route or interspecies extrapolations. Considerations include the use of parent compound vs. total metabolites generated vs. concentrations of specific metabolites, and opting to use peak values, time-weighted average (TWA) values; or cumulative values. For example, why did EPA use TCA produced rather than TWA liver TCA concentration to evaluate the potential dose-response relationship between TCE administration and liver weight increases in mice (Section 4.5)? Until the relationship between TCA and hepatomegaly is properly analyzed, it is premature to assert that TCA is insufficient to account for the rodent liver tumors.</p>	AUTHOR: Lisa M. Sweeney, Ph.D., DABT -
4.5.2	2	EPA-HQ-ORD-2009-0791-0010.1	ARCADIS on behalf of Deltrex Corporation	<p>To improve the clarity and transparency of the meta-analysis description in this document, a number of basic epidemiology terms need to be defined and their relevance to the meta-analysis provided. At the very least, a glossary of terms should be added with definitions for terms such as case-control study, cohort study, odds ratio, relative risk, causation, strength of association, etc. This is very important because the U.S. EPA's use of epidemiology tools in toxicological reviews is limited, and this document assumes the reader already has a good working knowledge of epidemiology.</p>	- -
4.5.2	8	EPA-HQ-ORD-2009-0791-0010.1	ARCADIS on behalf of Deltrex Corporation	<p>"The following provides a brief review of the meta-analysis for kidney, lymphoma, and liver cancers as shown in Appendix C, Tables C-1 through C-11.".....</p> <p>"Liver and Biliary Tract Cancer: The evidence for liver and biliary tract cancer is even more limited. The overall TCE exposure relative risk estimate for the nine studies used in the meta-analysis was 1.33 (95% CI: 1.09, 1.64). But the pooled RRp estimate for the highest TCE exposure group was lower at 1.28 (95% CI: 0.93, 1.77). Two of the nine studies had individual RR estimates below 1.0, and two studies had RR estimates for the highest TCE exposure group that were lower than the overall TCE exposure RR estimates. The overall TCE exposure individual study RR ranged from 0.54 to 2.1. The U.S. EPA acknowledges that the data for liver cancer are uncertain mainly because only cohort studies are available, and most of these studies have small numbers of cases.".....</p> <p>"Therefore, it can be agreed that the liver cancer meta-analysis is limited and conclusions by the U.S. EPA that the human epidemiology evidence of TCE exposure is "convincing" for kidney cancer and "compelling" for lymphoma are overreaching.".....</p>	- -

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>“The meta-analysis human epidemiology database for each of the three types of cancer (14 studies for kidney, 16 studies for lymphoma, and 9 studies for liver) is relatively small compared to the volumes of data reviewed for other chemicals such as arsenic, asbestos, dioxin, perchlorate, ethylene oxide, etc. The U.S. EPA should perform an internal quality review of its own practices or standards of care for the use of human epidemiology data for developing toxicity values.”</p>	
4.5.2	198	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>When examining the data for TCE and non-Hodgkin lymphoma, kidney cancer, and liver cancer, associations were inconsistent across occupational groups (summary results differed between aerospace/aircraft worker cohorts compared with workers from other industries), study design, location of the study, quality of exposure assessment (e.g., evaluating studies that relied upon biomonitoring to estimate exposure vs. semi-quantitative estimates vs. self-report, etc.), and by incidence vs. mortality endpoints. Although EPA examined high dose categories, it did not evaluate any potential dose-response relationships across the epidemiologic studies (except for the Charbotel et al. 2006 study). In our reviews of the epidemiologic data reported in various studies for different exposure levels (e.g. cumulative exposure and duration of exposure metrics): we did not find consistent dose-response associations between TCE and the three cancer sites under review (Mandel et al., 2006; Alexander et al., 2007; Kelsh et al., 2010) Ail established dose-response trend is one of the more important factors when making assessments of causation in epidemiologic literature. These issues are addressed in greater detail in the accompanying comments by Michael Kelsh and Dominic Alexander.</p>	<p>AUTHORS: Michael Dourson, Ph.D., DABT and Lynne Haber, Ph.D., DABT from Toxicology Excellence for Risk Assessment and Michael Kelsh, Ph.D., MPH and Dominik Alexander, Ph.D., MPH from Exponent, Health Sciences</p> <p>Charbotel B, Fevotte J, Hours M, martin J, Beregeret A. Case-Control Study on Renal Cell Cancer and Occupational Exposure to Trichloroethylene. Part 11: Epidemiological Aspects. Ann.Occup.Hyg. 2006.</p> <p>Mandel JH, Kelsb MA, Mink PJ, Alexander D, Kalms RM, Weingart M, Yost L Goodman M. Occupational trichloroethylene exposure and non-Hodgkins lymphoma: A meta-analysis and review. Occup Environ Med 2006; 63(9):597-607.</p> <p>Alexander DD, Kelsh MA, Mink PJ, Mandel JH. Basu R, Weingart W. A meta-analysis of occupational trichloroethylene exposure and liver cancer. Int Arch Occup Environ Health 2007; 81(2):127-143.</p> <p>Kelsh MA, Alexander DD, Mink PJ, Mandel JH. Occupational trichloroethylene exposure and kidney cancer: a meta-analysis. Epidemiology. 2010 Jan;21(1):95-102.</p>
4.5.2	278	EPA-HQ-ORD-2009-0791-0014.1	Exponent Health Services	<p>EPA’s meta-analysis methods and summaries, for the most part, are consistent with recent published summaries of this literature – however, EPA’s interpretation of the meta-analysis findings is not consistent with the general approaches used in evaluating causality from epidemiologic research study evaluation. Epidemiologic causal evaluation considers not only the presence of a statistical association, but also the strength of that association, whether exposure response trends are present, the consistency of study findings, biologic plausibility, coherence, and other factors (Hill 1965; Weed 2005). Although EPA considers these factors, their conclusions are not supported once these factors are applied to the epidemiologic literature. The epidemiologic literature on TCE exposure and cancer cannot be categorized as “strong” or “robust” or of sufficient quality to provide definitive evidence of a causal association between TCE exposure and cancer. The observed summary relative risk estimates from the meta-analyses of kidney cancer, liver cancer, and non-Hodgkin’s lymphoma (NHL) are not sufficiently strong to be able to rule out other potential explanations such as bias due to confounding, exposure misclassification, or other factors (e.g. selection bias in case control studies). The consistency of the findings is not as robust as characterized in the EPA review. For example, in the kidney cancer analyses, the evaluation of cohorts defined from biomonitoring data, a source of exposure information considered more accurate than other exposure assessment characterizations, found no association with kidney cancer. Although these studies were small, these results merit consideration. In addition, several large cohort studies of aerospace/aircraft maintenance workers (e.g. Radican et al. 2008; Boice et al. 1999) reported no association between TCE exposure and kidney cancer. The EPA review recognizes the significant limitations of several German studies of TCE exposure and kidney cancer (e.g., Henchler et al., Vamvakas et al.) and did not include them in their meta-analysis summaries; a decision consistent with a recently published meta-analysis of TCE and kidney cancer (Kelsh et al., 2010). In summary, it is important to emphasize that the magnitude of the summary estimate in the EPA meta-analysis of kidney cancer was modest (relative risk =1.25). Furthermore given the range and imprecision of the individual study findings, with many studies reporting no increased risks, it is more accurate to report the study results as “mixed” rather than consistent or robust.</p> <p>In the latest EPA Toxicological Review of TCE, it is apparent that many of the issues and concerns raised in the methodological review of the inter-agency draft with respect to the metaanalysis of epidemiologic studies of TCE exposure and cancer of have been addressed. However, some important matters remain, particularly regarding the interpretation of the currently available epidemiologic evidence. In the widely read textbook Modern Epidemiology (Rothman, Greenland and Lash 2008), Greenland and O’Rourke describe the two main goals of meta-analysis: to estimate differences among study-specific effects (analytic goal) and/or to estimate an</p>	<p>-</p> <p>Boice JD, Jr. et al. Mortality among aircraft manufacturing workers. Occup.Environ.Med. 1999;56:581-97.</p> <p>Hill AB. The Environment and Disease: Association or Causation? Proc R Soc Med 1965; 58:295-300.</p> <p>Kelsh MA, Alexander DD, Mink PJ, Mandel JH. Occupational trichloroethylene exposure and kidney cancer: a meta-analysis. Epidemiology. 2010 Jan;21(1):95–102.</p> <p>Lash TL. Bias analysis applied to Agricultural Health Study publications to estimate non-random sources of uncertainty. J Occup Med Toxicol. 2007 Nov 26;2:15.</p> <p>Radican L, Blair A, Stewart P, Wartenberg D. Mortality of aircraft maintenance workers exposed to trichloroethylene and other hydrocarbons and chemicals: An extended follow-up. J Occup Environ Med 2008; 50(11): 1306–19.</p> <p>Weed DL. Weight of Evidence: A Review of Concept and Methods. Risk Analysis, Vol. 25, No. 6, 2005.</p> <p>Alexander DD, Wagner ME. Benzene exposure and Non-Hodgkin Lymphoma: A meta-analysis of epidemiologic studies. J Occup Environ Med 2009, in press.</p> <p>Alexander DD, Mink PJ, Mandel JH, Kelsh M. A meta-analysis of occupational trichloroethylene exposure and multiple myeloma or leukemia. Occup Med (Lond) 2006; 56(7):485–493.</p> <p>Kelsh MA, Alexander DD, Mink PJ, Mandel JH. Occupational trichloroethylene exposure and kidney cancer: a meta-analysis. Epidemiology. 2010 Jan;21(1):95–102.</p> <p>Mandel JH Kelsh MA, Mink P, Alexander DD. Occupational trichloroethylene exposure and non-Hodgkin’s lymphoma: a meta-analysis and review. Occup.Environ.Med. 2006;63:597–607.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>average effect across studies (synthetic goal). They further remind readers that “a sound meta-analysis needs to assess each study’s limitations as well as gaps in the entire literature being assessed.” Thus, while a meta-analysis may serve as a valuable tool for analyzing data across a large body of scientific studies to produce a more precise estimate of relative risk, interpretation of summary findings should be made in consideration of several important methodological factors (e.g. exposure misclassification, confounding and selection bias) and guidelines for evaluation of causality based on epidemiologic data (Hill 1965; Weed 2005). Indeed, meta-analysis and causal inference are separate endeavours with different methods.</p> <p>Most epidemiologic studies of TCE exposure and cancer observed associations that were not statistically significant and most studies lacked quantitative exposure assessments. Across epidemiologic studies, different exposure metrics were used, exposure-response patterns were inconsistently observed, and uncontrolled (or incompletely controlled) confounding and other sources of systematic error likely influenced effect estimates. EPA conducted various sensitivity analyses (excluding individual studies to assess their impact on summary relative risk estimates); however, important evaluations such as summarization by sub-group characteristics, study design differences, or findings by exposure measurement method were not presented or fully considered. It is unfortunate that EPA did not conduct exposure-response analyses by specific exposure metrics, such as cumulative dose or years of exposure. Because “dose-response” is an important consideration in the evaluation of epidemiologic studies for causality, we evaluated exposure-response data to the extent possible in our published meta-analyses and observed no clear pattern of increasing cancer risk with increasing exposure level or duration (Kelsh et al 2010; Mandel et al 2006; Alexander et al. 2007; Alexander et al., 2006). Such an analysis by EPA would provide helpful information in the consideration of potential relationships between TCE and cancer. In summary, although EPA conducted a comprehensive meta-analysis and examined many issues in the epidemiologic data, EPA’s conclusions regarding the carcinogenicity of TCE are not supported by the studies they cite.</p>	
4.5.2	299	EPA-HQ-ORD-2009-0791-0014.1	Exponent Health Services	<p>Liver Cancer</p> <ul style="list-style-type: none"> The summary association for the high exposure analysis was slightly lower (and not statistically significant) compared with the overall analysis, which is not characteristic of a causal relationship. This implies that the epidemiologic data do not provide evidence of a causal association between TCE exposure and liver cancer. 	-
4.5.4.1	84	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	EPA’s detailed analysis of liver weight increases suffers from the same overestimates of TCA bioavailability discussed in section 2.3.	AUTHOR: Paul H. Dugard, Halogenated Solvents Industry Alliance, Inc. -
4.5.4.1	85	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>2.3 Potency of TCA as a Mouse Liver Carcinogen: As explained by Prof. Dekant, and as analyzed by Sweeney et al (2009), EPA has misinterpreted the bioavailability of TCA from drinking water, the mode of administration used in mouse carcinogenicity studies employed to establish the potency of TCA. Since the bioavailability of TCA falls with rising concentration in drinking water, not taking this into account leads to a lower estimate of potency of an internal dose of TCA than if correct values for bioavailability are employed. Using a correct estimate of the potency of TCA shows that sufficient TCA is generated from TCE to explain the incidence of mouse liver tumors (Fisher and Dugard, unpublished).</p> <p>EPA should recalculate the potency of internal doses of TCA (based on an improved estimate of bioavailability in TCA drinking water studies) and reassess the role of TCA in the generation of mouse liver tumors by TCE.</p>	AUTHOR: Paul H. Dugard, Halogenated Solvents Industry Alliance, Inc. -
4.5.5.1	202	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	Of the 4 primary tissues that EPA evaluates for carcinogenicity, only one or perhaps two of them, liver and lung tumors in mice, rises to the level of biological significance. Discussion of the remaining tumor types appears to presuppose that TCE is carcinogenic. The resulting text appears then to overly discount negative data, of which there are many, and to highlight marginal findings. The text does not appear to be a dispassionate rendering of the available data. (FOOTNOTE 1)	<p>FOOTNOTE 1: For example, EPA (page 4.261) states "For rats, Maltoni et al. (1986) reported 4 liver angiosarcomas (1 in a control male rat, 1 both in a TCE-exposed male and female at 600 ppmTCE for 8 weeks, and 1 in a female rat exposed to 600-ppm TCE for 104 weeks), but the specific results for incidences of hepatocellular "hepatomas" in treated and control rats were not given. Although Maltoni et al. (1986) concluded that the small number was not treatment related, the findings were brought forward [emphasis added] because of the extreme rarity of this tumor in control Sprague-Dawley rats, untreated or treated with vehicle materials." Perhaps we missed them in EPA's tome, but these data were not shown.</p> <p>Another example of this tendency to discount negative findings is found on Page 4-263. "Although the</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
					<p>mice in the two experiments [Maltoni et al., 1988, Table 4-55, page 4-2583 in males were of the same strain, the background level of liver cancer was significantly different between mice from the different sources (1/90 versus 19/90), though the early mortality may have led to some censoring." Perhaps we missed EPA's point, but it appears that the Table 4-55 only presented one of the two control groups. Inclusion of the control group with the higher background level would suggest that there was no chemical-related increase.</p> <p>AUTHORS: Michael Dourson, Ph.D., DABT and Lynne Haber, Ph.D., DABT from Toxicology Excellence for Risk Assessment and Michael Kelsh, Ph.D., MPH and Dominik Alexander, Ph.D., MPH from Exponent, Health Sciences</p> <p>U.S. Environmental Protection Agency. 2005. Guidelines for carcinogen risk assessment Washington D.C. EPA/630/P-03/001R.</p>
4.5.5.1	203	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	EPA states that liver tumors are statistically significant in mice. This statement is confirmed by a biological judgment of all available data as shown in Tables 5 and 6. (FOOTNOTE 2)	<p>FOOTNOTE 2: EPA (page 4-261) also states that "The NTP (1990) study of TCE exposure in male and female F344/N rats, and B6C3F1 mice (500 and 1,000 mg/kg for rats) is limited in the ability to demonstrate a dose- response for hepatocarcinogenicity. For rats, the NTP (1990) study reported no treatment-related non-neoplastic liver lesions in males and a decrease in basophilic cytological change reported from TCE- exposure in female rats. The results for detecting a carcinogenic response in rats were considered to be equivocal because both groups receiving TCE showed significantly reduced survival compared to vehicle controls and because of a high rate (e.g., 20% of the animals in the high-dose group) of death by gavage error [emphasis added].</p> <p>Note well, however, that NTP (1990) is the same study in which the sole statistically significant finding of kidney cancer in rats was made by EPA (page 4-179, Table 4-41). Thus, EPA appears to accept the findings of NTP (1990) when the result is positive (kidney), but not when the result is negative (liver).</p> <p>Authors: Michael Dourson, Ph.D., DABT and Lynne Haber, Ph.D., DABT from Toxicology Excellence for Risk Assessment and Michael Kelsh, Ph.D., MPH and Dominik Alexander, Ph.D., MPH from Exponent, Health Sciences</p> <p>-</p>
4.5.6	81	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>2.2 The Role of DCA in the Induction of Mouse Liver Tumors by TCE:</p> <p>As discussed by Prof. Dekant, the amount of DCA generated from TCE is very small or even non-existent. If this low level of production is combined with the weak genotoxic potential and the relatively low potency of DCA as a mouse liver carcinogen in its own right, there seems to be no justification for assuming DCA contributes significantly to mouse liver tumors induced by TCE. Bull et al (2002) report a clear difference in the phenotypes of tumors induced by DCA versus TCA. A proportion of DCA tumors contained c-Jun but none of the TCA tumors examined showed this character. Tumors from TCE treated animals were reported to show a mixture of TCA and DCA phenotypes with quite a high proportion relating to DCA. The problem with this study is that the TCE tumors are much later stage than those examined for TCA and DCA (79 weeks versus 52 weeks). It is well known that later stage tumors develop complex genetic composition; thus a contribution from DCA to tumor induction by TCE cannot be supported by this study. The only true conclusion that can be drawn is that there is no evidence that conversion of TCA to DCA occurs to affect the nature of tumors seen, and this can be applied to TCA derived from TCE – conversion of TCA to DCA is unlikely to be significant for induction of mouse liver tumors. EPA's detailed analysis of liver weight increases suffers from the same overestimates of TCA bioavailability discussed in section 2.3.</p> <p>There is no convincing reason to believe that DCA contributes to mouse liver tumor induction by TCE.</p>	<p>AUTHOR: Paul H. Dugard, Halogenated Solvents Industry Alliance, Inc.</p> <p>-</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
4.5.6	83	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>2.3 Potency of TCA as a Mouse Liver Carcinogen: As explained by Prof. Dekant, and as analyzed by Sweeney et al (2009), EPA has misinterpreted the bioavailability of TCA from drinking water, the mode of administration used in mouse carcinogenicity studies employed to establish the potency of TCA. Since the bioavailability of TCA falls with rising concentration in drinking water, not taking this into account leads to a lower estimate of potency of an internal dose of TCA than if correct values for bioavailability are employed. Using a correct estimate of the potency of TCA shows that sufficient TCA is generated from TCE to explain the incidence of mouse liver tumors (Fisher and Dugard, unpublished).</p> <p>EPA should recalculate the potency of internal doses of TCA (based on an improved estimate of bioavailability in TCA drinking water studies) and reassess the role of TCA in the generation of mouse liver tumors by TCE.</p>	<p>AUTHOR: Paul H. Dugard, Halogenated Solvents Industry Alliance, Inc.</p> <p>Sweeney, L. M., Kirman, C. R., Gargas, M. L., and Dugard, P. H. (2009). Contribution of trichloroacetic acid to liver tumors observed in perchloroethylene (perc)-exposed mice. <i>Toxicology</i> 260, 77-83.</p>
4.5.6	106	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>3. Mode of action for liver carcinogenesis</p> <p>* EPA spends considerable effort to correlate liver tumor induction by TCE in mice with liver tumor induction observed after administration of the TCE metabolites TCA and DCA. Again, such comparisons are inherently complex. Both DCA and TCA were administered with drinking water and TCE studies applied gavage in oil. The different administration regimens will result in different time courses of the administered compounds or metabolites in blood and dose-dependent bioavailability may further complicate the interpretation.</p> <p>* It is highly questionable whether DCA is involved in liver tumor induction by TCE since it is only formed in very low concentrations from TCE in rodents (Dekant et al., 1986a; Kim et al., 2009). In mice, DCA is formed in concentrations several orders of magnitude below those of TCA. Thus, DCA would be required to be a highly potent liver carcinogen, which it is not. Therefore, the potency data on DCA do not suggest that the high liver tumor incidence induced by TCE in mice is related to DCA formation. In addition, DCA is not a human urinary metabolite of TCE (Bernauer et al., 1996; Bloemen et al., 2001).</p> <p>* For TCA, EPA derives a dose-dependence from tumor incidence data in drinking water studies. Apparently, EPA assumes a dose-independent high bioavailability of TCA. However, the oral bioavailability of TCA from drinking water is limited, concentration-dependent and significantly reduced at higher concentrations of TCA (Larson and Bull, 1992; Templin et al., 1993; Sweeney et al., 2009). The incidence data therefore need to be corrected to account for the limited bioavailability of TCA at higher concentrations in drinking water.</p> <p>* The mostly negative data in mutagenicity testing with TCE using liver specific activation and negative in vivo genotoxicity data including a very low DNA-binding in liver of mice (Bergman, 1983; Kautiainen et al., 1997) also do not support a mutagenic MoA for liver tumors. Due to intensive metabolism by oxidation and reduction, chloral hydrate concentrations in the liver are low and chloral hydrate is a very weak mutagen. Therefore, chloral hydrate mutagenicity cannot adequately explain the formation of liver tumors by TCE in mice.</p>	<p>AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany</p> <p>Dekant, W., Schulz, A., Metzler, M., and Henschler, D. (1986a). Absorption, elimination and metabolism of trichloroethylene: a quantitative comparison between rats and mice. <i>Xenobiotica</i> 16, 143-152.</p> <p>Kim, S., Kim, D., Pollack, G. M., Collins, L. B., and Rusyn, I. (2009). 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. <i>Toxicol Appl Pharmacol</i> 238, 90-99.</p> <p>Bernauer, U., Birner, G., Dekant, W., and Henschler, D. (1996). Biotransformation of trichloroethene: dose-dependent excretion of 2,2,2-trichloro-metabolites and mercapturic acids in rats and humans after inhalation. <i>Arch Toxicol</i> 70, 338-346.</p> <p>Bloemen, L. J., Monster, A. C., Kezic, S., Commandeur, J. N., Veulemans, H., Vermeulen, N. P., and Wilmer, J. W. (2001). Study on the cytochrome P-450- and glutathione-dependent biotransformation of trichloroethylene in humans. <i>Int Arch Occup Environ Health</i> 74, 102-108.</p> <p>Larson, J. L., and Bull, R. J. (1992). Species differences in the metabolism of trichloroethylene to the carcinogenic metabolites trichloroacetate and dichloroacetate. <i>Toxicology and Applied Pharmacology</i> 115, 278-285.</p> <p>Templin, M. V., Parker, J. C., and Bull, R. J. (1993). Relative formation of dichloroacetate and trichloroacetate from trichloroethylene in male B6C3F1 mice. <i>Toxicology and Applied Pharmacology</i> 123, 1-8.</p> <p>Sweeney, L. M., Kirman, C. R., Gargas, M. L., and Dugard, P. H. (2009). Contribution of trichloroacetic acid to liver tumors observed in perchloroethylene (perc)-exposed mice. <i>Toxicology</i> 260, 77-83.</p> <p>Bergman, K. (1983). Interactions of trichloroethylene with DNA in vitro and with RNA and DNA of various mouse tissues in vivo. <i>Arch Toxicol</i> 54, 181-193.</p> <p>Kautiainen, A., Vogel, J. S., and Turteltaub, K. W. (1997). Dose-dependent binding of trichloroethylene to hepatic DNA and protein at low doses in mice. <i>Chem Biol Interact</i> 106, 109-121.</p>
4.5.7	80	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>2. Mouse Liver Tumors, Mode of Action</p> <p>2.1 General: It is well recognized that TCE induces mouse liver tumors in some strains of mouse but not in rats. There is no convincing support for hepatocarcinogenicity in epidemiology studies. It has been reasonably concluded that a product of oxidative metabolism of TCE is responsible for mouse liver tumors. The more significant metabolites generated from TCE via the oxidative pathway are either weakly genotoxic, at most, or non-genotoxic (see Moore and Harrington-Brock, 2000 for a comprehensive review). It is highly likely that</p>	<p>AUTHOR: Paul H. Dugard, Halogenated Solvents Industry Alliance, Inc.</p> <p>-</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>mouse liver tumors are generated by a non-genotoxic mechanism and many consider that the major circulating metabolite of TCE, trichloroacetic acid (TCA) is responsible acting via factors associated with peroxisome proliferation mediated through PPAR ALPHA. Acceptance of a PPAR ALPHA-related MoA could lead to a conclusion that the mouse liver tumors are not relevant to man. At the very least a non-linear MoA for mouse liver tumors should be accepted if TCA operates via a PPAR ALPHA-related MoA.</p> <p>EPA has two main reasons for rejecting a PPAR ALPHA-related mechanism that are specific for TCE and a general position regarding the interpretation of cases where PPAR ALPHA and rodent liver tumors are linked. The two specific reasons are 1) That dichloroacetic acid (DCA) is a metabolite of TCE; it is a rodent liver carcinogen; it is a genotoxin and makes an unknown but possibly significant contribution to mouse liver tumors induced by TCE. 2) That TCA is not sufficiently potent as a mouse liver carcinogen to explain the number of mouse liver tumors generated by TCE. The general position taken by EPA's NCEA Washington Office is that even if rodent tumors are generated via a PPAR ALPHA-related MoA, it has not been sufficiently well established that this MoA is not relevant to man and, since the mechanism is not fully understood, a linear dose response extrapolation is appropriate.</p>	
4.5.7	105	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>3. Mode of action for liver carcinogenesis</p> <p>* EPA spends considerable effort to correlate liver tumor induction by TCE in mice with liver tumor induction observed after administration of the TCE metabolites TCA and DCA. Again, such comparisons are inherently complex. Both DCA and TCA were administered with drinking water and TCE studies applied gavage in oil. The different administration regimens will result in different time courses of the administered compounds or metabolites in blood and dose-dependent bioavailability may further complicate the interpretation.</p> <p>* It is highly questionable whether DCA is involved in liver tumor induction by TCE since it is only formed in very low concentrations from TCE in rodents (Dekant et al., 1986a; Kim et al., 2009). In mice, DCA is formed in concentrations several orders of magnitude below those of TCA. Thus, DCA would be required to be a highly potent liver carcinogen, which it is not. Therefore, the potency data on DCA do not suggest that the high liver tumor incidence induced by TCE in mice is related to DCA formation. In addition, DCA is not a human urinary metabolite of TCE (Bernauer et al., 1996; Bloemen et al., 2001).</p> <p>* For TCA, EPA derives a dose-dependence from tumor incidence data in drinking water studies. Apparently, EPA assumes a dose-independent high bioavailability of TCA. However, the oral bioavailability of TCA from drinking water is limited, concentration-dependent and significantly reduced at higher concentrations of TCA (Larson and Bull, 1992; Templin et al., 1993; Sweeney et al., 2009). The incidence data therefore need to be corrected to account for the limited bioavailability of TCA at higher concentrations in drinking water.</p> <p>* The mostly negative data in mutagenicity testing with TCE using liver specific activation and negative in vivo genotoxicity data including a very low DNA-binding in liver of mice (Bergman, 1983; Kautiainen et al., 1997) also do not support a mutagenic MoA for liver tumors. Due to intensive metabolism by oxidation and reduction, chloral hydrate concentrations in the liver are low and chloral hydrate is a very weak mutagen. Therefore, chloral hydrate mutagenicity cannot adequately explain the formation of liver tumors by TCE in mice.</p>	<p>AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany</p> <p>Dekant, W., Schulz, A., Metzler, M., and Henschler, D. (1986a). Absorption, elimination and metabolism of trichloroethylene: a quantitative comparison between rats and mice. <i>Xenobiotica</i> 16, 143-152.</p> <p>Kim, S., Kim, D., Pollack, G. M., Collins, L. B., and Rusyn, I. (2009). 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. <i>Toxicol Appl Pharmacol</i> 238, 90-99.</p> <p>Bernauer, U., Birner, G., Dekant, W., and Henschler, D. (1996). Biotransformation of trichloroethene: dose-dependent excretion of 2,2,2-trichloro-metabolites and mercapturic acids in rats and humans after inhalation. <i>Arch Toxicol</i> 70, 338-346.</p> <p>Bloemen, L. J., Monster, A. C., Kezic, S., Commandeur, J. N., Veulemans, H., Vermeulen, N. P., and Wilmer, J. W. (2001). Study on the cytochrome P-450- and glutathione-dependent biotransformation of trichloroethylene in humans. <i>Int Arch Occup Environ Health</i> 74, 102-108.</p> <p>Larson, J. L., and Bull, R. J. (1992). Species differences in the metabolism of trichloroethylene to the carcinogenic metabolites trichloroacetate and dichloroacetate. <i>Toxicology and Applied Pharmacology</i> 115, 278-285.</p> <p>Templin, M. V., Parker, J. C., and Bull, R. J. (1993). Relative formation of dichloroacetate and trichloroacetate from trichloroethylene in male B6C3F1 mice. <i>Toxicology and Applied Pharmacology</i> 123, 1-8.</p> <p>Sweeney, L. M., Kirman, C. R., Gargas, M. L., and Dugard, P. H. (2009). Contribution of trichloroacetic acid to liver tumors observed in perchloroethylene (perc)-exposed mice. <i>Toxicology</i> 260, 77-83.</p> <p>Bergman, K. (1983). Interactions of trichloroethylene with DNA in vitro and with RNA and DNA of various mouse tissues in vivo. <i>Arch Toxicol</i> 54, 181-193.</p> <p>Kautiainen, A., Vogel, J. S., and Turteltaub, K. W. (1997). Dose-dependent binding of trichloroethylene to hepatic DNA and protein at low doses in mice. <i>Chem Biol Interact</i> 106, 109-121.</p>
4.5.7.2	62	EPA-HQ-ORD-2009-	Natural Resources	We support the findings of the publication by EPA scientists,13 as well as by others in the scientific literature that: 1) there are no reliable epidemiology data on human liver cancer risk from exposure to PPAR- α agonists, 2)	- 13 Guyton KZ, Chiu WA, Bateson TF, Jinot J, Scott CS, Brown RC, Caldwell JC. A reexamination of

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
		0791-0007.1	Defense Council (NRDC) and Supoprters	<p>humans are not PPARα-knockout mice, 3) there are no data to suggest that there should be site concordance between human and animal tumors following exposure to PPARα-agonists, and 4) hepatic Kupffer cells are required for the proliferative response to PPARα agonists, via a PPARα-independent mechanism, but the mechanism of this dependency is unclear. We therefore support IRIS scientific staff in their conclusion that there are insufficient data to disregard cancers observed in rodent studies.¹⁴</p> <p>While DNA synthesis and apoptosis are key events in carcinogenesis, some scientists have proposed that the balance between cell replication and cell loss in precancerous liver tissue may be more relevant to PPAR-induced cancer outcome.¹⁵ For example, treatment of older rats with the peroxisome proliferator Wy-14,643 induced a 5-7 fold higher yield of grossly visible hepatic tumors when compared to younger rats, whereas there was no age-related differences in peroxisome proliferation or sustained liver cell proliferation.¹⁶ This suggests that there are critical processes relevant to carcinogenesis that are incompletely understood, beyond peroxisomal and cellular proliferation. While DNA synthesis and decreased apoptosis may be necessary, they may not be sufficient, to predict cancer risk from exposure to PPAR-agonists.</p> <p>Most importantly, TCE is a multi-site carcinogen. Robust studies reviewed by the International Agency for Research on Cancer (IARC) in 1995 (Vol 63) reviewed evidence of TCE-associated cancer of the liver, lung, cervix, and blood. That working group of international cancer experts concluded that “Although the hypothesis linking the formation of mouse liver tumours with peroxisome proliferation is plausible, trichloroethylene also induced tumours at other sites in mice and rats” which cannot be explained away.</p>	<p>the PPAR-alpha activation mode of action as a basis for assessing human cancer risks of environmental contaminants. Environ Health Perspect. 2009 Nov;117(11):1664-72. Epub 2009 May 15.</p> <p>14 Melnick RL. Is peroxisome proliferation an obligatory precursor step in the carcinogenicity of di(2-ethylhexyl)phthalate (DEHP)? Environ Health Perspect. 2001 May;109(5):437-42. Review. Melnick RL, Huff J. Liver carcinogenesis is not a predicted outcome of chemically induced hepatocyte proliferation. Toxicol Ind Health. 1993 May-Jun;9(3):415-38. Review. Melnick RL. Does chemically induced hepatocyte proliferation predict liver carcinogenesis? FASEB J. 1992 Jun;6(9):2698-706. Review.</p> <p>15 Melnick RL. Is peroxisome proliferation an obligatory precursor step in the carcinogenicity of di(2-ethylhexyl)phthalate (DEHP)? Environ Health Perspect. 2001 May;109(5):437-42. Review. Melnick RL, Huff J. Liver carcinogenesis is not a predicted outcome of chemically induced hepatocyte proliferation. Toxicol Ind Health. 1993 May-Jun;9(3):415-38. Review. Melnick RL. Does chemically induced hepatocyte proliferation predict liver carcinogenesis? FASEB J. 1992 Jun;6(9):2698-706. Review.</p> <p>16 Cattley RC, Marsman DS, Popp JA. Age-related susceptibility to the carcinogenic effect of the peroxisome proliferator WY-14,643 in rat liver. Carcinogenesis. 1991 Mar;12(3):469-73.</p>
4.5.7.2	79	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>2. Mouse Liver Tumors, Mode of Action</p> <p>2.1 General: It is well recognized that TCE induces mouse liver tumors in some strains of mouse but not in rats. There is no convincing support for hepatocarcinogenicity in epidemiology studies. It has been reasonably concluded that a product of oxidative metabolism of TCE is responsible for mouse liver tumors. The more significant metabolites generated from TCE via the oxidative pathway are either weakly genotoxic, at most, or non-genotoxic (see Moore and Harrington-Brock, 2000 for a comprehensive review). It is highly likely that mouse liver tumors are generated by a non-genotoxic mechanism and many consider that the major circulating metabolite of TCE, trichloroacetic acid (TCA) is responsible acting via factors associated with peroxisome proliferation mediated through PPAR ALPHA. Acceptance of a PPAR ALPHA-related MoA could lead to a conclusion that the mouse liver tumors are not relevant to man. At the very least a non-linear MoA for mouse liver tumors should be accepted if TCA operates via a PPAR ALPHA-related MoA.</p> <p>EPA has two main reasons for rejecting a PPAR ALPHA-related mechanism that are specific for TCE and a general position regarding the interpretation of cases where PPAR ALPHA and rodent liver tumors are linked. The two specific reasons are 1) That dichloroacetic acid (DCA) is a metabolite of TCE; it is a rodent liver carcinogen; it is a genotoxin and makes an unknown but possibly significant contribution to mouse liver tumors induced by TCE. 2) That TCA is not sufficiently potent as a mouse liver carcinogen to explain the number of mouse liver tumors generated by TCE. The general position taken by EPA’s NCEA Washington Office is that even if rodent tumors are generated via a PPAR ALPHA-related MoA, it has not been sufficiently well established that this MoA is not relevant to man and, since the mechanism is not fully understood, a linear dose response extrapolation is appropriate.</p>	<p>AUTHOR: Paul H. Dugard, Halogenated Solvents Industry Alliance, Inc.</p> <p>-</p>
4.5.7.2	86	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>2.4 MoA of TCA Hepatocarcinogenicity and Implications for Human Exposure to TCE: At the time of writing, release of the report of an NRC committee review of the draft IRIS support document for perchloroethylene is imminent. The issue of TCA MoA is expected to be addressed in that review. The evidence strongly indicates a PPAR ALPHA-related MoA for the induction of mouse liver tumors by TCA and thus also by TCE. This would leave the issue of the implications of such a MoA for human exposures to TCE. At this time EPA’s NCEA Washington Office is becoming increasingly isolated in its opinion that PPAR ALPHA-related rodent liver tumors remain fully relevant to man and that linear dose-response extrapolations are appropriate. This isolation is apparent within EPA as well as from other regulatory federal agencies in the US and around the world.</p> <p>It remains to be seen how this debate plays out, but the majority opinion among respected scientists seems to</p>	<p>AUTHOR: Paul H. Dugard, Halogenated Solvents Industry Alliance, Inc.</p> <p>-</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
4.6	88	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>support a diminished concern regarding rodent liver tumors associated with a PPAR ALPHA-related MoA.</p> <p>3. Immunotoxicity</p> <p>Two immunotoxicity studies have been used to support very low RfC and RfD values. The effect chosen from the study of Keil et al (2009) is a reduced thymus weight in mice seen at relatively low dose levels. This stands in contrast to a number of studies (immunotoxicity and other) in which no effect on thymus weight was evident in rats and mice following relatively high dose levels of TCE. The other study used to develop the reference values is the developmental immunotoxicity study reported by Peden-Adams et al (2006) in which effects were reported in mouse offspring following exposure of dams and, post-weaning, the pups to 1.4 ppm TCE in drinking water. The study appears to have been well conducted and stands as the only one of its kind. The reason for concern is that the effect is apparently seen at such a low dose which stands in contrast with the same effects seen only at relatively high dose levels in adult rodents. It is important for the substantially higher sensitivity of fetus or pup to be confirmed in separate investigation.</p> <p>After comments on other endpoints driving low reference values have been taken into account, it is possible that only these immunotoxicity studies would be left supporting very low RfD and RfC values. At this time, the findings do not appear to be sufficiently robust to carry that responsibility.</p>	<p>AUTHOR: Paul H. Dugard, Halogenated Solvents Industry Alliance, Inc.</p> <p>-</p>
4.6.1.2	7	EPA-HQ-ORD-2009-0791-0010.1	ARCADIS on behalf of Deltrex Corporation	<p>“The following provides a brief review of the meta-analysis for kidney, lymphoma, and liver cancers as shown in Appendix C, Tables C-1 through C-11.”.....</p> <p>“Lymphoma Cancers: This same trend is noted with the meta-analysis for lymphomas. Two of the 16 studies reviewed (Greenland et al. 1994; Miligi et al. 2006) had individual study RR estimates for overall TCE exposure below 1.0, and all of the other studies used in the analysis except Hardell (1994) and Hansen (2001) had RR estimates between 1.0 and 1.24. The pooled RRp estimate for overall TCE exposure was 1.23 (95% CI: 1.04, 1.44). Further, for the highest exposed group, five of the 16 studies (Anttila et al. 1995; Hansen et al. 2001; Morgan et al. 1998; Zhao et al. 2005; and Siemiatycki 1991) showed lower RR estimates than the overall TCE exposure. The pooled RRp estimate for the highest TCE exposure group was 1.57 (95% CI: 1.27, 1.94). The U.S. EPA acknowledges that issues of (non-statistically significant) study heterogeneity, potential publication bias, and weaker exposure-response results contribute greater uncertainty for the lymphoma analysis”.....</p> <p>“Therefore, it can be agreed that the liver cancer meta-analysis is limited and conclusions by the U.S. EPA that the human epidemiology evidence of TCE exposure is “convincing” for kidney cancer and “compelling” for lymphoma are overreaching.”.....</p> <p>“The meta-analysis human epidemiology database for each of the three types of cancer (14 studies for kidney, 16 studies for lymphoma, and 9 studies for liver) is relatively small compared to the volumes of data reviewed for other chemicals such as arsenic, asbestos, dioxin, perchlorate, ethylene oxide, etc. The U.S. EPA should perform an internal quality review of its own practices or standards of care for the use of human epidemiology data for developing toxicity values.”</p>	<p>-</p> <p>Greenland, S., A. Salvan, D.H. Wegman et al. 1994. A case-control study of cancer mortality at the transformer-assembly facility. <i>Int Arch Occup Environ Health</i> 66:49–54.</p> <p>Miligi, L., A.S. Costantini, A. Benvenuti et al. 2006. Occupational exposure to solvents and the risk of lymphomas. <i>Epidemiology</i> 17:552–561.</p> <p>Hardell, L., M. Eriksson, A. Degerman. 1994. Exposure to phenoxyacetic acids, chlorophenols, or organic solvents in relation to histopathology, stage, and anatomical localization of non-Hodgkin's lymphoma. <i>Cancer Res</i> 54:2386–2389.</p> <p>Hansen, J., O. Raaschou-Nielsen, J.M. Christensen et al. 2001. Cancer incidence among Danish workers exposed to trichloroethylene. <i>J Occup Environ Med</i> 43:133–139.</p> <p>Anttila, A., E. Pukkala, M. Sallmen et al. 1995. Cancer incidence among Finnish workers exposed to halogenated hydrocarbons. <i>J Occup Environ Med</i> 37:797–806.</p> <p>Morgan, R.W., M.A. Kelsh, K. Zhao et al. 1998. Mortality of aerospace workers exposed to trichloroethylene. <i>Epidemiology</i> 9:424–431.</p> <p>Zhao, Y., A. Krishnadasan, N. Kennedy et al. 2005. Estimated effects of solvents and mineral oils on cancer incidence and Mortality in a cohort of aerospace workers. <i>Am J Ind Med</i> 48:249–258.</p> <p>Siemiatycki, J. 1991. Risk factors for cancer in the workplace. Boca Raton: CRC Press.</p>
4.6.1.2	26	EPA-HQ-ORD-2009-0791-0010.1	ARCADIS on behalf of Deltrex Corporation	<p>The human epidemiology studies reviewed in this assessment exhibit external inconsistency relative to each other and internal inconsistencies relative to their own study subgroups. While meta-analysis provides a more formal statistical approach to the criterion of consistency, both internal consistency and external consistency are important. For instance, Do the increases in risk occur in the categories of exposure when expected and in all the subgroups where expected? Or do the results of the various studies provide the same or consistent results? The same or similar results in several studies add support to arguments concerning causality. However, the strength of each study should be individually taken into account. Often negative studies do not get published, so several studies suggesting a weak association do not automatically lead to acceptance of causation.</p>	<p>-</p> <p>-</p>
4.6.1.2	197	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>When examining the data for TCE and non-Hodgkin lymphoma, kidney cancer, and liver cancer, associations were inconsistent across occupational groups (summary results differed between aerospace/aircraft worker cohorts compared with workers from other industries), study design, location of the study, quality of exposure assessment (e.g., evaluating studies that relied upon biomonitoring to estimate exposure vs. semi-quantitative estimates vs. self-report, etc.), and by incidence vs. mortality endpoints. Although EPA examined high dose categories, it did not evaluate any potential dose-response relationships across the epidemiologic studies (except for the Charbotel et al. 2006 study). In our reviews of the epidemiologic data reported in various studies for different exposure levels (e.g. cumulative exposure and duration of exposure metrics): we did not find consistent dose-response associations between TCE and the three cancer sites under review (Mandel et al., 2006; Alexander</p>	<p>AUTHORS: Michael Dourson, Ph.D., DABT and Lynne Haber, Ph.D., DABT from Toxicology Excellence for Risk Assessment and Michael Kelsh, Ph.D., MPH and Dominik Alexander, Ph.D., MPH from Exponent, Health Sciences</p> <p>Charbotel B, Fevotte J, Hours M, martin J, Beregeret A. Case-Control Study on Renal Cell Cancer and Occupational Exposure to Trichloroethylene. Part 11: Epidemiological Aspects. <i>Ann.Occup.Hyg.</i> 2006.</p> <p>Mandel JH, Kelsb MA, Mink PJ, Alexander D, Kalmes RM, Weingart M, Yost L Goodman M. Occupational trichloroethylene exposure and non-Hodgkins lymphoma: A meta-analysis and review.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				et al., 2007; Kelsh et al., 2010) Ail established dose-response trend is one of the more important factors when making assessments of causation in epidemiologic literature. These issues are addressed in greater detail in the accompanying comments by Michael Kelsh and Dominic Alexander.	Occup Environ Med 2006; 63(9):597-607. Alexander DD, Kelsh MA, Mink PJ, Mandel JH, Basu R, Weingart W. A meta-analysis of occupational trichloroethylene exposure and liver cancer. Int Arch Occup Environ Health 2007; 81(2):127-143. Kelsh MA, Alexander DD, Mink PJ, Mandel JH. Occupational trichloroethylene exposure and kidney cancer: a meta-analysis. Epidemiology. 2010 Jan;21(1):95-102.
4.6.1.2	238	EPA-HQ-ORD-2009-0791-0016.1	Jerome M. Ensminger	My daughter Janey was the only one of my four children to have been conceived and/or carried while being exposed to this contaminant at Camp Lejeune. When Janey was six years old, she was diagnosed with ALL and while she fought a valiant battle against her malignancy she ultimately lost the war. Janey died shortly after her ninth birthday on 24 September 1985, she suffered greatly!	- -
4.6.1.2	279	EPA-HQ-ORD-2009-0791-0014.1	Exponent Health Services	<p>EPA's meta-analysis methods and summaries, for the most part, are consistent with recent published summaries of this literature – however, EPA's interpretation of the meta-analysis findings is not consistent with the general approaches used in evaluating causality from epidemiologic research study evaluation. Epidemiologic causal evaluation considers not only the presence of a statistical association, but also the strength of that association, whether exposure response trends are present, the consistency of study findings, biologic plausibility, coherence, and other factors (Hill 1965; Weed 2005). Although EPA considers these factors, their conclusions are not supported once these factors are applied to the epidemiologic literature. The epidemiologic literature on TCE exposure and cancer cannot be categorized as “strong” or “robust” or of sufficient quality to provide definitive evidence of a causal association between TCE exposure and cancer. The observed summary relative risk estimates from the meta-analyses of kidney cancer, liver cancer, and non-Hodgkin's lymphoma (NHL) are not sufficiently strong to be able to rule out other potential explanations such as bias due to confounding, exposure misclassification, or other factors (e.g. selection bias in case control studies). The consistency of the findings is not as robust as characterized in the EPA review. For example, in the kidney cancer analyses, the evaluation of cohorts defined from biomonitoring data, a source of exposure information considered more accurate than other exposure assessment characterizations, found no association with kidney cancer. Although these studies were small, these results merit consideration. In addition, several large cohort studies of aerospace/aircraft maintenance workers (e.g. Radican et al. 2008; Boice et al. 1999) reported no association between TCE exposure and kidney cancer. The EPA review recognizes the significant limitations of several German studies of TCE exposure and kidney cancer (e.g., Henchler et al., Vamvakas et al.) and did not include them in their meta-analysis summaries; a decision consistent with a recently published meta-analysis of TCE and kidney cancer (Kelsh et al., 2010). In summary, it is important to emphasize that the magnitude of the summary estimate in the EPA meta-analysis of kidney cancer was modest (relative risk =1.25). Furthermore given the range and imprecision of the individual study findings, with many studies reporting no increased risks, it is more accurate to report the study results as “mixed” rather than consistent or robust.</p> <p>In the latest EPA Toxicological Review of TCE, it is apparent that many of the issues and concerns raised in the methodological review of the inter-agency draft with respect to the metaanalysis of epidemiologic studies of TCE exposure and cancer of have been addressed. However, some important matters remain, particularly regarding the interpretation of the currently available epidemiologic evidence. In the widely read textbook Modern Epidemiology (Rothman, Greenland and Lash 2008), Greenland and O'Rourke describe the two main goals of meta-analysis: to estimate differences among study-specific effects (analytic goal) and/or to estimate an average effect across studies (synthetic goal). They further remind readers that “a sound meta-analysis needs to assess each study's limitations as well as gaps in the entire literature being assessed.” Thus, while a meta-analysis may serve as a valuable tool for analyzing data across a large body of scientific studies to produce a more precise estimate of relative risk, interpretation of summary findings should be made in consideration of several important methodological factors (e.g. exposure misclassification, confounding and selection bias) and guidelines for evaluation of causality based on epidemiologic data (Hill 1965; Weed 2005). Indeed, meta-analysis and causal inference are separate endeavours with different methods.</p> <p>Most epidemiologic studies of TCE exposure and cancer observed associations that were not statistically</p>	<p>-</p> <p>Boice JD, Jr. et al. Mortality among aircraft manufacturing workers. Occup.Environ.Med. 1999;56:581-97.</p> <p>Hill AB. The Environment and Disease: Association or Causation? Proc R Soc Med 1965; 58:295-300.</p> <p>Kelsh MA, Alexander DD, Mink PJ, Mandel JH. Occupational trichloroethylene exposure and kidney cancer: a meta-analysis. Epidemiology. 2010 Jan;21(1):95-102.</p> <p>Lash TL. Bias analysis applied to Agricultural Health Study publications to estimate non-random sources of uncertainty. J Occup Med Toxicol. 2007 Nov 26;2:15.</p> <p>Radican L, Blair A, Stewart P, Wartenberg D. Mortality of aircraft maintenance workers exposed to trichloroethylene and other hydrocarbons and chemicals: An extended follow-up. J Occup Environ Med 2008; 50(11): 1306-19.</p> <p>Weed DL. Weight of Evidence: A Review of Concept and Methods. Risk Analysis, Vol. 25, No. 6, 2005.</p> <p>Alexander DD, Wagner ME. Benzene exposure and Non-Hodgkin Lymphoma: A meta-analysis of epidemiologic studies. J Occup Environ Med 2009, in press.</p> <p>Alexander DD, Mink PJ, Mandel JH, Kelsh M. A meta-analysis of occupational trichloroethylene exposure and multiple myeloma or leukemia. Occup Med (Lond) 2006; 56(7):485-493.</p> <p>Kelsh MA, Alexander DD, Mink PJ, Mandel JH. Occupational trichloroethylene exposure and kidney cancer: a meta-analysis. Epidemiology. 2010 Jan;21(1):95-102.</p> <p>Mandel JH Kelsh MA, Mink P, Alexander DD. Occupational trichloroethylene exposure and non-Hodgkin's lymphoma: a meta-analysis and review. Occup.Environ.Med. 2006;63:597-607.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				significant and most studies lacked quantitative exposure assessments. Across epidemiologic studies, different exposure metrics were used, exposure-response patterns were inconsistently observed, and uncontrolled (or incompletely controlled) confounding and other sources of systematic error likely influenced effect estimates. EPA conducted various sensitivity analyses (excluding individual studies to assess their impact on summary relative risk estimates); however, important evaluations such as summarization by sub-group characteristics, study design differences, or findings by exposure measurement method were not presented or fully considered. It is unfortunate that EPA did not conduct exposure-response analyses by specific exposure metrics, such as cumulative dose or years of exposure. Because “dose-response” is an important consideration in the evaluation of epidemiologic studies for causality, we evaluated exposure-response data to the extent possible in our published meta-analyses and observed no clear pattern of increasing cancer risk with increasing exposure level or duration (Kelsh et al 2010; Mandel et al 2006; Alexander et al. 2007; Alexander et al., 2006). Such an analysis by EPA would provide helpful information in the consideration of potential relationships between TCE and cancer. In summary, although EPA conducted a comprehensive meta-analysis and examined many issues in the epidemiologic data, EPA’s conclusions regarding the carcinogenicity of TCE are not supported by the studies they cite.	
4.6.1.2	292	EPA-HQ-ORD-2009-0791-0014.1	Exponent Health Services	The p-values for heterogeneity are not presented across the meta-analyses in Appendix C. It is indicated that no heterogeneity was observed, however, the specific quantitative information is not presented for the reader. These data should be reported.	- -
4.6.1.2	296	EPA-HQ-ORD-2009-0791-0014.1	Exponent Health Services	Non-Hodgkin Lymphoma (NHL) · Mortality data from Zhao et al. 2005 are used in the primary meta-analyses. EPA selected mortality data rather than incidence data because there more were deaths than there were incident cases. However, incidence data is the optimum choice of data to evaluate cause and effect and, thus, should have been selected for the primary analyses. In the EPA analysis for kidney cancer, the researchers used mortality data “to avoid the appearance of cherry-picking.” This does not appear to be a systematic method for data inclusion. Furthermore, the IRIS report notes the limitations of mortality data including misclassification (p. 4-159). · As with kidney cancer, it was stated that the robustness of their findings “lends substantial support to a conclusion that TCE exposure increases the risk of lymphoma.” Indeed, the EPA’s “high-exposure” analysis results were stronger in magnitude than the overall results; however, summary associations were sensitive to study design. Furthermore, dose-response was not examined so one cannot conclude that risk of NHL increases with increasing levels of exposure. In a recent published meta-analysis, where exposure-response patterns were examined (recognizing the limitations of these data), there was no evidence for increasing duration or intensity of exposure (Mandel et al., 2006). In addition, the heterogeneity of NHL and changing classification schemes over the past few decades make interpretation of available epidemiologic data challenging. Given the lack of exposure response patterns and heterogeneity of findings by study design, it is inappropriate to conclude that there is “substantial” support that TCE increases the risk of lymphoma (Mandel et al., 2006).	- Mandel JH Kelsh MA, Mink P, Alexander DD. Occupational trichloroethylene exposure and non-Hodgkin's lymphoma: a meta-analysis and review. <i>Occup. Environ. Med.</i> 2006;63:597–607.
4.7.4	108	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	4. Mode of action for lung tumorigenesis. EPA considers the lung tumors induced by TCE in specific strains of mice as relevant to humans and implies a genotoxic mode-of action. EPA tries to devalue the hypothesis that chloral may reach high concentrations in mouse lung cells. However, the arguments by EPA are not convincing. Rat and guinea pig data should not be used to conclude on biotransformation in mouse lung. * A delivery of TCE from the systemic circulation in mice also causes lung toxicity due to the high metabolic capacity in the target cell. If TCE-metabolites formed in the liver are transported to the lung to cause toxicity there, the species-specificity is difficult to explain since the same metabolites are also present in rats, which do	AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany Odum, J., Foster, J. R., and Green, T. (1992). A mechanism for the development of clara cell lesions in the mouse lung after exposure to trichloroethylene. <i>Chem. Biol. Interact.</i> 83, 135-153. Green, T., Mainwaring, G. W., and Foster, J. R. (1997b). Trichloroethylene induced mouse lung tumours: studies of the mode of action and comparisons between species. <i>Fundamental and Applied Toxicology</i> 37, 125-130. Villaschi, S., Giovanetti, A., Lombardi, C. C., Nicolai, G., Garbati, M., and Andreozzi, U. (1991). Damage and repair of mouse bronchial epithelium following acute inhalation of trichloroethylene. <i>Exp</i>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>not show lung toxicity.</p> <p>* A high rate of chloral formation from TCE and limited capacity for further metabolism of chloral (low capacity for reduction of chloral hydrate to trichloroethanol, low capacity for conjugation of trichloroethanol) will result in much higher steady state levels of chloral hydrate in mouse lung Clara cells as compared to rat or human lung (Odum et al., 1992; Green et al., 1997b). The high steady state levels may result in cytotoxicity.</p> <p>* Cells damaged by the high chloral concentrations formed by TCE-metabolism initiate regeneration and replication to repair and replace the damaged Clara cells (Villaschi et al., 1991) and repeated cycles of damage and regeneration may finally result in lung tumor formation.</p> <p>Support for a cytotoxic MoA regarding the mouse lung tumors induced by TCE can also be derived from observations with other chemicals. The consequences of Clara cell specific cytotoxicity for tumor induction has been assessed with a number of other chemicals and the very high capacity of the mouse lung Clara cell for biotransformation is also the basis for the mouse-specific lung toxicity. The assessment therefore should integrate this information.</p> <p>* Styrene, naphthalene, and coumarin induce lung tumors in mice and chronic damage of Clara cells including hyperplasia, often with a time- and dose-related increase in bronchiolar hyperplasia in terminal bronchioles. As with TCE, lung lesions are induced by short term administration, recess after repeated exposures and reappear after continuing exposures. None of these chemical induced lung tumors or histopathologic changes in rat lung (Cruzan et al., 1998; Cruzan et al., 2001).</p> <p>* Major species differences in lung tumor induction and lung anatomy are one likely basis for the selective tumorigenicity of these chemicals in mice. Lung tumors occur spontaneously in several mouse strains and the incidences of benign lung tumors in control mice are often very high. In general, murine lung tumors are mostly adenomas originating from bronchiolar Clara cells. The adenomas may progress to adenocarcinomas. (Witschi, 1991).</p> <p>* Clara cells are the major site of xenobiotic metabolism in the mouse lung (Chichester et al., 1991; Buckpitt et al., 1995). In addition to marked species differences in metabolic capacity of Clara cells in different species, species differences in Clara cell abundance and function may contribute to selective pulmonary toxicity in mice. Clara cell number is significantly higher within the terminal bronchioles of mice relative to rats and humans (Plopper et al., 1980; Lumsden et al., 1984). Clara cells represent approximately 5 % of all cell types and are distributed throughout the airways in mice. In humans, only very few Clara cells are present and are localized in specific regions. Moreover, Clara cells differ morphologically among species, with human cells containing little smooth endoplasmic reticulum.</p> <p>* TCE and the other chemicals inducing selective lung damage and lung tumors in mice require biotransformation by pulmonary CYP2F and CYP2E1 (Green et al., 1997b; Shultz et al., 1999; Shultz et al., 2001; Born et al., 2002; West et al., 2002; Forkert et al., 2005).</p> <p>* In mice, both CYP2E1 and CYP2F1 are preferentially localized in Clara cells (Forkert et al., 1989; Buckpitt et al., 1995; Forkert, 1995; Shultz et al., 2001). In rat lung, the expression of CYP2F4, an ortholog of mouse CYP2F2 (Baldwin et al., 2004) is app. 30-fold lower consistent with a much lower turnover of CYP2F substrates in rat. Evidence for the presence of the human ortholog CYP2F1 in human lung is lacking. In rhesus monkeys, CYP2F1 was not detected in the respiratory tract except in the nasal epithelium (Ding and Kaminsky, 2003; Baldwin et al., 2004). CYP2E1 catalytic activity is present in human lung with an activity app. 100-fold lower than in human liver (Bernauer et al., 2006).</p> <p>In summary, the available information on the presence and catalytic activities of CYP2E1 and CYP2F enzymes in the lung of different species suggest a much higher activity of these enzymes in the mouse, the species susceptible to the pneumotoxicity. Studies directly quantifying relevant metabolite formation from the different pneumotoxic compounds show that mice consistently have a much higher capacity for oxidation as compared to rats and humans. The available data on the mode-of-action for induction of lung tumors share many common</p>	<p>Lung Res 17, 601-614.</p> <p>Cruzan, G., Cushman, J. R., Andrews, L. S., Granville, G. C., Johnson, K. A., Bevan, C., Hardy, C. J., Coombs, D. W., Mullins, P. A., and Brown, W. R. (2001). Chronic toxicity/oncogenicity study of styrene in CD-1 mice by inhalation exposure for 104 weeks. <i>J Appl Toxicol</i> 21, 185-198.</p> <p>Cruzan, G., Cushman, J. R., Andrews, L. S., Granville, G. C., Johnson, K. A., Hardy, C. J., Coombs, D. W., Mullins, P. A., and Brown, W. R. (1998). Chronic toxicity/oncogenicity study of styrene in CD rats by inhalation exposure for 104 weeks. <i>Toxicol Sci</i> 46, 266-281.</p> <p>Witschi, H. (1991). Lung tumor susceptibility in mice: an overview. <i>Exp Lung Res</i> 17, 281-282.</p> <p>Chichester, C. H., Philpot, R. M., Weir, A. J., Buckpitt, A. R., and Plopper, C. G. (1991). Characterization of the cytochrome P-450 monooxygenase system in nonciliated bronchiolar epithelial (Clara) cells isolated from mouse lung. <i>Am J Respir Cell Mol Biol</i> 4, 179-186.</p> <p>Buckpitt, A., Chang, A. M., Weir, A., Van Winkle, L., Duan, X., Philpot, R., and Plopper, C. (1995). Relationship of cytochrome P450 activity to Clara cell cytotoxicity. IV. Metabolism of naphthalene and naphthalene oxide in microdissected airways from mice, rats, and hamsters. <i>Mol Pharmacol</i> 47, 74-81.</p> <p>Plopper, C. G., Mariassy, A. T., and Hill, L. H. (1980). Ultrastructure of the nonciliated bronchiolar epithelial (Clara) cell of mammalian lung: I. A comparison of rabbit, guinea pig, rat, hamster, and mouse. <i>Exp Lung Res</i> 1, 139-154.</p> <p>Lumsden, A. B., McLean, A., and Lamb, D. (1984). Goblet and Clara cells of human distal airways: evidence for smoking induced changes in their numbers. <i>Thorax</i> 39, 844-849.</p> <p>Shultz, M. A., Choudary, P. V., and Buckpitt, A. R. (1999). Role of murine cytochrome P-450 2F2 in metabolic activation of naphthalene and metabolism of other xenobiotics. <i>J Pharmacol Exp Ther</i> 290, 281-288.</p> <p>Shultz, M. A., Morin, D., Chang, A. M., and Buckpitt, A. (2001). Metabolic capabilities of CYP2F2 with various pulmonary toxicants and its relative abundance in mouse lung subcompartments. <i>J Pharmacol Exp Ther</i> 296, 510-519.</p> <p>Born, S. L., Caudill, D., Fliter, K. L., and Purdon, M. P. (2002). Identification of the cytochromes P450 that catalyze coumarin 3,4-epoxidation and 3-hydroxylation. <i>Drug Metab Dispos</i> 30, 483-487.</p> <p>West, J. A., Williams, K. J., Toskala, E., Nishio, S. J., Fleschner, C. A., Forman, H. J., Buckpitt, A. R., and Plopper, C. G. (2002). Induction of tolerance to naphthalene in Clara cells is dependent on a stable phenotypic adaptation favoring maintenance of the glutathione pool. <i>Am J Pathol</i> 160, 1115-1127.</p> <p>Forkert, P. G., Baldwin, R. M., Millen, B., Lash, L. H., Putt, D. A., Shultz, M. A., and Collins, K. S. (2005). Pulmonary bioactivation of trichloroethylene to chloral hydrate: relative contributions of CYP2E1, CYP2F, and CYP2B1. <i>Drug Metab Dispos</i> 33, 1429-1437.</p> <p>Forkert, P. G., Vessey, M. L., Park, S. S., Gelboin, H. V., and Cole, S. P. (1989). Cytochromes P-450 in murine lung. An immunohistochemical study with monoclonal antibodies. <i>Drug Metab Dispos</i> 17, 551-555.</p> <p>Forkert, P. G. (1995). CYP2E1 is preferentially expressed in Clara cells of murine lung: localization by in situ hybridization and immunohistochemical methods. <i>Am J Respir Cell Mol Biol</i> 12, 589-596.</p> <p>Baldwin, R. M., Jewell, W. T., Fanucchi, M. V., Plopper, C. G., and Buckpitt, A. R. (2004). Comparison of pulmonary/nasal CYP2F expression levels in rodents and rhesus macaque. <i>J Pharmacol</i></p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>features with regard to the induction of Clara cell lesions in the mouse and a number of observations support a non-genotoxic mode-of-action: Glutathione depletion is a major determinant of the toxic responses in the mouse Clara toxicity (West et al., 2000a; West et al., 2000b; Plopper et al., 2001; Phimister et al., 2004; Turner et al., 2005). Glutathione-depletion induced cell death induced by mouse specific Clara cell toxicants initiates extensive cell replication and subsequent hyperplasia which are considered important steps in the multi-step progression to tumor development (Gadberry et al., 1996; Green et al., 1997b; Green et al., 2001).</p>	<p>Exp Ther 309, 127-136.</p> <p>Ding, X., and Kaminsky, L. S. (2003). Human extrahepatic cytochromes P450: function in xenobiotic metabolism and tissue-selective chemical toxicity in the respiratory and gastrointestinal tracts. <i>Annu Rev Pharmacol Toxicol</i> 43, 149-173.</p> <p>Bernauer, U., Heinrich-Hirsch, B., Tonnie, M., Peter-Matthias, W., and Gundert-Remy, U. (2006). Characterisation of the xenobiotic-metabolizing Cytochrome P450 expression pattern in human lung tissue by immunochemical and activity determination. <i>Toxicol Lett</i> 164, 278-288.</p> <p>West, J. A., Buckpitt, A. R., and Plopper, C. G. (2000a). Elevated airway GSH resynthesis confers protection to Clara cells from naphthalene injury in mice made tolerant by repeated exposures. <i>J Pharmacol Exp Ther</i> 294, 516-523.</p> <p>West, J. A., Chichester, C. H., Buckpitt, A. R., Tyler, N. K., Brennan, P., Helton, C., and Plopper, C. G. (2000b). Heterogeneity of clara cell glutathione. A possible basis for differences in cellular responses to pulmonary cytotoxicants. <i>Am J Respir Cell Mol Biol</i> 23, 27-36.</p> <p>Plopper, C. G., Van Winkle, L. S., Fanucchi, M. V., Malburg, S. R., Nishio, S. J., Chang, A., and Buckpitt, A. R. (2001). Early events in naphthalene-induced acute Clara cell toxicity. II. Comparison of glutathione depletion and histopathology by airway location. <i>Am J Respir Cell Mol Biol</i> 24, 272-281.</p> <p>Phimister, A. J., Lee, M. G., Morin, D., Buckpitt, A. R., and Plopper, C. G. (2004). Glutathione depletion is a major determinant of inhaled naphthalene respiratory toxicity and naphthalene metabolism in mice. <i>Toxicol Sci</i> 82, 268-278.</p> <p>Turner, M., Mantick, N. A., and Carlson, G. P. (2005). Comparison of the depletion of glutathione in mouse liver and lung following administration of styrene and its metabolites styrene oxide and 4-vinylphenol. <i>Toxicology</i> 206, 383-388.</p> <p>Gadberry, M. G., DeNicola, D. B., and Carlson, G. P. (1996). Pneumotoxicity and hepatotoxicity of styrene and styrene oxide. <i>J Toxicol Environ Health</i> 48, 273-294.</p> <p>Green, T., Toghiani, A., and Foster, J. R. (2001). The role of cytochromes P-450 in styrene induced pulmonary toxicity and carcinogenicity. <i>Toxicology</i> 169, 107-117.</p>
4.7.4.1	128	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>Page 4-433: Lines 6 -7, the reactivity of chloral hydrate and chloroacetaldehyde are highly different and should not be compared. Chloroacetaldehyde is highly reactive with DNA-constituents (Green and Hathway, 1978), whereas chloral hydrate is not.</p>	<p>AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany</p> <p>Green, T., and Hathway, D. E. (1978). Interactions of vinyl chloride with rat-liver DNA in vivo. <i>Chem Biol Interact</i> 22, 211-224.</p>
4.8	178	EPA-HQ-ORD-2009-0791-0017.1	Michael Partain	<p>One thing I wish to point out to the EPA concerning their work on chemicals such as TCE. Your risk assessments are based on adult exposures. What about the children? What about in-utero babies such as myself. Why isn't the EPA assessing exposures at the most critical phase of a person's development?</p>	<p>-</p> <p>-</p>
4.8.2	177	EPA-HQ-ORD-2009-0791-0017.1	Michael Partain	<p>I am speaking today as a living witness to the dangers of VOCs such as (TCE).</p> <p>My name is Mike Partain. I am the son of Captain Warren B Partain Jr. USMC, USNA class of 1966. My parents arrived aboard Camp Lejeune in April 1967. I was conceived shortly after their arrival, carried and was born at the base naval hospital on January 30th 1968. I am one of the 16,500 in-utero children from Camp Lejeune Marine Corps Base targeted for study by the Agency for Toxic Substances and Disease Registry for our exposures to VOCs including TCE and PCE in the base's potable drinking water.</p> <p>During my mother's entire pregnancy we were exposed to high levels of VOCs in the base's potable water</p>	<p>-</p> <p>-</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>system while we lived in base housing at Camp Lejeune. Last January I attended a meeting of the NRC'S PCE Committee. At the time of the January 2009 meeting we identified 9 other men with male breast cancer from Camp Lejeune. Now here we are a year later. Since then we have now identified a total of 55 men who either lived or served aboard Camp Lejeune and now have male breast cancer. Our only commonality is that we all have male breast cancer and at one point of our lives, we all drank and were exposed to the toxic water aboard Camp Lejeune. Male breast cancer has also been observed at other TCE/PCE sites including Woburn Ma, Cape Cod Ma, Endicott NY and now Camp Lejeune.</p> <p>Male breast cancer is rare and even rarer in young men such as myself. Typically the disease strikes men between the ages of 60 and 70 and/or within certain risk groups. One of these groups is carriers of the BRCA one and two mutations. My doctors felt that I was a carrier due to my young age at diagnosis. They urged me to be genetically tested. I tested negative for the mutation and do not fall within any of the risk groups for male breast cancer</p>	
4.8.2.1	304	EPA-HQ-ORD-2009-0791-0017.1	Michael Partain	<p>Good morning, First, I would like to thank the EPA for hosting this listening session and for their time and efforts in this most important task involving the public trust. I am speaking today as a living witness to the dangers of VOCs such as (TCE).</p> <p>My name is Mike Partain. I am the son of Captain Warren B Partain Jr. USMC, USNA class of 1966. My parents arrived aboard Camp Lejeune in April 1967. I was conceived shortly after their arrival, carried and was born at the base naval hospital on January 30th 1968. I am one of the 16,500 in-utero children from Camp Lejeune Marine Corps Base targeted for study by the Agency for Toxic Substances and Disease Registry for our exposures to VOCs including TCE and PCE in the base's potable drinking water.</p> <p>During my mother's entire pregnancy we were exposed to high levels of VOCs in the base's potable water system while we lived in base housing at Camp Lejeune. Last January I attended a meeting of the NRC'S PCE Committee. At the time of the January 2009 meeting we identified 9 other men with male breast cancer from Camp Lejeune. Now here we are a year later. Since then we have now identified a total of 55 men who either lived or served aboard Camp Lejeune and now have male breast cancer. Our only commonality is that we all have male breast cancer and at one point of our lives, we all drank and were exposed to the toxic water aboard Camp Lejeune. Male breast cancer has also been observed at other TCE/PCE sites including Woburn Ma, Cape Cod Ma, Endicott NY and now Camp Lejeune.</p> <p>Male breast cancer is rare and even rarer in young men such as myself. Typically the disease strikes men between the ages of 60 and 70 and/or within certain risk groups. One of these groups is carriers of the BRCA one and two mutations. My doctors felt that I was a carrier due to my young age at diagnosis. They urged me to be genetically tested. I tested negative for the mutation and do not fall within any of the risk groups for male breast cancer</p>	- -
4.8.3	184	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	Development of a Reference Dose (RfD) based on heart defects. AIA agrees with DOD that the RfD derived for heart defects is not based upon a transparent evaluation and appropriate interpretation of all of the relevant data.	AUTHOR: Lisa Goldberg -
4.8.3	205	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>"Comments on the Public Review Draft of EPA's IRIS Toxicological Review for TCE: Developmental Effects." Carole A. Kimmel, PhD Gary L. Kimmel, PhD John M. DeSesso, PhD</p> <p>Exponent 1800 Diagonal Road, Suite 300 Alexandria, Virginia 22314</p> <p>29 January 2010</p> <p>EPA's assessment of TCE uses data on heart defects as a major endpoint for setting the RfD and RfC. The data</p>	<p>AUTHORS: Carole A. Kimmel, PhD; Gary L. Kimmel, PhD; John M. DeSesso, PhD from Exponent</p> <p>Bove FJ, Fulcomer MC, Klotz JB, Esmart J, Dufficy EM, Savrin JE. Public drinking water contamination and birth outcomes. Am J Epidemiol. 1995; 141:850-862.</p> <p>Goldberg SJ, Lebowitz MD, Graver EJ, Hicks S. An association of human congenital cardiac malformations and drinking water contaminants. J Am Coll Cardiol. 1990; 16:155-64.</p> <p>Wilson PD, Loffredo CA, Correa-Villaseñor A, Ferencz C. Attributable Fraction for Cardiac Malformations. Am J Epidemiol 1998; 148:414-23.</p> <p>Johnson PD, Goldberg SJ, Mays MZ, Dawson BV. Threshold of trichloroethylene contamination in</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics																																																								
				<p>selected to support this decision are from studies that are poorly designed and flawed. Furthermore, EPA neither incorporates nor accounts for more robust data from guideline- and GLP- compliant studies that show no increase in congenital heart defects.</p> <p>* The human data are based on studies with inadequate exposure information, making it impossible to determine whether or not exposure occurred and, if it did, to what levels of TCE.</p> <p>- There are also deficiencies in the human data in terms of the background rates of cardiac malformations (Bove et al., 1995), and differences in the outcome of different studies (Goldberg et al., 1990, versus the Baltimore Washington Infant Study -Wilson et al., 1998).</p> <p>* The animal data reporting a link between TCE and heart defects all come from the same laboratory and were an accumulation of data over ten years (Johnson et al. 2003, Dawson et al. 1993).</p> <p>- In the Johnson and Dawson studies, there were a number of deficiencies in study design and reporting of data that make the interpretation of data tentative at best.</p> <p>- The major effect reported in the Johnson and Dawson studies was an increase in the incidence of atrial septal defects (or the foramen ovale, which closes around the time of birth) which may be related to the procedure for examining fetuses or the timing of the dissection relative to the development of the fetus, rather than actual heart defects.</p> <p>* Two additional GLP- and guideline-compliant studies showing no effect on heart development were conducted by Fisher et al. (2001) and Carney et al. (2006).</p> <p>* Thus, EPA uses weak human data: incomplete and flawed animal data; and in vitro data (which are of questionable relevance to environmental exposures) to make a mechanistic argument that TCE causes heart defects. Although EPA notes some of the database deficiencies, EPA uses a "strength of evidence" approach, rather than a "weight of evidence" analysis, by basing the RfD only on the studies reporting a positive effect and ignoring the data from subsequent well-conducted GLP studies that show no increase in heart defects associated with TCE (Fisher et al., 2001; Carney et al., 2006).</p>	<p>maternal drinking waters affecting fetal heart development in the rat. Environ Health Perspect. 2003; 111:289-92.</p> <p>Dawson BV, Johnson PD, Goldberg 81, Ulreich JB. Cardiac teratogenesis of halogenated hydrocarbon-contaminated drinking water. J Am Coll Cardiol. 1993; 21:1466-72.</p> <p>Fisher JW, Chappel SR, Eggers JS, Johnson PD, MacMahon IKL, Goodyear CD, Sudberry GL, Warren DA, Latendresse JR, Graeter U. Trichloroethylene, trichloroacetic acid, and dichloroacetic acid: Do they affect fetal rat heart development? Int J Toxicol. 2001; 20:257-67.</p> <p>Carney, E.W., B.A. Thorsrud, P.H. Dugard, and C.L. Zablony. 2006. Developmental toxicity studies in Crl:CD (SD) rats following inhalation exposure to trichloroethylene and perchloroethylene. Birth Defects Research, Part B: Developmental and Reproductive Toxicology 77:405-412.</p>																																																								
4.8.3	208	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>EPA Evaluation of Animal Data on Heart Defects and Comments</p> <p>The EPA review of TCE (US EPA, 2009) uses the Johnson et al. (2003) and Dawson et al. (1993) data to establish reference levels for exposure -an RfC of 0.001 ppm and an RfD of 0.0004 mg/kg/day. The fetal heart malformation data reported in Johnson et al. (2003) are used to support both of these values (US EPA, 2009; see Tables 5.1.23 and 5.1.24 and the associated text). There are several limitations with this approach:</p> <p>* The Johnson et al. (2003) publication includes the Dawson et al. (1993) data and appears to be an accumulation of data over an approximate 10-year period.</p> <p>- This was not made clear in the Johnson paper, and it required a letter to the editor (Hardin et al., 2004) for the authors to respond and explain this situation (Johnson et al., 2004). There is no indication in the paper reporting the combined data (Johnson et al., 2003) about which data came from Dawson et al. (1993) and which data came from subsequent studies. Over the course of a decade, there could have changes in the lot of TCE used in the studies, differences in the animal supplier or animal health, changes in the experience of investigators and technicians, and changes in the procedure used for head examination. All of these could affect the results.</p> <p>- Dawson et al. (1993) do not mention the number of pregnant dams that were assigned to each treatment group and Dawson et al. (1993) used the fetus as the unit for statistical analysis. In developmental toxicity studies, the unit for statistical analysis is based on the dam or litter. This method helps to account for the litter effect (based on the concept that offspring of a given female tend to react more similarly to challenges than offspring from different females) and prevents inappropriate inflation of statistical significance.</p>	<p>Table 2. Comparison of Atrial Septal Defects in the Three Papers*</p> <table border="1" data-bbox="1634 976 2459 1307"> <thead> <tr> <th data-bbox="1634 976 1776 995">Study/Data</th> <th colspan="7" data-bbox="2059 976 2179 995">Treatment Groups</th> </tr> <tr> <th data-bbox="1634 995 1776 1052">Dawson et al. 1993</th> <th data-bbox="1776 995 1870 1052">Control Tap water</th> <th data-bbox="1870 995 1964 1052">TCE - Prepreg only 1.5 ppm</th> <th data-bbox="1964 995 2059 1052">TCE - Prepreg only 1100 ppm</th> <th data-bbox="2059 995 2153 1052">TCE - Preg only 1.5 ppm</th> <th data-bbox="2153 995 2247 1052">TCE - Preg only 1100 ppm</th> <th data-bbox="2247 995 2341 1052">TCE - Prepreg & Preg 1.5 ppm</th> <th data-bbox="2341 995 2459 1052">TCE - Prepreg & Preg 1100 ppm</th> </tr> </thead> <tbody> <tr> <td data-bbox="1634 1052 1776 1101">No. of atrial septal defects/no hearts examined (%)</td> <td data-bbox="1776 1052 1870 1101">1/232 (0.4)</td> <td data-bbox="1870 1052 1964 1101">3/130 (2.3)</td> <td data-bbox="1964 1052 2059 1101">7/147 (4.8)</td> <td data-bbox="2059 1052 2153 1101">4/181 (2.2)</td> <td data-bbox="2153 1052 2247 1101">7/105 (6.7)</td> <td data-bbox="2247 1052 2341 1101">5/256 (2.0)</td> <td data-bbox="2341 1052 2459 1101">19/435 (4.4)</td> </tr> <tr> <th data-bbox="1634 1101 1776 1149">Johnson et al. 2003</th> <th data-bbox="1776 1101 1870 1149">Control Distilled water</th> <th data-bbox="1870 1101 1964 1149">TCE - 2.5 ppb</th> <th data-bbox="1964 1101 2059 1149">TCE - 250 ppb</th> <th data-bbox="2059 1101 2153 1149">TCE - 1.5 ppm</th> <th data-bbox="2153 1101 2247 1149">TCE - 1100 ppm</th> <td></td> <td></td> </tr> <tr> <td data-bbox="1634 1149 1776 1198">No. of atrial septal defects/no hearts examined (%)</td> <td data-bbox="1776 1149 1870 1198">7/606 (1.2)</td> <td data-bbox="1870 1149 1964 1198">0/144 (0)</td> <td data-bbox="1964 1149 2059 1198">1/110 (1.0)</td> <td data-bbox="2059 1149 2153 1198">4/181 (2.2)</td> <td data-bbox="2153 1149 2247 1198">7/105 (6.7)</td> <td></td> <td></td> </tr> <tr> <th data-bbox="1634 1198 1776 1247">Fisher et al. 2001</th> <th data-bbox="1776 1198 1870 1247">Control IERO** Water</th> <th data-bbox="1870 1198 1964 1247">TCA 300 mg/kg in IERO water</th> <th data-bbox="1964 1198 2059 1247">DCA 300 mg/kg in IERO water</th> <th data-bbox="2059 1198 2153 1247">Control Soybean oil</th> <th data-bbox="2153 1198 2247 1247">TCE 500 mg/kg in soybean oil</th> <th data-bbox="2247 1198 2341 1247">Retinoic acid - 15 mg/kg in soybean oil</th> <td></td> </tr> <tr> <td data-bbox="1634 1247 1776 1307">No. of atrial septal defects/no hearts examined (%)</td> <td data-bbox="1776 1247 1870 1307">2/273 (1.0)</td> <td data-bbox="1870 1247 1964 1307">2/269 (1.0)</td> <td data-bbox="1964 1247 2059 1307">3/298 (1.0)</td> <td data-bbox="2059 1247 2153 1307">6/367 (1.6)</td> <td data-bbox="2153 1247 2247 1307">4/290 (1.4)</td> <td data-bbox="2247 1247 2341 1307">3/155 (1.9)</td> <td></td> </tr> </tbody> </table> <p data-bbox="1634 1307 2306 1323">*Data in the shaded boxes were reported in both the Dawson et al. 1993 and the Johnson et al. 2003 papers.</p> <p data-bbox="1634 1323 1895 1339">**IERO = ion exchange/reverse osmosis</p> <p data-bbox="1610 1372 2521 1481">FOOTNOTE 1: For purposes of estimating the comparability of the dosages in the Fisher and Johnson studies, the following rough estimates can be made, in the Johnson drinking water study, the high dose was 1100 ppm TCE in the water. If the rats drank 20 mL/day, they received ~22 mg TCE/day. In the Fisher gavage study, the rats were administered 500 mg/kg/day. If the rats weighed 350 g, they received ~175 mg TCE/day.</p>	Study/Data	Treatment Groups							Dawson et al. 1993	Control Tap water	TCE - Prepreg only 1.5 ppm	TCE - Prepreg only 1100 ppm	TCE - Preg only 1.5 ppm	TCE - Preg only 1100 ppm	TCE - Prepreg & Preg 1.5 ppm	TCE - Prepreg & Preg 1100 ppm	No. of atrial septal defects/no hearts examined (%)	1/232 (0.4)	3/130 (2.3)	7/147 (4.8)	4/181 (2.2)	7/105 (6.7)	5/256 (2.0)	19/435 (4.4)	Johnson et al. 2003	Control Distilled water	TCE - 2.5 ppb	TCE - 250 ppb	TCE - 1.5 ppm	TCE - 1100 ppm			No. of atrial septal defects/no hearts examined (%)	7/606 (1.2)	0/144 (0)	1/110 (1.0)	4/181 (2.2)	7/105 (6.7)			Fisher et al. 2001	Control IERO** Water	TCA 300 mg/kg in IERO water	DCA 300 mg/kg in IERO water	Control Soybean oil	TCE 500 mg/kg in soybean oil	Retinoic acid - 15 mg/kg in soybean oil		No. of atrial septal defects/no hearts examined (%)	2/273 (1.0)	2/269 (1.0)	3/298 (1.0)	6/367 (1.6)	4/290 (1.4)	3/155 (1.9)	
Study/Data	Treatment Groups																																																												
Dawson et al. 1993	Control Tap water	TCE - Prepreg only 1.5 ppm	TCE - Prepreg only 1100 ppm	TCE - Preg only 1.5 ppm	TCE - Preg only 1100 ppm	TCE - Prepreg & Preg 1.5 ppm	TCE - Prepreg & Preg 1100 ppm																																																						
No. of atrial septal defects/no hearts examined (%)	1/232 (0.4)	3/130 (2.3)	7/147 (4.8)	4/181 (2.2)	7/105 (6.7)	5/256 (2.0)	19/435 (4.4)																																																						
Johnson et al. 2003	Control Distilled water	TCE - 2.5 ppb	TCE - 250 ppb	TCE - 1.5 ppm	TCE - 1100 ppm																																																								
No. of atrial septal defects/no hearts examined (%)	7/606 (1.2)	0/144 (0)	1/110 (1.0)	4/181 (2.2)	7/105 (6.7)																																																								
Fisher et al. 2001	Control IERO** Water	TCA 300 mg/kg in IERO water	DCA 300 mg/kg in IERO water	Control Soybean oil	TCE 500 mg/kg in soybean oil	Retinoic acid - 15 mg/kg in soybean oil																																																							
No. of atrial septal defects/no hearts examined (%)	2/273 (1.0)	2/269 (1.0)	3/298 (1.0)	6/367 (1.6)	4/290 (1.4)	3/155 (1.9)																																																							

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>- These mistakes give the appearance that the authors were unaware of how to design studies, or how to analyze and present developmental toxicity data.</p> <p>* For the purposes of risk assessment and setting of regulatory standards, studies like Johnson et al. (2003) and Dawson et al. (1993), with deficiencies such as those mentioned above, should only be used in a support role when a database of other, more well-designed studies is available. Johnson et al. (2003) should be used as the critical study for establishing regulatory exposure levels.</p> <p>* The Johnson et al. (2003) and Dawson et al. (1993) studies have significant limitations regarding the reporting of standard maternal and fetal parameters.</p> <p>- Johnson et al. (2003) do not provide data on maternal and fetal parameters other than cardiac malformations, only mentioning that "maternal and fetal variables, including noncardiac congenital abnormalities, showed no significant differences between treated and control groups."</p> <p>- Dawson et al. (1993) did not provide any control data for maternal and fetal parameters, other than cardiac abnormalities. Consequently, there is no way to assess the impact of exposure on any parameter other than cardiac abnormalities, including such parameters as maternal body weight and body weight gain, fetal weight, and fetal viability.</p> <p>- Johnson et al. (2004) note that "Control values were consistent throughout our studies." However, there is no way for the reader to determine this.</p> <p>- 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 (e.g. cardiac defects) are within historical ranges.</p> <p>* Studies where major components of the results are not reported or the missing data have not been evaluated by the risk assessors may be useful in supporting other, more complete, data sets, but are of questionable value as primary studies in establishing an exposure standard.</p> <p>* Johnson et al. (2003) indicate that their goal was to determine whether there was a threshold level of TCE in drinking water above which the incidence of congenital cardiac defects in the rodent increased significantly. The doses reported were 0, 2.5, 250, 1,500, and 1,100,000 ppb. Does their study design and statistical analysis permit the testing of a hypothesis derived from this goal?</p> <p>- Their study pools discrete data from at least two separate studies and an accumulation of data over several years and is an unbalanced design (55 dams in the control vs. 9-13 in the treatment groups).</p> <p>- They report that their data could indicate that a threshold effect exists at a level between 1.5 and 1,100 ppm.</p> <p>* It would be prudent to have a qualified statistician look at this database and the statistical evaluations used to determine if the analysis was appropriate. The reported "threshold effect" has a range of three orders of magnitude. This is not very useful in establishing reference levels.</p> <p>* In discussing the dose-response pattern in Johnson et al. (2003), the authors specifically mention the response observed at the highest exposure level (1,100,000 ppb) relative to control. With regard to the results seen in the other three dose levels, they only mention that "Intermediate exposure levels produced intermediate response rates." While the latter statement may be true, the intermediate levels did not produce a clear dose-response relationship.</p> <p>- The incidence of heart defects in fetuses was 2.1, 0, 4.5, 5.0 and 10.5% in controls, 2.5, 250, 1500 and 1,100,000 ppb exposure groups, respectively. The extreme range of exposure levels (440,000-fold difference</p>	<p>AUTHORS: Carole A. Kimmel, PhD; Gary L. Kimmel, PhD; John M. DeSesso, PhD from Exponent US EPA (2009). Toxicological Review of Trichloroethylene. Public Review Draft.</p> <p>Johnson PD, Goldberg SJ, Mays MZ, Dawson BV. Threshold of trichloroethylene contamination in maternal drinking waters affecting fetal heart development in the rat. Environ Health Perspect. 2003; 111:289-92.</p> <p>Dawson BV, Johnson PD, Goldberg SJ, Ulreich JB. Cardiac teratogenesis of halogenated hydrocarbon-contaminated drinking water. J Am Coll Cardiol. 1993; 21:1466-72.</p> <p>Hardin BD, Kelman BJ, Brent RL. Trichloroethylene and cardiac malformations, a correspondence in Environ Health Perspect. 2004; 112:A607-8.</p> <p>Johnson PD, Dawson B, Goldberg SJ, Mays MZ, Trichloroethylene: Johnson et al.'s Response. Environ Health Perspect. 2004; 112:A608-9.</p> <p>NRC (1994). Science and Judgment in Risk Assessment. National Research Council; National Academy Press, Washington, DC; 1994.</p> <p>Fisher JW, Channel SR, Eggers JS, Johnson PD, MacMahon IKL, Goodyear CD, Sudberry GL, Warren DA, Latendresse JR, Graeter IJ. Trichloroethylene, trichloroacetic acid, and dichloroacetic acid: Do they affect fetal rat heart development? Int J Toxicol. 2001; 20:257-67.</p> <p>Carney EW, Zablony CL, Clements CM. Trichloroethylene: inhalation developmental toxicity. The Dow Chemical Company, Study ID: 981129. Midland, Michigan; 2001.</p> <p>Carney, E.W., B.A. Thorsrud, P.H. Dugard, and C.L. Zablony. 2006. Developmental toxicity studies in Crl:CD (SD) rats following inhalation exposure to trichloroethylene and perchloroethylene. Birth Defects Research, Part B: Developmental and Reproductive Toxicology 77:405-412.</p> <p>Smith MK, Randall JL, Read EJ, Stober JA. Teratogenic activity of trichloroacetic acid in the rat. Teratology 1989; 40:445-51.</p> <p>Smith MK, Randall JL, Read EF, Stober JA. Developmental toxicity of dichloroacetate in the rat. Teratology 1992; 46(3):217-23.</p> <p>Momma K, Ito T, Ando M. In situ morphology of the foramen ovale in the fetal and neonatal rat. Pediatr Res 1992; 32: 669-672.</p> <p>NRC (2006). Assessing the Human Health Risks of Trichloroethylene: Key Scientific Issues. National Research Council: National Academies Press, Washington, DC.</p> <p>American Heart Association (2005b) Congenital cardiovascular defects statistics. Available online at http://www.americanheart.org/presenter.jhtml?identifier=4576.</p> <p>Hoffman, J. I. E. and S. Kaplan (2002) "The incidence of congenital heart disease" J Am Coll Cardiol 39: 1890-1900.</p> <p>Drake VJ, Koprowski SL, Hu N, Smith SM, Lough J. (2006a). Cardiogenic effects of trichloroethylene and trichloroacetic acid following exposure during heart specification of avian development. Toxicol Sci 94: 153-164.</p> <p>Drake VJ, Koprowski SL, Lough J, Hu N, Smith SM. (2006b) Trichloroethylene exposure during cardiac valvuloseptal morphogenesis alters cushion formation and cardiac hemodynamics in the avian</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>between low and high exposure levels, and >700-fold between the 1500 and 1,100,000 ppb exposure levels) is not mirrored by a remarkable difference in the incidence of heart defects (2.1% in controls and only 10.5% incidence at the highest exposure level).</p> <p>* To make the analysis more difficult to interpret independently, the fetus and not the dam (litter) was used as the experimental unit. EPA has 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 EPA refers to "Section 6, dose-response" regarding this additional data, since it does not appear that anything in this section/sub-section details these data or how they were used. It is unclear if EPA has examined these data. At a minimum, EPA should make the data available and explain how it has been incorporated into EPA's risk assessment.</p> <p>* The dose-response pattern is another area where the input of a qualified statistician/modeler would be prudent.</p> <p>* Johnson et al. (2003) comment that TCE exposure using an in vitro chick model has been shown to have effects on several elements of epithelial-mesenchymal cell transformation in endocardial cushions (tissue that becomes part of the atrioventricular valves and septum) at concentration ranges that correlate with their findings.</p> <p>- They note a concentration range of 50-250 ppm (although it isn't clear if this is the only concentration range used in the referenced studies), which is bounded by the Johnson et al. (2003) concentration range, but then, almost any range would be, given the extreme range that Johnson et al. used.</p> <p>- More importantly, an application of X ppm in an in vitro chick embryo study is in no way comparable to an application of X ppm in drinking water in an in vivo rat study.</p> <p>* Use of in vitro data with questionable relevance to environmental exposures as mechanistic support for heart defects reported in poorly conducted whole animal studies and weak human studies does not build a strong case for using heart defects as the basis for risk assessment, and compounds the problem of overstating the importance of the data.</p> <p>* Generally, the draft assessment focuses too much on one set of studies that show a putative positive response to low-exposure levels of TCE, instead of considering the overall data base and the limitations of the focus studies.</p> <p>- The draft assessment is not a "weight of evidence" evaluation but a "strength of evidence" evaluation (NRC, 1994). All the focus is on those studies that found a compound-related effect and no attention was given to the strengths and weaknesses of those studies that found no compound-related effects. Data from GLP-compliant animal studies that were carefully designed to probe the existence of potential links between TCE or its metabolites and heart or eye defects have shown no associations at exposure levels that are several orders of magnitude higher than those expected in environmental or occupational settings.</p> <p>-- Fisher et al. (2001) specifically investigated the cardiac teratogenic potential of TCE, TCA, and DCA in groups of 19 -20 pregnant Sprague-Dawley rats. The rats received oral bolus doses of TCE (500 mg/kg/day, in soybean oil), TCA (300 mg/kg/day, in water) or DCA (300 mg/kg/day, in water) on gestational days 6 -15. On gestational day 21, fetuses were removed by laparohysterectomy and hearts were examined and microdissected under a stereomicroscope by an investigator experienced in the procedure (Dr. Paula Johnson, author of Johnson et al. (2003)). The rates of cardiac malformations among treated animals did not differ from control rates. Also, TCE caused no change in the weight of fetuses and did not inhibit maternal weight gain at the high dose level [FOOTNOTE 1] used in this study.</p> <p>-- An inhalation study of TCE in pregnant Charles River CD IGS rats (Carney et al., 2001; 2006) exposed groups of 27 animals to filtered air or to atmospheric concentrations of TCE up to and including the limit dose (600 ppm) for 6 hours/day on each of gestational days 6 -20. Although maternal toxicity (decreased body weight gain) was elicited at the highest dose, TCE exposure caused no increase in gross, skeletal, or visceral (including heart and eye) malformations at any of the concentrations tested.</p>	<p>embryo. Environ Health Perspect 114: 842-847.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>-- Some early studies of TCA and DCA in pregnant Long-Evans rats (Smith et al., 1989, 1992) reported ocular malformations. In a follow-up to the Fisher et al. (2001) study, Warren et al. (2006) reported that examination of the heads showed that none of the chemicals used in the Fisher et al. (2001) study elicited gross ocular malformations. Morphometric analysis of the lens area, globe area and interocular distances revealed reductions of these parameters only in the TCA- and DCA-treated fetuses, but the overall smaller sizes of the fetuses in those groups were sufficient to explain the reductions.</p> <p>- Weight of evidence clearly must consider all of the data, both positive and no effect data. When the majority of the positive data are derived from clearly flawed studies using methods that give results that are not replicable in other laboratories, it is difficult to understand how the Agency can justify using only these data as the basis for a regulatory assessment.</p> <p>* While there were similar methods used for examining hearts in fetuses in the Dawson and Johnson laboratories and Dr. Johnson collaborated on the Fisher et al. (2001) study, there were several differences among the 3 studies as noted in the EPA review, as well as possibly significant differences in heart preparation not noted by EPA (see Table 1 below).</p> <p>* Table 1 details differences in preparation of the heart for dissection, Dawson et al. (1993) and Johnson et al. (2003) both removed the heart first, then flushed with a fixative, Fisher et al. (2001) flushed the heart in situ via the left ventricle with a staining solution for better visualization (1:3 hematoxylin-saline solution), perhaps a more physiologically normal situation, then removed the heart and immersion fixed it in 10% buffered formalin.</p> <p>* One major difference in the data from the Dawson/Johnson laboratory versus the Fisher laboratory appears to be the incidence of atrial septal defects (Table 2), The types of atrial septal defects reported by Dawson/Johnson et al. are not detailed in any of the papers except for the statement that they are "secundum in type" (Dawson et al., 1993).</p> <p>- Since the septum primum and septum secundum both grow rapidly around the time of birth to close the foramen ovale (Momma et al., 1992), this may represent normal in developmental timing such as occurs with other structures that are maturing around the time of birth in the rat, (e.g" skeletal ossification of sternebrae, vertebral centra, etc" or development of the renal papilla).</p> <p>- Whether the different methods of flushing the hearts may have disturbed the position of the septum which would not be closed on the day of sacrifice is unclear.</p> <p>- Even more troubling, however, is that neither Dawson et al. (1993) nor Johnson et al. (2003) provide maternal or fetal weight data, so it is impossible to know whether there were differences in fetal weight that would suggest a delay in development. Also, data on other aspects of fetal development (e.g., skeletal ossification) were not presented to give any clues about developmental stage.</p> <p>- Fisher et al. (2001) report no significant difference from water-treated control animals in maternal weight, uterine weight, number of implantations or fetal weight for TCE at 500 mg/kg, In that study, the percent of fetuses with atrial septal defects was approximately the same in the two groups. Thus, there are a lot of questions about the incompleteness of the data presented in the Dawson et al. (1993) and Johnson et al. (2003) papers, in addition to the obvious design flaws and protracted length of time over which the studies were conducted. Without concurrent control data, it is very difficult to evaluate small changes in head development that may or may not be related to TCE exposure.</p> <p>* Another difference is in the incidence of ventricular septal defects (VSDs).</p> <p>- Johnson et al. (2003) reported membranous VSD occurrences as 0.33% in controls; 1.7% at 1.5 ppm; and 2.9% at 1,100 ppm. For muscular VSDs, they reported 0.33% in controls; 0.55% at 1.5 ppm; and 0.95% at 1,100 ppm.</p> <p>* In the Fisher et al. (2003) study, there are no cases of VSD in TCE-treated fetuses, even though there were 2 cases of membranous VSD and one case of muscular VSD in soybean-treated controls (incidence of 0.54% and</p>	

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>0.27% respectively).</p> <p>* There are significant questions about examination of the hearts in the Dawson/Johnson studies, as well as questions about whether effects on the atrial septum (the primary defect reported) are actually a reflection of developmental delays, because the atrial septum is developing around the time of birth. In addition, there was no increase in VSDs in a carefully-controlled study (Fisher et al. ZOO?), while Johnson et al. (2003) reported a low increase in incidence with TCE exposure. Unfortunately, data on maternal and fetal body weight or other indicators of development (e.g., skeletal ossification) are missing from the reports by Dawson/Johnson. Consequently, it is not possible to assess the developmental importance of their findings.</p> <p>* The NRC (2006) report states that ventricular septal defects (VSDs) were the most commonly observed cardiac problems in both animal studies and the epidemiological studies. This observation is provided as support to the idea that TCE can induce heart defects. However, as indicated earlier, the Johnson et al. (2003) study reported a much higher incidence of atrial septal defects than VSDs.</p> <p>- There are serious questions about whether or not atrial septal defects are actual defects or simply due to delays in development (an adaptive response that is usually reversible). In addition, VSDs are the most common heart defect in the human population, making up anywhere from -14.25% of CHD cases (American Heart Association, 2005b; Hoffman and Kaplan, 2002), regardless of whether or not TCE exposure is involved.</p> <p>- TCE reportedly alters endocardial cushion proliferation at low doses when administered in ovo, but whether or not this in turn increases the incidence of CHD is unclear. An increase in cellular proliferation in the cardiac cushion and outflow tract has been noted in the in ovo study by Drake et al. (2006a). In this study, 0.2, 4, and 200 nm/egg concentrations of TCE were injected into the yolks of eggs during cardiac cushion formation at Hamburger Hamilton (HH) stages 13, 15, 17, and 20. At the 4 nm/egg concentration and higher, an increase in cardiac cushion proliferation was observed in parallel with alterations in cardiac blood flow patterns. However, the same authors also noted in a later paper that this same increase in cellular proliferation was observed when TCE was administered at HH 18, 21, and 23, but this latter experiment the increased proliferation was not linked to any kind of functional cardiac alterations, illustrating that the two are not necessarily linked (Drake et al., 2006b).</p> <p>* Thus, it is unclear whether the effects on cellular proliferation of endocardial cushions seen in chick studies are related to septal defects, and it is unlikely that the changes reported from direct egg injection studies with high levels of TCE are relevant to whole animal or human exposure levels.</p>	
4.8.3	211	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>EPA Evaluation of Human Data on Heart Defects and Comments</p> <p>The existing human data are deficient for risk assessment, but even so they do not support an association between TCE exposure and cardiac defects in human infants.</p> <p>* A shortcoming that is common to all of the epidemiology studies is the lack of accurate exposure information and poor control of confounding factors. In the instance of the Arizona aquifer, the authors were clear to point out that their data showed "a significant association but not a cause and effect relation between parental exposure to the contaminated water area" and cardiac defects. By this, they meant that the parents of affected children were present in the land area overlying the aquifer during early gestation -but not that they had necessarily drunk or used contaminated water. Thus, it is not clear whether exposure occurred or to how much. With respect to the Baltimore-Washington Infant Study, interviews with parents identified activities and occupations that were likely to have involved organic solvents and degreasing substances. TCE is among the substances that could have been used, but it was not singled out as a causative agent and there is no information on levels of exposure. These data sets fail to clearly identify a specific causative agent and do not quantify exposure levels, making these data sets insufficient for an assessment of risk for a particular chemical (i.e., TCE).</p> <p>* NRC (2006) cited the findings in Bove et al. (2002), a study that re-analyzed the data presented in the widely disputed Goldberg et al. (1990) study. Goldberg et al. (1990) reported an increased incidence of congenital heart defects (CHD) in Tucson, AZ, but this report was criticized for its data analysis and sampling techniques. Bove</p>	<p>AUTHORS: Carole A. Kimmel, PhD; Gary L. Kimmel, PhD; John M. DeSesso, PhD from Exponent</p> <p>NRC (2006). Assessing the Human Health Risks of Trichloroethylene: Key Scientific Issues. National Research Council: National Academies Press, Washington, DC.</p> <p>Bove et al. (2002). Drinking water contaminants and adverse pregnancy outcomes. Environ Health Perspect 110 (Suppl 1):61-74.</p> <p>Goldberg SJ, Lebowitz MD, Graver EJ, Hicks S. An association of human congenital cardiac malformations and drinking water contaminants. J Am Coll Cardiol. 1990; 16:155-64.</p> <p>American Heart Association (2005a) Congenital heart defects in children factsheet. Available online at http://www.americanheart.org/presenter.jhtml?identifier=12012.</p> <p>NRC (2009). Contaminated Water Supplies at Camp LeJeune: Assessing Potential Health Effects. National Research Council: National Academies Press, Washington, DC.</p> <p>IOM (2003). Gulf War and Health, Vol. 2, Insecticides and Solvents. Washington, DC: National Academies Press.</p>

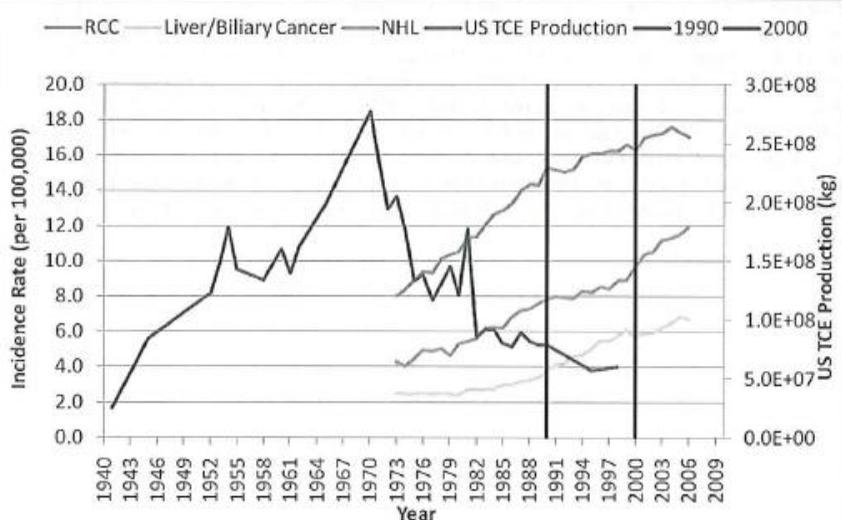
TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>et al. (2002) reported that 10-11% of households in Tucson had at least one member that had worked or resided in the TCE contaminated area. In contrast, it was stated that 39.2% of babies born with CHD had at least one parent who had resided or worked in a contaminated area. This was based on interviews of 143 of the 365 CHD cases. Bove et al. (2002) claimed that if it was assumed that the remaining 172 cases had a similar proportion of exposed parents, then the prevalence of CHD in the exposed areas during the first trimester of pregnancy would be about 2.3 times that in the uncontaminated areas. No confidence interval for this was provided. One major problem with this evaluation is that whether the mother and/or father was exposed to the TCE was not considered, and the pathway by which paternal exposure would contribute to an increase in CHD is unclear. Additionally; because socioeconomic status and demographics were not integrated with the geographical distribution of the population, it is possible that a higher proportion of births occurred in the part of town with TCE-contaminated water. In many parts of the county, certain areas of a region are more heavily populated with households with children. The control group here is for the overall Tucson population and not childbearing families. The absence of an appropriate control group is a potential confounding factor that was not considered. Another issue is that the control incidence of CHDs was stated to be 2.6/1,000 births, which is well below the expected U.S. background CHD rate of 811,000 births as reported by the American Heart Association (2005a). Therefore, it appears that the Bove et al. (2002) study suffers from many of the same problems as the original Goldberg et al. (1990) study.</p> <p>* The NRC (2009) report updated the conclusions of the IOM (2003) report and concluded that "there continues to be inadequate/insufficient evidence" for a link between TCE and congenital malformations in humans.</p> <p>* As discussed above, the human data cited by the assessment are inadequate for risk assessment and do not support a link between TCE and heart defects.</p> <p>CONCLUSIONS</p> <p>* EPA used a strength of evidence rather than a weight of evidence in their assessment of the data on cardiac defects. That is, only the positive data showing effects were considered in selecting data as the basis for the RfD and RfC rather than considering the whole body of data. EPA's guidelines clearly indicate the importance of using a weight of evidence approach.</p> <p>* All of the data showing cardiac defects in whole animal studies come from a single lab and have significant study design flaws and inadequate data reporting.</p> <p>* More carefully controlled GLP-studies did not show an increase in cardiac defects, including the study by Fisher et al. (2001) in which Dr. Johnson (of Johnson et al. 2003) participated.</p> <p>* The human data used by EPA as support for a link between TCE and heart defects are inadequate</p>	<p>Fisher JW, Channel SR, Eggers JS, Johnson PD, MacMahon IKL, Goodyear CD, Sudberry GL, Warren DA, Latendresse JR, Graeter JJ. Trichloroethylene, trichloroacetic acid, and dichloroacetic acid: Do they affect fetal rat heart development? Int J Toxicol. 2001; 20:257-67.</p> <p>Johnson PD, Goldberg SJ, Mays MZ, Dawson BV. Threshold of trichloroethylene contamination in maternal drinking waters affecting fetal heart development in the rat. Environ Health Perspect. 2003; 111:289-92.</p>
4.8.3	263	EPA-HQ-ORD-2009-0791-0012.1	McKenna, Long & Aldrige, LLP	<p>EPA does not use the entire database in its assessment of heart defects</p> <ul style="list-style-type: none"> • Animal studies are severely limited methodologically and in the reporting of data. • Human data suffers from inadequate exposure definition and inconsistent findings. • Mechanistic argument needs better support than seemingly irrelevant in vitro data and flawed in vivo data. • Data are seemingly ignored from well-conducted studies that show no increase in heart defects. <p>EPA should not say that heart defects may occur at environmentally relevant TCE doses in humans.</p> <p>A full weight of evidence evaluation (not a strength of evidence argument) should be provided for risk managers.</p>	<p>-</p> <p>-</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
4.10	60	EPA-HQ-ORD-2009-0791-0007.1	Natural Resources Defense Council (NRDC) and Supoprters	<p>It is likely that individuals will vary in their response to chemical toxicants according to differences in genetic factors, diet, lifestyle, health status, and age or gestational stage of exposure. These parameters may reduce the ability to detoxify or excrete TCE. In particular, the elder and the very young are both likely to be more susceptible to TCE toxicity because of reduced organ function, and therefore reduced ability to detoxify or excrete TCE.</p> <p>In addition, duration of exposure is likely to influence the pharmacokinetics of TCE toxicity. People who live or work in TCE contaminated areas are more susceptible to TCE toxicity due to chronic exposures.</p> <p>A review of TCE and PCE by the Agency for Toxic Substances & Disease Registry (ATSDR) reports on studies in animals and humans that provide some evidence that the developing fetus may be susceptible to maternal exposure to TCE, PCE and their common carcinogenic metabolite TCA.9 ATSDR reported in their review that physiologically-based pharmacokinetic (PB/PK) models have been developed to predict fetal exposures to PCE, TCE, and TCA (in utero) resulting from maternal exposure.10 The same ATSDR review pointed out that in studies of pregnant rats exposed to high doses of TCE via inhalation (618 ppm), ingestion (350 µg/ml or 350 ppm) or gavage (2.3 mg/kg or 2.3 ppm), both TCE and TCA were found in fetal blood at levels greater than 60% of the maternal blood level.11</p> <p>According to a public health statement from the CDC ATSDR, about 400,000 workers in the US are routinely exposed to TCE.12 This kind of chronic or routine exposure scenario makes them a vulnerable subpopulation because of increased exposure above background levels. It means that if these workers are also experiencing routine exposures to TCE through drinking water, showering, or home vapor intrusion, they could be exceeding acceptable limits and putting their health at great risk.</p>	<p>9 Agency for Toxic Substances and Disease Registry (ATSDR). 1997. Toxicological profile for Trichloroethylene (TCE). Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. Complete profile available at http://www.atsdr.cdc.gov/toxprofiles/tp19.html</p> <p>10 Agency for Toxic Substances and Disease Registry (ATSDR). 1997. Toxicological profile for Trichloroethylene (TCE). Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. Complete profile available at http://www.atsdr.cdc.gov/toxprofiles/tp19.html</p> <p>11 ATSDR Health Consultation: Evaluation of Health Impacts from Potential Past Exposure to Tetrachloroethylene in the Natick Public Water Supply (1998). Available at http://www.atsdr.cdc.gov/hac/pha/natick/nla_p2.html</p> <p>12 ATSDR Public Health Statement for trichloroethylene. Updated in 2008. Available at http://www.atsdr.cdc.gov/toxprofiles/phs19.html</p>
4.11.2	4	EPA-HQ-ORD-2009-0791-0010.1	ARCADIS on behalf of Deltrex Corporation	<p>The U.S. EPA has stated ...”TCE is characterized as “Carcinogenic to 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 U.S. EPA further states that “the evidence is ‘compelling’ for lymphoma and limited for liver and biliary tract cancers.” This conclusion overstates the results of the meta-analysis. Meta-analysis can be used in a systematic review of epidemiologic data regarding exposure and potential harm. Elements of this analysis should include a clearly stated purpose, careful literature searches, explicit inclusion and exclusion criteria, assessments of study validity and thus bias, and well-articulated definitions and rules of inference for selected causal criteria. The U.S. EPA has made a good attempt to follow these guidelines (Weed 2000; Blair et al. 1995) for the meta-analysis contained in their document, but the discussion in Appendix B is not clear about the U.S. EPA’s criteria for choosing the specific literature. It is equally important for the U.S. EPA to explain the hypothesis under investigation in the meta-analysis. In other words, what is the specific scientific study question to be answered? The U.S. EPA provides a sizable body of literature that may be complete, but the document lacks clarity. Choice of literature must support the basic study question, and criteria to use or exclude specific studies can have a profound effect on the results of the risk assessment. This may be a contributing factor in the U.S. EPA’s overreaching interpretation of the data and conclusions.</p>	-
4.11.2	15	EPA-HQ-ORD-2009-0791-0010.1	ARCADIS on behalf of Deltrex Corporation	<p>The following provides a brief review of the meta-analysis for kidney, lymphoma, and liver cancers as shown in Appendix C, Tables C-1 through C-11.</p> <p>Kidney Cancer: For overall TCE exposures, four of the 14 studies (Anttila et al. 1995; Boice et al. 1999; Greenland et al. 1994; and Siemiatycki 1991) used in the kidney meta-analysis had individual study relative risks (RRs) less than 1.0, and the other 10 studies had individual RRs between 1.0 and 2.47. The pooled relative risk (RRp) estimates for overall TCE exposure was 1.25 (95% Confidence Intervals [CI]: 1.11, 1.41). Further, for the highest TCE exposed groups within the 12 studies pooled for RRp estimates, three of the studies (Boice et al., 1999; Radican et al., 2008; and Siemiatycki 1991) had individual study RRs lower than for the overall TCE exposure. The pooled RRp estimate for the highest TCE exposure group was 1.53 (95% CI: 1.23, 1.91).</p> <p>Lymphoma Cancers: This same trend is noted with the meta-analysis for lymphomas. Two of the 16 studies reviewed (Greenland et al. 1994; Miligi et al. 2006) had individual study RR estimates for overall TCE exposure below 1.0, and all of the other studies used in the analysis except Hardell (1994) and Hansen (2001) had RR estimates between 1.0 and 1.24. The pooled RRp estimate for overall TCE exposure was 1.23 (95% CI: 1.04, 1.44). Further, for the highest exposed group, five of the 16 studies (Anttila et al. 1995; Hansen et al. 2001;</p>	<p>-</p> <p>Anttila, A., E. Pukkala, M. Sallmen et al. 1995. Cancer incidence among Finnish workers exposed to halogenated hydrocarbons. <i>J Occup Environ Med</i> 37:797–806.</p> <p>Boice, J.D., D.E. Marano, J.P Fryzek et al. 1999. Mortality among aircraft manufacturing workers. <i>Occup Environ Med</i> 56:581–597.</p> <p>Greenland, S., A. Salvan, D.H. Wegman et al. 1994. A case-control study of cancer mortality at the transformer-assembly facility. <i>Int Arch Occup Environ Health</i> 66:49–54.</p> <p>Siemiatycki, J. 1991. Risk factors for cancer in the workplace. Boca Raton: CRC Press.</p> <p>Anttila, A., E. Pukkala, M. Sallmen et al. 1995. Cancer incidence among Finnish workers exposed to halogenated hydrocarbons. <i>J Occup Environ Med</i> 37:797–806.</p> <p>Boice, J.D., D.E. Marano, J.P Fryzek et al. 1999. Mortality among aircraft manufacturing workers. <i>Occup Environ Med</i> 56:581–597.</p> <p>Greenland, S., A. Salvan, D.H. Wegman et al. 1994. A case-control study of cancer mortality at the transformer-assembly facility. <i>Int Arch Occup Environ Health</i> 66:49–54.</p> <p>Siemiatycki, J. 1991. Risk factors for cancer in the workplace. Boca Raton: CRC Press.</p> <p>Greenland, S., A. Salvan, D.H. Wegman et al. 1994. A case-control study of cancer mortality at the</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>Morgan et al. 1998; Zhao et al. 2005; and Siemiatycki 1991) showed lower RR estimates than the overall TCE exposure. The pooled RRp estimate for the highest TCE exposure group was 1.57 (95% CI: 1.27, 1.94). The U.S. EPA acknowledges that issues of (non-statistically significant) study heterogeneity, potential publication bias, and weaker exposure-response results contribute greater uncertainty for the lymphoma analysis.</p> <p>Liver and Biliary Tract Cancer: The evidence for liver and biliary tract cancer is even more limited. The overall TCE exposure relative risk estimate for the nine studies used in the meta-analysis was 1.33 (95% CI: 1.09, 1.64). But the pooled RRp estimate for the highest TCE exposure group was lower at 1.28 (95% CI: 0.93, 1.77). Two of the nine studies had individual RR estimates below 1.0, and two studies had RR estimates for the highest TCE exposure group that were lower than the overall TCE exposure RR estimates. The overall TCE exposure individual study RR ranged from 0.54 to 2.1. The U.S. EPA acknowledges that the data for liver cancer are uncertain mainly because only cohort studies are available, and most of these studies have small numbers of cases.</p> <p>Therefore, it can be agreed that the liver cancer meta-analysis is limited and conclusions by the U.S. EPA that the human epidemiology evidence of TCE exposure is “convincing” for kidney cancer and “compelling” for lymphoma are overreaching.</p>	<p>transformer-assembly facility. Int Arch Occup Environ Health 66:49–54.</p> <p>Miligi, L., A.S. Costantini, A. Benvenuti et al. 2006. Occupational exposure to solvents and the risk of lymphomas. Epidemiology 17:552–561.</p> <p>Hardell, L., M. Eriksson, A. Degerman. 1994. Exposure to phenoxyacetic acids, chlorophenols, or organic solvents in relation to histopathology, stage, and anatomical localization of non-Hodgkin's lymphoma. Cancer Res 54:2386–2389.</p> <p>Hansen, J., O. Raaschou-Nielsen, J.M. Christensen et al. 2001. Cancer incidence among Danish workers exposed to trichloroethylene. J Occup Environ Med 43:133–139.</p> <p>Morgan, R.W., M.A. Kelsh, K. Zhao et al. 1998. Mortality of aerospace workers exposed to trichloroethylene. Epidemiology 9:424–431.</p> <p>Zhao, Y., A. Krishnadasan, N. Kennedy et al. 2005. Estimated effects of solvents and mineral oils on cancer incidence and Mortality in a cohort of aerospace workers. Am J Ind Med 48:249–258.</p>
4.11.2	20	EPA-HQ-ORD-2009-0791-0010.1	ARCADIS on behalf of Deltrex Corporation	<p>The majority of RR estimates for the individual studies are at or below 2.0 for the overall TCE exposure and the highest TCE exposure group. In addition, the meta-analysis for each of the cancer types showed RRp estimates below 2.0.</p> <p>Risk measurements in epidemiology studies infer causality, but the strength of that association provides the public health significance of the inference. The basic rule is the higher the observed increase in risk, “the less likely that other factors explain the excess, unless the other factors are themselves likely to produce a similar high risk.” Cole (1980) points out that a relative risk of less than 2.0 may be readily explicable by some unperceived bias or confounding factor, while those above 5.0 are less likely to be so explained. While it is not impossible for an agent to pose a low risk and be the causal agent, conclusions that an association is causal when relative risks are low at high exposure may be in error.</p> <p>Further, an RR of 2 or less whether it is from a quantitative meta-analysis or qualitative application of Hill’s criteria still remains on the borderline of what is typically called a “weak” association. Even the authors of the individual studies acknowledge this in their study discussions/conclusions. For example, Charbotel (2006) states: “The results of the present study do not agree with the negative results obtained by a number of large cohort studies... Although this study shows a possible link between high levels of exposure to TCE and increased risk of RCC, further epidemiological studies are necessary to assess the effect of lower levels of exposure.” Further, the highest exposure groups’ meta-analysis RRs, while slightly higher, also still remain in the weak association category. Even if this were to be considered significant, the U.S. EPA needs to further explain why possible high-dose industrial/workplace inhalation exposures are of public health significance for extrapolation to low dose environmental exposures through other environmental media (water, soil, etc.)</p>	<p>-</p> <p>- Cole, P. 1980. Introduction In: Breslow NE and Day NE (Ed. W. Davis) Statistical Methods in Cancer Research. International Agency for Research on Cancer (IARC) Science Publication No. 32. IARC Lyon, France, pp 14-39.</p> <p>- Charbotel, B., J. Fevotte, M. Hours et al. (2006) Case-control study on renal cell cancer and occupational exposure to trichloroethylene. Part II: Epidemiological aspects. Ann Occup Hyg 50(8):777–787.</p>
4.11.2	27	EPA-HQ-ORD-2009-0791-0010.1	ARCADIS on behalf of Deltrex Corporation	<p>The human epidemiology studies reviewed in this assessment exhibit external inconsistency relative to each other and internal inconsistencies relative to their own study subgroups. While meta-analysis provides a more formal statistical approach to the criterion of consistency, both internal consistency and external consistency are important. For instance, Do the increases in risk occur in the categories of exposure when expected and in all the subgroups where expected? Or do the results of the various studies provide the same or consistent results? The same or similar results in several studies add support to arguments concerning causality. However, the strength of each study should be individually taken into account. Often negative studies do not get published, so several studies suggesting a weak association do not automatically lead to acceptance of causation.</p>	<p>-</p> <p>-</p>
4.11.2	29	EPA-HQ-ORD-2009-0791-0010.1	ARCADIS on behalf of Deltrex Corporation	<p>Input from the TCE Subregistry of the Agency for Toxic Substances and Disease Registry’s (ATSDR’s) National Exposure Registry is absent in this document with no explanation. This subregistry of over 4,000 individuals contains information on exposure to TCE in drinking water, as well as associated health effects (Agency for Toxic Substances and Disease Registry 1996). A specific goal of the subregistry is to obtain, maintain, disseminate, and analyze longitudinal data; that is, data collected on the same people over time that have documented exposure to a specific chemical. To date, this goal has been pursued for the TCE subregistry by the collection of baseline and at least three follow-up collections of data from the subregistry population. The results</p>	<p>-</p> <p>-</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>of the statistical analysis of Baseline and Follow-up 1 data do not show increases in reported cancer cases except for a general increase for female registrants in the 19 to 25 years of age group, but this increase was not statistically significant. Other systemic health problems have indicated a statistically significant increase from Baseline to Follow-up 1, but this trend has not been noted for cancer. However, future evaluations are planned, including analyses of Follow-up 2 and 3 data. If the U.S. EPA is to use human epidemiology data as a major line of evidence in this TCE review, it would seem critical to obtain input from epidemiologists at ATSDR's TCE subregistry.</p> <p>It should further be noted that the registry is designed to account for many of the difficulties inherent in drawing conclusions from individual epidemiology studies. The registry design includes a clearly stated purpose, careful literature searches, explicit inclusion and exclusion criteria, assessments of data collection for study validity and thus bias, and well-articulated definitions and rules of inference for selected causal criteria; in essence, a meta-analysis constructed for public health decision-making. Given that the TCE subregistry is now 20+ years post exposure of human populations to various levels of TCE in drinking water, the information contained within this registry should not be dismissed. If there are reasons for not including this information in this document, it should be stated.</p> <p>At the very least, this information should be used to challenge the hypothesis under investigation in the meta-analysis and explain clearly why the RRs estimated from a high-dose industrial inhalation epidemiology study are used to extrapolate an oral cancer value to be used in site risk assessments and drinking water regulations.</p>	
4.11.2	34	EPA-HQ-ORD-2009-0791-0011.1	ARCADIS	<p>In its External Review Draft: Toxicological Review of Trichloroethylene (EPA/635/R-09/011A), the United States Environmental Protection Agency (EPA) has characterized trichloroethylene (TCE) as "carcinogenic to humans" based on human epidemiological data on renal cell carcinoma (RCC). Specifically, EPA (2009) states: "Following EPA (2005a) Guidelines for Carcinogen Risk Assessment, based on the available data as of 2009, TCE is characterized as "Carcinogenic to 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 human evidence of carcinogenicity from epidemiologic studies of TCE exposure is compelling for lymphoma but less convincing than for kidney cancer, and more limited for liver and biliary tract cancer." Thus, EPA is basing its characterization on RCC. While EPA felt that there was some evidence that TCE was causally associated with non-Hodgkin's lymphoma (NHL), their carcinogenic characterization was not based on the lymphoma carcinogenic endpoint. Also, EPA characterized the potential association between TCE exposure and human liver and biliary tract cancer as "less convincing," so clearly their carcinogenic classification was not based on data concerning the causation of liver and biliary tract cancer.....</p> <p>More importantly, EPA has derived an inhalation Unit Risk Factor (URF) for RCC using the data from a human epidemiological study published by Charbotel et al. (2006). EPA's proposed URF for RCC was 1.02×10^{-6} per $\mu\text{g}/\text{m}^3$. EPA states strongly that data from all available studies can only support the dose-response modeling of RCC, not other cancer endpoints, such as liver and biliary tract cancer and NHL. However, EPA then proceeds to, in essence, derive URFs for liver and biliary tract cancer and NHL, despite the fact that: (1) the characterization of TCE as "Carcinogenic to Humans" is based on RCC, not on liver and biliary tract cancer or NHL and (2) the required data on other tumor endpoints are not available for dose-response modeling. Specifically, EPA states:....</p> <p>Using both methods, EPA concluded that liver and biliary tract cancer had similar risk to humans as RCC, and NHL had double the risk to humans as RCC. Accordingly, EPA multiplied the URF based on RCC by a factor of 4 to arrive at a multi-site URF of 4×10^{-6} per $\mu\text{g}/\text{m}^3$. In essence, EPA is stating that they think they following site-specific URFs are reasonable estimates of the human health risk posed by inhalation of TCE:</p> <ul style="list-style-type: none"> - Renal cell carcinoma 1×10^{-6} per $\mu\text{g}/\text{m}^3$ - Liver & biliary cancer 1×10^{-6} per $\mu\text{g}/\text{m}^3$ - Non-Hodgkin's lymphoma 2×10^{-6} per $\mu\text{g}/\text{m}^3$ - Total URF 4×10^{-6} per $\mu\text{g}/\text{m}^3$ 	<p>- Environmental Protection Agency (EPA). 2005a. As cited in U.S. Environmental Protection Agency (EPA). 2009. Charbotel et al. 2006. As cited in U.S. Environmental Protection Agency (EPA) 2009.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>The proposed URF of 4×10^{-6} per $\mu\text{g}/\text{m}^3$ is totally illogical. First EPA states that the evidence that TCE causes liver and biliary tract cancer in humans is weak and insufficient to conclude that TCE is carcinogenic to humans. Then, they derive a URF that states that the risks for liver and biliary tract cancer are equal to the risks for RCC. Similarly, EPA states that the evidence that TCE causes NHL in humans is only suggestive, but then they derive a URF that will predict increased human risks for NHL despite the fact that the evidence that TCE causes NHL at all is less than the evidence that it causes RCC in humans.</p> <p>ARCADIS finds that EPA has not performed a validation exercise to determine if the classification of TCE as “Carcinogenic to Humans” and the proposed estimates of the quantitative risk to humans are consistent with the observable facts concerning human cancer rates and other known risk factors for the tumor types listed above.</p>	

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
4.11.2	44	EPA-HQ-ORD-2009-0791-0011.1	ARCADIS	<p data-bbox="610 147 962 170">Time Course of Cancer Incidence Rates</p> <p data-bbox="610 196 1602 464">As noted in Figure 1, which summarizes historical US incidence rates of RCC, liver and biliary cancer, and NHL from the NCI SEER database, the incidence rates for all three tumor types has been increasing steadily for years. Given that TCE production and use in the US peaked in 1970, the observed time course of incidence rates is not consistent with TCE being a major cause of any of these cancers in the US population. Figure 1 also shows production statistics and shows the time points that are 20 years and 30 years after the peak in production. Given that any cancers caused by TCE would be expected to be observable in the national cancer incidence statistics 20-30 years after critical exposure events, one would expect that incidence rates would be decreasing, not increasing, if TCE were a major cause. Of course, decreases in the incidence rates of any TCE-caused cancers could be masked by increasing rates of cancers associated with other causal agents. Whether such masking is occurring or not, the conclusion is the same: the time courses of RCC, liver and biliary cancer, and NHL do not provide support for any hypothesis that TCE poses a great risk of cancer in the human population.</p> <p data-bbox="610 490 1602 586">Figure 1: US TCE production (1941-1998) and US incidence rates of RCC, liver and biliary cancer, and NHL (1973-2006). Lines at 1990 and 2000 indicate 20-year and 30-year latency periods, respectively, from peak TCE production in 1970. US production data from Bakke et al. (2007), IARC (1995), Doherty (2000), and EPA (2009). Incidence rates from SEER (2009 a,b,c).</p>	<p data-bbox="1620 170 2462 219">FIGURE 1 PRODUCTION OF TCE VERSUS TIME COURSE OF SELECTED TUMOR INCIDENCE RATES</p> 

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
4.11.2	55	EPA-HQ-ORD-2009-0791-0007.1	Natural Resources Defense Council (NRDC) and Supoprters	<p>We strongly support the determination that TCE causes kidney cancer in humans, based on multiple robust lines of scientific evidence. The assessment reviews scientific evidence linking TCE exposure with kidney cancer in both human and animal studies. It is especially significant that a meta-analysis of 14 high-quality studies found a statistically significant pooled relative risk estimate for kidney cancer of 1.25 (95%CI 1.11, 1.41). Importantly, the association was dose-dependent, with the highest exposed group having a relative risk of 1.53 (95% CI 1.23, 1.91). This means that the risk of getting kidney cancer from TCE exposure is on average 53% higher than background (without TCE exposure) in the highest exposed group, and possibly as high as 91%.</p> <p>Epidemiology studies are usually biased towards the null, meaning that they tend to err on the side of not finding a true causal relationship between an exposure and an outcome, rather than finding a causal relationship where none exists. This design bias makes it harder to detect a true causal relationship between an exposure and an outcome when one exists. This often happens because of a common error called exposure misclassification that occurs when exposed individuals accidentally end up in the control groups (no or low exposure) and unexposed individuals accidentally get put into the “exposed” or “high exposed” groups. This misclassification error results in exposed individuals with the measured outcome (kidney cancer in this case) in the control groups, and unexposed individuals without the measured outcome in the exposure groups, ultimately falsely reducing the risk differences between the two groups. Thus, the meta-analysis of 14 robust studies that finds a statistically significant causal relationship, reported by EPA in this TCE assessment, is a powerful scientific statement supporting a causal relationship between TCE exposure and kidney cancer.</p>	- -
4.11.2	59	EPA-HQ-ORD-2009-0791-0007.1	Natural Resources Defense Council (NRDC) and Supoprters	<p>We strongly support EPA’s determination that TCE is a human carcinogen by all routes of exposure. Robust studies reviewed by the International Agency for Research on Cancer (IARC) in 1995 (Vol 63) provide compelling evidence of cancer from oral exposure studies in both mice (liver cancer) and rats (kidney cancer), and inhalation exposure in mice (lung cancer) and rats (kidney cancer and testicular cancer). Epidemiologic studies of workplace exposures reviewed by IARC in 1995 reported on a statistically significant increase in skin cancer (SIR 2.4, 95%CI 1.0-4.7), providing evidence that dermal exposures are likely to be carcinogenic. Other human cancers reviewed by IARC to be associated with TCE workplace exposures include cervical cancer (SIR 2.4, 95%CI 1.1-4.8), non-Hodgkin’s lymphoma, and liver cancer.</p>	- -
4.11.2	69	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>1. Kidney Toxicity and Carcinogenicity</p> <p>1.1 General: EPA has followed a recommendation of the NRC in the review of the 2001 IRIS draft released in 2006 to accord greater weight to kidney toxicity and tumorigenesis than to liver responses in the mouse. In general, we support the change in emphasis recommended by the NRC but EPA has now applied unbalanced and incorrect interpretations to the data from epidemiological and toxicity studies to generate unfounded concerns about exposure to TCE and effects on the kidney.</p>	AUTHOR: Paul H. Dugard, Halogenated Solvents Industry Alliance, Inc. -
4.11.2	82	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>2.2 The Role of DCA in the Induction of Mouse Liver Tumors by TCE:</p> <p>As discussed by Prof. Dekant, the amount of DCA generated from TCE is very small or even non-existent. If this low level of production is combined with the weak genotoxic potential and the relatively low potency of DCA as a mouse liver carcinogen in its own right, there seems to be no justification for assuming DCA contributes significantly to mouse liver tumors induced by TCE. Bull et al (2002) report a clear difference in the phenotypes of tumors induced by DCA versus TCA. A proportion of DCA tumors contained c-Jun but none of the TCA tumors examined showed this character. Tumors from TCE treated animals were reported to show a mixture of TCA and DCA phenotypes with quite a high proportion relating to DCA. The problem with this study is that the TCE tumors are much later stage than those examined for TCA and DCA (79 weeks versus 52 weeks). It is well known that later stage tumors develop complex genetic composition; thus a contribution from DCA to tumor induction by TCE cannot be supported by this study. The only true conclusion that can be drawn is that there is no evidence that conversion of TCA to DCA occurs to affect the nature of tumors seen, and this can be applied to TCA derived from TCE – conversion of TCA to DCA is unlikely to be significant for induction of mouse liver tumors. EPA’s detailed analysis of liver weight increases suffers from the same overestimates of TCA bioavailability discussed in section 2.3.</p> <p>There is no convincing reason to believe that DCA contributes to mouse liver tumor induction by TCE.</p>	AUTHOR: Paul H. Dugard, Halogenated Solvents Industry Alliance, Inc. -
4.11.2	182	EPA-HQ-	Aerospace	Classification of TCE as "carcinogenic to humans". AIA supports both the Department of Defense (DOD) and	AUTHOR: Lisa Goldberg

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
		ORD-2009-0791-0009.1	Industries Association (AIA)	the National Aeronautics and Space Administration (NASA) position that the classification of TCE as a known human carcinogen is neither supported by the evidence nor consistent with EPA's Guidelines for Carcinogen Risk Assessment (2005).	-
4.11.2	190	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>Comments on the Weight of Evidence Cancer Conclusions in the Trichloroethylene: Consideration of Both Toxicological and Epidemiologic Evidence -External Review Draft</p> <p>Michael Dourson, Ph.D., DABT Lynne Haber, Ph.D., DABT Toxicology Excellence for Risk Assessment</p> <p>Michael Kelsh, Ph.D, MPH Dominik Alexander, Ph.D, MPH Exponent, Health Sciences</p> <p>These comments address the question of whether the overall toxicological and epidemiologic data provide sufficient evidence for description of TCE as "Carcinogenic to Humans." First we review the Environmental Protection Agency's (EPA's) 2005 guidelines for weight of evidence descriptors regarding carcinogenic potential . We then consider where the scientific evidence from toxicological and epidemiologic research best fits under these criteria.</p> <p>Our key overall observations and conclusions are as follows: EPA has proposed a cancer descriptor of "carcinogenic to humans" for TCE "based on convincing evidence of a causal association between TCE exposure in humans and kidney cancer."</p> <p>Upon a critical scientific assessment, we find that the currently available are clearly not convincing of a causal association between TCE exposure and cancer in humans. This is because neither the epidemiologic data nor the animal and mechanistic data meet EPA's criteria of "carcinogenic to humans" as described in the 2005 EPA Guidelines for Carcinogen Risk Assessment. Moreover, we find that EPA has not judged any other chemical as a "human carcinogen" or its equivalent (using older guidelines) on such inconsistent support and such a lack of strong and convincing epidemiologic evidence. EPA's proposal to use the classification "carcinogenic to humans" for TCE would be a poorly supported precedent in the application of its own guidelines.</p> <p>Rather, our judgment based on the 2005 EPA Guidelines for Carcinogen Risk Assessment, which EPA has established to make such determinations consistent across chemical assessments, indicates that a more correct classification for EPA to make for TCE would either be "likely to be carcinogenic to humans" or "suggestive evidence of carcinogenicity" depending on how one considers the "adequacy" of evidence to demonstrate carcinogenic potential.</p>	<p>AUTHORS: Michael Dourson, Ph.D., DABT and Lynne Haber, Ph.D., DABT from Toxicology Excellence for Risk Assessment and Michael Kelsh, Ph.D., MPH and Dominik Alexander, Ph.D., MPH from Exponent, Health Sciences</p> <p>-</p>
4.11.2	192	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>Application of the Guidelines to Trichloroethylene</p> <p>In considering the data in the context of applying the "carcinogenic to humans" descriptor, one first considers the weight of the epidemiological evidence. We judge the epidemiologic evidence to be neither "convincing" nor "strong," two key terms in the guidelines. This judgment is based on four recent reviews and meta-analyses of occupational TCE exposures and cancer as well as other reviews of this literature (Alexander et al., 2006, 2007; Mandel et al., 2006; Kelsh et al., 2010). The recent review and meta-analysis by Kelsh et al., 2010 focuses on occupational TCE exposure and kidney cancer; and includes the recent Charbotel 2006 study that is emphasized in the EPA assessment and used by EPA scientists to conduct a quantitative risk assessment. Both the EPA meta-analysis and the recently published Kelsh et al. meta-analysis of the TCE-kidney cancer epidemiologic literature produced similar summary results. However in Kelsh et al., the limitations of this body of research, namely exposure assessment limitations, potential unmeasured confounding, potential selection biases, and inconsistent findings across groups of studies, did not allow for a conclusion that there is sufficient evidence of a casual association, despite a modest overall association. In addition, although the recent Charbotel et al. 2006 study has made important improvements in exposure assessment, it still has important potential limitations that do not permit an appropriate use in quantitative risk assessment.</p>	<p>AUTHORS: Michael Dourson, Ph.D., DABT and Lynne Haber, Ph.D., DABT from Toxicology Excellence for Risk Assessment and Michael Kelsh, Ph.D., MPH and Dominik Alexander, Ph.D., MPH from Exponent, Health Sciences</p> <p>Alexander DD, Kelsh MA, Mink PJ, Mandel JH, Basu R, Weingart W. A meta-analysis of occupational trichloroethylene exposure and liver cancer. <i>Int Arch Occup Environ Health</i> 2007; 81(2):127-143.</p> <p>Alexander DD, Mink PJ, Mandel JH; Kelsh MA. A meta-analysis of occupational trichloroethylene exposure and multiple myeloma or leukemia. <i>Occup Med</i> 2006; 56(7):485-93.</p> <p>Mandel JH, Kelsh MA, Mink PJ, Alexander D, Kalmes RM, Weingart M, Yost L Goodman M. Occupational trichloroethylene exposure and non-Hodgkins lymphoma: A meta-analysis and review. <i>Occup Environ Med</i> 2006; 63(9):597-607.</p> <p>Kelsh MA, Alexander DD, Mink PJ, Mandel JH. Occupational trichloroethylene exposure and kidney cancer: a meta-analysis. <i>Epidemiology</i>. 2010 Jan;21(1):95-102.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
					Charbotel B, Fevotte J, Hours M, martin J, Beregeret A. Case-Control Study on Renal Cell Cancer and Occupational Exposure to Trichloroethylene. Part 11: Epidemiological Aspects. Ann.Occup.Hyg. 2006.
4.11.2	194	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>There are reasonably well designed and well conducted epidemiologic studies that report no association between TCE and cancer, some reasonably well designed and conducted studies that did report associations between TCE and cancer, and finally some relatively poorly designed studies reporting both positive and negative findings. Overall, the summary relative risks or odds ratios in the meta-analysis studies (EPA or published meta-analyses) generally ranged between 1.2 and 1.4. The IRIS document refers to these associations as "small;" a term not typically consistent with "convincing" and strong." Weak or small associations may be more likely to be influenced or be the result of confounding or bias. Smoking and body mass index are well-established risk factors for kidney cancer, and smoking and alcohol are risk factors for liver cancer, yet the potential impact of these factors on the meta-analysis associations was not fully considered. There were suggestions that these factors may have impacted findings (e.g. in the large Danish cohort study of TCE exposed workers, tile researchers noted that smoking was more prevalent among the TCE exposed populations however little empirical data were provided (Raachou-Nielson et al., 2003). In addition, colinearity of occupational exposures (i.e. TCE exposure correlated with chemical and/or other exposures) may make it difficult to isolate potential effects of TCE from those of other exposures within a given study, and hinder interpretation across studies. For example, although Charbotel et al. (2006) reposted potential exposure response trends; while controlling for many confounders of concern (which strengthens the weight of evidence), they also reported attenuated associations for cumulative TCE exposure after adjustment for exposure to cutting fluids and other petroleum oils (weakening the weight of the evidence). This study is also be limited due to other by potential study design considerations such as selection bias, self report of work histories, residual confounding and other design factors.</p>	<p>AUTHORS: Michael Dourson, Ph.D., DABT and Lynne Haber, Ph.D., DABT from Toxicology Excellence for Risk Assessment and Michael Kelsh, Ph.D., MPH and Dominik Alexander, Ph.D., MPH from Exponent, Health Sciences</p> <p>Raaschou-Nielsen O et al. Cancer risk among workers at Danish companies using trichloroethylene: a cohort study. Am.J.Epidemiol. 2003;158:1182-92.</p> <p>Charbotel B, Fevotte J, Hours M, martin J, Beregeret A. Case-Control Study on Renal Cell Cancer and Occupational Exposure to Trichloroethylene. Part 11: Epidemiological Aspects. Ann.Occup.Hyg. 2006.</p>
4.11.2	199	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>When examining the data for TCE and non-Hodgkin lymphoma, kidney cancer, and liver cancer, associations were inconsistent across occupational groups (summary results differed between aerospace/aircraft worker cohorts compared with workers from other industries), study design, location of the study, quality of exposure assessment (e.g., evaluating studies that relied upon biomonitoring to estimate exposure vs. semi-quantitative estimates vs. self-report, etc.), and by incidence vs. mortality endpoints. Although EPA examined high dose categories, it did not evaluate any potential dose-response relationships across the epidemiologic studies (except for the Charbotel et al. 2006 study). In our reviews of the epidemiologic data reported in various studies for different exposure levels (e.g. cumulative exposure and duration of exposure metrics): we did not find consistent dose-response associations between TCE and the three cancer sites under review (Mandel et al., 2006; Alexander et al., 2007; Kelsh et al., 2010) Ail established dose-response trend is one of the more important factors when making assessments of causation in epidemiologic literature. These issues are addressed in greater detail in the accompanying comments by Michael Kelsh and Dominic Alexander.</p> <p>Thus, based on an overall WOE analysis of the epidemiologic research, these data do not support the conclusion that there is "strong" or "convincing" evidence of a causal association between human exposure and cancer.</p>	<p>AUTHORS: Michael Dourson, Ph.D., DABT and Lynne Haber, Ph.D., DABT from Toxicology Excellence for Risk Assessment and Michael Kelsh, Ph.D., MPH and Dominik Alexander, Ph.D., MPH from Exponent, Health Sciences</p> <p>Charbotel B, Fevotte J, Hours M, martin J, Beregeret A. Case-Control Study on Renal Cell Cancer and Occupational Exposure to Trichloroethylene. Part 11: Epidemiological Aspects. Ann.Occup.Hyg. 2006.</p> <p>Mandel JH, Kelsb MA, Mink PJ, Alexander D, Kalmes RM, Weingart M, Yost L Goodman M. Occupational trichloroethylene exposure and non-Hodgkins lymphoma: A meta-analysis and review. Occup Environ Med 2006; 63(9):597-607.</p> <p>Alexander DD, Kelsh MA, Mink PJ, Mandel JH. Basu R, Weingart W. A meta-analysis of occupational trichloroethylene exposure and liver cancer. Int Arch Occup Environ Health 2007; 81(2):127-143.</p> <p>Kelsh MA, Alexander DD, Mink PJ, Mandel JH. Occupational trichloroethylene exposure and kidney cancer: a meta-analysis. Epidemiology. 2010 Jan;21(1):95-102.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics												
4.11.2	201	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>The EPA's 2005 guidelines also state that a chemical may be described as carcinogenic to humans with a lesser weight of epidemiologic evidence that is strengthened by other lines of evidence, all of which must be met. One of these lines of evidence is "extensive evidence of carcinogenicity in animals." Therefore, we now turn to an evaluation of the animal data.</p> <p>In weighing the evidence in experimental animals and addressing the impact of the metabolites produced, EPA states that</p> <p>"A greater variability of response is expected than from exposure to a single agent making it particularly important to look at the TCE database in a holistic fashion rather than the results of a single study, especially for quantitative inferences." (EPA, page 4-233)</p> <p>We agree with EPA that the database needs to be viewed holistically. EPA goes on to surmise that evidence for cancer is found in two species (rats and mice) and for more than one tumor endpoint (kidney, liver, lung and immune system). However, EPA's description of this evidence is unconvincing when starting from the neutral question of: "Does TCE cause cancer in experimental animals?" Of the 4 primary tissues that EPA evaluates for carcinogenicity, only one or perhaps two of them, liver and lung tumors in mice, rises to the level of biological significance. Discussion of the remaining tumor types appears to presuppose that TCE is carcinogenic. The resulting text appears then to overly discount negative data, of which there are many, and to highlight marginal findings. The text does not appear to be a dispassionate rendering of the available data. (FOOTNOTE 1)</p> <p>Specifically, EPA's conclusion that kidney cancer is evident in rats rests on one statistically significant finding in over 70 dose/tumor endpoint comparisons and references to exceedances of historical control values (NTP, 1990) Using a 0.05 p-value for statistical significance, a frequency of 1 or even several statistically or biologically significant events is expected in such a large number of dosed/tumor groups. This expectation is met, but not exceeded, as shown in Tables 1 and 2, which present the percent response for the various studies of kidney tumors, grouped by exposure level. EPA notes several other occurrences of kidney tumors, but tile incidence was either not statistically significant or of borderline significance in comparison with concurrent controls. The presentation of data vs. the historical NTP controls is very useful. But historical control data needs to be presented in the context of both the study and year, since drift occurs in animal colonies (e.g., it is likely that the historical control data were different for the NCI 1976 study than for the NTP 1988-1990 studies). At least as importantly, historical control data is needed for each strain, particularly in light of the relatively high control response (7% in the inhalation study in Han:Wistar rats (Henschler et al., 1980). The statements about consistent increases of a rare tumor seem to assume that the background for all strains is the same as that reported by NTP for F344 rats. Moreover, each of the studies EPA cites has problems. Although EPA generally does a good job of identifying these problems, its overall conclusion, based on these flawed studies cannot be that TCE is a known kidney tumorigen. The best that can be said is that the data are inconsistent.</p> <p>EPA states that liver tumors are statistically significant in mice. This statement is confirmed by a biological judgment of all available data as shown in Tables 5 and 6. (FOOTNOTE 2)</p> <p>EPA finds three statistically significant occurrences of lung tumors in mice, 1 of them in a study with known epichlorohydrin contamination. Findings in other studies might be considered as biologically significant (see highlights in Tables 9 and 10 of these comments). The rest of the studies show no statistically significant increase, or show no lung tumors, or show a decrease in lung tumors as shown in Tables 7, 8, 9 and 10. Briefly, these data are either equivocal or marginally positive. EPA might consider revising its lung tumor table (Table 4-73) in order to make this information more readily transparent.</p> <p>EPA states on page 4-397 that:</p> <p>"Cancers of the immune system that have been observed in animal studies and are associated with TCE exposure are summarized in Tables 4-68 and 4-69. The specific tumor types observed are malignant lymphomas, lymphosarcomas, and reticulum cell sarcomas in mice and leukemias in rats..."</p> <p>EPA then continues on page 4-399 with:</p>	<table border="1" data-bbox="1623 147 2252 261"> <tr> <td data-bbox="1623 147 1749 201">Vinyl Chloride (2000)</td> <td data-bbox="1757 147 1843 201">11(16)</td> <td data-bbox="1852 147 1884 201">2</td> <td data-bbox="1892 147 1978 201">8(10)</td> <td data-bbox="1986 147 2045 201">6(8)</td> <td data-bbox="2053 147 2252 201">Y (angio-sarcoma)</td> </tr> <tr> <td data-bbox="1623 206 1749 261">1,3-Butadiene (2001)</td> <td data-bbox="1757 206 1843 261">7(9)</td> <td data-bbox="1852 206 1884 261">ND</td> <td data-bbox="1892 206 1978 261">1</td> <td data-bbox="1986 206 2045 261">1</td> <td data-bbox="2053 206 2252 261">N</td> </tr> </table> <p>¹ First number is the best estimate of number of unique cohorts, based on the IRIS summary. The number in parentheses is total number of citations of studies.</p> <p>² ND = not determinable from writeup; no studies were mentioned, but it is not clear from the writeup whether negative studies exist, but were not included because a strength of evidence approach was in use at the time.</p> <p>³ Tumor associated with the chemical exposure has a very low background in humans, increasing the specificity of the association.</p> <p>⁴ There is one IRIS assessment for benzene, with portions from 1998 and 2000. The human data are presented in the initial 1998 assessment, while inhalation data for animals were presented in the 1998 document, and oral animal data presented in a 2000 document.</p> <p>FOOTNOTE 1: For example, EPA (page 4.261) states "For rats, Maltoni et al. (1986) reported 4 liver angiosarcomas (1 in a control male rat, 1 both in a TCE-exposed male and female at 600 ppmTCE for 8 weeks, and 1 in a female rat exposed to 600-ppm TCE for 104 weeks), but the specific results for incidences of hepatocellular "hepatomas" in treated and control rats were not given. Although Maltoni et al. (1986) concluded that the small number was not treatment related, the findings were brought forward [emphasis added] because of the extreme rarity of this tumor in control Sprague-Dawley rats, untreated or treated with vehicle materials." Perhaps we missed them in EPA's tome, but these data were not shown.</p> <p>Another example of this tendency to discount negative findings is found on Page 4-263. "Although the mice in the two experiments [Maltoni et al., 1988, Table 4-55, page 4-2583 in males were of the same strain, the background level of liver cancer was significantly different between mice from the different sources (1/90 versus 19/90), though the early mortality may have led to some censoring." Perhaps we missed EPA's point, but it appears that the Table 4-55 only presented one of the two control groups. Inclusion of the control group with the higher background level would suggest that there was no chemical-related increase.</p> <p>FOOTNOTE 2: EPA (page 4-261) also states that "The NTP (1990) study of TCE exposure in male and female F344/N rats, and B6C3F1 mice (500 and 1,000 mg/kg for rats) is limited in the ability to demonstrate a dose-response for hepatocarcinogenicity. For rats, the NTP (1990) study reported no treatment-related non-neoplastic liver lesions in males and a decrease in basophilic cytological change reported from TCE- exposure in female rats. The results for detecting a carcinogenic response in rats were considered to be equivocal because both groups receiving TCE showed significantly reduced survival compared to vehicle controls and because of a high rate (e.g., 20% of the animals in the high-dose group) of death by gavage error [emphasis added].</p> <p>Note well, however, that NTP (1990) is the same study in which the sole statistically significant finding of kidney cancer in rats was made by EPA (page 4-179, Table 4-41). Thus, EPA appears to accept the</p>	Vinyl Chloride (2000)	11(16)	2	8(10)	6(8)	Y (angio-sarcoma)	1,3-Butadiene (2001)	7(9)	ND	1	1	N
Vinyl Chloride (2000)	11(16)	2	8(10)	6(8)	Y (angio-sarcoma)												
1,3-Butadiene (2001)	7(9)	ND	1	1	N												

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>"In summary, overall there is limited available data in animals on the role of TCE in lymphomas and leukemias. There are few studies that analyze for lymphomas and/or leukemias. Lymphomas were described in four studies (NTP, 1990; NCI, 1976; Henschler et al., 1980, 1984) but study limitations (high background rate) in most studies make it difficult to determine if these are TCE-induced. Three studies found positive trends in leukemia in specific strains and/or gender (Maltoni et al., 1986, 1988; NTP, 1988). Due to study limitations, these trends cannot be determined to be TCE-induced."</p> <p>In reading the text between these two apparently disparate quotes, the data for these cancers is overwhelmingly negative; some data might be statistically significant negative (Henschler et al., 1984). The use of EPA (2005) would suggest that these experimental animals findings are negative.</p> <p>As currently written, the best argument that EPA can make with these experimental animal data is that the data provide suggestive evidence of carcinogenicity. A holistic viewpoint, one that EPA espouses, limits the interpretation and reliability of the animal data, and/or decreases the weight of evidence for carcinogenicity in rodents. Based on these considerations, the animal data for these four tumors do not meet the criterion of "extensive evidence of carcinogenicity in animals." Multiple marginal findings do not constitute "extensive evidence." We encourage EPA to either revise its text, with appropriate supporting data, to support a judgment of "likely to cause cancer in humans," or reconsider its conclusion based on these experimental animal data.</p> <p>The epidemiologic literature on TCE can be characterized by many of the terms used to describe characteristics of the "suggestive" descriptor. These include the findings of a small increase in risk of tumors (kidney, NHL, liver) combined with the possibility that these cancers can be attributable to other known and unknown factors, and where there are studies that report positive responses, the limitations in study power, design, or conduct limit the ability to draw "confident" conclusions. As shown in the data extracted from IRIS and presented in Table 11, the epidemiological data supporting a conclusion of "known" human carcinogen, or "A carcinogen" for other chemicals under the 1986 guidelines, is typically much stronger than the data for TCE.</p> <p>The available experimental animal evidence can be interpreted in various ways depending on how EPA chooses to revise its text. As currently written, this evidence is primarily negative or conflicting for kidney and immune tumors, and positive for mouse liver tumors and lung tumors, and thus the overall weight of evidence considering both epidemiology and experimental animal evidence would be best seen as "suggestive." However, a more complete presentation and analysis of the animal data may push the overall classification into the "likely" category based on a "suggestive" characterization of the epidemiologic literature and consideration of the weight of evidence from the animal tumor data, particularly the data on liver tumors in mice.</p> <p>However, in no circumstance is it scientifically reasonable to judge that TCE is "carcinogenic to humans" based on the available human and experimental animal data.</p>	<p>findings of NTP (1990) when the result is positive (kidney), but not when tile result is negative (liver).</p> <p>AUTHORS: Michael Dourson, Ph.D., DABT and Lynne Haber, Ph.D., DABT from Toxicology Excellence for Risk Assessment and Michael Kelsh, Ph.D., MPH and Dominik Alexander, Ph.D., MPH from Exponent, Health Sciences</p> <p>U.S. Environmental Protection Agency. 2005. Guidelines for carcinogen risk assessment Washington D.C. EPA/630/P-03/001R.</p>
4.11.2	204	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>In summary, 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 male that case. Description of TCE as a known human carcinogen is precluded by:</p> <ul style="list-style-type: none"> * Methodological and analytical inconsistencies in the epidemiologic literature, such as weak summary associations, differences in results by sub-groups, lack of evidence or dose-response relationships or insufficient data to fully evaluate exposure trends, and the potential influence of confounding by lifestyle or occupational factors. <p>Description of TCE as a likely carcinogen based on the draft EPA text is:</p> <ul style="list-style-type: none"> * Downweighted by the conflicting or negative experimental animal data for kidney and immune tumors, and weakly supported by the positive findings for mouse liver and lung tumors. * EPA could improve its determination of kidney tumors findings by conducting a complete historical control analysis for each study that it deems scientifically credible, but it will need to re-evaluate NTP 1990 to determine whether this study meets these criteria. EPA should not discount the negative findings for NTP (1990) for rat 	<p>FOOTNOTE 2: EPA (page 4-261) also states that "The NTP (1990) study of TCE exposure in male and female F344/N rats, and B6C3F1 mice (500 and 1,000 mg/kg for rats) is limited in the ability to demonstrate a dose- response for hepatocarcinogenicity. For rats, the NTP (1990) study reported no treatment-related non-neoplastic liver lesions in males and a decrease in basophilic cytological change reported from TCE- exposure in female rats. The results for detecting a carcinogenic response in rats were considered to be equivocal because both groups receiving TCE showed significantly reduced survival compared to vehicle controls and because of a high rate (e.g., 20% of the animals in the high-dose group) of death by gavage error [emphasis added].</p> <p>Note well, however, that NTP (1990) is the same study in which the sole statistically significant finding of kidney cancer in rats was made by EPA (page 4-179, Table 4-41). Thus, EPA appears to accept the findings of NTP (1990) when the result is positive (kidney), but not when tile result is negative (liver).</p> <p>Authors: Michael Dourson, Ph.D., DABT and Lynne Haber, Ph.D., DABT from Toxicology Excellence for Risk Assessment and Michael Kelsh, Ph.D., MPH and Dominik Alexander, Ph.D., MPH from Exponent, Health Sciences</p> <p>-</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				liver tumors, but then accept the same study for findings of rat kidney tumors. (FOOTNOTE 2)	
4.11.2	240	EPA-HQ-ORD-2009-0791-0019.1	Patton Boggs LLP	NAS/EPA Interpretations Completely Inconsistent * EPA: "Carcinogenic to humans," based on "convincing evidence of a causal association between TCE exposure in humans and kidney cancer" * NAS: Several TCE cohort studies reported increased risk of kidney cancer... Results often based on a relatively small number of exposed persons and varied quality of exposure data... The Committee concludes that "there is limited/suggestive evidence of an association between chronic exposure to TCE or PCE and kidney cancer."	- -
4.11.2	245	EPA-HQ-ORD-2009-0791-0012.1	McKenna, Long & Aldrige, LLP	New Policy: EPA is... *Lowering the bar on what may be considered "known human." -The evidence for TCE is not in the same league as plutonium and asbestos. -TCE would be the new floor to the "known human carcinogen" group in terms of supporting evidence.	- -
4.11.2	249	EPA-HQ-ORD-2009-0791-0012.1	McKenna, Long & Aldrige, LLP	Main messages: Cancer findings *The data do not support "known" carcinogen under the 2005 EPA Cancer Guidelines. - New policy interpretation on cancer classification pushes the data too far and sets an unevaluated precedent for lower weight of evidence. - Charbotel et al 2006 found that consideration of cutting oil exposures removed the association between TCE and kidney cancer.	- -
4.11.2	251	EPA-HQ-ORD-2009-0791-0012.1	McKenna, Long & Aldrige, LLP	Main messages: Cancer findings *Give risk managers a more complete description of the weight of evidence, not less, and not a bump up to a higher category.	- -
4.11.2	272	EPA-HQ-ORD-2009-0791-0014.1	Exponent Health Services	EPA's Toxicological Review of Trichloroethylene (TCE) External Review Draft: Comments Regarding Meta-Analysis of Epidemiologic Studies and Use of the Charbotel et al. 2006 Study in Quantitative Risk Assessment EPA concluded that the epidemiologic data were robust and consistent, and, in some cases, strongly supportive of providing evidence of trichloroethylene (TCE) carcinogenicity. Other reviews and meta-analyses have not reached these same conclusions, noting heterogeneity of findings (i.e. lack of consistent findings), lack of consistent exposure response evidence, and other methodological problems of the epidemiologic studies. With respect to the case-control studies of Charbotel et al. 2006, EPA considered this sufficient data for quantitative doseresponse modeling. Although Charbotel et al. 2006 have provided individual level TCE exposure estimates, limitations in the exposure assessment and study design features of this study do not permit use of Charbotel et al. 2006 data in more quantitative dose response or cancer slope factor modeling. Selection bias, where renal cell cancers among screw-cutting industry workers are more likely to be enrolled in the case control study than other renal cell cancers, is a concern, the fact that forty percent of exposure assignments of renal cancer case are based on qualitative TCE exposure assessment procedures, and the reliance on self-reported work history are important limitations that do not permit use of Charbotel et al 2006 data in quantitative risk analysis. Based on full consideration of guidelines used to determine causality from epidemiologic data, a more appropriate classification of TCE carcinogenicity would be either "suggestive evidence of carcinogenicity" or "likely carcinogenic."	- Charbotel, B; Fevotte, J; Hours, M; et al. (2006) Case-control study on renal cell cancer and occupational exposure to trichloroethylene. Part II: Epidemiological aspects. Ann Occup Hyg 50(8):777-787.
4.11.2	276	EPA-HQ-ORD-2009-0791-0014.1	Exponent Health Services	We were asked to provide comments to the recent EPA External Review Draft for the Toxicological Review of TCE (dated October 2009) by companies and associations involved as users of TCE or in TCE remediation. Our work in the evaluation of the epidemiologic literature of occupational TCE exposure and cancer has provided us with in-depth knowledge and familiarity with much of the epidemiologic research on this chemical. EPA staff	- Charbotel, B; Fevotte, J; Hours, M; et al. (2006) Case-control study on renal cell cancer and occupational exposure to trichloroethylene. Part II: Epidemiological aspects. Ann Occup Hyg 50(8):777-787.

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>have prepared a comprehensive review of the epidemiologic studies of TCE exposure and cancer and non-cancer outcomes. In addition, they performed a quantitative risk assessment of cancer relying on one epidemiologic study, Charbotel et al. 2006, which is a case-control study that was conducted in a region in France where workers in the screw cutting industry likely experienced relatively high TCE exposures. These comments focus on various issues relating to epidemiologic studies of TCE exposure and cancer and the use of the Charbotel study data in a quantitative cancer risk assessment.</p> <p>EPA’s meta-analysis methods and summaries, for the most part, are consistent with recent published summaries of this literature – however, EPA’s interpretation of the meta-analysis findings is not consistent with the general approaches used in evaluating causality from epidemiologic research study evaluation. Epidemiologic causal evaluation considers not only the presence of a statistical association, but also the strength of that association, whether exposure response trends are present, the consistency of study findings, biologic plausibility, coherence, and other factors (Hill 1965; Weed 2005). Although EPA considers these factors, their conclusions are not supported once these factors are applied to the epidemiologic literature. The epidemiologic literature on TCE exposure and cancer cannot be categorized as “strong” or “robust” or of sufficient quality to provide definitive evidence of a causal association between TCE exposure and cancer. The observed summary relative risk estimates from the meta-analyses of kidney cancer, liver cancer, and non-Hodgkin’s lymphoma (NHL) are not sufficiently strong to be able to rule out other potential explanations such as bias due to confounding, exposure misclassification, or other factors (e.g. selection bias in case control studies). The consistency of the findings is not as robust as characterized in the EPA review. For example, in the kidney cancer analyses, the evaluation of cohorts defined from biomonitoring data, a source of exposure information considered more accurate than other exposure assessment characterizations, found no association with kidney cancer. Although these studies were small, these results merit consideration. In addition, several large cohort studies of aerospace/aircraft maintenance workers (e.g. Radican et al. 2008; Boice et al. 1999) reported no association between TCE exposure and kidney cancer. The EPA review recognizes the significant limitations of several German studies of TCE exposure and kidney cancer (e.g., Henchler et al., Vamvakas et al.) and did not include them in their meta-analysis summaries; a decision consistent with a recently published meta-analysis of TCE and kidney cancer (Kelsh et al., 2010). In summary, it is important to emphasize that the magnitude of the summary estimate in the EPA meta-analysis of kidney cancer was modest (relative risk =1.25). Furthermore given the range and imprecision of the individual study findings, with many studies reporting no increased risks, it is more accurate to report the study results as “mixed” rather than consistent or robust.</p> <p>In the latest EPA Toxicological Review of TCE, it is apparent that many of the issues and concerns raised in the methodological review of the inter-agency draft with respect to the metaanalysis of epidemiologic studies of TCE exposure and cancer of have been addressed. However, some important matters remain, particularly regarding the interpretation of the currently available epidemiologic evidence. In the widely read textbook Modern Epidemiology (Rothman, Greenland and Lash 2008), Greenland and O’Rourke describe the two main goals of meta-analysis: to estimate differences among study-specific effects (analytic goal) and/or to estimate an average effect across studies (synthetic goal). They further remind readers that “a sound meta-analysis needs to assess each study’s limitations as well as gaps in the entire literature being assessed.” Thus, while a meta-analysis may serve as a valuable tool for analyzing data across a large body of scientific studies to produce a more precise estimate of relative risk, interpretation of summary findings should be made in consideration of several important methodological factors (e.g. exposure misclassification, confounding and selection bias) and guidelines for evaluation of causality based on epidemiologic data (Hill 1965; Weed 2005). Indeed, meta-analysis and causal inference are separate endeavours with different methods.</p> <p>Most epidemiologic studies of TCE exposure and cancer observed associations that were not statistically significant and most studies lacked quantitative exposure assessments. Across epidemiologic studies, different exposure metrics were used, exposure-response patterns were inconsistently observed, and uncontrolled (or incompletely controlled) confounding and other sources of systematic error likely influenced effect estimates. EPA conducted various sensitivity analyses (excluding individual studies to assess their impact on summary relative risk estimates); however, important evaluations such as summarization by sub-group characteristics, study design differences, or findings by exposure measurement method were not presented or fully considered. It is unfortunate that EPA did not conduct exposure-response analyses by specific exposure metrics, such as cumulative dose or years of exposure. Because “dose-response” is an important consideration in the evaluation of</p>	<p>Boice JD, Jr. et al. Mortality among aircraft manufacturing workers. <i>Occup. Environ. Med.</i> 1999;56:581-97.</p> <p>Hill AB. The Environment and Disease: Association or Causation? <i>Proc R Soc Med</i> 1965; 58: 295-300.</p> <p>Kelsh MA, Alexander DD, Mink PJ, Mandel JH. Occupational trichloroethylene exposure and kidney cancer: a meta-analysis. <i>Epidemiology.</i> 2010 Jan;21(1):95–102.</p> <p>Lash TL. Bias analysis applied to Agricultural Health Study publications to estimate non-random sources of uncertainty. <i>J Occup Med Toxicol.</i> 2007 Nov 26;2:15.</p> <p>Radican L, Blair A, Stewart P, Wartenberg D. Mortality of aircraft maintenance workers exposed to trichloroethylene and other hydrocarbons and chemicals: An extended follow-up. <i>J Occup Environ Med</i> 2008; 50(11): 1306–19</p> <p>Weed DL. Weight of Evidence: A Review of Concept and Methods. <i>Risk Analysis</i>, Vol. 25, No. 6, 2005</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				epidemiologic studies for causality, we evaluated exposure-response data to the extent possible in our published meta-analyses and observed no clear pattern of increasing cancer risk with increasing exposure level or duration (Kelsh et al 2010; Mandel et al 2006; Alexander et al. 2007; Alexander et al., 2006). Such an analysis by EPA would provide helpful information in the consideration of potential relationships between TCE and cancer. In summary, although EPA conducted a comprehensive meta-analysis and examined many issues in the epidemiologic data, EPA's conclusions regarding the carcinogenicity of TCE are not supported by the studies they cite.	
4.11.2	286	EPA-HQ-ORD-2009-0791-0014.1	Exponent Health Services	<p>Use of Epidemiologic Data for Quantitative Cancer Risk Assessment</p> <p>Epidemiologic data are frequently limited, especially in the area of detailed and accurate exposure information for quantitative risk assessment and slope factor estimation. Consideration of the representativeness of the population studied, generalizability of the study results, and the overall strengths and limitations of the epidemiologic study should also be considered in selecting data for quantitative risk assessment. Although Charbotel et al. made significant improvements in their exposure assessment compared to other epidemiologic studies of TCE and cancer, it is still at best a semi-quantitative method for screw cutting workers and a qualitative method for other TCE exposed workers, who comprised 40% of the exposed cases. In addition, potential limitations in the study design such as representativeness of the study population, reliance on self-report of work history information, potential selection and confounding bias concerns, and the fact that the better exposure assessment procedures do not apply to approximately 40% of the exposed cases are important reasons why it is inappropriate to rely only on Charbotel et al. data for slope factor estimation purposes.</p>	- -
4.11.2	289	EPA-HQ-ORD-2009-0791-0014.1	Exponent Health Services	<p>Specific Comments on Use of Charbotel et al. 2006 Study for Dose Response Modeling in EPA's External Review Draft of Trichloroethylene</p> <p>EPA relied on epidemiologic and exposure data reported in the Charbotel et al. study of renal cell cancers to conduct dose response modeling and to estimate the cancer slope factor for TCE. Specifically, this case-control study evaluated renal cell cancer among residents in the Arve Valley region of France. This region had been selected for study because of the prominent screw cutting industry where TCE was used as a degreaser and solvent and for which relatively high TCE exposure occurred among workers (Fevotte et al., 2006). It was estimated that there were approximately 650 shops employing about 7,000 workers in the 1970s (500 of the shops employed less than five workers), and 750 shops employing about 12,000 workers in 1982 (600 employed less than 10 workers) [Fevotte et al., 2006].</p> <p>Although the Charbotel et al. study was able to take advantage of TCE exposure data collected over the years by occupational physicians in the region, numerous uncertainties exist that argue against relying only upon these data and the reported epidemiologic findings from this study for use in quantitative risk assessment. In addition, exposure data from other studies (e.g. Scandinavian studies, aerospace workers studies) should be further explored to assess whether more refined semi-quantitative job exposure matrices can be developed and used rather than relying exclusively on the Charbotel et al. study findings. Many of these limitations and uncertainties are noted in the EPA assessment; however, some were not discussed in the EPA report. These important methodological concerns include the following:</p> <ul style="list-style-type: none"> · Potential selection bias. No cancer registry was available for this region to identify all relevant renal cell cancer cases from the target population. Case ascertainment relied on records of local urologists and regional medical centers; therefore, selection bias is possible as a result of this process. Given the concerns of the medical community in this region regarding renal cell cancer (RCC) among screw cutting industry workers, it is likely that any cases of renal cell cancer among these workers would likely be diagnosed earlier. It is also much more unlikely that a RCC case among these workers would be missed compared to the chance of missing an RCC case among other workers not exposed to TCE. This preference in identifying cases among screw cutting industry workers would bias findings in an upward direction. · General uncertainties in retrospective exposure assessment. Industrial hygiene data have to be linked to self-reported (or proxy reported) work histories, which may be 	- - Anttila, A; Pukkala, E; Sallmén, M; et al. (1995) Cancer incidence among Finnish workers exposed to halogenated hydrocarbons. J Occup Environ Med 37:797-806. Axelson, O; Selden, A; Andersson, K; et al. (1994) Updated and expanded 1 Swedish cohort study on trichloroethylene and cancer risk. J Occup Med 36:556-562. Boice JD, Jr. et al. Mortality among aircraft manufacturing workers. Occup.Environ.Med. 1999;56:581-97. Charbotel, B; Fevotte, J; Hours, M; et al. (2006) Case-control study on renal cell cancer and occupational exposure to trichloroethylene. Part II: Epidemiological aspects. Ann Occup Hyg 50(8):777-787. Fevotte, J; Charbotel, B; Muller-Beaute, P; et al. (2006) Case-control study on renal cell cancer and occupational exposure to trichloroethylene. Part I: Exposure assessment. Ann Occup Hyg 50:765-775. Hansen, J; Raaschou-Nielsen, O; Christensen, JM; et al. (2001) Cancer incidence among Danish workers exposed to trichloroethylene. J Occup Environ Med 43:133-139. Radican L, Blair A, Stewart P, Wartenberg D. Mortality of aircraft maintenance workers exposed to trichloroethylene and other hydrocarbons and chemicals: An extended follow-up. J Occup Environ Med 2008; 50(11): 1306-19

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>inaccurate resulting in exposure misclassification. It is not possible to predict with certainty whether such bias is more likely to be differential or non-differential. Given that there were numerous screw cutting shops in the region employing a small number of employees at each shop, substantial exposure variation can be expected that may not have been captured in the exposure assessment process. The EPA report recognizes this limitation, but did not sufficiently consider its potential impact, which should be evaluated in further sensitivity analyses that consider potential recall bias and exposure variability across the many different screw-cutting industry sites.</p> <ul style="list-style-type: none"> · The quality of TCE exposure information, and the type of questionnaire instrument used to collect TCE exposure and work history information varied between the screw-cutting workers and other workers. The Charbotel et al. study relied upon different questionnaires and exposure assessment methods to collect data from screwcutting industry workers and other workers who may have been exposed to TCE. <p>Roughly 75% (64 of 86) of the cases had TCE exposure from non-screw cutting exposures [Table 3 in Charbotel et al. 2006]. Non-screw cutting industry workers had a much less specific work history questionnaire and TCE exposure matrix than the screw cutting industry workers. Thus the TCE exposure information in the Charbotel et al. study that is supported by industrial hygiene and biomonitoring data is accurate for about 60% of the exposed cases – and still relies on linkage to self-reported work history information. The other 40%, a significant proportion of the number of cases, was due to exposures from other work, for which the exposure assessment process was much less quantitative. This information bias may have impacted observed associations in the study.</p> <ul style="list-style-type: none"> · Potential confounding due to other workplace exposures. Screw cutting industry workers used a variety of oils and other solvents. Charbotel et al. reported lower risks for TCE exposure and renal cell cancer once data were adjusted for cutting oils. In fact, they noted, “Indeed, many patient 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.” This uncertainty questions the reliability of using data from Charbotel et al. in TCE risk assessment. · Representativeness of the Arve Valley population. The health and exposure experience of the Arve Valley residents, including screw cutting industry employees, may be distinct from other populations. It may not be appropriate to rely on this one unique population to generalize about health risks in the more heterogeneous worker populations in the United States. EPA acknowledged this potential limitation. · Relatively small sample size. In the Charbotel et al. case-control study, there were 16 exposed cases (out of a total of 84 cases who were assigned semi-quantitative TCE exposure scores) in the high exposure level category that essentially drives the findings for “TCE exposure response patterns.” Generalizing interpretations from a relatively small sample size from a specific workforce may result in biased risk assessments across broader populations. In fact the epidemiology of TCE exposure and cancer is in general limited by small numbers of exposed cases from which relative risks are calculated. The EPA report acknowledges this limitation. · Control selection procedures may have produced bias. It is well known that hospitalbased controls, like those selected in the Charbotel et al. study, may not provide a good reflection of the exposure or confounder prevalence in the source population. In this study, controls were selected from urologist patients or specialized treatment centers and likely had a higher prevalence of kidney cancer confounders such as smoking, obesity, use of diuretics, and hypertension than a population-based control sample would have. Thus the confounder presence among cases may be diluted by the fact that the prevalence of confounders if over represented among controls. The impact of this is not directly predictable, but it is plausible that this may act to overestimate renal cell cancer risks due to TCE. <p>EPA has selected the Charbotel et al. study on the basis that it provided individual human exposure data. However, it should be noted that three Scandinavian studies used worker specific biomonitoring</p>	

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>data (more quantitative and specific than the semi-quantitative data used in Charbotel) to define the exposure cohorts and estimate health risks EPA should consider trying to incorporate these data into the quantitative evaluation. These three Scandinavian studies (Anttila et al. 1995; Axelson et al. 1994; Hansen et al. 2001), individually or in the aggregate, did not find elevated relative risks of TCE exposure and kidney cancer. It is appropriate to consider the Charbotel study as one of the stronger epidemiologic studies of TCE exposed workers because of more extensive efforts to assess TCE exposure. However, despite these efforts, as apparent from the list of limitations and uncertainties above, it is clear that the Charbotel data alone should not be relied upon as the basis for cancer slope factors and quantitative estimates of potential risk. The potential biases noted (e.g. selection bias, confounder bias) call for more careful sensitivity analyses (e.g. using methods proposed by Lash et al 2007) to assess the robustness of the reported epidemiologic findings in the Charbotel study.</p> <p>Before such sensitivity analyses are conducted, reliance upon the Charbotel study as a source of quantitative TCE exposure information for risk assessment purposes is not appropriate given the limitations of the study itself, the lack of consistent findings compared with biomonitoring studies, and the higher relative risks observed in this study compared to meta-analysis results as well as results of other high TCE exposure cohorts (e.g. aerospace and aircraft maintenance workers (Radican et al., 2008; Boice et al., 1999).</p>	
4.11.2	295	EPA-HQ-ORD-2009-0791-0014.1	Exponent Health Services	<p>In EPA's External Draft Report, it was stated that the meta-analysis of TCE and kidney cancer produced a small and statistically significant increase in risk, with a stronger effect observed in the highest exposure analysis. The association between TCE and kidney cancer was judged as robust, which does not reflect the inconsistencies in these data. For example, the summary association for all studies is 1.25, and for cohort studies is 1.16, and for case-control studies is 1.41. Thus, the summary findings appear sensitive to the study design being used. The findings are also sensitive to the type of sub-group or exposure classification being analyzed. As mentioned above, in the case of kidney cancer, biomonitoring studies showed different results (no association, with summary relative risk very close to 1.0 (Kelsh et al., 2010) than case control studies based on self-reported information. In summary, there are too many inconsistencies between the data and exposure differences across studies to conclude that the findings are robust.</p>	<p>- Kelsh MA, Alexander DD, Mink PJ, Mandel JH. Occupational trichloroethylene exposure and kidney cancer: a meta-analysis. <i>Epidemiology</i>. 2010 Jan;21(1):95-102.</p>
4.11.2	297	EPA-HQ-ORD-2009-0791-0014.1	Exponent Health Services	<p>Non-Hodgkin Lymphoma (NHL)</p> <ul style="list-style-type: none"> · Mortality data from Zhao et al. 2005 are used in the primary meta-analyses. EPA selected mortality data rather than incidence data because there were more deaths than there were incident cases. However, incidence data is the optimum choice of data to evaluate cause and effect and, thus, should have been selected for the primary analyses. In the EPA analysis for kidney cancer, the researchers used mortality data "to avoid the appearance of cherry-picking." This does not appear to be a systematic method for data inclusion. Furthermore, the IRIS report notes the limitations of mortality data including misclassification (p. 4-159). · As with kidney cancer, it was stated that the robustness of their findings "lends substantial support to a conclusion that TCE exposure increases the risk of lymphoma." Indeed, the EPA's "high-exposure" analysis results were stronger in magnitude than the overall results; however, summary associations were sensitive to study design. Furthermore, dose-response was not examined so one cannot conclude that risk of NHL increases with increasing levels of exposure. In a recent published meta-analysis, where exposure-response patterns were examined (recognizing the limitations of these data), there was no evidence for increasing duration or intensity of exposure (Mandel et al., 2006). In addition, the heterogeneity of NHL and changing classification schemes over the past few decades make interpretation of available epidemiologic data challenging. Given the lack of exposure response patterns and heterogeneity of findings by study design, it is inappropriate to conclude that there is "substantial" support that TCE increases the risk of lymphoma (Mandel et al., 2006). 	<p>- Mandel JH, Kelsh MA, Mink P, Alexander DD. Occupational trichloroethylene exposure and non-Hodgkin's lymphoma: a meta-analysis and review. <i>Occup. Environ. Med.</i> 2006;63:597-607.</p>
4.11.2	300	EPA-HQ-ORD-2009-	Exponent Health	Liver Cancer	<p>-</p> <p>-</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
		0791-0014.1	Services	· The summary association for the high exposure analysis was slightly lower (and not statistically significant) compared with the overall analysis, which is not characteristic of a causal relationship. This implies that the epidemiologic data do not provide evidence of a causal association between TCE exposure and liver cancer.	
5.1	50	EPA-HQ-ORD-2009-0791-0007.1	Natural Resources Defense Council (NRDC) and Supoprters	<p>Infants and others may exceed acceptable exposure limits</p> <p>Here we present the dose response estimates that are provided in this draft assessment, with some attempt to translate them to plain language. A reference dose (RfD, oral exposure) or a reference concentration (RfC, inhalation exposure) are estimates (with uncertainty spanning perhaps an order of magnitude) of a continuous exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious non-cancer effects during a lifetime. For this TCE assessment the RfC/RfD are based on observed effects on the kidney, the adult immune system, the developing fetal heart, and the developing immune system.</p> <ul style="list-style-type: none"> •Non-cancer inhalation RfC is 0.001 ppm (5 µg/m3) •Non-cancer oral RfD is 0.0004 mg/kg/day (0.4 µg/kg/day) <p>To put these numbers into some context, the current drinking water limit (MCL, or maximum contaminant level) for TCE is 5 ppb (µg/L). At this level, a 70 kg adult drinking 2 L of water daily (EPA standard assumptions) would ingest 0.14 µg/kg/day, or 0.00014 mg/kg/day, from water alone. This is still below the draft oral RfD of 0.0004 mg/kg/d. However, an infant with a body weight of 4 kg drinking 0.78 L of fluids daily (EPA standard assumptions) would ingest 0.975 µg/kg/day, or 0.000975 mg/kg/day, above the draft oral RfD.....</p> <p>.....In addition to drinking water, exposure to TCE can also take place at significant levels through breathing air in and around homes that are contaminated with TCE vapors, and from showering in water contaminated with TCE. In groundwater plumes, TCE has been shown to vaporize and migrate to the surface, where it can collect in residential basements at dangerous levels. If an infant or child is living in a house where drinking water is contaminated and vapor intrusion is present, the addition of exposures through both routes would almost certainly exceed the RfD/RfC.</p>	<p>2 A slope factor is an estimate of a carcinogen's potency, characterized as a plausible upper bound on the increased human cancer risk from lifetime exposure to an average dose of 1 mg/kg-d. That is, the slope factor estimates a bound on the risk per mg/kg-d, accordingly, the slope factor is expressed in units of inverse lifetime-average dose, or (mg/kg-d)⁻¹. Multiplying a slope factor by a lifetime-average dose (in mg/kg-d) yields a plausible upper bound on the increased probability of developing cancer from exposure to the carcinogen. A unit risk is analogous to a slope factor, but expressed in units of inverse lifetime-average ambient air concentration (ug/m3)-1 or inverse lifetime average drinking water concentration (ug/L)-1 instead of inverse lifetime-average dose (mg/kg-d)-1. Unit risks are convenient when exposure is expressed in terms of environmental concentrations (g/m3 or g/L). Unit risk estimates are based on particular exposure assumptions, specifically, a 70-kg adult drinking 2L/d and breathing 20m3/d. When applied to other propulations with different exposure factors-for example, children-unit risk estimates should be adjusted accordingly.</p> <p>-</p>
5.1	65	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>Taken together, our comments show that RfC and RfD values selected by EPA are unreasonably low and that critical information regarding cancer induction by TCE has been misinterpreted.</p>	<p>AUTHOR: Paul H. Dugard, Halogenated Solvents Industry Alliance, Inc.</p> <p>-</p>
5.1	89	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>3. Immunotoxicity</p> <p>Two immunotoxicity studies have been used to support very low RfC and RfD values. The effect chosen from the study of Keil et al (2009) is a reduced thymus weight in mice seen at relatively low dose levels. This stands in contrast to a number of studies (immunotoxicity and other) in which no effect on thymus weight was evident in rats and mice following relatively high dose levels of TCE. The other study used to develop the reference values is the developmental immunotoxicity study reported by Peden-Adams et al (2006) in which effects were reported in mouse offspring following exposure of dams and, post-weaning, the pups to 1.4 ppm TCE in drinking water. The study appears to have been well conducted and stands as the only one of its kind. The reason for concern is that the effect is apparently seen at such a low dose which stands in contrast with the same effects seen only at relatively high dose levels in adult rodents. It is important for the substantially higher sensitivity of fetus or pup to be confirmed in separate investigation.</p> <p>After comments on other endpoints driving low reference values have been taken into account, it is possible that only these immunotoxicity studies would be left supporting very low RfD and RfC values. At this time, the findings do not appear to be sufficiently robust to carry that responsibility.</p>	<p>AUTHOR: Paul H. Dugard, Halogenated Solvents Industry Alliance, Inc.</p> <p>-</p>
5.1	130	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>The Draft TCE Reassessment (as I will call the document in question), is a complex and far-reaching one, with many novel analytical aspects and treating many relevant scientific issues. Although many of these aspects bear comment, I have chosen to focus my comments on one particular area: the methodology used in quantitative risk assessment for non-cancer effects of TCE.</p> <p>Overall, the Draft TCE Reassessment reflects considerable effort and thoughtfulness on the part of US EPA in that it considered and incorporated a wide range of data in support of the proposed RfC and RfD for TCE. I respect the level of effort that was required to interpret and process this large body of data and the need to, in the end, propose one RfC and one RfD. However, although in the end a choice needs to be made, it is important,</p>	<p>AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp.</p> <p>-</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>particularly in cases where a very large body of complicated data exists, that the process of making those choices involves a careful weight-of-evidence approach, so that the consequences of the various alternatives to those choices can be carefully worked through and considered as part of the overall analysis. Moreover, it is important that the process of evaluating the various alternatives be transparent to the reader, and to the risk manager who ultimately will use the resulting criteria.</p> <p>The four overarching comments I have on the assessment are: (1) it is important to carefully consider and clearly communicate how human variability was characterized in the assessment; (2) it is important to have a high level of confidence in the pharmacokinetic (PK) model assumption that humans generate higher levels of dichlorovinyl cysteine (DCVC) than rats; (3) a sufficient weight-of-evidence approach is needed for ascribing and communicating confidence across the large array of candidate RfDs/RfCs; and (4) clear communication of the entire process is needed.</p>	
5.1	131	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>The following bullets summarize the specific comments, which are discussed in more detail below.</p> <ul style="list-style-type: none"> * The allowance for inter-human PK variability double counts and misconstrues the nature of the dose-response curve. * The reassessment document should specifically call out and individually characterize elements of its analysis that make particularly big differences to the RfC and RfD determination. * The assessment should discuss proportionality between applied and internal dose, the circumstances under which that proportionality is seen as changing, and the impact of the changes on the quantitative risk analysis. * It is not clear that DCVC constitutes an appropriate basis for an internal dose metric for kidney non-cancer toxicity. * The document's conclusion that humans have high flux through the conjugative pathway is at odds with previous assessments, and is not well supported by evidence; yet, this assumption markedly lowers RfC/D values compared to those using traditional applied-dose approaches. * Reliable estimates of the extent of variability among humans in DCVC activation have not been established, yet this factor is very influential in lowering the RfC/D. * A weight-of-evidence approach should have been applied, and made transparent, to ascribe a level of confidence for each of the potential RfCs/RfDs derived in the assessment. * There is considerable uncertainty in the proposed RfC of 0.001 ppm for TCE, particularly related to potential uncertainty in the Physiologically Based Pharmacokinetic (PBPK) modeling of the DCVC dose metric in humans, and the relationship of that dose metric with increased kidney weight. 	<p>AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp.</p> <p>-</p>
5.1	137	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>The allowance for inter-human PK variability double counts and misconstrues the nature of the dose-response curve.</p> <p>There are two questions about the allowance for human variability in metabolic activation. The first, addressed elsewhere in these comments, is whether the extent of variability has been reliably estimated. The second, addressed here, is how allowance for variability has been entered in to the RfD/C calculations. It would appear that allowance for human variability has been double-counted because inter-individual variability is built in to the tolerance distribution-based dose-response curve.</p> <p>The method employed in the document is to set a point of departure (PoD) on the animal-based dose-response curve, using central estimates of "standard rat" internal doses as the dose measure. That is, inter-individual PK variation among rats, even though it exists, was not estimated and not considered in the dose-response curve estimation. For non-cancer endpoints, the dose-response curve is interpreted as a tolerance distribution – as the cumulative distribution of individual sensitivity variation. The reason that some animals respond at a given (externally applied) dose and others do not is that some have their individual tolerances exceeded while others do</p>	<p>AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp.</p> <p>-</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>not, and higher doses exceed the individual tolerances of a greater fraction of the variable population, thereby yielding higher disease incidences.</p> <p>Some of this variation is in PK, and so to some extent, the rats that respond do so because they are more vulnerable owing to their individual PK variation that makes them have a higher proportionality of internal to external dose. The contribution of this effect is captured in the fitted dose-response curve, which also reflects variation in sensitivity for other, non-PK reasons, but the contributions of PK variation are already incorporated, and are not readily split out without some attempt to characterize PK variation among individual rats.</p> <p>The rat dose-response curve is then used to determine a PoD by finding a dose that yields a low predicted response, say 1%. Because the dose scale is measured in average internal dose among the rats, the dose associated with a 1% response level is the average internal dose for rats such that 1% of them are expected to have their individual tolerances exceeded. For the sake of argument, if we hypothetically say that there is absolutely no inter-rat variation in PK, then all the rats in a hypothetical experiment at the 1% response dose will have the same internal dose, and which rats respond and which do not will be ruled entirely by variation in pharmacodynamic (PD) sensitivity to this fixed internal dose. But, if one instead hypothesizes that variation in sensitivity is entirely ruled by PK variation (with no contribution of PD variability) then the 1% of rats responding are that same 1% that are most sensitive owing to their PK variation – that is, they are the 99th percentile of the internal dose distribution.</p> <p>The reality is somewhere in between, with both PK and PD variability contributing to variation in ability to tolerate the dose. But without characterization of PK variation among individual rats, we have no way to split the components out (though there is the conventional split between PK and PD that we apply to Uncertainty Factors).</p> <p>Staying with the hypothetical case that sensitivity variation is all in PK, then the only reason to make further allowance for human PK variation is if variation in PK among humans is greater than variation among rats, and even then the correction should only be for the degree to which it is greater – that is, the ratio of the 99th percentile in humans versus the 99th percentile in rats rather than the ratio of the 99th to the 50th percentile in humans.</p> <p>The hypothetical case of pure PK dependence of sensitivity variation is made to clarify the argument, but in the real case of contributions from both PK and PD, the principle illustrated still applies. There is some mix of influence of PK- and PD-based sensitivity among the responding rats, and the effect of this is captured in the fitted dose-response curve, for which the dose variable is the average internal dose. That internal dose is likely higher on average among the 1% of rats responding, because of the contribution of PK to their sensitivity; but, since this is unmeasured, all the analysis can say is that when a group of rats is dosed at a given external level, the average internal dose among them has some level estimated by the rat PBPK model. In view of the (unknown) contribution of PK to sensitivity and the (unknown) degree to which PK varies among rats, there is some (unknown) degree to which some rats have higher-than-average internal doses and thereby have an increased response probability (which is dictated by PD sensitivity to internal dose levels).</p> <p>When the rat PoD is extrapolated to a human PoD based on average PK in the two species, it implicitly assumes that the mix of PK and PD, and the extent of inter-individual variation in PK, are the same in humans as in the rats. If one then makes a correction for the difference between the 50th percentile of PK in humans and the 99th percentile (as the draft reassessment does) it essentially implicitly assumes that all of the variation in sensitivity reflected in the dose-response curve is attributable to PK alone.</p> <p>If one assumes that the mix of PK and PD influence is similar across species, then the correct correction is the ratio of 99th percentiles across species, but since the 99th percentile in rats is not estimated, this cannot be calculated. If one cannot assume that the mix of PK and PD is the same, then it is doubly impossible to calculate a correction.</p> <p>The method that has been employed in the draft reassessment seems to implicitly assume that all of the dose-response in rats is attributable to PD (and this drives the PoD down as far as possible in internal-dose terms) and</p>	

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				that all of the dose-response in humans is attributable to PK (and this drives the sensitive human allowance down as far as possible). The net result is to yield an RfC that is overcorrected for human inter-individual variation to a degree that is not possible to know with the analyses available.	
5.1	138	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>The reassessment document should specifically call out and individually characterize elements of its analysis that make particularly big differences to the RfC and RfD determination.</p> <p>The analyses in the draft reassessment document are complex and in many cases novel. Findings and conclusions from various chapters come to bear as they are applied to the RfD/C determination. It is difficult for a reader – and more importantly, for a risk manager using the document as a reference – to trace the sources of and reasoning behind analytical findings that are subsequently used in calculations and to gauge the impact of specific judgments or conclusions from earlier chapters on the final RfD/C determinations. Moreover, the impacts of specific choices or judgments on the final calculation – and the differences that would arise if different choices were made – need to be isolated and documented. Only in this way can a risk manager understand where the changes from earlier assessments are coming from, what they are based on, how reliable is the basis for that change, and how different the analysis would be under other arguably appropriate alternatives.</p> <p>Transparency means more than just showing all the calculations in large appendices; there is a critical need for effective communication about the impact of choices and judgments that are made, about the basis for those judgments, and about the impacts of those judgments vis-à-vis possible alternatives on the final outcome.</p> <p>For example, it should be made clear that the chief impact on changing the RfD/C from what they would be under default procedures (and from how they were previously characterized) is the invocation of much greater flux through the conjugative metabolic pathway in humans than had previously been estimated. As discussed further elsewhere in these comments, this result is the chief reason that an internal-dose basis for an RfC based on kidney toxicity comes out much lower than if the RfC were based on other endpoints or on applied dose, though this conclusion is not obvious without deep reading of the document and detailed tracing of the calculations. There are reasons to question whether this finding of high human flux through the conjugative pathway is correct (as discussed elsewhere), but any discussion of that question and any documentation of the basis for that conclusion is far removed from its application in a later chapter. The discussion of what pathway, and what measure of that pathway's activity, is best used as an internal dose metric for kidney toxicity is in yet another place, and these conclusions can also be questioned. But again, that discussion (to the extent it exists anywhere) is far removed from its place of application.</p> <p>A truly transparent analysis would (1) make it clear why the use of the particular internal dose metric changes the outcome; (2) describe how much it changes the outcome; (3) explain why the estimate of the flux in humans is now much greater than it had been in previous analyses; (4) articulate the main pros and cons of the basis for this increased estimate, the judgment as to its reliability, and the basis for that judgment; and (5) characterize the impact of having made other reasonable choices. It should do this in a concise and consolidated way as a commentary on the RfC calculation, available for a risk manager to use in understanding the basis and reliability of the number, with specific references (not just chapter numbers) to places in the document where the details are discussed.</p>	AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp. -
5.1	141	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>The assessment should discuss proportionality between applied and internal dose, the circumstances under which that proportionality is seen as changing, and the impact of the changes on the quantitative risk analysis.</p> <p>If the internal dose measure at the level of a target organ or tissue is strictly proportional to the externally applied dose or to the exposure level, then analyses based on internal or external doses should be identical. It is only when this proportionality changes that doing an internal-dose basis to the calculations changes; and this should be examined, not just as a "bottom line," but in a way that allows ascribing impacts to different parts of the calculation. The components to be considered are as follows:</p> <p>* Change in proportionality of external to internal dose over the dose range of the bioassay experiments – these will affect the shape of the dose-response curve and its interpretation, since in the case of external dose, proportionality changes are incorporated into the estimated curvature;</p>	AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp. -

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>* Change in proportionality of external to internal dose in low-dose extrapolations – this includes extrapolation down to a PoD and also any extrapolations below the PoD, since it will differ in outcome and interpretation if these are done on an internal- or external-dose basis;</p> <p>* Change in proportionality of external to internal dose between routes of exposure – this influences the impact of using an internal-dose basis for route extrapolation, in particular the oral-to-inhalation extrapolation that is heavily used in the document, and it is needed to judge whether route-extrapolated endpoints are in accord with what was observed in bioassays by the route extrapolated to (for instance, whether the kidney toxicity in rats extrapolated from oral bioassays to inhalation are in accord with what was seen in rats in inhalation bioassays at internal doses comparable to those inferred in the extrapolation);</p> <p>* Change in proportionality of external to internal dose over time patterns of exposure – animal bioassays often have five days/wk dosing, and human exposures are often intermittent and varying. To the extent that proportionality changes with the rate of dose delivery, this may affect calculations or the applicability of extrapolations;</p> <p>* Change in proportionality of external to internal dose between experimental animals and humans – the difference between the modal animals and modal humans affects the cross-species extrapolation. As noted earlier, this is a large contributor to the low RfC calculated for TCE using internal dose, and the validity of the result hangs on the reliability of the estimate of relative human vs. rat metabolic activation, and on the choice of pathway to use as an internal dose measure; and</p> <p>* Change in proportionality of external to internal dose among people (or animals) in a variable human population – both animals and humans will have some variation in the proportionality of internal to external dose, though the document only tries to estimate the extent of this in humans. A key question, however (as discussed below) is whether and by how much humans exceed the test animals in inter-individual variation in PK.</p> <p>It is not that these questions are not discussed in the document, but many of the discussions are buried in details. Making these questions explicit, and evaluating their individual roles in altering the RfD/C calculations, is important to understanding how and why PK calculations and assumptions are affecting the outcome. The robustness of the calculations can then be judged according to the robustness of the basis for invoking changes in proportionality of external to internal dose.</p>	
5.1	145	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>It is not clear that DCVC constitutes an appropriate basis for an internal dose metric for kidney non-cancer toxicity.</p> <p>The kidney is seen as a sensitive target, and low RfC values drive the consideration of an overall RfC. The incorporation of internal doses makes the calculated RfC much lower than it would be if based on administered doses. It is therefore critically important that the internal-dose basis of kidney toxicity characterization be correct and reliable. The changes in non-cancer toxicity standards implied by the analyses in the Draft Reassessment hinge largely on assumptions about the PK of internal doses in kidney in rats and humans; and, if these assumptions are wrong, the basis for lowering the RfC is lost.</p> <p>This being said, there are many questions about the PK assumptions that have been employed. First is the choice of DCVC as the basis for the dose metric. Just because DCVC is used for kidney cancer evaluation does not mean that the same dose measure is appropriate for non-cancer toxicity. Indeed, Lash et al. (2000) describe formic acid as a potential mode of action (MOA) for kidney damage for TCE, distinguishing the case of cancer and non-cancer kidney effects, stating, "Hence, although formic acid formation may contribute to TCE-induced renal damage, this is not likely to be a significant MOA in TCE-induced kidney carcinogenesis" (emphasis added). While the beta-lyase pathway may play a predominant role in kidney carcinogenesis, the possible roles of other chemical actors (formic acid and trichloroethanol) are not adequately addressed. The PBPK modeling effort focuses solely on the products of the beta-lyase pathway and apparently ignores these other possibilities. The conclusions are accordingly dependent on this being the correct dose metric. If alternative pathways could</p>	<p>AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp.</p> <p>Lash, LH; Parker, JC; Scott, CS. 2000. "Modes of action of trichloroethylene for kidney tumorigenesis." Environ. Health Perspect. 108(Suppl. 2):225-240.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>be addressed via the model, this could either provide some support for US EPA's position that they are not relevant or it could show that a different dose metric is warranted. The current argument, i.e., that there are differences in kidney histopathology between TCE- and trichloroethanol-treated rats, and that this indicates a different MOA, is not particularly compelling.</p>	
5.1	148	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>The document's conclusion that humans have high flux through the conjugative pathway is at odds with previous assessments, and is not well supported by evidence; yet, this assumption markedly lowers RfC/D values compared to those using traditional applied-dose approaches.</p> <p>The consensus of scientific opinion had been that humans have low flux through the conjugative pathway, which would lead to low internal doses to the kidney. It was also the consensus that it is difficult to pin down the extent of flux through this pathway for experimental reasons. The draft reassessment document indicates that the human flux through the conjugation pathway can be concluded to be much greater than in rats. In view of the importance of this judgment to the eventual RfD/C, it must be clearly explained why this altered conclusion is warranted.</p> <p>As stated on page 3-128, the PBPK model reports one to two orders of magnitude more glutathione (GSH) conjugation and DCVC bioactivation in humans relative to rats. US EPA acknowledges that the 95% confidence intervals of the predicted population means for the two species overlap but there is little discussion of how this result is inconsistent with much of the previous data on TCE metabolism and TCE health effects in both humans and animals. For example, Lash et al. (2000) state that metabolic studies of PCE and Compound A indicate greater flux through the beta-lyase pathway in rats compared to humans (i.e., several fold higher in rodents). It would be unusual if TCE were somehow different from these structurally similar compounds such that the flux in humans was many times higher than in rats. Along similar lines, Lash et al. (2007) state that the flux of tetrachloroethylene (PCE) through the GSH pathway is approximately fivefold faster in rodents than that of TCE. They also indicate that the reactive intermediates derived via the beta-lyase pathway from PCE are more reactive than those derived from TCE. This would suggest that PCE should be a much stronger kidney toxicant than TCE in the rat; yet, to our knowledge, neither chemical could be regarded as a very potent nephrotoxicant. For example, in the National Toxicology Program (NTP) and National Institute of Health (NIH) oral bioassays (NTP, 1990; NIH, 1977) toxic nephrosis was observed in rats treated with either chemical and at similar doses. In human studies, neither chemical is consistently shown to be a potent nephrotoxicant (if anything, studies such as that by Henschler et al. (1995) would suggest TCE is more potent). This line of reasoning argues against the primary role of the beta-lyase pathway in PCE/TCE nephrotoxicity, and should be discussed in the document.</p> <p>The basis for finding such large human flux through the conjugative pathway is also questionable. The result comes from the hierarchical Bayesian analysis of the PBPK model. The US EPA PBPK model yields good fits to the rat and human urinary DCVC excretion data and also to S-dichlorovinyl glutathione (DCVG) measured in human blood. We would suggest caution, however, in assuming that just because the model, as formulated and parameterized, fits the available DCVC/DCVG data, that highly quantitative predictions can then be made concerning the mean and variation of the various model parameters. This is particularly of concern given the huge changes resulting from the Bayesian updating of the DCVC bioactivation constants (i.e., from 0.14 to 0.0087 in the rat and from 0.0021 to 0.023 in the human). The basis for the prior is not clear, but what is evident is that something other than direct experimental characterization is driving the updated DCVC bioactivation result, and some direct confirmation that such large flux actually occurs would seem critical to using this result in so influential a manner.</p> <p>Given the disparity between the model results and prior general scientific opinion about rat vs. human differences in GSH conjugation towards TCE, it would be valuable to use the model to predict what possible DCVC target organ doses would be for some of the key epidemiology studies. The reported prevalence of kidney damage could then be compared across studies for logical consistency with estimated DCVC concentrations. This would serve as a useful "reality check" for a model that is making novel claims regarding chemical toxicity. In any case, a clear and convincing case must be made as to why the previous scientific consensus about human DCVC activation and its estimation is being overturned.</p>	<p>AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp.</p> <p>Lash, LH; Parker, JC; Scott, CS. 2000. "Modes of action of trichloroethylene for kidney tumorigenesis." Environ. Health Perspect. 108(Suppl. 2):225-240.</p> <p>National Toxicology Program (NTP). 1990. "Carcinogenesis studies of trichloroethylene (without epichlorohydrin) (CAS No. 79-01-6) in F344/N rats and B6C3F1 mice (gavage studies)." Research Triangle Park, NC. National Institutes of Health. NTP TR 243; NIH Publication No. 90-1779. 174p., May.</p> <p>National Institute of Health (NIH). 1977. "Bioassay of tetrachloroethylene for possible carcinogenicity." Bethesda, MD. National Technical Information Service (NTIS), Springfield, VA. NCI-CG-TR-13; NIH 77-813.</p> <p>Lash, LH; Putt, DA; Huang, P; Hueni, SE; Parker, JC. 2007. "Modulation of hepatic and renal metabolism and toxicity of trichloroethylene and perchloroethylene by alterations in status of cytochrome P450 and glutathione." Toxicology 235(1-2):11-26.</p> <p>Henschler, D; Vamvakas, S; Lammert, M; Dekant, W; Kraus, B; Thomas, B; Ulm, K. 1995. "Increased incidence of renal cell tumors in a cohort of cardboard workers exposed to trichloroethene." Arch. Toxicol. 69(5):291-299.</p>
5.1	151	EPA-HQ-ORD-2009-	Halogenated Solvents	<p>Reliable estimates of the extent of variability among humans in DCVC activation have not been established, yet this factor is very influential in lowering the RfC/D.</p>	<p>AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp.</p> <p>-</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
		0791-0018.1	Industry Alliance, Inc.	<p>It is not only the high estimate of the average amount of human DCVC activation via flux through the conjugative pathway that results in markedly lowered reference values, it is also the calculation of the impact of estimated variability among humans in this rate. Elsewhere in these comments it is argued that the method for considering the impact of inter-human variability is flawed; but, in addition, there is the question of how reliably its extent has been estimated. In the previous comment it was noted that the soundness of the basis for estimating a much-changed average DCVC activation is unclear in view of widely acknowledged experimental difficulties and the evident influence of the Bayesian updating procedure. This concern applies even more to the characterization of variation among individuals, and great care must be taken to avoid attributing to genuine inter-individual variability differences that are really just due to experimental error, which can have marked effects for measurements on single individuals.</p> <p>US EPA notes that the variability in the renal GSH conjugation and bioactivation of DCVC is substantial due to the data set of Lash et al. (1999, as cited in the assessment). The Lash et al. data set, consisting of eight males and eight females in the 100-ppm dose group and five individuals (three males, two females) in the 50-ppm dose group is indeed very limited for characterizing such an important parameter in the model. The stability of any variance estimate drawn from such a small sample size (when developing a model meant to characterize the whole human population) should be viewed as tentative. This has fairly important implications when attempting to use the PBPK model for RfC calculations in ways meant to protect large fractions (i.e., 99%) of the human population. It would also be helpful to show the model predictions as compared to Lash et al.'s results for the 50-ppm dose group (Figure 3-10 only shows the 100-ppm group) to get a better sense of the model's predictive ability at lower exposure concentrations.</p>	
5.1	152	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>A weight-of-evidence approach should have been applied, and made transparent, in order to ascribe a level of confidence for each of the potential RfCs/RfDs that were derived in this assessment.</p> <p>The Draft TCE Reassessment takes the approach of conducting dose-response analysis on virtually every available data set on every non-cancer endpoint and turning each into a candidate RfC or RfD; it then winnows these down based largely on criteria of goodness-of-fit of dose-response models and of giving low ("most sensitive") RfD/RfC values. There is some advantage in this approach in that it allows one to look at the array of values that potentially reflect each endpoint. What such an approach deemphasizes, however, is the judgment about the representativeness of data sets in characterizing a potential human toxicity and about the consistency among studies that investigate the same endpoint. Not all effects appearing in animals have an equally compelling case as potential effects in humans. A well behaved data set that can be closely fitted by conventional models does not necessarily represent the best estimate of that effect among several studies that examine it, and the analysis showing elevated responses at the lowest level is not necessarily the most reliable.</p> <p>A weight-of-evidence approach should have been applied more rigorously and transparently, in which each endpoint or group of related endpoints is examined for consistency among studies and potential human relevance (Lewandowski and Rhomberg, 2005). An unreplicable effect, even if fitted well by dose-response analysis, does not provide a meaningful guide for human risk evaluation. It may be that a study that is not the most amenable to dose-response curve fitting or other quantitative analysis is nonetheless judged the best at fairly representing the body of studies on an endpoint for purposes of projecting potential human risk. It is appropriate to use the ability to fit good dose-response curves as a key criterion, but it should not be the only criterion. That is, the choice of studies on which to base RfD/RfC values is a judgment based on biological insights as well as on statistical curve fitting, and it must strike a balance between biological meaningfulness and representativeness on the one hand and well-behaved curve fitting on the other when these two aspects are in some degree of conflict. It must be made clear that all of the relevant studies for each endpoint were carefully considered and that the choices for data sets to represent particular endpoints are justifiable on both statistical and toxicological criteria.</p> <p>Furthermore, the weight-of-evidence evaluation could have been incorporated into a quantitative level of confidence for each proposed RfC/RfD, so that there is a means for communicating the level of confidence represented by the weight-of-evidence for each endpoint. Given the large number of RfCs/RfDs derived in this assessment, and the implicit utility of these values by risk managers and decision makers, the level of confidence in each RfC/RfD relative to those chosen as the final proposed values is something that needs to be carefully</p>	<p>AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp.</p> <p>Lewandowski, TA; Rhomberg, LR. 2005. "A proposed methodology for selecting a trichloroethylene inhalation unit risk value for use in risk assessment." Regul. Toxicol. Pharmacol. 41:39-54.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>considered through a weight-of-evidence evaluation for each endpoint, and then clearly communicated. However, it appears that more weight was placed on the most sensitive endpoint, and the goodness-of-fit for the dose-response data, in the absence of sufficient consideration of the weight of evidence in support of that endpoint as the critical effect.</p> <p>This is particularly relevant in derivation of the proposed RfC (discussed more below), where the drivers of the lowest RfCs appear to be from six studies, only one of which is an unpublished rat inhalation study where kidney effects were observed (Woolhiser et al., 2006, as cited in the Draft TCE Reassessment). The remaining studies were rodent oral studies from which route-to-route extrapolations were conducted to derive the RfC, a process that should affect their weight in the overall analysis of kidney effects since they include the added uncertainties inherent in the extrapolation, especially in the PK-based extrapolation, which must assume that the models are accurate and dependable for different routes, and that the measure of internal dose chosen is correct and comparable in toxicity even under the different time-patterns of tissue exposure inherent in the oral and inhalation exposures.</p> <p>Additional uncertainties should be noted in a weight-of-evidence evaluation of kidney toxicity. As described above, there is uncertainty in extrapolation from rodents to humans in the DCVC bioactivation portion of the PBPK model that is the basis of the proposed RfC for kidney effects. There is additional uncertainty regarding whether the kidney effect endpoint from the Woolhiser et al. (2006) rat inhalation study (increased kidney weight) is in fact related to DCVC bioactivation. If an associated level of confidence, based on the weight of evidence, had been derived and presented for the RfC based on the Woolhiser et al. (2006) study (and for each proposed RfC and RfD), the reader, and risk managers and decision makers could evaluate the level of confidence in the proposed toxicity values against other potential RfCs/RfDs that may reflect what appear to be less sensitive endpoints, but perhaps with a higher associated level of confidence based on the weight of evidence.</p>	
5.1	154	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>There is considerable uncertainty in the proposed RfC of 0.001 ppm for TCE, particularly related to potential uncertainty in the PBPK modeling of the DCVC dose metric in humans, and the relationship of that dose metric with increased kidney weight.</p> <p>There is uncertainty in choosing the p-cRfCs in the lower end of the candidate RfC range.</p> <p>The Draft TCE Reassessment presents a range of p-cRfCs (based on PBPK modeled internal dose metrics) and c-RfCs (based on applied dose) in Table 5-19. The values in this table reflect the lowest RfCs for the various effect domains. As discussed in section 5.1.5.2, US EPA suggests that although the range of lowest candidate RfCs within each health effect spans 3,000-fold (from 0.0003 to 0.9 ppm), there are</p> <p>"[S]ix p-cRfCs from both oral and inhalation studies [that] are in the relatively narrow range of 0.0003 – 0.003 ppm at the low end of the overall range."</p> <p>It further suggests, in the context of discussing the advantage of deriving multiple RfCs from multiple studies, that</p> <p>"[W]hen multiple candidate values happen to fall within a narrow range at the low end of the overall range ... that it leads to a more robust RfC (less sensitive to limitations of individual studies) and that it provides the important characterization that the RfC exposure level is similar for multiple noncancer effects rather than being based on a sole explicit critical effect."</p> <p>Although more studies resulting in similar RfCs will provide, to some extent, more confidence in that range of RfCs, the confidence associated with each of those RfCs in that range should also be carefully considered using a weight-of-evidence approach (as discussed in the comment above), and in comparison to other proposed RfCs that may not be as low, but for which there may be more confidence based on the weight of evidence for those endpoints.</p> <p>In fact, compared with these six RfCs that reflect the lowest range of candidate RfCs, five of which are oral</p>	AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp. -

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>studies (uncertainty in the route-to-route extrapolation is discussed below), there is another range of p-cRfCs on Table 5-19 that might suggest a more robust RfC range. Although without carefully reviewing the weight of evidence for each of these RfCs (and we did not conduct that level of review), we cannot state with certainty that this range would provide a more robust RfC in the end. However, there are six inhalation studies that represent another relatively narrow range of RfCs, from 0.013 to 0.12 ppm, two representing reproductive effects (0.013 and 0.017 ppm), one representing a neurological effect (0.016 ppm), one representing a developmental effect (0.062 ppm), and two representing immunological effects (0.11 and 0.12 ppm). It is not clear that this range of RfCs was considered, as a group, in comparison to the lower range of RfCs, as it was not discussed in the Draft TCE Reassessment. A discussion of the level of confidence in these six RfCs, based on a weight-of-evidence evaluation of the studies for those endpoints, in comparison to the level of confidence in the lower range of RfCs, might suggest that these RfCs as a group are more robust than the six that reflect the lower range of RfCs.</p> <p>There is uncertainty in the oral to inhalation route-to-route extrapolation.</p> <p>As discussed, although the six RfCs at the lower end of the range do fall within a narrow range of values, only one of these studies was a rat inhalation study (Woolhiser et al., 2006) in which increased kidney weight was the observed effect. The studies that were the basis of the other five RfCs were rodent oral gavage (NTP, 1976 and NTP, 1988, as cited in the Draft TCE Reassessment) or drinking water (Keil et al., 2009 and Johnson et al., 2003, as cited in the Draft TCE Reassessment) studies, two of which were based on kidney effects (toxic nephropathy and toxic nephrosis), two of which were based on immunological effects (increased thymus weight and increased anti-dsDNA & anti-ssDNA Abs), and one of which was based on developmental effects (heart malformations). These five RfCs were all derived from a route-to-route extrapolation, and are therefore (on the exposure route basis alone) less certain than the one RfC derived from an inhalation study. In fact, in extrapolating tissue doses from the oral to inhalation route, one could check to see how the extrapolated tissue doses compare with what would be calculated as tissue doses in inhalation rodent studies. To the extent that similar internal doses were indeed examined in the oral and inhalation studies, similar toxicity should have been observed under the logic of the route-to-route extrapolation. In fact, toxicity in the inhalation studies is largely seen at high doses that, at least on an applied-dose basis, are large compared to the doses showing toxicity in oral studies. This casts doubt on the validity of the gavage-to-inhalation extrapolations.</p> <p>There is uncertainty in the PBPK model reflecting a higher DCVC bioactivation in humans than in rodents.</p> <p>In addition, the one p-cRfC that was based on an inhalation study (Woolhiser et al., 2006) was 400-fold lower than the cRfC derived from the applied dose default methodology from the same study. US EPA discusses how this difference is due to a 30- to 100-fold difference between rats and humans in DCVC bioactivation that is reflected in the PBPK modeling, with humans having a higher level of DCVC bioactivation in the model. As discussed above, there is uncertainty in this difference that needs careful consideration before placing such emphasis on this model as the basis of an inhalation RfC. Given that the Woolhiser et al. (2006) study is the only inhalation study in this narrow lower end of the range, this study inherently provides more weight to the proposed RfC than the other four oral studies, and is discussed in more detail below.</p> <p>There are limitations, and lack of transparency, in using the Woolhiser et al. (2006) as the basis of one of the candidate RfCs.</p> <p>The Woolhiser et al. (2006) study is an unpublished rat inhalation study that was designed to examine immunotoxicity of TCE, but also contained information on kidney weights. Therefore, there is no way for the reader to easily review the results of this study. As discussed in the Draft TCE Reassessment, rats were exposed to 0, 100, 300, and 1,000 ppm TCE for 6 hours/day, 5 days/week, for four weeks. The authors observed significantly elevated kidney weights at 1,000 ppm TCE exposure. But the Draft TCE Reassessment notes that the "small number of animals and the variation in initial animal weight limit the ability of this study to determine statistically significant increases." Therefore, this study provides weak evidence that inhalation of TCE results in increased kidney weight.</p> <p>There is uncertainty in the relevance of increased kidney weight as a critical effect for non-cancer effects of TCE.</p>	

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>The observed effect from the Woolhiser et al. (2006) study was increased kidney weight relative to body weight. One other rodent inhalation study (Kjellstrand et al., 1983) discussed in the Draft TCE Reassessment also observed increased kidney weight from TCE inhalation, and another (Maltoni et al., 1988) observed meganucleocytosis. It is not clear that increased kidney weight or meganucleocytosis is directly related to kidney toxicity. Although some older studies seem to suggest that kidney weight increase is related to kidney toxicity (Feron et al., 1973), more recent studies (Bailey et al., 2004) suggest that the kidney weight to body weight ratio is uncertain, and other methods should be used to confirm weight increases. Barton and Clewell (2000) note that "Although short exposures produced increased kidney weight, it is unclear if this represents a reliable indicator of chronic toxicity (53,54)." As discussed by Hayes (2008), organ weight to body weight changes are typically secondary effects and not necessarily adverse. In addition, there does not appear to be any evidence to suggest that DCVC bioactivation is related to increased kidney weight, at least this is not discussed in the Draft Reassessment.</p> <p>Summary</p> <p>Although derivation and consideration of a range of RfCs is a sound approach to deriving an RfC, choosing the lowest range of RfCs (without a sufficient weight-of-evidence evaluation of the RfCs in that range), reflected by only one inhalation study for which the effect of increased kidney weight is questionable, is not strongly supported by the scientific evidence for TCE non-cancer effects. This is based on: (1) the fact that the significance of the observed effect in the Woolhiser study was weak and based on a small sample size; (2) uncertainty in the oral to inhalation route-to-route extrapolation for the five other RfCs in the range; (3) uncertainty in the PBPK model reflecting a higher DCVC bioactivation in humans than in rodents that was used for three of these RfCs; (4) uncertainty in the relevance of increased kidney weight as a critical effect for non-cancer effects of TCE; and finally, (5) the fact that there is another narrow range of six RfCs (from 0.013 to 0.12 ppm) that are all based on inhalation studies and for which, had a level of confidence in those RfCs been presented, might in fact reflect a more robust set of RfCs, base on a weight-of-evidence analysis of those endpoints.</p>	
5.1	159	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>Although derivation and consideration of a range of RfCs is a sound approach to deriving an RfC, choosing the lowest range of RfCs (without a sufficient weight-of-evidence evaluation of the RfCs in that range), reflected by only one inhalation study for which the effect of increased kidney weight is questionable, is not strongly supported by the scientific evidence for TCE non-cancer effects. This is based on: (1) the fact that the significance of the observed effect in the Woolhiser study was weak and based on a small sample size; (2) uncertainty in the oral to inhalation route-to-route extrapolation for the five other RfCs in the range; (3) uncertainty in the PBPK model reflecting a higher DCVC bioactivation in humans than in rodents that was used for three of these RfCs; (4) uncertainty in the relevance of increased kidney weight as a critical effect for non-cancer effects of TCE; and finally, (5) the fact that there is another narrow range of six RfCs (from 0.013 to 0.12 ppm) that are all based on inhalation studies and for which, had a level of confidence in those RfCs been presented, might in fact reflect a more robust set of RfCs, base on a weight-of-evidence analysis of those endpoints.</p>	AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp. -
5.1	185	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	Development of a Reference Dose (RfD) based on heart defects. AIA agrees with DOD that the RfD derived for heart defects is not based upon a transparent evaluation and appropriate interpretation of all of the relevant data.	AUTHOR: Lisa Goldberg -
5.1	188	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	Lack of sensitivity analyses to identify key data sets and assumptions in models and numerical derivations. The key risk outcomes of the assessment are based on multiple assumptions and data sets. AIA agrees with DOD and NASA that sensitivity analyses are needed to test the effects of these assumptions and to enable evaluation of the most important assumptions.	AUTHOR: Lisa Goldberg -
5.1	206	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>"Comments on the Public Review Draft of EPA's IRIS Toxicological Review for TCE: Developmental Effects." Carole A. Kimmel, PhD Gary L. Kimmel, PhD John M. DeSesso, PhD</p> <p>Exponent</p>	<p>AUTHORS: Carole A. Kimmel, PhD; Gary L. Kimmel, PhD; John M. DeSesso, PhD from Exponent</p> <p>Bove FJ, Fulcomer MC, Klotz JB, Esmart J, Dufficy EM, Savrin JE. Public drinking water contamination and birth outcomes. Am J Epidemiol. 1995; 141:850-862.</p> <p>Goldberg SJ, Lebowitz MD, Graver EJ, Hicks S. An association of human congenital cardiac</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>1800 Diagonal Road, Suite 300 Alexandria, Virginia 22314</p> <p>29 January 2010</p> <p>EPA's assessment of TCE uses data on heart defects as a major endpoint for setting the RfD and RfC. The data selected to support this decision are from studies that are poorly designed and flawed. Furthermore, EPA neither incorporates nor accounts for more robust data from guideline- and GLP- compliant studies that show no increase in congenital heart defects.</p> <p>* The human data are based on studies with inadequate exposure information, making it impossible to determine whether or not exposure occurred and, if it did, to what levels of TCE.</p> <p>- There are also deficiencies in the human data in terms of the background rates of cardiac malformations (Bove et al., 1995), and differences in the outcome of different studies (Goldberg et al., 1990, versus the Baltimore Washington Infant Study -Wilson et al., 1998).</p> <p>* The animal data reporting a link between TCE and heart defects all come from the same laboratory and were an accumulation of data over ten years (Johnson et al. 2003, Dawson et al. 1993).</p> <p>- In the Johnson and Dawson studies, there were a number of deficiencies in study design and reporting of data that make the interpretation of data tentative at best.</p> <p>- The major effect reported in the Johnson and Dawson studies was an increase in the incidence of atrial septal defects (or the foramen ovale, which closes around the time of birth) which may be related to the procedure for examining fetuses or the timing of the dissection relative to the development of the fetus, rather than actual heart defects.</p> <p>* Two additional GLP- and guideline-compliant studies showing no effect on heart development were conducted by Fisher et al. (2001) and Carney et al. (2006).</p> <p>* Thus, EPA uses weak human data: incomplete and flawed animal data; and in vitro data (which are of questionable relevance to environmental exposures) to make a mechanistic argument that TCE causes heart defects. Although EPA notes some of the database deficiencies, EPA uses a "strength of evidence" approach, rather than a "weight of evidence" analysis, by basing the RfD only on the studies reporting a positive effect and ignoring the data from subsequent well-conducted GLP studies that show no increase in heart defects associated with TCE (Fisher et al., 2001; Carney et al., 2006).</p>	<p>malformations and drinking water contaminants. J Am Coll Cardiol. 1990; 16:155-64.</p> <p>Wilson PD, Loffredo CA, Correa-Villaseñor A, Ferencz C. Attributable Fraction for Cardiac Malformations. Am J Epidemiol 1998; 148:414-23.</p> <p>Johnson PD, Goldberg SJ, Mays MZ, Dawson BV. Threshold of trichloroethylene contamination in maternal drinking waters affecting fetal heart development in the rat. Environ Health Perspect. 2003; 111:289-92.</p> <p>Dawson BV, Johnson PD, Goldberg 81, Ulreich JB. Cardiac teratogenesis of halogenated hydrocarbon-contaminated drinking water. J Am Coll Cardiol. 1993; 21:1466-72.</p> <p>Fisher JW, Channel SR, Eggers JS, Johnson PD, MacMahon IKL, Goodyear CD, Sudberry GL, Warren DA, Latendresse JR, Graeter IJ. Trichloroethylene, trichloroacetic acid, and dichloroacetic acid: Do they affect fetal rat heart development? Int J Toxicol. 2001; 20:257-67.</p> <p>Carney, E.W., B.A. Thorsrud, P.H. Dugard, and C.L. Zablony. 2006. Developmental toxicity studies in Crl:CD (SD) rats following inhalation exposure to trichloroethylene and perchloroethylene. Birth Defects Research, Part B: Developmental and Reproductive Toxicology 77:405-412.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics																																																	
5.1	209	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>EPA Evaluation of Animal Data on Heart Defects and Comments</p> <p>The EPA review of TCE (US EPA, 2009) uses the Johnson et al. (2003) and Dawson et al. (1993) data to establish reference levels for exposure -an RfC of 0.001 ppm and an RfD of 0.0004 mg/kg/day. The fetal heart malformation data reported in Johnson et al. (2003) are used to support both of these values (US EPA, 2009; see Tables 5.1.23 and 5.1.24 and the associated text). There are several limitations with this approach:</p> <p>* The Johnson et al. (2003) publication includes the Dawson et al. (1993) data and appears to be an accumulation of data over an approximate 10-year period.</p> <p>- This was not made clear in the Johnson paper, and it required a letter to the editor (Hardin et al., 2004) for the authors to respond and explain this situation (Johnson et al., 2004). There is no indication in the paper reporting the combined data (Johnson et al., 2003) about which data came from Dawson et al. (1993) and which data came from subsequent studies. Over the course of a decade, there could have changes in the lot of TCE used in the studies, differences in the animal supplier or animal health, changes in the experience of investigators and technicians, and changes in the procedure used for head examination. All of these could affect the results.</p> <p>- Dawson et al. (1993) do not mention the number of pregnant dams that were assigned to each treatment group and Dawson et al. (1993) used the fetus as the unit for statistical analysis. In developmental toxicity studies, the unit for statistical analysis is based on the dam or litter. This method helps to account for the litter effect (based on the concept that offspring of a given female tend to react more similarly to challenges than offspring from different females) and prevents inappropriate inflation of statistical significance.</p> <p>- These mistakes give the appearance that the authors were unaware of how to design studies, or how to analyze and present developmental toxicity data.</p> <p>* For the purposes of risk assessment and setting of regulatory standards, studies like Johnson et al. (2003) and Dawson et al. (1993), with deficiencies such as those mentioned above, should only be used in a support role when a database of other, more well- designed studies is available. Johnson et al. (2003) should be used as the critical study for establishing regulatory exposure levels.</p> <p>* The Johnson et al. (2003) and Dawson et al. (1993) studies have significant limitations regarding the reporting of standard maternal and fetal parameters.</p> <p>- Johnson et al. (2003) do not provide data on maternal and fetal parameters other than cardiac malformations, only mentioning that "maternal and fetal variables, including noncardiac congenital abnormalities, showed no significant differences between treated and control groups."</p> <p>- Dawson et al. (1993) did not provide any control data for maternal and fetal parameters, other than cardiac abnormalities. Consequently, there is no way to assess the impact of exposure on any parameter other than cardiac abnormalities, including such parameters as maternal body weight and body weight gain, fetal weight, and fetal viability.</p> <p>- Johnson et al. (2004) note that "Control values were consistent throughout our studies." However, there is no way for the reader to determine this.</p> <p>- 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 (e.g. cardiac defects) are within historical ranges.</p> <p>* Studies where major components of the results are not reported or the missing data have not been evaluated by the risk assessors may be useful in supporting other, more complete, data sets, but are of questionable value as primary studies in establishing an exposure standard.</p>	<p>Table 2. Comparison of Atrial Septal Defects in the Three Papers*</p> <table border="1" data-bbox="1634 191 2459 527"> <thead> <tr> <th data-bbox="1634 191 1776 212">Study/Data</th> <th colspan="6" data-bbox="2053 191 2179 212">Treatment Groups</th> </tr> </thead> <tbody> <tr> <td data-bbox="1634 217 1776 261">Dawson et al. 1993</td> <td data-bbox="1784 217 1927 261">Control Tap water</td> <td data-bbox="1935 217 2077 261">TCE – Prepreg only 1.5 ppm</td> <td data-bbox="2085 217 2228 261">TCE – Prepreg only 1100 ppm</td> <td data-bbox="2236 217 2378 261">TCE – Preg only 1.5 ppm</td> <td data-bbox="2386 217 2529 261">TCE – Preg only 1100 ppm</td> <td data-bbox="2537 217 2679 261">TCE – Prepreg & Preg 1.5 ppm</td> </tr> <tr> <td data-bbox="1634 266 1776 310">No. of atrial septal defects/no hearts examined (%)</td> <td data-bbox="1784 266 1927 310">1/232 (0.4)</td> <td data-bbox="1935 266 2077 310">3/130 (2.3)</td> <td data-bbox="2085 266 2228 310">7/147 (4.8)</td> <td data-bbox="2236 266 2378 310">4/181 (2.2)</td> <td data-bbox="2386 266 2529 310">7/105 (6.7)</td> <td data-bbox="2537 266 2679 310">5/256 (2.0)</td> </tr> <tr> <td data-bbox="1634 315 1776 358">Johnson et al. 2003</td> <td data-bbox="1784 315 1927 358">Control Distilled water</td> <td data-bbox="1935 315 2077 358">TCE – 2.5 ppb</td> <td data-bbox="2085 315 2228 358">TCE – 250 ppb</td> <td data-bbox="2236 315 2378 358">TCE – 1.5 ppm</td> <td data-bbox="2386 315 2529 358">TCE – 1100 ppm</td> <td data-bbox="2537 315 2679 358"></td> </tr> <tr> <td data-bbox="1634 363 1776 407">No. of atrial septal defects/no hearts examined (%)</td> <td data-bbox="1784 363 1927 407">7/606 (1.2)</td> <td data-bbox="1935 363 2077 407">0/144 (0)</td> <td data-bbox="2085 363 2228 407">1/110 (1.0)</td> <td data-bbox="2236 363 2378 407">4/181 (2.2)</td> <td data-bbox="2386 363 2529 407">7/105 (6.7)</td> <td data-bbox="2537 363 2679 407"></td> </tr> <tr> <td data-bbox="1634 412 1776 456">Fisher et al. 2001</td> <td data-bbox="1784 412 1927 456">Control IERO** Water</td> <td data-bbox="1935 412 2077 456">TCA 300 mg/kg in IERO water</td> <td data-bbox="2085 412 2228 456">DCA 300 mg/kg in IERO water</td> <td data-bbox="2236 412 2378 456">Control Soybean oil</td> <td data-bbox="2386 412 2529 456">TCE 500 mg/kg in soybean oil</td> <td data-bbox="2537 412 2679 456">Retinoic acid – 15 mg/kg in soybean oil</td> </tr> <tr> <td data-bbox="1634 461 1776 505">No. of atrial septal defects/no hearts examined (%)</td> <td data-bbox="1784 461 1927 505">2/273 (1.0)</td> <td data-bbox="1935 461 2077 505">2/269 (1.0)</td> <td data-bbox="2085 461 2228 505">3/298 (1.0)</td> <td data-bbox="2236 461 2378 505">6/367 (1.6)</td> <td data-bbox="2386 461 2529 505">4/290 (1.4)</td> <td data-bbox="2537 461 2679 505">3/155 (1.9)</td> </tr> </tbody> </table> <p>*Data in the shaded boxes were reported in both the Dawson et al. 1993 and the Johnson et al. 2003 papers. **IERO = ion exchange/reverse osmosis</p> <p>FOOTNOTE 1: For purposes of estimating the comparability of the dosages in the Fisher and Johnson studies, the following rough estimates can be made, in the Johnson drinking water study, the high dose was 1100 ppm TCE in the water. If the rats drank 20 mL/day, they received ~22 mg TCE/day. In the Fisher gavage study, the rats were administered 500 mg/kg/day. If the rats weighed 350 g, they received ~175 mg TCE/day.</p> <p>AUTHORS: Carole A. Kimmel, PhD; Gary L. Kimmel, PhD; John M. DeSesso, PhD from Exponent US EPA (2009). Toxicological Review of Trichloroethylene. Public Review Draft.</p> <p>Johnson PD, Goldberg SJ, Mays MZ, Dawson BV. Threshold of trichloroethylene contamination in maternal drinking waters affecting fetal heart development in the rat. Environ Health Perspect. 2003; 111:289-92.</p> <p>Dawson BV, Johnson PD, Goldberg SJ, Ulreich JB. Cardiac teratogenesis of halogenated hydrocarbon-contaminated drinking water. J Am Coll Cardiol. 1993; 21:1466-72.</p> <p>Hardin BD, Kelman BJ, Brent RL. Trichloroethylene and cardiac malformations, a correspondence in Environ Health Perspect. 2004; 112:A607-8.</p> <p>Johnson PD, Dawson B, Goldberg SJ, Mays MZ. Trichloroethylene: Johnson et al.'s Response. Environ Health Perspect. 2004; 112:A608-9.</p> <p>NRC (1994). Science and Judgment in Risk Assessment. National Research Council; National Academy Press, Washington, DC; 1994.</p> <p>Fisher JW, Chappel SR, Eggers JS, Johnson PD, MacMahon IKL, Goodyear CD, Sudberry GL, Warren DA, Latendresse JR, Graeter IJ. Trichloroethylene, trichloroacetic acid, and dichloroacetic acid: Do they affect fetal rat heart development? Int J Toxicol. 2001; 20:257-67.</p> <p>Carney EW, Zablony CL, Clements CM. Trichloroethylene: inhalation developmental toxicity. The Dow Chemical Company, Study ID: 981129. Midland, Michigan; 2001.</p> <p>Carney, E.W., B.A. Thorsrud, P.H. Dugard, and C.L. Zablony. 2006. Developmental toxicity studies in Crl:CD (SD) rats following inhalation exposure to trichloroethylene and perchloroethylene. Birth Defects Research, Part B: Developmental and Reproductive Toxicology 77:405-412.</p> <p>Smith MK, Randall JL, Read EJ, Stober JA. Teratogenic activity of trichloroacetic acid in the rat.</p>	Study/Data	Treatment Groups						Dawson et al. 1993	Control Tap water	TCE – Prepreg only 1.5 ppm	TCE – Prepreg only 1100 ppm	TCE – Preg only 1.5 ppm	TCE – Preg only 1100 ppm	TCE – Prepreg & Preg 1.5 ppm	No. of atrial septal defects/no hearts examined (%)	1/232 (0.4)	3/130 (2.3)	7/147 (4.8)	4/181 (2.2)	7/105 (6.7)	5/256 (2.0)	Johnson et al. 2003	Control Distilled water	TCE – 2.5 ppb	TCE – 250 ppb	TCE – 1.5 ppm	TCE – 1100 ppm		No. of atrial septal defects/no hearts examined (%)	7/606 (1.2)	0/144 (0)	1/110 (1.0)	4/181 (2.2)	7/105 (6.7)		Fisher et al. 2001	Control IERO** Water	TCA 300 mg/kg in IERO water	DCA 300 mg/kg in IERO water	Control Soybean oil	TCE 500 mg/kg in soybean oil	Retinoic acid – 15 mg/kg in soybean oil	No. of atrial septal defects/no hearts examined (%)	2/273 (1.0)	2/269 (1.0)	3/298 (1.0)	6/367 (1.6)	4/290 (1.4)	3/155 (1.9)
Study/Data	Treatment Groups																																																					
Dawson et al. 1993	Control Tap water	TCE – Prepreg only 1.5 ppm	TCE – Prepreg only 1100 ppm	TCE – Preg only 1.5 ppm	TCE – Preg only 1100 ppm	TCE – Prepreg & Preg 1.5 ppm																																																
No. of atrial septal defects/no hearts examined (%)	1/232 (0.4)	3/130 (2.3)	7/147 (4.8)	4/181 (2.2)	7/105 (6.7)	5/256 (2.0)																																																
Johnson et al. 2003	Control Distilled water	TCE – 2.5 ppb	TCE – 250 ppb	TCE – 1.5 ppm	TCE – 1100 ppm																																																	
No. of atrial septal defects/no hearts examined (%)	7/606 (1.2)	0/144 (0)	1/110 (1.0)	4/181 (2.2)	7/105 (6.7)																																																	
Fisher et al. 2001	Control IERO** Water	TCA 300 mg/kg in IERO water	DCA 300 mg/kg in IERO water	Control Soybean oil	TCE 500 mg/kg in soybean oil	Retinoic acid – 15 mg/kg in soybean oil																																																
No. of atrial septal defects/no hearts examined (%)	2/273 (1.0)	2/269 (1.0)	3/298 (1.0)	6/367 (1.6)	4/290 (1.4)	3/155 (1.9)																																																

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>* Johnson et al. (2003) indicate that their goal was to determine whether there was a threshold level of TCE in drinking water above which the incidence of congenital cardiac defects in the rodent increased significantly. The doses reported were 0, 2.5, 250, 1,500, and 1,100,000 ppb. Does their study design and statistical analysis permit the testing of a hypothesis derived from this goal?</p> <p>- Their study pools discrete data from at least two separate studies and an accumulation of data over several years and is an unbalanced design (55 dams in the control vs. 9-13 in the treatment groups).</p> <p>- They report that their data could indicate that a threshold effect exists at a level between 1.5 and 1,100 ppm.</p> <p>* It would be prudent to have a qualified statistician look at this database and the statistical evaluations used to determine if the analysis was appropriate. The reported "threshold effect" has a range of three orders of magnitude. This is not very useful in establishing reference levels.</p> <p>* In discussing the dose-response pattern in Johnson et al. (2003), the authors specifically mention the response observed at the highest exposure level (1,100,000 ppb) relative to control. With regard to the results seen in the other three dose levels, they only mention that "Intermediate exposure levels produced intermediate response rates." While the latter statement may be true, the intermediate levels did not produce a clear dose-response relationship.</p> <p>- The incidence of heart defects in fetuses was 2.1, 0, 4.5, 5.0 and 10.5% in controls, 2.5, 250, 1500 and 1,100,000 ppb exposure groups, respectively. The extreme range of exposure levels (440,000-fold difference between low and high exposure levels, and >700-fold between the 1500 and 1,100,000 ppb exposure levels) is not mirrored by a remarkable difference in the incidence of heart defects (2.1% in controls and only 10.5% incidence at the highest exposure level).</p> <p>* To make the analysis more difficult to interpret independently, the fetus and not the dam (litter) was used as the experimental unit. EPA has 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 EPA refers to "Section 6, dose-response" regarding this additional data, since it does not appear that anything in this section/sub-section details these data or how they were used. It is unclear if EPA has examined these data. At a minimum, EPA should make the data available and explain how it has been incorporated into EPA's risk assessment.</p> <p>* The dose-response pattern is another area where the input of a qualified statistician/modeler would be prudent.</p> <p>* Johnson et al. (2003) comment that TCE exposure using an in vitro chick model has been shown to have effects on several elements of epithelial-mesenchymal cell transformation in endocardial cushions (tissue that becomes part of the atrioventricular valves and septum) at concentration ranges that correlate with their findings.</p> <p>- They note a concentration range of 50-250 ppm (although it isn't clear if this is the only concentration range used in the referenced studies), which is bounded by the Johnson et al. (2003) concentration range, but then, almost any range would be, given the extreme range that Johnson et al. used.</p> <p>- More importantly, an application of X ppm in an in vitro chick embryo study is in no way comparable to an application of X ppm in drinking water in an in vivo rat study.</p> <p>* Use of in vitro ovo data with questionable relevance to environmental exposures as mechanistic support for heart defects reported in poorly conducted whole animal studies and weak human studies does not build a strong case for using heart defects as the basis for risk assessment, and compounds the problem of overstating the importance of the data.</p> <p>* Generally, the draft assessment focuses too much on one set of studies that show a putative positive response to low-exposure levels of TCE, instead of considering the overall data base and the limitations of the focus studies.</p>	<p>Teratology 1989; 40:445-51.</p> <p>Smith MK, Randall JL, Read EF, StoberJA. Developmental toxicity of dichloroacetate in the rat. Teratology 1992; 46(3):217-23.</p> <p>Momma K, Ito T, Ando M. In situ morphology of the foramen ovale in the fetal and neonatal rat. Pediatr Res 1992; 32: 669-672.</p> <p>NRC (2006). Assessing the Human Health Risks of Trichloroethylene: Key Scientific Issues. National Research Council: National Academies Press, Washington, DC.</p> <p>American Heart Association (2005b) Congenital cardiovascular defects statistics. Available online at http://www.americanheart.org/presenter.jhtml?identifier=4576.</p> <p>Hoffman, J. I. E. and S. Kaplan (2002) "The incidence of congenital heart disease"1 Am Coll Cardiol 39: 1890-1900.</p> <p>Drake VJ, Koprowski SL, Hu N, Smith SM, Lough J. (2006a). Cardiogenic effects of trichloroethylene and trichloroacetic acid following exposure during heart specification of avian development. Toxicol Sci 94: 153-164.</p> <p>Drake VJ, Koprowski SL, Lough J, Hu N, Smith SM. (2006b) Trichloroethylene exposure during cardiac valvuloseptal morphogenesis alters cushion formation and cardiac hemodynamics in the avian embryo. Environ Health Perspect 114: 842-847.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>- The draft assessment is not a "weight of evidence" evaluation but a "strength of evidence" evaluation (NRC, 1994). All the focus is on those studies that found a compound-related effect and no attention was given to the strengths and weaknesses of those studies that found no compound-related effects. Data from GLP-compliant animal studies that were carefully designed to probe the existence of potential links between TCE or its metabolites and heart or eye defects have shown no associations at exposure levels that are several orders of magnitude higher than those expected in environmental or occupational settings.</p> <p>-- Fisher et al. (2001) specifically investigated the cardiac teratogenic potential of TCE, TCA, and DCA in groups of 19 -20 pregnant Sprague-Dawley rats. The rats received oral bolus doses of TCE (500 mg/kg/day, in soybean oil), TCA (300 mg/kg/day, in water) or DCA (300 mg/kg/day, in water) on gestational days 6 -15. On gestational day 21, fetuses were removed by laparohysterectomy and hearts were examined and microdissected under a stereomicroscope by an investigator experienced in the procedure (Dr. Paula Johnson, author of Johnson et al. (2003)). The rates of cardiac malformations among treated animals did not differ from control rates. Also, TCE caused no change in the weight of fetuses and did not inhibit maternal weight gain at the high dose level [FOOTNOTE 1] used in this study.</p> <p>-- An inhalation study of TCE in pregnant Charles River CD IGS rats (Carney et al., 2001; 2006) exposed groups of 27 animals to filtered air or to atmospheric concentrations of TCE up to and including the limit dose (600 ppm) for 6 hours/day on each of gestational days 6 -20. Although maternal toxicity (decreased body weight gain) was elicited at the highest dose, TCE exposure caused no increase in gross, skeletal, or visceral (including heart and eye) malformations at any of the concentrations tested.</p> <p>-- Some early studies of TCA and DCA in pregnant Long-Evans rats (Smith et al., 1989, 1992) reported ocular malformations. In a follow-up to the Fisher et al. (2001) study, Warren et al. (2006) reported that examination of the heads showed that none of the chemicals used in the Fisher et al. (2001) study elicited gross ocular malformations. Morphometric analysis of the lens area, globe area and interocular distances revealed reductions of these parameters only in the TCA- and DCA-treated fetuses, but the overall smaller sizes of the fetuses in those groups were sufficient to explain the reductions.</p> <p>- Weight of evidence clearly must consider all of the data, both positive and no effect data. When the majority of the positive data are derived from clearly flawed studies using methods that give results that are not replicable in other laboratories, it is difficult to understand how the Agency can justify using only these data as the basis for a regulatory assessment.</p> <p>* While there were similar methods used for examining hearts in fetuses in the Dawson and Johnson laboratories and Dr. Johnson collaborated on the Fisher et al. (2001) study, there were several differences among the 3 studies as noted in the EPA review, as well as possibly significant differences in heart preparation not noted by EPA (see Table 1 below).</p> <p>* Table 1 details differences in preparation of the heart for dissection, Dawson et al. (1993) and Johnson et al. (2003) both removed the heart first, then flushed with a fixative, Fisher et al. (2001) flushed the heart in situ via the left ventricle with a staining solution for better visualization (1:3 hematoxylin-saline solution), perhaps a more physiologically normal situation, then removed the heart and immersion fixed it in 10% buffered formalin.</p> <p>* One major difference in the data from the Dawson/Johnson laboratory versus the Fisher laboratory appears to be the incidence of atrial septal defects (Table 2), The types of atrial septal defects reported by Dawson/Johnson et al. are not detailed in any of the papers except for the statement that they are "secundum in type" (Dawson et al., 1993).</p> <p>- Since the septum primum and septum secundum both grow rapidly around the time of birth to close the foramen ovale (Momma et al., 1992), this may represent normal in developmental timing such as occurs with other structures that are maturing around the time of birth in the rat, (e.g" skeletal ossification of sternebrae, vertebral centra, etc" or development of the renal papilla).</p> <p>- Whether the different methods of flushing the hearts may have disturbed the position of the septum which</p>	

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>would not be closed on the day of sacrifice is unclear.</p> <ul style="list-style-type: none"> - Even more troubling, however, is that neither Dawson et al. (1993) nor Johnson et al. (2003) provide maternal or fetal weight data, so it is impossible to know whether there were differences in fetal weight that would suggest a delay in development. Also, data on other aspects of fetal development (e.g., skeletal ossification) were not presented to give any clues about developmental stage. - Fisher et al. (2001) report no significant difference from water-treated control animals in maternal weight, uterine weight, number of implantations or fetal weight for TCE at 500 mg/kg. In that study, the percent of fetuses with atrial septal defects was approximately the same in the two groups. Thus, there are a lot of questions about the incompleteness of the data presented in the Dawson et al. (1993) and Johnson et al. (2003) papers, in addition to the obvious design flaws and protracted length of time over which the studies were conducted. Without concurrent control data, it is very difficult to evaluate small changes in head development that may or may not be related to TCE exposure. * Another difference is in the incidence of ventricular septal defects (VSDs). - Johnson et al. (2003) reported membranous VSD occurrences as 0.33% in controls; 1.7% at 1.5 ppm; and 2.9% at 1,100 ppm. For muscular VSDs, they reported 0.33% in controls; 0.55% at 1.5 ppm; and 0.95% at 1,100 ppm. * In the Fisher et al. (2003) study, there are no cases of VSD in TCE-treated fetuses, even though there were 2 cases of membranous VSD and one case of muscular VSD in soybean-treated controls (incidence of 0.54% and 0.27% respectively). * There are significant questions about examination of the hearts in the Dawson/Johnson studies, as well as questions about whether effects on the atrial septum (the primary defect reported) are actually a reflection of developmental delays, because the atrial septum is developing around the time of birth. In addition, there was no increase in VSDs in a carefully-controlled study (Fisher et al. ZOO?), while Johnson et al. (2003) reported a low increase in incidence with TCE exposure. Unfortunately, data on maternal and fetal body weight or other indicators of development (e.g., skeletal ossification) are missing from the reports by Dawson/Johnson. Consequently, it is not possible to assess the developmental importance of their findings. * The NRC (2006) report states that ventricular septal defects (VSDs) were the most commonly observed cardiac problems in both animal studies and the epidemiological studies. This observation is provided as support to the idea that TCE can induce heart defects. However, as indicated earlier, the Johnson et al. (2003) study reported a much higher incidence of atrial septal defects than VSDs. - There are serious questions about whether or not atrial septal defects are actual defects or simply due to delays in development (an adaptive response that is usually reversible). In addition, VSDs are the most common heart defect in the human population, making up anywhere from -14.25% of CHD cases (American Heart Association, 2005b; Hoffman and Kaplan, 2002), regardless of whether or not TCE exposure is involved. - TCE reportedly alters endocardial cushion proliferation at low doses when administered in ovo, but whether or not this in turn increases the incidence of CHD is unclear. An increase in cellular proliferation in the cardiac cushion and outflow tract has been noted in the in ovo study by Drake et al. (2006a). In this study, 0.2, 4, and 200 nm/egg concentrations of TCE were injected into the yolks of eggs during cardiac cushion formation at Hamburger Hamilton (HH) stages 13, 15, 17, and 20. At the 4 nm/egg concentration and higher, an increase in cardiac cushion proliferation was observed in parallel with alterations in cardiac blood flow patterns. However, the same authors also noted in a later paper that this same increase in cellular proliferation was observed when TCE was administered at HH 18, 21, and 23, but this latter experiment the increased proliferation was not linked to any kind of functional cardiac alterations, illustrating that the two are not necessarily linked (Drake et al., 2006b). * Thus, it is unclear whether the effects on cellular proliferation of endocardial cushions seen in chick studies are related to septal defects, and it is unlikely that the changes reported from direct egg injection studies with high 	

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
5.1	212	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>levels of TCE are relevant to whole animal or human exposure levels.</p> <p>EPA Evaluation of Human Data on Heart Defects and Comments</p> <p>The existing human data are deficient for risk assessment, but even so they do not support an association between TCE exposure and cardiac defects in human infants.</p> <p>* A shortcoming that is common to all of the epidemiology studies is the lack of accurate exposure information and poor control of confounding factors. In the instance of the Arizona aquifer, the authors were clear to point out that their data showed "a significant association but not a cause and effect relation between parental exposure to the contaminated water area" and cardiac defects. By this, they meant that the parents of affected children were present in the land area overlying the aquifer during early gestation -but not that they had necessarily drunk or used contaminated water. Thus, it is not clear whether exposure occurred or to how much. With respect to the Baltimore-Washington Infant Study, interviews with parents identified activities and occupations that were likely to have involved organic solvents and degreasing substances. TCE is among the substances that could have been used, but it was not singled out as a causative agent and there is no information on levels of exposure. These data sets fail to clearly identify a specific causative agent and do not quantify exposure levels, making these data sets insufficient for an assessment of risk for a particular chemical (i.e., TCE).</p> <p>* NRC (2006) cited the findings in Bove et al. (2002), a study that re-analyzed the data presented in the widely disputed Goldberg et al. (1990) study. Goldberg et al. (1990) reported an increased incidence of congenital heart defects (CHD) in Tucson, AZ, but this report was criticized for its data analysis and sampling techniques. Bove et al. (2002) reported that 10-11% of households in Tucson had at least one member that had worked or resided in the TCE contaminated area. In contrast, it was stated that 39.2% of babies born with CHD had at least one parent who had resided or worked in a contaminated area. This was based on interviews of 143 of the 365 CHD cases. Bove et al. (2002) claimed that if it was assumed that the remaining 172 cases had a similar proportion of exposed parents, then the prevalence of CHD in the exposed areas during the first trimester of pregnancy would be about 2.3 times that in the uncontaminated areas. No confidence interval for this was provided. One major problem with this evaluation is that whether the mother and/or father was exposed to the TCE was not considered, and the pathway by which paternal exposure would contribute to an increase in CHD is unclear. Additionally, because socioeconomic status and demographics were not integrated with the geographical distribution of the population, it is possible that a higher proportion of births occurred in the part of town with TCE-contaminated water. In many parts of the county, certain areas of a region are more heavily populated with households with children. The control group here is for the overall Tucson population and not childbearing families. The absence of an appropriate control group is a potential confounding factor that was not considered. Another issue is that the control incidence of CHDs was stated to be 2.6/1,000 births, which is well below the expected U.S. background CHD rate of 811,000 births as reported by the American Heart Association (2005a). Therefore, it appears that the Bove et al. (2002) study suffers from many of the same problems as the original Goldberg et al. (1990) study.</p> <p>* The NRC (2009) report updated the conclusions of the IOM (2003) report and concluded that "there continues to be inadequate/insufficient evidence" for a link between TCE and congenital malformations in humans.</p> <p>* As discussed above, the human data cited by the assessment are inadequate for risk assessment and do not support a link between TCE and heart defects.</p> <p>CONCLUSIONS</p> <p>* EPA used a strength of evidence rather than a weight of evidence in their assessment of the data on cardiac defects. That is, only the positive data showing effects were considered in selecting data as the basis for the RfD and RfC rather than considering the whole body of data. EPA's guidelines clearly indicate the importance of using a weight of evidence approach.</p> <p>* All of the data showing cardiac defects in whole animal studies come from a single lab and have significant</p>	<p>AUTHORS: Carole A. Kimmel, PhD; Gary L. Kimmel, PhD; John M. DeSesso, PhD from Exponent</p> <p>NRC (2006). Assessing the Human Health Risks of Trichloroethylene: Key Scientific Issues. National Research Council: National Academies Press, Washington, DC.</p> <p>Bove et al. (2002). Drinking water contaminants and adverse pregnancy outcomes. Environ Health Perspect 110 (Suppl 1):61-74.</p> <p>Goldberg SJ, Lebowitz MD, Graver EJ, Hicks S. An association of human congenital cardiac malformations and drinking water contaminants. J Am Coll Cardiol. 1990; 16:155-64.</p> <p>American Heart Association (2005a) Congenital heart defects in children factsheet. Available online at http://www.americanheart.org/presenter.jhtml?identifier=12012.</p> <p>NRC (2009). Contaminated Water Supplies at Camp LeJeune: Assessing Potential Health Effects. National Research Council: National Academies Press, Washington, DC.</p> <p>IOM (2003). Gulf War and Health, Vol. 2, Insecticides and Solvents. Washington, DC: National Academies Press.</p> <p>Fisher JW, Channel SR, Eggers JS, Johnson PD, MacMahon IKL, Goodyear CD, Sudberry GL, Warren DA, Latendresse JR, Graeter IJ. Trichloroethylene, trichloroacetic acid, and dichloroacetic acid: Do they affect fetal rat heart development? Int J Toxicol. 2001; 20:257-67.</p> <p>Johnson PD, Goldberg SJ, Mays MZ, Dawson BV. Threshold of trichloroethylene contamination in maternal drinking waters affecting fetal heart development in the rat. Environ Health Perspect. 2003; 111:289-92.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>study design flaws and inadequate data reporting.</p> <p>* More carefully controlled GLP-studies did not show an increase in cardiac defects, including the study by Fisher et al. (2001) in which Dr. Johnson (of Johnson et al. 2003) participated.</p> <p>* The human data used by EPA as support for a link between TCE and heart defects are inadequate</p>	
5.1	216	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>Lisa M. Sweeney, Ph.D., DABT Toxicology Excellence for Risk Assessment</p> <p>The extensive use of complex modeling in the trichloroethylene (TCE) assessment presents a formidable challenge to scientific peer review. EPA should facilitate peer review by providing an analysis of the most influential assumptions (commonly referred to as a "sensitivity analysis"). Such an analysis would not have to be complex itself, or delay the review of tile draft excessively. However, a sensitivity analysis is necessary to provide a sufficient review of this document.</p> <p>Some key assumptions in the physiologically based pharmacokinetic (PBPK) and dose response modeling in the assessment provide an example of why such an analysis is needed. For example, the assumption of glutathione (GSH) conjugation rate differences between humans and rodents apparently has a several hundred fold effect on the derived values for the inhalation reference concentrations. This assumption appears to be only weakly supported by the weight of the evidence; EPA's own statistical analysis of the related dose metrics also casts doubt on its validity. EPA should use other data in the literature to improve this parameter estimate.</p> <p>Other examples that show tile value of a sensitivity analysis are presented. Please consider the value of providing such an analysis to the Scientific Advisory Board reviewers and provide them with the information they need to conduct a full and scientifically robust peer review of this document.</p>	AUTHOR: Lisa M. Sweeney, Ph.D., DABT -
5.1	221	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>WHY IS SCRUTINY OF THE TCE PBPK MODEL IMPORTANT?</p> <p>The use of PBPK model-derived estimates of GSH metabolism as a metric (rather than applied dose) for kidney toxicity had a 300- to 400-fold impact on the cRfC and RID (p. 5-51), after taking into account dose-response and interspecies differences. The use of internal dose metrics is generally preferred over applied dose when the data are sufficient, support the choice of dose metric, and tie the dose metric to the endpoint of interest, because such internal dose metrics are more predictive of the observed toxicity. Although there is not necessarily an inherent problem with dose metrics that differ markedly from applied dose measures, such barge differences call for greater scrutiny of the reasons for the differences, and increase the importance of the consideration of the implications of uncertainties. The use of GSH metabolism (calculated using the PBPK model) as the dose metric for the kidney resulted in kidney effects being identified as one of the key noncancer effects. Intuitively, the 300 to 400-fold difference in the calculated cRfC and cRfD must somehow be related to the values of the parameters in the PBPK model, most likely those pertaining to GSH metabolism, but it is not necessarily clear which parameters arc the key drivers, and whether large interspecies differences in these parameters are supportable based on the available data.</p>	AUTHOR: Lisa M. Sweeney, Ph.D., DABT -
5.1	230	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>Regarding 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, RID, and a chosen cancer risk level (e.g., 1 in 10⁵) under conditions of continuous exposure. We recommend that these analyses be conducted for tile key endpoints (is., those from which the risk values were derived) and tile candidate RfCs and RfDs that are within approximately 3-10x of the final RfC and RfD.</p>	AUTHOR: Lisa M. Sweeney, Ph.D., DABT -
5.1	231	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>OTHER KEY CHOICES IN THE RISK ASSESSMENT NOT RELATED TO PBPK MODEL PARAMETER VALUES.</p> <p>One of the many parameters to be considered in a sensitivity analysis is the dose or exposure concentration.</p>	AUTHOR: Lisa M. Sweeney, Ph.D., DABT -

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>Clearly, the value of the iPOD will be related to the dose, especially at doses below saturating levels. Many risk assessment choices feed into identifying the point of departure for the RfCs/RfDs and slope factors, some of which will be discussed below.</p> <p>First, the study considered for use as the basis for the potential risk value needs to be evaluated to determine if it is suitable for risk assessment. Considerations include the use of suitable test species, numbers of animals, appropriate test material (e.g., acceptable purity or a standardized mixture), adequate documentation, and ethical conduct of the study. Even if a single study is inadequate by itself, it may be possible to combine studies to yield adequate information, or use the study to support findings from mother study. Toxicity studies of key metabolites should also be considered. For the endpoint of hepatomegaly EPA appears to have considered evaluating the dose-response relationship for a TCE metabolite (in this case, TCA) via direct dosing and the effect of interest, in order to compare that relationship to the relationship between the same metabolite and the effect of interest when that compound is produced from TCE metabolism. Evaluation of the dose-response from direct-dosing studies of key metabolites and demonstration of consistency with the dose response seen from dosing with TCE would provide a more scientifically-supported analysis.</p>	
5.1	233	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>Suitable endpoints within the study need to be selected. Endpoints should be reproducible adverse effects relevant to humans. EPA's decision to not consider non-numerical data ("e.g., data presented in line or bar graphs rather than in tabular form", page 5-4, line 4) for Benchmark Dose analyses seems arbitrary and inappropriately limiting.</p> <p>Next, an appropriate response level needs to be chosen. The response level could be qualitative (e.g., mild irritation) or quantitative (percent affected). For example, why should EPA use a benchmark response (BMR) of 1% for heart defects, when higher BMRs were used for other endpoints? An appropriate dose-response model (or models) also needs to be selected (e.g., linearized multi-stage model or others in EPA BenchMark Dose Software (BMDS)).</p> <p>An important consideration, especially when PBPK modeling is to be used, is the choice of dose metric. Assumptions/beliefs about the mode of action are embedded within the choice of dose metric used for dose-response analyses and route-to-route or interspecies extrapolations. Considerations include the use of parent compound vs. total metabolites generated vs. concentrations of specific metabolites, and opting to use peak values, time-weighted average (TWA) values; or cumulative values. For example, why did EPA use TCA produced rather than TWA liver TCA concentration to evaluate the potential dose-response relationship between TCE administration and liver weight increases in mice (Section 4.5)? Until the relationship between TCA and hepatomegaly is properly analyzed, it is premature to assert that TCA is insufficient to account for the rodent liver tumors.</p> <p>Uncertainty factors (UFs) obviously have an impact on the RfC/RfD. In cases where the relationship between external dose and internal dose is nonlinear, RfC values may differ depending on whether one first applies UFs to the test species point of departure and then completes the interspecies extrapolation or if one reverses the sequence, first extrapolating to human external dose, they dividing by the UFs. As a replacement for the use of default values of the pharmacokinetic variability component of UFH, EPA used the 99th percentile of the population distribution as the "sensitive" individual, based on toxicokinetic variability. EPA defends the choice of the 99th percentile rather than the 95th percentile based on the inclusion of both uncertainty and variability in the distribution, but does not explain why the inclusion of variability suggests the need to use a higher percentile value from the distribution or how they concluded that the 99th percentile was the appropriate value. They should provide information on how their choice of the 99th percentile, rather than other well-supported values, such as the 95th percentile, affected the outcome of the analysis. While the choice of the percentile to use to characterize human variability is a scientific policy choice, uncertainty in the distribution is larger at the tails, and therefore has a much larger impact on the 99th percentile than on the 95th percentile.</p>	AUTHOR: Lisa M. Sweeney, Ph.D., DABT -

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
5.1	248	EPA-HQ-ORD-2009-0791-0012.1	McKenna, Long & Aldrige, LLP	New policy: EPA is... *Using a new approach of deriving multiple RfDs and RfCs that mixes toxicology with policy.	- -
5.1	255	EPA-HQ-ORD-2009-0791-0012.1	McKenna, Long & Aldrige, LLP	Main messages: Non-cancer findings The new inhalation reference concentrations depend too heavily on assumptions in the PbPk and dose-response modeling Assuming higher human production of DCVC is a critical part of the complicated analysis of RfC, RfD, and cancer dose response – It is disputed science and EPA’s analysis appears to show that it does not fit the modeling well The standard and well-tested approach for deriving RfCs directly from the study data should still be presented and preferred for now	- -
5.1	264	EPA-HQ-ORD-2009-0791-0012.1	McKenna, Long & Aldrige, LLP	EPA does not use the entire database in its assessment of heart defects • Animal studies are severely limited methodologically and in the reporting of data. • Human data suffers from inadequate exposure definition and inconsistent findings. • Mechanistic argument needs better support than seemingly irrelevant in vitro data and flawed in vivo data. • Data are seemingly ignored from well-conducted studies that show no increase in heart defects. EPA should not say that heart defects may occur at environmentally relevant TCE doses in humans. A full weight of evidence evaluation (not a strength of evidence argument) should be provided for risk managers.	- -
5.1	265	EPA-HQ-ORD-2009-0791-0012.1	McKenna, Long & Aldrige, LLP	EPA needs to show the effect of their assumptions and modeling choices • The inter-related PbPk and dose-response modeling for multiple endpoints and dose metrics is so complex that even experts have trouble sifting through it. • The support for multiple dose metrics and route-to-route extrapolation requires a very complex set of weight of evidence evaluations for modes of action. • Even a simple narrative of the most influential assumptions and data sets (and their support) would be helpful. – The narrative does not have to be exhaustive and time consuming. – Scientists at EPA may already know the most sensitive parameters.	- -
5.2	37	EPA-HQ-ORD-2009-0791-0011.1	ARCADIS	Need for Assessment of Policy Implications and Validation Exercises It is critical for all organizations, including governmental agencies, to assess the real world implications of their proposed actions. This is done routinely when major actions of government are planned. For instance, the National Environmental Policy Act of 1969 (42 USC 4321) requires that the consequences of planned actions be carefully assessed before the actions are taken. NEPA requires that the Federal government “attain the widest range of beneficial uses of the environment without degradation, risk to health or safety, or other undesirable and unintended consequences.” Procedurally, NEPA requires that the Federal government shall: “Include in every recommendation or report on proposals for legislation and other major Federal actions significantly affecting the quality of the human environment, a detailed statement by the responsible official on – (i) the environmental impact of the proposed action, (ii) any adverse environmental effects which cannot be avoided should the proposal be implemented, (iii) alternatives to the proposed action...” The U.S. Department of Housing and Urban Development (2005) also routinely performs environmental	-

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>assessments of its proposed housing projects that include assessment of safety hazards, noise, air quality, socioeconomic consequences such as displacement, and effects on community facilities and services, among others.</p> <p>More importantly, federal laws and regulations governing the remediation of hazardous waste require that the risks posed by proposed remedial actions be carefully considered before decisions are made. CERCLA (Superfund) regulations (40 CFR 300.430) state:</p> <p>“The short-term impacts of alternatives shall be assessed considering the following: (1) short-term risks that might be posed to the community during implementation of an alternative; (2) potential impacts on workers during remedial action and the effectiveness and reliability of protective measures; (3) potential environmental impacts of the remedial action and the effectiveness and reliability of mitigative measures during implementation.”</p> <p>EPA elaborates on interpretation of these regulations in their guidance for conducting remedial investigations and feasibility studies under CERCLA (EPA 1988) by requiring that alternative remedies be evaluated with respect to their respective effects on human health and the environment. EPA guidance says that the following factors should be addressed as appropriate for each alternative:</p> <ul style="list-style-type: none"> • Protection of the community during remedial actions – this aspect of short-term effectiveness addresses any risk that results from implementation of the proposed remedial action, such as dust from excavation, transportation of hazardous materials, or air-quality impacts from a stripping tower operation that may affect human health. • Protection of workers during remedial actions – this factor assesses threats that may be posed to workers and the effectiveness and reliability of protective measures that would be taken. • Environmental impacts – this factor addresses the potential adverse environmental impacts that may result from the construction and implementation of an alternative and evaluates the reliability of the available mitigation measures in preventing or reducing the potential impacts. <p>EPA (1988) states: “Alternatives should consider the potential threat to human health and the environment associated with excavation, transportation and re-disposal, or containment.</p> <p>Offsite transport and disposal without treatment is the least favored alternative where practicable treatment technologies are available.”</p> <p>Thus, the laws of the land generally require federal agencies, such as EPA, to evaluate the real world implications of their proposed actions. In the case of the External Review Draft: Toxicological Review of Trichloroethylene, EPA has not performed any sort of analysis that evaluates the costs or benefits of the proposed action or the relative risks to the population of implementing the proposed action, or that evaluates the proposed action in a real world context in any manner whatsoever.</p> <p>EPA has not validated its proposals to determine if they make any sense in the context of the real world. EPA routinely demands that validation exercises be performed whenever anyone develops a mathematical or biologically-based model. For instance, when hydrogeological experts develop a model to explain the movement of volatile chemicals through the subsurface environment and into the basement of dwellings, EPA demands that the models be validated with empirical measurements of soil gas and indoor air. When in vitro models are developed to measure the dissolution of lead from a soil matrix into synthetic gastrointestinal fluids to mimic the action of the animal gastrointestinal tract, EPA demands that the models be validated by running in vitro and in vivo studies side by side. When complicated groundwater flow models are developed, they, too, must be validated by the collection of actual measurement data to determine if the models are valid.</p> <p>EPA’s requirements for model validation are applied both internally and externally. Hundreds of cases of EPA-sponsored validation exercises can be cited. Yet, curiously, when EPA proposes to classify a substance as “Carcinogenic to Humans” and proposes a URF that will govern environmental decision making for decades with regard to the safety of the nation’s drinking water, the safety of consumer products, the clean-up of soil and groundwater at hundreds of sites that were affected by chemical spills and releases, and the safety of air in industrial, commercial, and residential buildings, EPA does not take the time to perform even the simplest of validation exercises.</p> <p>ARCADIS finds that a validation exercise is absolutely required as part of a document that proposes a carcinogenic classification and URF for any chemical. Such an exercise is even more important for a chemical</p>	

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>such as TCE, which affects so many products, processes, sites, and buildings across the country. Because of the lack of any validation exercise, ARCADIS finds the EPA draft document on TCE to be deficient.</p> <p>In its Charge to External Peer Reviewers, EPA (2009) specifically asks the reviewers to comment on whether the proposal is “technically/scientifically adequate to support EPA’s draft inhalation and oral unit risks.” ARCADIS finds that without any validation assessment of any sort, the approach presented in the draft document is not “technically/scientifically adequate to support EPA’s draft inhalation and oral unit risks.”</p>	
5.2	46	EPA-HQ-ORD-2009-0791-0011.1	ARCADIS	<p>ARCADIS finds EPA’s proposed action to be deficient because the implications of the proposal were not discussed, and no validation exercise was performed to determine if cancer incidence predictions made with the proposed URF match the known incidence rates of RCC, liver and biliary cancer, and NHL in the context of the many well-characterized risk factors for these cancers. The preliminary information presented above is provided for EPA’s consideration, because ARCADIS is recommending that EPA not issue a carcinogen classification and a URF for an important chemical such as TCE without assessing the implications of the action and validating the proposed action against the known facts.</p> <p>In addition, ARCADIS notes that the TCE concentration that poses a residential excess lifetime cancer risk of 1×10^{-6} is $0.25 \mu\text{g}/\text{m}^3$. According to the EPA’s 1999 TO-15 method, the method detection limits for TCE in indoor air are $2.42 \mu\text{g}/\text{m}^3$, or $0.38 \mu\text{g}/\text{m}^3$ if Selective Ion Monitoring is used. A target risk of 1×10^{-6} is used by EPA and State governments when defining vapor intrusion screening levels. Thus, the practical implications of EPA’s proposed URF will be to set national policy for vapor intrusion such that TCE concentrations below detection limits will drive costly and time consuming investigations.</p> <p>ARCADIS is aware that some laboratories now offer, at additional cost, analytical methods that have reporting limits less than $0.25 \mu\text{g}/\text{m}^3$. However, $0.25 \mu\text{g}/\text{m}^3$ is well below the typical indoor air concentrations of TCE detected in many different indoor air quality studies. Applying a vapor intrusion screening level that is less than typical indoor background levels will derail the goals of vapor intrusion studies, which are to detect, study, and mitigate vapor intrusion into homes from nearby spills and releases of volatile constituents, not indoor sources of VOCs.</p>	- -
5.2	76	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>1.3 Mode of Action for Kidney Toxicity and Carcinogenicity (for additional technical detail see the comments of Prof. Dekant): EPA considers that the formation of DCVC from TCE and its activation in kidneys of rats, mice and humans to be the cause of toxicity and, through genotoxicity, tumor formation. A balanced evaluation of the evidence simply does not support these opinions. The summary of Prof. Dekant’s review is as follows:</p> <p>From the known potency of DCVC administered directly to rats, the toxicity of TCE in chronic or long term experiments in rats cannot be explained solely on the extent of DCVC production and activation. The generation of a flood of formic acid through the kidney of rats exposed to TCE (by a mechanism fully understood) does lead to recognizable kidney damage. Although EPA dismisses formic acid because histopathological damage appears to be different between that seen for trichloroethanol (generates formic acid only – no DCVC component) and TCE, it appears highly likely that a combination of DCVC and formic acid damage underlies kidney toxicity in the rat. In mice, less formic acid is released following TCE administration and DCVC activation is greater in mouse kidney which suggests that DCVC may play a greater role in mouse kidney toxicity. Since DCVC is not a highly potent kidney toxicant, the very low levels generated in man are unlikely to cause kidney toxicity. Human experience supports this: Despite historical occupational exposures greater than 100 ppm on an 8 hour time-weighted-average with peak exposures reaching many thousand ppm, kidney disease has not been associated with TCE. Those studies in which markers of kidney damage have been studied have not provided clear evidence of an effect of TCE in man. The conclusion must be that kidney damage is highly unlikely to occur at current occupational exposure levels (ACGIH TLV is 10 ppm, 8 hour TWA) and of no concern for the general population.</p> <p>EPA considers that kidney tumors in rats result from the genotoxicity following DCVC activation. The reasons to consider this to be improbable are 1) That DCVC, although positive in in vitro bacterial mutagenicity tests (following activation by endogenous bacterial enzymes or enhanced by exogenous rat kidney preparations), has</p>	<p>AUTHOR: Paul H. Dugard, Halogenated Solvents Industry Alliance, Inc.</p> <p>Terracini, B., and Parker, V. H. (1965). A Pathological Study on the Toxicity of S-Dichlorovinyl-L-Cysteine. Food Cosmet Toxicol 3, 67-74.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>not been found, in credible studies, to be anything more than weakly genotoxic in vivo. 2) Combining the weak genotoxicity with the low levels generated in rats does not indicate a primary role for generation of tumors by a genotoxic mechanism. 3) The single long term experiment involving direct administration of DCVC to rats did not generate tumors in a protocol which would have been expected to show induction of tumors by a genotoxic mechanism (Terracini and Parker, 1965). This study cannot be used to “prove the negative” (i.e. DCVC is not a kidney carcinogen) but, despite its age, was well designed and conducted. 4) DCVC activation in the mouse kidney is greater than in rat kidney but kidney tumors have not been induced by TCE in any study. A genotoxic mode of action might have been expected to induce tumors in mice.</p> <p>On balance, rat kidney tumors are unlikely to have arisen via a genotoxic mechanism following TCE administration. Since tumors have only been induced at dose levels of TCE that cause frank kidney toxicity, and male rats have a recognized tendency to develop kidney tumors under circumstances of repeated damage-repair cycles, this seems to be the most plausible mode of action.</p> <p>Whether the incidence of rat kidney tumors should be used to calculate human cancer risk is debatable, but if such calculations are employed, a non-linear MoA should be assumed.</p>	
5.2	77	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>1.4 Use of Epidemiological Data to Calculate Cancer Potency: The NRC (2006) review of the 2001 IRIS draft document stated that epidemiology studies available at that time were unsuitable for calculations of cancer slope factors to be used for regulatory purposes. Calculations using epidemiological data were considered acceptable for comparison with animal-based calculations only. The 2009 IRIS draft document derives a slope factor based upon the Charbotel et al. (2006) case control study of renal cell carcinoma and TCE exposure. This study is better than many TCE epidemiology studies but it must be questioned whether it provides a sufficiently robust starting point for calculation of a slope factor that will form the basis of regulations, setting vapor intrusion limits and other factors having significant impact on societal resources. The Charbotel et al (2006) study shows the significance of confounders on the outcome of the analysis and, with confounders taken into account, the elevation of incidence above unity is too small and uncertain to be used in a firm calculation. The dose response relationship reported in the study is heavily dependent upon the exposure assessment for a very small number of individuals and is therefore less robust than statistical evaluation would suggest. It is interesting that EPA takes the Charbotel et al (2006) study as the primary evidence for a causal relationship between TCE and renal cell carcinoma; Charbotel herself concludes that the study “...suggests an association between exposures to high levels of TCE and increased risk of RCC.”</p> <p>The supposed agreement between the cancer slope factors derived from rat data and the Charbotel study is not real. The slope factor derived from rat data involves an inter-species conversion based on the erroneous estimate of high DCVG production and activation of DCVC in humans and the slope factor is higher because of that. As discussed above, rat kidney tumors are most likely to have developed as a result of a non-genotoxic MoA and a non-linear dose response relationship, if any should be assumed.</p> <p>It is recommended that a calculation of cancer slope factor based on Charbotel et al (2006) is used only for comparison with results from animal studies.</p>	<p>AUTHOR: Paul H. Dugard, Halogenated Solvents Industry Alliance, Inc.</p> <p>-</p>
5.2	104	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>2. The role of glutathione S-conjugates in nephrotoxicity and renal tumor formation by TCE</p> <p>Since S-conjugates of TCE are nephrotoxic in rodents and genotoxic in vitro, it is appealing to conclude that S-conjugate formation is involved in nephrotoxicity of TCE and that the MoA for kidney tumor formation is genotoxicity. However, a number of contradictory findings are not adequately considered in the IRIS-document:</p> <p>* Formation rates for DCVC in subcellular fractions from mice and rats are similar (or even higher in mice) suggesting similar doses of DCVC to the kidney in both species (Green et al., 1997a; Kim et al., 2009). Moreover, activation of TCE by the β-lyase pathway is higher in mice (Eyre et al., 1995), DCVC is more nephrotoxic in mice, and causes higher rates of cell replication and covalent binding in mice as compared to rats (Eyre et al., 1995; Green et al., 1997a). Yet, mice are not sensitive to TCE induced renal tumor formation.</p> <p>* Based on the nephrotoxicity of DCVC and the low rates of formation of DCVC both in rats and mice in vivo, it is questionable if the very low concentrations of DCVG formed in rodents can explain nephrotoxicity and tumor</p>	<p>AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany</p> <p>Green, T., Dow, J., Ellis, M. K., Foster, J. R., and Odum, J. (1997a). The role of glutathione conjugation in the development of kidney tumours in rats exposed to trichloroethylene. <i>Chemico-Biological Interactions</i> 105, 99-117.</p> <p>Kim, S., Kim, D., Pollack, G. M., Collins, L. B., and Rusyn, I. (2009). 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. <i>Toxicol Appl Pharmacol</i> 238, 90-99.</p> <p>Eyre, R. J., Stevens, D. K., Parker, J. C., and Bull, R. J. (1995). Acid-labile adducts to protein can be used as indicators of the cysteine S-conjugate pathway of trichloroethene metabolism. <i>J Toxicol Environ Health</i> 46, 443-464.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>formation. Extrapolating the DCVC blood concentrations observed after single doses to the doses applied in the carcinogenicity studies with TCE in rats, daily DCVC-doses in the two year studies were less than 0.03 mg/kg bw. This is orders of magnitude below the doses of DCVC required to induce nephrotoxicity during chronic administration (Terracini and Parker, 1965) and further questions an involvement of this pathway in nephrotoxicity of TCE.</p> <p>* EPA concludes that trichloroethanol and formic acid formation may not be involved in the toxicity of TCE to the kidney due to differences in pathology observed between TCE and trichloroethanol treated rats. In my opinion, such comparisons are difficult since differences in the kinetic profiles of a compound formed as a metabolite or administered per se are likely major confounders. The mode of action for TCE-induced renal tumors due to effects of increased formic acid excretion due to disturbances in intermediary metabolism by trichloroethanol is supported by renal toxicity of trichloroethanol, insufficient rates of DCVC/DCVC-formation to account for renal toxicity and the absence of genotoxic effects of TCE on rat kidney in vivo.</p> <p>* EPA states that data on VHL gene mutations support a mutagenic MoA in TCE-induced kidney tumors. This is based on studies (Bruning et al., 1997; Brauch et al., 2004) reporting VHL mutations in renal tumors of TCE-exposed individuals. It is concluded that comparison of TCE-exposed and non-exposed patients (Brauch et al., 2004) revealed clear differences with respect to (1) frequency of somatic VHL mutations, (2) incidence of C454T transition, and (3) incidence of multiple mutations. As discussed in Brauch et al. (2004), the mutation frequency in the non-exposed patients (10%) was considerably lower than that commonly observed in sporadic renal tumors, e.g. 82% (Nickerson et al., 2008) or 71% (Banks et al., 2006), and technical problems using archived tissue samples may be one of the causes. Given that exon 3, which harbors the multiple mutations seen in TCE exposed patients, did not amplify in most of the controls, there is only limited evidence for a difference in the incidence of multiple mutations and frequency of somatic VHL mutations, although the C454T transition appears to be characteristic of tumors in TCE exposed patients. However, the presence of mutations in human tumors does not lead to the conclusion that VHL mutations occur early during carcinogenesis. Hence, they are not evidence for a direct genotoxicity of TCE in the kidney. In contrast, experimental data in rats show that neither TCE nor its active metabolite DCVC induce VHL mutations (Mally et al., 2006), suggesting that VHL mutations in humans may be acquired at later stages of tumor development. While the document argues that the VHL gene may not be a target gene in rodent models of renal carcinogenesis, only few studies have looked at VHL in rats and there is no support for the hypothesis that the role of VHL is different in rats and humans.</p> <p>* The Eker rat may be a useful rodent model for renal cell carcinoma (RCC), but the molecular basis for chemically induced tumor formation in rats and RCC in humans may be widely different from spontaneous tumor formation in this rat strain, as high-grade RCCs can develop in the absence of mutations in the Tsc2 gene in rats (Toyokuni et al., 1998). Development of high-grade renal cell carcinomas in rats independently of somatic mutations in the Tsc2 and VHL tumor suppressor genes (Toyokuni et al., 1998) demonstrates that mutational inactivation of TSC2 or VHL is not a prerequisite for renal carcinogenesis. The similar pathway activation in Eker rat RCC as that seen in humans with VHL mutations reported (Liu et al., 2003) involves deregulation of HIFalpha and VEGF expression which frequently occur in various cancers and provide little evidence to suggest that Tsc-2 inactivation in rats is “analogous” to inactivation of VHL in human RCC.</p> <p>* Epidemiological data may support an association between specific VHL mutations and TCE exposure, this does not indicate an early event in RCC and – in the absence of experimental support - should not be taken as support for a mutational MoA.</p> <p>* EPA uses micronucleus and comet assay data in rat kidney after TCE-administration as support for a genotoxic MoA. However, the positive micronucleus (Robbiano et al., 2004) assay applied a very high dose and used an inappropriate route of administration (ip injection of ½ of the LD50). Due to the high dose applied and the route of administration, the results may be confounded by inflammatory responses and should not be used for conclusions. A comet assay in the kidney using repeated inhalation exposures to TCE was negative (Clay, 2008). The decision to not use this study in the assessment is insufficiently justified. The inhalation study used a higher number of animals (5/group) as compared to the ip study, which states n > 3 with an apparent maximum of 5. The comet assay also shows that administered DCVC is no more than weakly active in the kidney.</p>	<p>Terracini, B., and Parker, V. H. (1965). A Pathological Study on the Toxicity of S-Dichlorovinyl-L-Cysteine. <i>Food Cosmet Toxicol</i> 3, 67-74.</p> <p>Bruning, T., Weirich, G., Hornauer, M. A., Hofler, H., and Brauch, H. (1997). Renal cell carcinomas in trichloroethene (TRI) exposed persons are associated with somatic mutations in the von Hippel-Lindau (VHL) tumour suppressor gene. <i>Arch Toxicol</i> 71, 332-335.</p> <p>Brauch, H., Weirich, G., Klein, B., Rabstein, S., Bolt, H. M., and Bruning, T. (2004). VHL mutations in renal cell cancer: does occupational exposure to trichloroethylene make a difference? <i>Toxicol Lett</i> 151, 301-310.</p> <p>Nickerson, M. L., Jaeger, E., Shi, Y., Durocher, J. A., Mahurkar, S., Zaridze, D., Matveev, V., Janout, V., Kollarova, H., Bencko, V., Navratilova, M., Szeszenia-Dabrowska, N., Mates, D., Mukeria, A., Holcatova, I., Schmidt, L. S., Toro, J. R., Karami, S., Hung, R., Gerard, G. F., Linehan, W. M., Merino, M., Zbar, B., Boffetta, P., Brennan, P., Rothman, N., Chow, W. H., Waldman, F. M., and Moore, L. E. (2008). Improved identification of von Hippel-Lindau gene alterations in clear cell renal tumors. <i>Clin Cancer Res</i> 14, 4726-4734.</p> <p>Banks, R. E., Tirukonda, P., Taylor, C., Hornigold, N., Astuti, D., Cohen, D., Maher, E. R., Stanley, A. J., Harnden, P., Joyce, A., Knowles, M., and Selby, P. J. (2006). Genetic and epigenetic analysis of von Hippel-Lindau (VHL) gene alterations and relationship with clinical variables in sporadic renal cancer. <i>Cancer Res</i> 66, 2000-2011.</p> <p>Mally, A., Walker, C. L., Everitt, J. I., Dekant, W., and Vamvakas, S. (2006). Analysis of renal cell transformation following exposure to trichloroethene in vivo and its metabolite S-(dichlorovinyl)-L-cysteine in vitro. <i>Toxicology</i> 224, 108-118.</p> <p>Toyokuni, S., Okada, K., Kondo, S., Nishioka, H., Tanaka, T., Nishiyama, Y., Hino, O., and Hiai, H. (1998). Development of high-grade renal cell carcinomas in rats independently of somatic mutations in the Tsc2 and VHL tumor suppressor genes. <i>Jpn J Cancer Res</i> 89, 814-820.</p> <p>Liu, M. Y., Poellinger, L., and Walker, C. L. (2003). Up-regulation of hypoxia-inducible factor 2alpha in renal cell carcinoma associated with loss of Tsc-2 tumor suppressor gene. <i>Cancer Res</i> 63, 2675-2680.</p> <p>Robbiano, L., Baroni, D., Carrozzino, R., Mereto, E., and Brambilla, G. (2004). DNA damage and micronuclei induced in rat and human kidney cells by six chemicals carcinogenic to the rat kidney. <i>Toxicology</i> 204, 187-195.</p> <p>Clay, P. (2008). Assessment of the genotoxicity of trichloroethylene and its metabolite, S-(1,2-dichlorovinyl)-L-cysteine (DCVC), in the comet assay in rat kidney. <i>Mutagenesis</i> 23, 27-33.</p> <p>Swenberg, J. A., and Lehman-McKeeman, L. D. (1999). a2u-Globulin associated nephropathy as a mechanism of renal tubular cell carcinogenesis in male rats. In <i>IARC-Scientific Publications: Species differences in thyroid, kidney and urinary bladder carcinogenesis</i> (C. C. Capen, E. Dybing, J. M. Rice, and J. D. Wilbourn, Eds.), pp. 95-118. International Agency on Cancer Research, Lyon.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>* EPA argues that there is no link between nephrotoxicity and renal tumor formation. However, there are a number of compounds that cause renal tumors in rats without being genotoxic. For example, cytotoxicity and regenerative cell proliferation (Swenberg and Lehman-McKeeman, 1999) is accepted as MoA for ALPHA2U-globulin binding agents (TCE does not bind to ALPHA2u-globulin, but is most likely to cause renal tumors through nephrotoxicity).</p> <p>In summary, the data do not support a genotoxic mode of action for kidney carcinogenicity via S-conjugates of TCE. The decision of EPA to employ S-conjugate-mediated genotoxicity in support of a linear dose response relationship for renal cell carcinoma should be revised to reflect the balance of the data. A non-linear dose response relationship is well supported by the available evidence.</p>	
5.2	183	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	Classification of TCE as "carcinogenic to humans". AIA supports both the Department of Defense (DOD) and the National Aeronautics and Space Administration (NASA) position that the classification of TCE as a known human carcinogen is neither supported by the evidence nor consistent with EPA's Guidelines for Carcinogen Risk Assessment (2005).	AUTHOR: Lisa Goldberg -
5.2	193	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>Application of the Guidelines to Trichloroethylene</p> <p>In considering the data in the context of applying the "carcinogenic to humans" descriptor, one first considers the weight of the epidemiological evidence. We judge the epidemiologic evidence to be neither "convincing" nor "strong," two key terms in the guidelines. This judgment is based on four recent reviews and meta-analyses of occupational TCE exposures and cancer as well as other reviews of this literature (Alexander et al., 2006, 2007; Mandel et al., 2006; Kelsh et al., 2010). The recent review and meta-analysis by Kelsh et al., 2010 focuses on occupational TCE exposure and kidney cancer; and includes the recent Charbotel 2006 study that is emphasized in the EPA assessment and used by EPA scientists to conduct a quantitative risk assessment. Both the EPA meta-analysis and the recently published Kelsh et al. meta-analysis of the TCE-kidney cancer epidemiologic literature produced similar summary results. However in Kelsh et al., the limitations of this body of research, namely exposure assessment limitations, potential unmeasured confounding, potential selection biases, and inconsistent findings across groups of studies, did not allow for a conclusion that there is sufficient evidence of a causal association, despite a modest overall association. In addition, although the recent Charbotel et al. 2006 study has made important improvements in exposure assessment, it still has important potential limitations that do not permit an appropriate use in quantitative risk assessment.</p>	<p>AUTHORS: Michael Dourson, Ph.D., DABT and Lynne Haber, Ph.D., DABT from Toxicology Excellence for Risk Assessment and Michael Kelsh, Ph.D., MPH and Dominik Alexander, Ph.D., MPH from Exponent, Health Sciences</p> <p>Alexander DD, Kelsh MA, Mink PJ, Mandel JH, Basu R, Weingart W. A meta-analysis of occupational trichloroethylene exposure and liver cancer. <i>Int Arch Occup Environ Health</i> 2007; 81(2):127-143.</p> <p>Alexander DD, Mink PJ, Mandel JH; Kelsh MA. A meta-analysis of occupational trichloroethylene exposure and multiple myeloma or leukemia. <i>Occup Med</i> 2006; 56(7):485-93.</p> <p>Mandel JH, Kelsh MA, Mink PJ, Alexander D, Kalmes RM, Weingart M, Yost L Goodman M. Occupational trichloroethylene exposure and non-Hodgkins lymphoma: A meta-analysis and review. <i>Occup Environ Med</i> 2006; 63(9):597-607.</p> <p>Kelsh MA, Alexander DD, Mink PJ, Mandel JH. Occupational trichloroethylene exposure and kidney cancer: a meta-analysis. <i>Epidemiology</i>. 2010 Jan;21(1):95-102.</p> <p>Charbotel B, Fevotte J, Hours M, martin J, Beregeret A. Case-Control Study on Renal Cell Cancer and Occupational Exposure to Trichloroethylene. Part 11: Epidemiological Aspects. <i>Ann.Occup.Hyg.</i> 2006.</p>
5.2	195	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>There are reasonably well designed and well conducted epidemiologic studies that report no association between TCE and cancer, some reasonably well designed and conducted studies that did report associations between TCE and cancer, and finally some relatively poorly designed studies reporting both positive and negative findings. Overall, the summary relative risks or odds ratios in the meta-analysis studies (EPA or published meta-analyses) generally ranged between 1.2 and 1.4. The IRIS document refers to these associations as "small;" a term not typically consistent with "convincing" and strong." Weak or small associations may be more likely to be influenced or be the result of confounding or bias. Smoking and body mass index are well-established risk factors for kidney cancer, and smoking and alcohol are risk factors for liver cancer, yet the potential impact of these factors on the meta-analysis associations was not fully considered. There were suggestions that these factors may have impacted findings (e.g. in the large Danish cohort study of TCE exposed workers, tile researchers noted that smoking was more prevalent among the TCE exposed populations however little empirical data were provided (Raachou-Nielson et al., 2003). In addition, collinearity of occupational exposures (i.e. TCE exposure correlated with chemical and/or other exposures) may make it difficult to isolate potential effects of TCE from those of other exposures within a given study, and hinder interpretation across studies. For example, although Charbotel et al. (2006) reported potential exposure response trends; while controlling for many confounders of concern (which strengthens the weight of evidence), they also reported attenuated associations for cumulative TCE exposure after adjustment for exposure to cutting fluids and other petroleum oils (weakening the weight of the evidence). This study is also limited due to other by potential study design considerations such as selection bias, self report of work histories, residual confounding and other design factors.</p>	<p>AUTHORS: Michael Dourson, Ph.D., DABT and Lynne Haber, Ph.D., DABT from Toxicology Excellence for Risk Assessment and Michael Kelsh, Ph.D., MPH and Dominik Alexander, Ph.D., MPH from Exponent, Health Sciences</p> <p>Raachou-Nielson O et al. Cancer risk among workers at Danish companies using trichloroethylene: a cohort study. <i>Am.J.Epidemiol.</i> 2003;158:1182-92.</p> <p>Charbotel B, Fevotte J, Hours M, martin J, Beregeret A. Case-Control Study on Renal Cell Cancer and Occupational Exposure to Trichloroethylene. Part 11: Epidemiological Aspects. <i>Ann.Occup.Hyg.</i> 2006.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
5.2	241	EPA-HQ-ORD-2009-0791-0019.1	Patton Boggs LLP	Charbotel et al. 2006 * Used by EPA to estimate dose-response * Considered in both EPA and NAS assessments * Cannot be considered "convincing evidence of a causal association" * Rather, "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 lower levels of exposure."	- -
5.2	252	EPA-HQ-ORD-2009-0791-0012.1	McKenna, Long & Aldrige, LLP	Quote from Charbotel et al 2006 "The results of the present study do not agree with the negative results obtained by a number of large cohort studies. ... Although this study shows a possible link between high levels of exposure to TCE and increased risk of RCC, further epidemiological studies are necessary to assess the effect of lower levels of exposure."	- -
5.2	254	EPA-HQ-ORD-2009-0791-0012.1	McKenna, Long & Aldrige, LLP	Data support nonlinear dose-response for cancer, at least in part of the dose-response range • The argument for linear is not strong enough to support it being the only model presented. • The 2005 EPA Cancer Guidelines say that both models should be presented, or a dual model used in a case like this. • Again, give risk managers more of the science and show the whole dose-response and the effects of considering both modes of action.	- -
5.2	271	EPA-HQ-ORD-2009-0791-0014.1	Exponent Health Services	EPA's Toxicological Review of Trichloroethylene (TCE) External Review Draft: Comments Regarding Meta-Analysis of Epidemiologic Studies and Use of the Charbotel et al. 2006 Study in Quantitative Risk Assessment EPA concluded that the epidemiologic data were robust and consistent, and, in some cases, strongly supportive of providing evidence of trichloroethylene (TCE) carcinogenicity. Other reviews and meta-analyses have not reached these same conclusions, noting heterogeneity of findings (i.e. lack of consistent findings), lack of consistent exposure response evidence, and other methodological problems of the epidemiologic studies. With respect to the case-control studies of Charbotel et al. 2006, EPA considered this sufficient data for quantitative doseresponse modeling. Although Charbotel et al. 2006 have provided individual level TCE exposure estimates, limitations in the exposure assessment and study design features of this study do not permit use of Charbotel et al. 2006 data in more quantitative dose response or cancer slope factor modeling. Selection bias, where renal cell cancers among screw-cutting industry workers are more likely to be enrolled in the case control study than other renal cell cancers, is a concern, the fact that forty percent of exposure assignments of renal cancer case are based on qualitative TCE exposure assessment procedures, and the reliance on self-reported work history are important limitations that do not permit use of Charbotel et al 2006 data in quantitative risk analysis. Based on full consideration of guidelines used to determine causality from epidemiologic data, a more appropriate classification of TCE carcinogenicity would be either "suggestive evidence of carcinogenicity" or "likely carcinogenic."	- Charbotel, B; Fevotte, J; Hours, M; et al. (2006) Case-control study on renal cell cancer and occupational exposure to trichloroethylene. Part II: Epidemiological aspects. Ann Occup Hyg 50(8):777-787.
5.2	277	EPA-HQ-ORD-2009-0791-0014.1	Exponent Health Services	We were asked to provide comments to the recent EPA External Review Draft for the Toxicological Review of TCE (dated October 2009) by companies and associations involved as users of TCE or in TCE remediation. Our work in the evaluation of the epidemiologic literature of occupational TCE exposure and cancer has provided us with in-depth knowledge and familiarity with much of the epidemiologic research on this chemical. EPA staff have prepared a comprehensive review of the epidemiologic studies of TCE exposure and cancer and non-cancer outcomes. In addition, they performed a quantitative risk assessment of cancer relying on one epidemiologic	- Charbotel, B; Fevotte, J; Hours, M; et al. (2006) Case-control study on renal cell cancer and occupational exposure to trichloroethylene. Part II: Epidemiological aspects. Ann Occup Hyg 50(8):777-787. Boice JD, Jr. et al. Mortality among aircraft manufacturing workers. Occup.Environ.Med.

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>study, Charbotel et al. 2006, which is a case-control study that was conducted in a region in France where workers in the screw cutting industry likely experienced relatively high TCE exposures. These comments focus on various issues relating to epidemiologic studies of TCE exposure and cancer and the use of the Charbotel study data in a quantitative cancer risk assessment.</p> <p>EPA’s meta-analysis methods and summaries, for the most part, are consistent with recent published summaries of this literature – however, EPA’s interpretation of the meta-analysis findings is not consistent with the general approaches used in evaluating causality from epidemiologic research study evaluation. Epidemiologic causal evaluation considers not only the presence of a statistical association, but also the strength of that association, whether exposure response trends are present, the consistency of study findings, biologic plausibility, coherence, and other factors (Hill 1965; Weed 2005). Although EPA considers these factors, their conclusions are not supported once these factors are applied to the epidemiologic literature. The epidemiologic literature on TCE exposure and cancer cannot be categorized as “strong” or “robust” or of sufficient quality to provide definitive evidence of a causal association between TCE exposure and cancer. The observed summary relative risk estimates from the meta-analyses of kidney cancer, liver cancer, and non-Hodgkin’s lymphoma (NHL) are not sufficiently strong to be able to rule out other potential explanations such as bias due to confounding, exposure misclassification, or other factors (e.g. selection bias in case control studies). The consistency of the findings is not as robust as characterized in the EPA review. For example, in the kidney cancer analyses, the evaluation of cohorts defined from biomonitoring data, a source of exposure information considered more accurate than other exposure assessment characterizations, found no association with kidney cancer. Although these studies were small, these results merit consideration. In addition, several large cohort studies of aerospace/aircraft maintenance workers (e.g. Radican et al. 2008; Boice et al. 1999) reported no association between TCE exposure and kidney cancer. The EPA review recognizes the significant limitations of several German studies of TCE exposure and kidney cancer (e.g., Henchler et al., Vamvakas et al.) and did not include them in their meta-analysis summaries; a decision consistent with a recently published meta-analysis of TCE and kidney cancer (Kelsh et al., 2010). In summary, it is important to emphasize that the magnitude of the summary estimate in the EPA meta-analysis of kidney cancer was modest (relative risk =1.25). Furthermore given the range and imprecision of the individual study findings, with many studies reporting no increased risks, it is more accurate to report the study results as “mixed” rather than consistent or robust.</p> <p>In the latest EPA Toxicological Review of TCE, it is apparent that many of the issues and concerns raised in the methodological review of the inter-agency draft with respect to the metaanalysis of epidemiologic studies of TCE exposure and cancer of have been addressed. However, some important matters remain, particularly regarding the interpretation of the currently available epidemiologic evidence. In the widely read textbook Modern Epidemiology (Rothman, Greenland and Lash 2008), Greenland and O’Rourke describe the two main goals of meta-analysis: to estimate differences among study-specific effects (analytic goal) and/or to estimate an average effect across studies (synthetic goal). They further remind readers that “a sound meta-analysis needs to assess each study’s limitations as well as gaps in the entire literature being assessed.” Thus, while a meta-analysis may serve as a valuable tool for analyzing data across a large body of scientific studies to produce a more precise estimate of relative risk, interpretation of summary findings should be made in consideration of several important methodological factors (e.g. exposure misclassification, confounding and selection bias) and guidelines for evaluation of causality based on epidemiologic data (Hill 1965; Weed 2005). Indeed, meta-analysis and causal inference are separate endeavours with different methods.</p> <p>Most epidemiologic studies of TCE exposure and cancer observed associations that were not statistically significant and most studies lacked quantitative exposure assessments. Across epidemiologic studies, different exposure metrics were used, exposure-response patterns were inconsistently observed, and uncontrolled (or incompletely controlled) confounding and other sources of systematic error likely influenced effect estimates. EPA conducted various sensitivity analyses (excluding individual studies to assess their impact on summary relative risk estimates); however, important evaluations such as summarization by sub-group characteristics, study design differences, or findings by exposure measurement method were not presented or fully considered. It is unfortunate that EPA did not conduct exposure-response analyses by specific exposure metrics, such as cumulative dose or years of exposure. Because “dose-response” is an important consideration in the evaluation of epidemiologic studies for causality, we evaluated exposure-response data to the extent possible in our published meta-analyses and observed no clear pattern of increasing cancer risk with increasing exposure level or duration</p>	<p>1999;56:581-97.</p> <p>Hill AB. The Environment and Disease: Association or Causation? Proc R Soc Med 1965; 58: 295-300.</p> <p>Kelsh MA, Alexander DD, Mink PJ, Mandel JH. Occupational trichloroethylene exposure and kidney cancer: a meta-analysis. Epidemiology. 2010 Jan;21(1):95–102.</p> <p>Lash TL. Bias analysis applied to Agricultural Health Study publications to estimate non-random sources of uncertainty. J Occup Med Toxicol. 2007 Nov 26;2:15.</p> <p>Radican L, Blair A, Stewart P, Wartenberg D. Mortality of aircraft maintenance workers exposed to trichloroethylene and other hydrocarbons and chemicals: An extended follow-up. J Occup Environ Med 2008; 50(11): 1306–19</p> <p>Weed DL. Weight of Evidence: A Review of Concept and Methods. Risk Analysis, Vol. 25, No. 6, 2005</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				(Kelsh et al 2010; Mandel et al 2006; Alexander et al. 2007; Alexander et al., 2006). Such an analysis by EPA would provide helpful information in the consideration of potential relationships between TCE and cancer. In summary, although EPA conducted a comprehensive meta-analysis and examined many issues in the epidemiologic data, EPA's conclusions regarding the carcinogenicity of TCE are not supported by the studies they cite.	
5.2	287	EPA-HQ-ORD-2009-0791-0014.1	Exponent Health Services	<p>Use of Epidemiologic Data for Quantitative Cancer Risk Assessment</p> <p>Epidemiologic data are frequently limited, especially in the area of detailed and accurate exposure information for quantitative risk assessment and slope factor estimation. Consideration of the representativeness of the population studied, generalizability of the study results, and the overall strengths and limitations of the epidemiologic study should also be considered in selecting data for quantitative risk assessment. Although Charbotel et al. made significant improvements in their exposure assessment compared to other epidemiologic studies of TCE and cancer, it is still at best a semi-quantitative method for screw cutting workers and a qualitative method for other TCE exposed workers, who comprised 40% of the exposed cases. In addition, potential limitations in the study design such as representativeness of the study population, reliance on self-report of work history information, potential selection and confounding bias concerns, and the fact that the better exposure assessment procedures do not apply to approximately 40% of the exposed cases are important reasons why it is inappropriate to rely only on Charbotel et al. data for slope factor estimation purposes.</p>	-
5.2	288	EPA-HQ-ORD-2009-0791-0014.1	Exponent Health Services	<p>Specific Comments on Use of Charbotel et al. 2006 Study for Dose Response Modeling in EPA's External Review Draft of Trichloroethylene</p> <p>EPA relied on epidemiologic and exposure data reported in the Charbotel et al. study of renal cell cancers to conduct dose response modeling and to estimate the cancer slope factor for TCE. Specifically, this case-control study evaluated renal cell cancer among residents in the Arve Valley region of France. This region had been selected for study because of the prominent screw cutting industry where TCE was used as a degreaser and solvent and for which relatively high TCE exposure occurred among workers (Fevotte et al., 2006). It was estimated that there were approximately 650 shops employing about 7,000 workers in the 1970s (500 of the shops employed less than five workers), and 750 shops employing about 12,000 workers in 1982 (600 employed less than 10 workers) [Fevotte et al., 2006].</p> <p>Although the Charbotel et al. study was able to take advantage of TCE exposure data collected over the years by occupational physicians in the region, numerous uncertainties exist that argue against relying only upon these data and the reported epidemiologic findings from this study for use in quantitative risk assessment. In addition, exposure data from other studies (e.g. Scandinavian studies, aerospace workers studies) should be further explored to assess whether more refined semi-quantitative job exposure matrices can be developed and used rather than relying exclusively on the Charbotel et al. study findings. Many of these limitations and uncertainties are noted in the EPA assessment; however, some were not discussed in the EPA report. These important methodological concerns include the following:</p> <ul style="list-style-type: none"> · Potential selection bias. No cancer registry was available for this region to identify all relevant renal cell cancer cases from the target population. Case ascertainment relied on records of local urologists and regional medical centers; therefore, selection bias is possible as a result of this process. Given the concerns of the medical community in this region regarding renal cell cancer (RCC) among screw cutting industry workers, it is likely that any cases of renal cell cancer among these workers would likely be diagnosed earlier. It is also much more unlikely that a RCC case among these workers would be missed compared to the chance of missing an RCC case among other workers not exposed to TCE. This preference in identifying cases among screw cutting industry workers would bias findings in an upward direction. · General uncertainties in retrospective exposure assessment. Industrial hygiene data have to be linked to self-reported (or proxy reported) work histories, which may be inaccurate resulting in exposure misclassification. It is not possible to predict with certainty whether such bias is more likely to be differential or non-differential. Given 	<p>-</p> <p>Anttila, A; Pukkala, E; Sallmén, M; et al. (1995) Cancer incidence among Finnish workers exposed to halogenated hydrocarbons. <i>J Occup Environ Med</i> 37:797–806.</p> <p>Axelsson, O; Selden, A; Andersson, K; et al. (1994) Updated and expanded 1 Swedish cohort study on trichloroethylene and cancer risk. <i>J Occup Med</i> 36:556–562.</p> <p>Boice JD, Jr. et al. Mortality among aircraft manufacturing workers. <i>Occup. Environ. Med.</i> 1999;56:581-97.</p> <p>Charbotel, B; Fevotte, J; Hours, M; et al. (2006) Case-control study on renal cell cancer and occupational exposure to trichloroethylene. Part II: Epidemiological aspects. <i>Ann Occup Hyg</i> 50(8):777–787.</p> <p>Fevotte, J; Charbotel, B; Muller-Beaute, P; et al. (2006) Case-control study on renal cell cancer and occupational exposure to trichloroethylene. Part I: Exposure assessment. <i>Ann Occup Hyg</i> 50:765–775.</p> <p>Hansen, J; Raaschou-Nielsen, O; Christensen, JM; et al. (2001) Cancer incidence among Danish workers exposed to trichloroethylene. <i>J Occup Environ Med</i> 43:133–139.</p> <p>Radican L, Blair A, Stewart P, Wartenberg D. Mortality of aircraft maintenance workers exposed to trichloroethylene and other hydrocarbons and chemicals: An extended follow-up. <i>J Occup Environ Med</i> 2008; 50(11): 1306–19</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>that there were numerous screw cutting shops in the region employing a small number of employees at each shop, substantial exposure variation can be expected that may not have been captured in the exposure assessment process. The EPA report recognizes this limitation, but did not sufficiently consider its potential impact, which should be evaluated in further sensitivity analyses that consider potential recall bias and exposure variability across the many different screw-cutting industry sites.</p> <ul style="list-style-type: none"> · The quality of TCE exposure information, and the type of questionnaire instrument used to collect TCE exposure and work history information varied between the screw-cutting workers and other workers. The Charbotel et al. study relied upon different questionnaires and exposure assessment methods to collect data from screwcutting industry workers and other workers who may have been exposed to TCE. Roughly 75% (64 of 86) of the cases had TCE exposure from non-screw cutting exposures [Table 3 in Charbotel et al. 2006]. Non-screw cutting industry workers had a much less specific work history questionnaire and TCE exposure matrix than the screw cutting industry workers. Thus the TCE exposure information in the Charbotel et al. study that is supported by industrial hygiene and biomonitoring data is accurate for about 60% of the exposed cases – and still relies on linkage to self-reported work history information. The other 40%, a significant proportion of the number of cases, was due to exposures from other work, for which the exposure assessment process was much less quantitative. This information bias may have impacted observed associations in the study. · Potential confounding due to other workplace exposures. Screw cutting industry workers used a variety of oils and other solvents. Charbotel et al. reported lower risks for TCE exposure and renal cell cancer once data were adjusted for cutting oils. In fact, they noted, “Indeed, many patient 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.” This uncertainty questions the reliability of using data from Charbotel et al. in TCE risk assessment. · Representativeness of the Arve Valley population. The health and exposure experience of the Arve Valley residents, including screw cutting industry employees, may be distinct from other populations. It may not be appropriate to rely on this one unique population to generalize about health risks in the more heterogeneous worker populations in the United States. EPA acknowledged this potential limitation. · Relatively small sample size. In the Charbotel et al. case-control study, there were 16 exposed cases (out of a total of 84 cases who were assigned semi-quantitative TCE exposure scores) in the high exposure level category that essentially drives the findings for “TCE exposure response patterns.” Generalizing interpretations from a relatively small sample size from a specific workforce may result in biased risk assessments across broader populations. In fact the epidemiology of TCE exposure and cancer is in general limited by small numbers of exposed cases from which relative risks are calculated. The EPA report acknowledges this limitation. · Control selection procedures may have produced bias. It is well known that hospitalbased controls, like those selected in the Charbotel et al. study, may not provide a good reflection of the exposure or confounder prevalence in the source population. In this study, controls were selected from urologist patients or specialized treatment centers and likely had a higher prevalence of kidney cancer confounders such as smoking, obesity, use of diuretics, and hypertension than a population-based control sample would have. Thus the confounder presence among cases may be diluted by the fact that the prevalence of confounders if over represented among controls. The impact of this is not directly predictable, but it is plausible that this may act to overestimate renal cell cancer risks due to TCE. <p>EPA has selected the Charbotel et al. study on the basis that it provided individual human exposure data. However, it should be noted that three Scandinavian studies used worker specific biomonitoring data (more quantitative and specific than the semi-quantitative data used in Charbotel) to define the exposure cohorts and estimate health risks EPA should consider trying to incorporate these data into the</p>	

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>quantitative evaluation. These three Scandinavian studies (Anttila et al. 1995; Axelson et al. 1994; Hansen et al. 2001), individually or in the aggregate, did not find elevated relative risks of TCE exposure and kidney cancer. It is appropriate to consider the Charbotel study as one of the stronger epidemiologic studies of TCE exposed workers because of more extensive efforts to assess TCE exposure. However, despite these efforts, as apparent from the list of limitations and uncertainties above, it is clear that the Charbotel data alone should not be relied upon as the basis for cancer slope factors and quantitative estimates of potential risk. The potential biases noted (e.g. selection bias, confounder bias) call for more careful sensitivity analyses (e.g. using methods proposed by Lash et al 2007) to assess the robustness of the reported epidemiologic findings in the Charbotel study. Before such sensitivity analyses are conducted, reliance upon the Charbotel study as a source of quantitative TCE exposure information for risk assessment purposes is not appropriate given the limitations of the study itself, the lack of consistent findings compared with biomonitoring studies, and the higher relative risks observed in this study compared to meta-analysis results as well as results of other high TCE exposure cohorts (e.g. aerospace and aircraft maintenance workers (Radican et al., 2008; Boice et al., 1999).</p>	
5.2	298	EPA-HQ-ORD-2009-0791-0014.1	Exponent Health Services	<p>Non-Hodgkin Lymphoma (NHL)</p> <ul style="list-style-type: none"> · Mortality data from Zhao et al. 2005 are used in the primary meta-analyses. EPA selected mortality data rather than incidence data because there more were deaths than there were incident cases. However, incidence data is the optimum choice of data to evaluate cause and effect and, thus, should have been selected for the primary analyses. In the EPA analysis for kidney cancer, the researchers used mortality data “to avoid the appearance of cherry-picking.” This does not appear to be a systematic method for data inclusion. Furthermore, the IRIS report notes the limitations of mortality data including misclassification (p. 4-159). · As with kidney cancer, it was stated that the robustness of their findings “lends substantial support to a conclusion that TCE exposure increases the risk of lymphoma.” Indeed, the EPA’s “high-exposure” analysis results were stronger in magnitude than the overall results; however, summary associations were sensitive to study design. Furthermore, dose-response was not examined so one cannot conclude that risk of NHL increases with increasing levels of exposure. In a recent published meta-analysis, where exposure-response patterns were examined (recognizing the limitations of these data), there was no evidence for increasing duration or intensity of exposure (Mandel et al., 2006). In addition, the heterogeneity of NHL and changing classification schemes over the past few decades make interpretation of available epidemiologic data challenging. Given the lack of exposure response patterns and heterogeneity of findings by study design, it is inappropriate to conclude that there is “substantial” support that TCE increases the risk of lymphoma (Mandel et al., 2006). 	<p>- Mandel JH Kelsh MA, Mink P, Alexander DD. Occupational trichloroethylene exposure and non-Hodgkin's lymphoma: a meta-analysis and review. Occup.Environ.Med. 2006;63:597–607.</p>
5.2	301	EPA-HQ-ORD-2009-0791-0014.1	Exponent Health Services	<p>Liver Cancer</p> <ul style="list-style-type: none"> · The summary association for the high exposure analysis was slightly lower (and not statistically significant) compared with the overall analysis, which is not characteristic of a causal relationship. This implies that the epidemiologic data do not provide evidence of a causal association between TCE exposure and liver cancer. 	<p>-</p>
7	30	EPA-HQ-ORD-2009-0791-0010.1	ARCADIS on behalf of Deltrex Corporation	<p>Input from the TCE Subregistry of the Agency for Toxic Substances and Disease Registry’s (ATSDR’s) National Exposure Registry is absent in this document with no explanation. This subregistry of over 4,000 individuals contains information on exposure to TCE in drinking water, as well as associated health effects (Agency for Toxic Substances and Disease Registry 1996). A specific goal of the subregistry is to obtain, maintain, disseminate, and analyze longitudinal data; that is, data collected on the same people over time that have documented exposure to a specific chemical. To date, this goal has been pursued for the TCE subregistry by the collection of baseline and at least three follow-up collections of data from the subregistry population. The results of the statistical analysis of Baseline and Follow-up 1 data do not show increases in reported cancer cases except for a general increase for female registrants in the 19 to 25 years of age group, but this increase was not statistically significant. Other systemic health problems have indicated a statistically significant increase from Baseline to Follow-up 1, but this trend has not been noted for cancer. However, future evaluations are planned,</p>	<p>-</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>including analyses of Follow-up 2 and 3 data. If the U.S. EPA is to use human epidemiology data as a major line of evidence in this TCE review, it would seem critical to obtain input from epidemiologists at ATSDR's TCE subregistry.</p> <p>It should further be noted that the registry is designed to account for many of the difficulties inherent in drawing conclusions from individual epidemiology studies. The registry design includes a clearly stated purpose, careful literature searches, explicit inclusion and exclusion criteria, assessments of data collection for study validity and thus bias, and well-articulated definitions and rules of inference for selected causal criteria; in essence, a meta-analysis constructed for public health decision-making. Given that the TCE subregistry is now 20+ years post exposure of human populations to various levels of TCE in drinking water, the information contained within this registry should not be dismissed. If there are reasons for not including this information in this document, it should be stated.</p> <p>At the very least, this information should be used to challenge the hypothesis under investigation in the meta-analysis and explain clearly why the RRs estimated from a high-dose industrial inhalation epidemiology study are used to extrapolate an oral cancer value to be used in site risk assessments and drinking water regulations.</p>	
7	31	EPA-HQ-ORD-2009-0791-0010.1	ARCADIS on behalf of Deltrex Corporation	<p>Input from the TCE Subregistry of the Agency for Toxic Substances and Disease Registry's (ATSDR's) National Exposure Registry is absent in this document with no explanation. This subregistry of over 4,000 individuals contains information on exposure to TCE in drinking water, as well as associated health effects (Agency for Toxic Substances and Disease Registry 1996). A specific goal of the subregistry is to obtain, maintain, disseminate, and analyze longitudinal data; that is, data collected on the same people over time that have documented exposure to a specific chemical. To date, this goal has been pursued for the TCE subregistry by the collection of baseline and at least three follow-up collections of data from the subregistry population. The results of the statistical analysis of Baseline and Follow-up 1 data do not show increases in reported cancer cases except for a general increase for female registrants in the 19 to 25 years of age group, but this increase was not statistically significant. Other systemic health problems have indicated a statistically significant increase from Baseline to Follow-up 1, but this trend has not been noted for cancer. However, future evaluations are planned, including analyses of Follow-up 2 and 3 data. If the U.S. EPA is to use human epidemiology data as a major line of evidence in this TCE review, it would seem critical to obtain input from epidemiologists at ATSDR's TCE subregistry.</p> <p>It should further be noted that the registry is designed to account for many of the difficulties inherent in drawing conclusions from individual epidemiology studies. The registry design includes a clearly stated purpose, careful literature searches, explicit inclusion and exclusion criteria, assessments of data collection for study validity and thus bias, and well-articulated definitions and rules of inference for selected causal criteria; in essence, a meta-analysis constructed for public health decision-making. Given that the TCE subregistry is now 20+ years post exposure of human populations to various levels of TCE in drinking water, the information contained within this registry should not be dismissed. If there are reasons for not including this information in this document, it should be stated.</p> <p>At the very least, this information should be used to challenge the hypothesis under investigation in the meta-analysis and explain clearly why the RRs estimated from a high-dose industrial inhalation epidemiology study are used to extrapolate an oral cancer value to be used in site risk assessments and drinking water regulations.</p>	-
7	32	EPA-HQ-ORD-2009-0791-0010.1	ARCADIS on behalf of Deltrex Corporation	<p>The two most recent studies by Charbotel et al. in 2007 and 2009 should be reviewed given the significance this Toxicological Review places on the 2006 study and its use in the derivation of the oral cancer toxicity value.</p> <p>1. Charbotel, B., J. Fevotte, J. Martin, and A. Bergeret. 2009. Renal cell carcinoma and exposure to trichloroethylene: Are French occupational exposure limits relevant? <i>Revue d'Epidemiologie et de Sante Publique</i> 57: 41-47.</p>	-

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				2. Charbotel, B., S. Gad, D. Caiola et al. 2007. Trichloroethylene exposure and somatic mutations of the VHL gene in patients with Renal Cell Carcinoma. Journal of Occupational Medicine and Toxicology, 2:13.	

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics																																																																																																																																								
7	40	EPA-HQ-ORD-2009-0791-0011.1	ARCADIS	<p>ARCADIS is in the process of performing an historical population risk assessment of TCE of the type that EPA should have presented in External Review Draft: Toxicological Review of Trichloroethylene. Because the risk assessment is not yet completed, ARCADIS outlines here a scoping exercise for such a validation exercise for EPA's consideration. When the risk assessment is completed, ARCADIS would be pleased to submit it to EPA to add to the body of information in its TCE files.</p> <p>Latency Period Any TCE-caused RCC, liver and biliary cancer or NHL that was observable in the National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER) statistics from 2000-2006 would have to have been caused by exposures that occurred years ago. It is generally recognized that chemicals exhibit a latency period of 20-30 years if they are causally associated with carcinogenesis. EPA (2009) has assessed human epidemiology studies in the External Review Draft: Toxicological Review of Trichloroethylene and has generally concluded that 25-35 years of study follow-up met their criteria for an adequate latency period. Thus, it is reasonable to assume</p> <p>According to Doherty (2000), TCE was not industrially significant until about 1930. For this preliminary validation exercise, it is assumed that the exposure period of interest is 1930-1980. The average US population during this period was 169,037,000.</p> <p>Current Incidence Statistics The SEER program of the NCI reports age-adjusted incidence rates of tumors in the US for each year from 1973 to 2006 (SEER 2009a,b,c). Four Registries were added to the SEER database in 2000, bringing the total to 17. The current incidence at the tumor sites of interest as stated by EPA are listed below for 2000-2006 using NCI's SEER 17 data set, as used by EPA (2009) in deriving the URF:</p> <ul style="list-style-type: none"> - RCC 10.9/100,000 - Liver and biliary tract 6.2/100,000 - NHL 17.1/100,000 - Total 34.2/100,000 <p>These rates represent the incidences of tumors in individuals from all races, both sexes, and reporting age groups under 85. RCC was defined as those tumors occurring in the kidney (site C64.9) and of ICD-O-3 histologic types 8255, 8260, 8310, 8312, 8316-8320, 8510, and 8959 as defined in EPA (2009). Liver and biliary tract tumors were defined as those occurring in the liver or intrahepatic bile ducts (sites C22.0 and C22.1). Non-Hodgkins lymphoma was defined as cancer occurring under broad histology groupings 9670-9699, 9700-9719, 9720-9729 or histologic type 9591.</p> <p>Clearly, all 34.2/100,000 of these cancer cases per year cannot be caused by TCE even if TCE really is carcinogenic in humans under certain circumstances because smoking, obesity, hypertension, bacterial and viral infections, and other risk factors are already known to cause many of these observed cases of cancer. The following section describes known risk factors in greater detail.</p> <p>Known Risk Factors RCC, liver and biliary cancer, and NHL all have many known human risk factors. These risk factors are summarized below.</p> <p>RCC: According to the American Cancer Society (http://www.cancer.org/docroot/home/index.asp) there are many causal factors that are associated with kidney cancer. These include:</p> <ul style="list-style-type: none"> •Smoking •Excess body weight •Chemical exposures: asbestos, cadmium, some herbicides, benzene, trichloroethylene •Inherited risk factors <ul style="list-style-type: none"> o von Hippel-Lindau disease o hereditary papillary renal cell carcinoma o hereditary leiomyomatosis and renal cell carcinoma o Birt-Hogg-Dube syndrome o hereditary renal oncocytoma • Family history •High blood pressure •Certain medicines: phenacetin, high blood pressure drugs •Diabetes 	<table border="1"> <thead> <tr> <th>Source of Exposure</th> <th>Year(s) of Measurement</th> <th>Arithmetic Mean (ppm)</th> <th>Maximum (ppm)</th> </tr> </thead> <tbody> <tr><td>Degreasing</td><td>1986</td><td>38</td><td>89</td></tr> <tr><td>Degreasing</td><td>1980</td><td><0.1</td><td></td></tr> <tr><td>Degreasing</td><td>1980</td><td>0.2</td><td>0.7</td></tr> <tr><td>Degreasing</td><td>1980</td><td><0.3</td><td></td></tr> <tr><td>Degreasing</td><td>1980</td><td>0.6</td><td></td></tr> <tr><td>Degreasing</td><td>1980-1989</td><td>7.9</td><td></td></tr> <tr><td>Degreasing</td><td>1960-1969</td><td>38</td><td></td></tr> <tr><td>Degreasing</td><td>1947-1959</td><td>24</td><td></td></tr> <tr><td>Degreasing</td><td>1990</td><td>19</td><td>50</td></tr> <tr><td>Degreasing</td><td>1990</td><td>4.1</td><td>11</td></tr> <tr><td>Degreasing</td><td>1982</td><td>0.7</td><td>1.1</td></tr> <tr><td>Degreasing</td><td>1982</td><td>5.3</td><td>23</td></tr> <tr><td>Degreasing</td><td>1982</td><td>62</td><td>234</td></tr> <tr><td>Degreasing</td><td>1982</td><td>4.1</td><td></td></tr> <tr><td>Degreasing</td><td>1982</td><td>5.7</td><td>39</td></tr> <tr><td>Degreasing</td><td>1983</td><td>7.8</td><td>25</td></tr> <tr><td>Degreasing</td><td>1981</td><td>1</td><td>3</td></tr> <tr><td>Degreasing</td><td>1981</td><td>1.2</td><td>1.7</td></tr> <tr><td>Degreasing</td><td>1988</td><td>28</td><td>64</td></tr> <tr><td>Degreasing</td><td>1988</td><td>25</td><td>33</td></tr> <tr><td>Degreasing</td><td>1981</td><td>1.4</td><td>1.7</td></tr> <tr><td>Degreasing</td><td>1940</td><td>134</td><td>342</td></tr> <tr><td>Vapor degreasing</td><td>1956</td><td>68</td><td>73</td></tr> <tr><td>Vapor degreasing</td><td>1956</td><td>398</td><td>423</td></tr> <tr><td>Vapor degreasing</td><td>1956</td><td>566</td><td>637</td></tr> <tr><td>Vapor degreasing</td><td>1974</td><td>57</td><td>65</td></tr> <tr><td>Vapor degreasing</td><td>1989</td><td>39</td><td>120</td></tr> <tr><td>Degreasing</td><td>1988-1999</td><td>5.1</td><td>27</td></tr> <tr><td>Spot remover</td><td>1997-1999</td><td></td><td>22</td></tr> <tr><td>Spot remover</td><td>1996</td><td>1.9</td><td>4.1</td></tr> <tr><td>Spot remover</td><td>1996</td><td>1.1</td><td>1.7</td></tr> <tr><td>Printing dyes</td><td>1980-1989</td><td>6.4</td><td></td></tr> <tr><td>Printina dves</td><td>1960-1969</td><td>81</td><td></td></tr> </tbody> </table>	Source of Exposure	Year(s) of Measurement	Arithmetic Mean (ppm)	Maximum (ppm)	Degreasing	1986	38	89	Degreasing	1980	<0.1		Degreasing	1980	0.2	0.7	Degreasing	1980	<0.3		Degreasing	1980	0.6		Degreasing	1980-1989	7.9		Degreasing	1960-1969	38		Degreasing	1947-1959	24		Degreasing	1990	19	50	Degreasing	1990	4.1	11	Degreasing	1982	0.7	1.1	Degreasing	1982	5.3	23	Degreasing	1982	62	234	Degreasing	1982	4.1		Degreasing	1982	5.7	39	Degreasing	1983	7.8	25	Degreasing	1981	1	3	Degreasing	1981	1.2	1.7	Degreasing	1988	28	64	Degreasing	1988	25	33	Degreasing	1981	1.4	1.7	Degreasing	1940	134	342	Vapor degreasing	1956	68	73	Vapor degreasing	1956	398	423	Vapor degreasing	1956	566	637	Vapor degreasing	1974	57	65	Vapor degreasing	1989	39	120	Degreasing	1988-1999	5.1	27	Spot remover	1997-1999		22	Spot remover	1996	1.9	4.1	Spot remover	1996	1.1	1.7	Printing dyes	1980-1989	6.4		Printina dves	1960-1969	81	
Source of Exposure	Year(s) of Measurement	Arithmetic Mean (ppm)	Maximum (ppm)																																																																																																																																										
Degreasing	1986	38	89																																																																																																																																										
Degreasing	1980	<0.1																																																																																																																																											
Degreasing	1980	0.2	0.7																																																																																																																																										
Degreasing	1980	<0.3																																																																																																																																											
Degreasing	1980	0.6																																																																																																																																											
Degreasing	1980-1989	7.9																																																																																																																																											
Degreasing	1960-1969	38																																																																																																																																											
Degreasing	1947-1959	24																																																																																																																																											
Degreasing	1990	19	50																																																																																																																																										
Degreasing	1990	4.1	11																																																																																																																																										
Degreasing	1982	0.7	1.1																																																																																																																																										
Degreasing	1982	5.3	23																																																																																																																																										
Degreasing	1982	62	234																																																																																																																																										
Degreasing	1982	4.1																																																																																																																																											
Degreasing	1982	5.7	39																																																																																																																																										
Degreasing	1983	7.8	25																																																																																																																																										
Degreasing	1981	1	3																																																																																																																																										
Degreasing	1981	1.2	1.7																																																																																																																																										
Degreasing	1988	28	64																																																																																																																																										
Degreasing	1988	25	33																																																																																																																																										
Degreasing	1981	1.4	1.7																																																																																																																																										
Degreasing	1940	134	342																																																																																																																																										
Vapor degreasing	1956	68	73																																																																																																																																										
Vapor degreasing	1956	398	423																																																																																																																																										
Vapor degreasing	1956	566	637																																																																																																																																										
Vapor degreasing	1974	57	65																																																																																																																																										
Vapor degreasing	1989	39	120																																																																																																																																										
Degreasing	1988-1999	5.1	27																																																																																																																																										
Spot remover	1997-1999		22																																																																																																																																										
Spot remover	1996	1.9	4.1																																																																																																																																										
Spot remover	1996	1.1	1.7																																																																																																																																										
Printing dyes	1980-1989	6.4																																																																																																																																											
Printina dves	1960-1969	81																																																																																																																																											

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics																																							
7	42	EPA-HQ-ORD-2009-0791-0011.1	ARCADIS	<p>Clearly, even if EPA’s conclusions are correct that TCE causes some of the RCC, liver and biliary cancer, and NHL in the human population, TCE can only be responsible for a small fraction of them. ARCADIS has attempted to find quantitative information in the literature to determine what fraction of the total RCC, liver and biliary cancer and NHL in the human population is not already explained by the above causative agents. Determining the etiologic fraction to various causal agents is an extremely difficult scientific problem. In their landmark 1981 paper, Richard Doll and Richard Peto (Doll and Peto 1981) made such quantitative estimates of the causes of human cancer. In Benchmarks, Volume 4, Issue 3 (2004), NCI summarized their work and concluded that the work has withstood the test of time. Specifically, NCI stated: “The estimates made by two English epidemiologists, Richard Doll and Richard Peto, in the early 1980s are still reasonable (see table below).” In the referenced table, Doll and Peto (1981) concluded that occupational exposures and exposures to pollutants in the air, water, and food could be responsible for causing 2-13% of all cancers, with the majority being caused by smoking, diet, and infections. Doll’s conclusions in 1998 (Doll 1998) were that 3-9% of all cancers could be caused by occupational exposures and exposures to pollutants in the air, water, and food. These statistics apply to total cancers and not the three specific cancers of interest in these comments. However, in the absence of site-specific information, it is not unreasonable to assume that the maximum fraction of total RCCs, liver and biliary cancers, and NHLs caused by occupational or environmental exposure to any chemicals is roughly 10%.</p> <p>As a test of the reasonableness of this assumption, ARCADIS performed a preliminary search of the literature to identify the etiologic fraction of kidney cancer attributed to selected causes. Two reports provide useful information. After reviewing eleven studies of excess body weight and kidney cancer, Bergstrom et al. (2001) concluded that 25% of kidney cancer in Europe was attributed to excess body weight. Setiawan et al. (2007) studied a cohort of over 160,000 people for over 8 years and found that at least 50% of the RCC was associated with smoking, obesity, and hypertension. Specifically, they found that smoking accounted for 32% of the RCC cases in males and 16% in the females. Obesity accounted for 10% of the RCC cases in males and 17% in the females. Finally, hypertension accounted for 15% of the RCC cases in males and 24% in the females.</p> <p>The above studies on kidney cancer reasonably support the assumption made for this validation exercise of EPA’s proposed URF. It is assumed here that 10% of the cases of all RCC, liver and biliary tract cancer, and NHL are caused by occupation and environmental chemical exposures.</p>	<p style="text-align: center;">TABLE 1 WORKPLACE EXPOSURE INFORMATION FROM EPA (2009)</p> <table border="1" data-bbox="1653 224 2440 605"> <thead> <tr> <th>Citation</th> <th>Worker Group</th> <th>Exposure Concentration (µg/m3)</th> </tr> </thead> <tbody> <tr> <td>Xu et al. (2009)</td> <td>Metal degreasing</td> <td>18,000 - 683,000</td> </tr> <tr> <td>Neghab et al. (1997)</td> <td>Metal degreasing</td> <td>47,800</td> </tr> <tr> <td>Kamijima, et al. (2007)</td> <td>Varied</td> <td><50,000 – 4,000,000</td> </tr> <tr> <td>Kamijima, et al. (2008)</td> <td>Varied</td> <td>164,000 – 2,330,000</td> </tr> <tr> <td>Iavicoli et al. (2005)</td> <td>Degreasing</td> <td>35,000</td> </tr> <tr> <td>Zielinski (1973)</td> <td>Electrical parts assembly</td> <td>200,000</td> </tr> <tr> <td>Radican et al. (2008); Blair et al. (1998)</td> <td>Aircraft maintenance</td> <td>53,700 (rag & bucket) 537,000 – 1,075,000 (vapor degreasing)</td> </tr> <tr> <td>Morgan et al. (1998)</td> <td>Aerospace</td> <td>>268,700</td> </tr> <tr> <td>Hansen et al. (2001)</td> <td>Varied</td> <td>64,500</td> </tr> <tr> <td>Anttila et al. (1995)</td> <td>Varied</td> <td>32,200</td> </tr> <tr> <td>Axelsson et al. (1994)</td> <td>Varied</td> <td><107,500</td> </tr> <tr> <td>Raaschou-Nielsen et al. (2003)</td> <td>Varied</td> <td>Pre-1970: 215,000 – 322,400 1970-1979: 53,700 – 1,075,000 1980-1989: 21,500</td> </tr> </tbody> </table> <p>Doll, R., and R. Peto. 1981. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. <i>Journal of the National Cancer Institute</i> 66: 1191-1308.</p> <p>Bergstrom, A., P. Pisani, V. Tenet, A. Wolk, and H.-O. Adami. 2001. Overweight as an avoidable cause of cancer in Europe. <i>International Journal of Cancer</i> 91: 421-430.</p> <p>Setiawan, V.W., D.O. Stram, A.M.Y. Nomura, L.N. Kolonel, and B.E. Henderson. 2007. Risk factors for renal cell cancer: the multiethnic cohort. <i>American Journal of Epidemiology</i> 166(8): 932-940.</p>	Citation	Worker Group	Exposure Concentration (µg/m3)	Xu et al. (2009)	Metal degreasing	18,000 - 683,000	Neghab et al. (1997)	Metal degreasing	47,800	Kamijima, et al. (2007)	Varied	<50,000 – 4,000,000	Kamijima, et al. (2008)	Varied	164,000 – 2,330,000	Iavicoli et al. (2005)	Degreasing	35,000	Zielinski (1973)	Electrical parts assembly	200,000	Radican et al. (2008); Blair et al. (1998)	Aircraft maintenance	53,700 (rag & bucket) 537,000 – 1,075,000 (vapor degreasing)	Morgan et al. (1998)	Aerospace	>268,700	Hansen et al. (2001)	Varied	64,500	Anttila et al. (1995)	Varied	32,200	Axelsson et al. (1994)	Varied	<107,500	Raaschou-Nielsen et al. (2003)	Varied	Pre-1970: 215,000 – 322,400 1970-1979: 53,700 – 1,075,000 1980-1989: 21,500
Citation	Worker Group	Exposure Concentration (µg/m3)																																										
Xu et al. (2009)	Metal degreasing	18,000 - 683,000																																										
Neghab et al. (1997)	Metal degreasing	47,800																																										
Kamijima, et al. (2007)	Varied	<50,000 – 4,000,000																																										
Kamijima, et al. (2008)	Varied	164,000 – 2,330,000																																										
Iavicoli et al. (2005)	Degreasing	35,000																																										
Zielinski (1973)	Electrical parts assembly	200,000																																										
Radican et al. (2008); Blair et al. (1998)	Aircraft maintenance	53,700 (rag & bucket) 537,000 – 1,075,000 (vapor degreasing)																																										
Morgan et al. (1998)	Aerospace	>268,700																																										
Hansen et al. (2001)	Varied	64,500																																										
Anttila et al. (1995)	Varied	32,200																																										
Axelsson et al. (1994)	Varied	<107,500																																										
Raaschou-Nielsen et al. (2003)	Varied	Pre-1970: 215,000 – 322,400 1970-1979: 53,700 – 1,075,000 1980-1989: 21,500																																										
7	162	EPA-HQ-ORD-2009-0791-0011.1	ARCADIS	<p>ARCADIS is in the process of performing an historical population risk assessment of TCE of the type that EPA should have presented in External Review Draft: Toxicological Review of Trichloroethylene. Because the risk assessment is not yet completed, ARCADIS outlines here a scoping exercise for such a validation exercise for EPA’s consideration. When the risk assessment is completed, ARCADIS would be pleased to submit it to EPA to add to the body of information in its TCE files.</p> <p>Latency Period Any TCE-caused RCC, liver and biliary cancer or NHL that was observable in the National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER) statistics from 2000-2006 would have to have been caused by exposures that occurred years ago. It is generally recognized that chemicals exhibit a latency period of 20-30 years if they are causally associated with carcinogenesis. EPA (2009) has assessed human epidemiology studies in the External Review Draft: Toxicological Review of Trichloroethylene and has generally concluded that 25-35 years of study follow-up met their criteria for an adequate latency period. Thus, it is reasonable to assume that any cancers observed in the 2000 – 2006 statistics that might have been caused by TCE exposure would have to have been caused by TCE exposures between prior to 1970-1976 for a 30 year latency period and prior to 1980-1986 for a 20 year latency period.</p> <p>According to Doherty (2000), TCE was not industrially significant until about 1930. For this preliminary validation exercise, it is assumed that the exposure period of interest is 1930-1980. The average US population during this period was 169,037,000.</p> <p>Current Incidence Statistics The SEER program of the NCI reports age-adjusted incidence rates of tumors in the US for each year from 1973 to 2006 (SEER 2009a,b,c). Four Registries were added to the SEER database in 2000, bringing the total to 17. The current incidence at the tumor sites of interest as stated by EPA are listed below for 2000-2006 using NCI’s</p>	<p style="text-align: center;">TABLE 1 WORKPLACE EXPOSURE INFORMATION FROM EPA (2009)</p> <table border="1" data-bbox="1653 954 2440 1336"> <thead> <tr> <th>Citation</th> <th>Worker Group</th> <th>Exposure Concentration (µg/m3)</th> </tr> </thead> <tbody> <tr> <td>Xu et al. (2009)</td> <td>Metal degreasing</td> <td>18,000 - 683,000</td> </tr> <tr> <td>Neghab et al. (1997)</td> <td>Metal degreasing</td> <td>47,800</td> </tr> <tr> <td>Kamijima, et al. (2007)</td> <td>Varied</td> <td><50,000 – 4,000,000</td> </tr> <tr> <td>Kamijima, et al. (2008)</td> <td>Varied</td> <td>164,000 – 2,330,000</td> </tr> <tr> <td>Iavicoli et al. (2005)</td> <td>Degreasing</td> <td>35,000</td> </tr> <tr> <td>Zielinski (1973)</td> <td>Electrical parts assembly</td> <td>200,000</td> </tr> <tr> <td>Radican et al. (2008); Blair et al. (1998)</td> <td>Aircraft maintenance</td> <td>53,700 (rag & bucket) 537,000 – 1,075,000 (vapor degreasing)</td> </tr> <tr> <td>Morgan et al. (1998)</td> <td>Aerospace</td> <td>>268,700</td> </tr> <tr> <td>Hansen et al. (2001)</td> <td>Varied</td> <td>64,500</td> </tr> <tr> <td>Anttila et al. (1995)</td> <td>Varied</td> <td>32,200</td> </tr> <tr> <td>Axelsson et al. (1994)</td> <td>Varied</td> <td><107,500</td> </tr> <tr> <td>Raaschou-Nielsen et al. (2003)</td> <td>Varied</td> <td>Pre-1970: 215,000 – 322,400 1970-1979: 53,700 – 1,075,000 1980-1989: 21,500</td> </tr> </tbody> </table> <p>American Cancer Society. 2009. <i>Cancer Prevention and Early Detection: Facts and Figures</i>.</p> <p>ATSDR (Agency for Toxic Substances and Disease Registry). 1997. <i>Toxicological Profile for Trichloroethylene</i>. U.S. Department of Health and Human Services, Public Health Service. September</p>	Citation	Worker Group	Exposure Concentration (µg/m3)	Xu et al. (2009)	Metal degreasing	18,000 - 683,000	Neghab et al. (1997)	Metal degreasing	47,800	Kamijima, et al. (2007)	Varied	<50,000 – 4,000,000	Kamijima, et al. (2008)	Varied	164,000 – 2,330,000	Iavicoli et al. (2005)	Degreasing	35,000	Zielinski (1973)	Electrical parts assembly	200,000	Radican et al. (2008); Blair et al. (1998)	Aircraft maintenance	53,700 (rag & bucket) 537,000 – 1,075,000 (vapor degreasing)	Morgan et al. (1998)	Aerospace	>268,700	Hansen et al. (2001)	Varied	64,500	Anttila et al. (1995)	Varied	32,200	Axelsson et al. (1994)	Varied	<107,500	Raaschou-Nielsen et al. (2003)	Varied	Pre-1970: 215,000 – 322,400 1970-1979: 53,700 – 1,075,000 1980-1989: 21,500
Citation	Worker Group	Exposure Concentration (µg/m3)																																										
Xu et al. (2009)	Metal degreasing	18,000 - 683,000																																										
Neghab et al. (1997)	Metal degreasing	47,800																																										
Kamijima, et al. (2007)	Varied	<50,000 – 4,000,000																																										
Kamijima, et al. (2008)	Varied	164,000 – 2,330,000																																										
Iavicoli et al. (2005)	Degreasing	35,000																																										
Zielinski (1973)	Electrical parts assembly	200,000																																										
Radican et al. (2008); Blair et al. (1998)	Aircraft maintenance	53,700 (rag & bucket) 537,000 – 1,075,000 (vapor degreasing)																																										
Morgan et al. (1998)	Aerospace	>268,700																																										
Hansen et al. (2001)	Varied	64,500																																										
Anttila et al. (1995)	Varied	32,200																																										
Axelsson et al. (1994)	Varied	<107,500																																										
Raaschou-Nielsen et al. (2003)	Varied	Pre-1970: 215,000 – 322,400 1970-1979: 53,700 – 1,075,000 1980-1989: 21,500																																										

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>SEER 17 data set, as used by EPA (2009) in deriving the URF:</p> <p>RCC 10.9/100,000 Liver and biliary tract 6.2/100,000 NHL 17.1/100,000 Total 34.2/100,000</p> <p>These rates represent the incidences of tumors in individuals from all races, both sexes, and reporting age groups under 85. RCC was defined as those tumors occurring in the kidney (site C64.9) and of ICD-O-3 histologic types 8255, 8260, 8310, 8312, 8316-8320, 8510, and 8959 as defined in EPA (2009). Liver and biliary tract tumors were defined as those occurring in the liver or intrahepatic bile ducts (sites C22.0 and C22.1). Non-Hodgkins lymphoma was defined as cancer occurring under broad histology groupings 9670-9699, 9700-9719, 9720-9729 or histologic type 9591.</p> <p>Clearly, all 34.2/100,000 of these cancer cases per year cannot be caused by TCE even if TCE really is carcinogenic in humans under certain circumstances because smoking, obesity, hypertension, bacterial and viral infections, and other risk factors are already known to cause many of these observed cases of cancer. The following section describes known risk factors in greater detail.</p> <p>Known Risk Factors RCC, liver and biliary cancer, and NHL all have many known human risk factors. These risk factors are summarized below.</p> <p>RCC: According to the American Cancer Society (http://www.cancer.org/docroot/home/index.asp) there are many causal factors that are associated with kidney cancer. These include:</p> <ul style="list-style-type: none"> •Smoking •Excess body weight •Chemical exposures: asbestos, cadmium, some herbicides, benzene, trichloroethylene •Inherited risk factors <ul style="list-style-type: none"> o von Hippel-Lindau disease o hereditary papillary renal cell carcinoma o hereditary leiomyomatosis and renal cell carcinoma o Birt-Hogg-Dube syndrome o hereditary renal oncocytoma • Family history •High blood pressure •Certain medicines: phenacetin, high blood pressure drugs • Dialysis <p>Cancer Prevention and Early Detection (American Cancer Society 2009) states that smoking and excess body weight are causally associated with kidney cancer.</p> <p>NCI (http://www.cancer.gov/cancertopics/wyntk/kidney/page4) states that there are many causal factors associated with kidney cancer, including:</p> <ul style="list-style-type: none"> • Smoking •Obesity •High blood pressure • Long-term dialysis • Chemical Exposures: Coke oven emissions, asbestos, cadmium <p>Liver and Biliary Tract Cancer: According to the American Cancer Society (http://www.cancer.org/docroot/home/index.asp) there are many causal factors that are associated with liver and biliary tract cancer. These include:</p> <ul style="list-style-type: none"> •Certain types of liver disease: hepatitis B virus, hepatitis C virus, certain inherited liver diseases, cirrhosis •Diabetes: diabetes •Excess body weight 	<p>1997.</p> <p>Bakke, B., Stewart, P.A., Waters, M.A. 2007. Uses of and exposure to trichloroethylene in US industry: a systematic literature review. <i>Journal of Occupational and Environmental Hygiene</i> 4: 375-390.</p> <p>Bergstrom, A., P. Pisani, V. Tenet, A. Wolk, and H.-O. Adami. 2001. Overweight as an avoidable cause of cancer in Europe. <i>International Journal of Cancer</i> 91: 421-430.</p> <p>Blair et al. 1998. As cited in U.S. Environmental Protection Agency (EPA) 2009.</p> <p>Boice et al. 1998. As cited in U.S. Environmental Protection Agency (EPA) 2009.</p> <p>Census Bureau. 2009. GCT-T1: Population Estimates. Data Set: 2009 Population Estimates. Accessed 22 January 2010, <http://factfinder.census.gov>.</p> <p>Corbett, T.H., G.C. Hamilton, M.K. Yoon, and J.L. Endres. 1973. Occupational exposure of operating room personnel to trichloroethylene. <i>Canadian Journal of Anesthesia</i> 20(5): 675-678.</p> <p>Department of Labor. 1972. Occupational Employment Statistics, 1960-1970. Bulletin 1738. Bureau of Labor Statistics.</p> <p>Environmental Protection Agency (EPA). 2009. Toxicological Review of Trichloroethylene (CAS No. 79-01-6) In Support of Summary Information on the Integrated Risk Information System (IRIS). External Review Draft. EPA/635/R-09/011A. October 2009.</p> <p>Doherty, R.E. 2000. A history of the production and use of carbon tetrachloride, tetrachloroethylene, trichloroethylene, and 1,1,1-trichloroethane in the United States: part 2 – trichloroethylene and 1,1,1-trichloroethane. <i>Journal of Environmental Forensics</i> 1: 83-93.</p> <p>Doll, R., and R. Peto. 1981. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. <i>Journal of the National Cancer Institute</i> 66: 1191-1308.</p> <p>Garabrant et al. 1988. As cited in U.S. Environmental Protection Agency (EPA) 2009.</p> <p>International Agency for Research on Cancer (IARC). 1995. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 63: Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals. World Health Organization, Lyon, France.</p> <p>Morgan et al. 1998. As cited in U.S. Environmental Protection Agency (EPA) 2009.</p> <p>NIOSH (National Institute for Occupational Safety and Health). 1978. Special Occupational Hazard Review with Control Recommendations: Trichloroethylene. US Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, Division of Criteria Documentation and Standards Development, Priorities and Research Analysis Branch. January 1978.</p> <p>Setiawan, V.W., D.O. Stram, A.M.Y. Nomura, L.N. Kolonel, and B.E. Henderson. 2007. Risk factors for renal cell cancer: the multiethnic cohort. <i>American Journal of Epidemiology</i> 166(8): 932-940.</p> <p>Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov). 2009a. SEER*Stat Database: Incidence - SEER 9 Regs Limited-Use, Nov 2008 Sub (1973-2006) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2006 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2009, based on the November 2008 submission.</p> <p>Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov). 2009b.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<ul style="list-style-type: none"> •Aflatoxins •Chemical exposures: vinyl chloride, thorium dioxide (Thorotrast), anabolic steroids, arsenic <p>Cancer Prevention and Early Detection (American Cancer Society 2009) states that smoking and alcohol consumption are causally associated with liver cancer.</p> <p>NCI (http://www.cancer.gov/cancertopics/wyntk/liver/page4) states that there are many causal factors associated with liver cancer, including:</p> <ul style="list-style-type: none"> •Certain infections: hepatitis B virus (HBV), hepatitis C virus (HPC) •Heavy alcohol use •Aflatoxin •Iron storage disease •Cirrhosis •Excess body weight • Diabetes <p>NHL: According to the Memorial Sloan-Kettering Cancer Center (http://www.mskcc.org:80/mskcc/html/5470.cfm), NHL is associated with numerous risk factors and chemical exposures. Reported risk factors include:</p> <ul style="list-style-type: none"> • Compromised immune systems (inherited genetic diseases, human immunodeficiency virus [HIV] infection, or immunosuppressive drugs) •Certain viruses and bacteria (Epstein-Barr virus, human T-cell leukemia/lymphoma virus, Helicobacter pylori bacteria) •Chemical exposures: specific herbicides and pesticides, solvents and fertilizers (nitrate) <p>According to the Leukemia and Lymphoma Society (http://www.leukemia-lymphoma.org/all_page?item_id=7030) NHL is associated with the following causal factors:</p> <ul style="list-style-type: none"> •Herbicides and pesticides (organochlorine, organophosphate and phenoxyacid compounds) •Epstein-Barr virus (EBV) •Human T-lymphotropic virus (HTLV) •Helicobacter pylori bacteria •Inherited syndromes <p>According to the American Cancer Society (http://www.cancer.org/docroot/home/index.asp) there are many causal factors that are associated with NHL. These include:</p> <ul style="list-style-type: none"> •Chemical exposures: benzene, certain herbicides and pesticides, certain cancer chemotherapeutic drugs •Radiation exposure •Weakened immune systems: immunosuppressive drugs, human immunodeficiency •Autoimmune diseases: rheumatoid arthritis, systemic lupus erythematosus and others •Certain infections: Human T-Cell Leukemia/lymphoma Virus Type 1 (HTLV-1), EBV, Helicobacter pylori bacteria, hepatitis C virus •Excess body weight <p>NCI (http://www.cancer.gov/cancertopics/wyntk/non-hodgkin-lymphoma/page3) states there are many causal factors associated with NHL, including:</p> <ul style="list-style-type: none"> •Weakened immune system: inherited conditions, immunosuppressant drugs •Certain infections: HIV, EBV, Helicobacter pylori bacteria, HTLV-1, hepatitis C •Excess body weight •Certain herbicides <p>The above information firmly demonstrates that for the three tumor sites that EPA states are causally linked to TCE exposure, there are a multitude of known causative agents. Many more information sources and primary scientific publications could be cited to provide a comprehensive summary of the known risk factors for these three tumor sites, but the above information is sufficient to make the general point.</p>	<p>SEER*Stat Database: Incidence - SEER 13 Regs Limited-Use, Nov 2008 Sub (1992-2006) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2006 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2009, based on the November 2008 submission.</p> <p>Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov). 2009c. SEER*Stat Database: Incidence - SEER 17 Regs Limited-Use + Hurricane Katrina Impacted Louisiana Cases, Nov 2008 Sub (2000-2006) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2006 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2009, based on the November 2008 submission.</p> <p>Spirtas et al. 1991. As cited in U.S. Environmental Protection Agency (EPA) 2009.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>Etiologic Fraction</p> <p>Clearly, even if EPA’s conclusions are correct that TCE causes some of the RCC, liver and biliary cancer, and NHL in the human population, TCE can only be responsible for a small fraction of them. ARCADIS has attempted to find quantitative information in the literature to determine what fraction of the total RCC, liver and biliary cancer and NHL in the human population is not already explained by the above causative agents. Determining the etiologic fraction to various causal agents is an extremely difficult scientific problem. In their landmark 1981 paper, Richard Doll and Richard Peto (Doll and Peto 1981) made such quantitative estimates of the causes of human cancer. In Benchmarks, Volume 4, Issue 3 (2004), NCI summarized their work and concluded that the work has withstood the test of time. Specifically, NCI stated: “The estimates made by two English epidemiologists, Richard Doll and Richard Peto, in the early 1980s are still reasonable (see table below).” In the referenced table, Doll and Peto (1981) concluded that occupational exposures and exposures to pollutants in the air, water, and food could be responsible for causing 2-13% of all cancers, with the majority being caused by smoking, diet, and infections. Doll’s conclusions in 1998 (Doll 1998) were that 3-9% of all cancers could be caused by occupational exposures and exposures to pollutants in the air, water, and food. These statistics apply to total cancers and not the three specific cancers of interest in these comments. However, in the absence of site-specific information, it is not unreasonable to assume that the maximum fraction of total RCCs, liver and biliary cancers, and NHLs caused by occupational or environmental exposure to any chemicals is roughly 10%.</p> <p>As a test of the reasonableness of this assumption, ARCADIS performed a preliminary search of the literature to identify the etiologic fraction of kidney cancer attributed to selected causes. Two reports provide useful information. After reviewing eleven studies of excess body weight and kidney cancer, Bergstrom et al. (2001) concluded that 25% of kidney cancer in Europe was attributed to excess body weight. Setiawan et al. (2007) studied a cohort of over 160,000 people for over 8 years and found that at least 50% of the RCC was associated with smoking, obesity, and hypertension. Specifically, they found that smoking accounted for 32% of the RCC cases in males and 16% in the females.</p> <p>Obesity accounted for 10% of the RCC cases in males and 17% in the females. Finally, hypertension accounted for 15% of the RCC cases in males and 24% in the females.</p> <p>The above studies on kidney cancer reasonably support the assumption made for this validation exercise of EPA’s proposed URF. It is assumed here that 10% of the cases of all RCC, liver and biliary tract cancer, and NHL are caused by occupation and environmental chemical exposures.</p> <p>The fraction of these three tumor types that could possibly be explained by one specific chemical agent, TCE, must be less than the assumed 10% for all chemicals because nationally recognized sources of information on cancer causes and prevention have listed the following chemicals as known risk factors for these three tumors:</p> <ul style="list-style-type: none"> •Asbestos •Cadmium •Certain herbicides •Benzene • Trichloroethylene •Phenacetin •High blood pressure drugs •Coke oven emissions •Aflatoxins •Vinyl chloride •Thorium dioxide •Anabolic steroids •Arsenic •Certain pesticides •Certain cancer chemotherapeutic drugs <p>In addition, EPA’s Integrated Risk Information System (IRIS) database was searched to identify all of the chemicals that EPA has concluded cause either kidney cancer, liver cancer, or lymphatic cancer. ARCADIS identified 55 chemicals, which are listed below:</p> <p>February 1, 2010</p>	

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<ul style="list-style-type: none"> •1,1,1,2-Tetrachloroethane •1,1,2,2-Tetrachloroethane •1,1,2-Trichloroethane •1,2,3-Trichloropropane •1,2-Diphenylhydrazine •1,3-Butadiene •1,3-Dichloropropene •2,2',3,3',4,4',5,5',6,6'-Decabromodiphenyl ether (BDE-209) •2,4,6-Trichlorophenol •2,4-/2,6-Dinitrotoluene mixture •Acephate •Aldrin •alpha-Hexachlorocyclohexane (alpha-HCH) •Aramite •beta-Hexachlorocyclohexane (beta-HCH) •Bis(chloroethyl)ether (BCEE) •Bromate •Bromodichloromethane •Carbon tetrachloride •Chlordane •Chlordecone (Kepone) •Chloroform •Di (2-ethylhexyl)phthalate (DEHP) •Di(2-ethylhexyl)adipate •Dibromochloromethane •Dichloroacetic acid •Dichloromethane •Dieldrin <p>February 1, 2010</p> <ul style="list-style-type: none"> •Fomesafen •Furmecyclox •Hepatochlor •Hepatochlor epoxide •Hexachlorobenzene •Hexachlorobutadiene •Hexachlorodibenzo-p-dioxin (HxCDD), mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD •Hexachloroethane • Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) •Nitrobenzene •N-Nitrosodiethanolamine • N-Nitrosodiethylamine •N-Nitrosodimethylamine •N-Nitrosodi-N-propylamine •N-Nitroso-N-methylethylamine •N-Nitrosopyrrolidine • p,p'-Dichlorodiphenyl dichloroethane (DDD) • p,p'-Dichlorodiphenyldichloroethylene (DDE) • p,p'-Dichlorodiphenyltrichloroethane (DDT) • Pentachlorophenol •Polychlorinated biphenyls (PCBs) • Prochloraz •Quinoline •technical Hexachlorocyclohexane (t-HCH) 	

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<ul style="list-style-type: none"> •Toxaphene •Trifluralin •Vinyl chloride <p>In toto, there are more than 70 chemicals that governmental bodies have stated are causally associated with the three cancer sites of interest. If they were all equally important as causes of the three tumor types designated by EPA, then each could be reasonably assumed to be responsible for ~1% of the occupational or environmental causes of these cancers. Thus, it is reasonable and conservative to assume that no more than 10% of RCC, liver and biliary cancer, and NHL that are caused by occupational or environmental exposures to chemicals are caused by one chemical, TCE. In conclusion, if 10% of all RCC, liver and biliary cancer, and NHL are caused by occupational or environmental chemical exposure and 10% of those are caused specifically by TCE, then that leads to a reasonable assumption that 1% (10% x 10%) of all RCC, liver and biliary cancer, and NHL might conceivably be caused by TCE exposures if TCE really is one of the causes of RCC, liver and biliary cancer, or NHL in the human population. Accordingly, if TCE were causally associated with the observed tumors in the human population, it could cause no more than about 0.01 x 34.2/100,000, which would be about 0.3/100,000. Assuming that the SEER Registries are representative of the entire US population, and given that the average US population from 2000 to 2006 was 290,396,564 (U.S. Census Bureau 2009), the estimated numbers of each tumor type are given below.</p> <p>RCC 317/year Liver & Biliary Tract 180/year NHL 497/year Total 994/year</p> <p>ARCADIS recommends that EPA perform an historical population risk assessment for all members of the population who were exposed to TCE during the years 1930-1980 and determine if the cancer incidence rate can be reasonably predicted by the use of EPA's proposed URF. If the predicted number of cancer cases per year exceeds the number presented above by a large margin, then EPA needs to conclude that the proposal does not pass a real world validation. If the predicted number of cancer cases per year are similar to the above values, then, despite the fact that causation is not proven, the validation exercise would conclude that EPA's proposed URFs are theoretically possible.</p> <p>Uses of Trichloroethylene Doherty (2000) described the history of the production and use of TCE in great detail. According to Doherty (2000), the uses of TCE included use as a cleaning and degreasing agent in "the electronics, defense, chemical, rail, automotive, boat, shoe, food processing, textile, and dry-cleaning industries." It was also used "as a refrigerant, a low-temperature heat transfer medium, a freezing point depressant in CTC fire extinguishers, an extraction agent in the decaffeination of coffee and a cleaner for optical lenses. TCE was used as an ingredient in printing inks, elastomers, industrial paints, paint strippers, lacquers, varnishes, lubricants, pesticides and adhesives."</p> <p>TCE was also used as a general anesthetic and as an analgesic in dental extractions, childbirth and other short surgical procedures, as well as for disinfecting surgical instruments. TCE was used as a grain fumigant, and TCE was in countless consumer products. Consumer products containing TCE included: "shoe polish, drain and pipe cleaners, household cleaners, spot removers, disinfectants, paint removers, wig cleaners, upholstery cleaners, deodorizers, type-writer correction fluid, adhesives, mildew preventives, and septic tank cleaners" (Doherty 2000).</p> <p>In the food industry, TCE was used as an extraction solvent for fats, vegetable oils, and caffeine for decaffeinated coffee. In the textile industry, TCE was used for a variety of purposes. In the chemical industry, TCE was used for the production of "polyvinyl chloride, chloroacetic acid, hydrofluorocarbons, pharmaceuticals, insecticides, flame-retardant chemicals, and fertilizers" (Doherty 2000).</p> <p>Historical TCE Exposures Because of the many uses to which TCE was employed over the years, many people have had considerable exposure to TCE in the work place and also in the home due to the use of TCE in numerous consumer products. In External Review Draft: Toxicological Review of Trichloroethylene, EPA (2009) has summarized a</p>	

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>considerable amount of exposure level information concerning exposures to TCE by various workers. The exposure values from EPA (2009) are summarized in Table 1.</p> <p>EPA has also made several general statements about historical TCE workplace exposures. Specifically, EPA stated: “Studies of aircraft workers show short term peak exposures in the hundreds of ppm (>540 mg/m3) and long term exposures in the low tens of ppm (>54 mg/m3) (Spirtas et al. 1991; Blair et al. 1998; Garabrant et al. 1988; Morgan et al. 1998; and Boice et al. 1998).” ARCADIS has not performed a detailed historical exposure assessment at this time. However, selected reports have been reviewed. For instance, Bakke et al. (2007) performed a systematic literature review and summarized over 100 exposure measurements by industrial process. Selected information from Bakke et al. (2007) is shown in Table 2 and summarized in Table 3.</p> <p>Average concentrations of TCE for degreasing and vapor degreasing ranged from <537 ug/m3 for samples taken in rooms that did not contain the degreaser to 3,039,420 ug/m3. Thirty-five out of 57 reports (61%) reported average TCE concentrations above 54,000 ug/m3, the level that EPA (2009) reported as the typical long-term exposure level for workers. Average exposures for many other exposure sources exceed the level that EPA reported as a typical long term exposure level for workers.</p> <p>From the above summaries of exposure measurements, ARCADIS concludes that it is a reasonable to assume that many workers in various industries who were working in or near metal degreasing operations were historically exposed for many years to average TCE concentrations of 200,000 ug/m3 or more. This is about one-half of the current OSHA Permissible Exposure Level of 100 ppm (537,000 ug/m3) and slightly less than about one-half of the current Threshold Limit Value of 50 ppm (268,500 ug/m3). In other work place settings, average exposure levels would have been lower. It is reasonable to assume that many workers in printing and dyes, spot removing, and adhesives were exposed routinely to 100,000 ug/m3 or more.</p> <p>To supplement the summaries of exposure information provided by EPA (2009) and Bakke et al. (2007), ARCADIS acquired exposure information for exposures to three additional receptor groups: (1) hospital personnel and patients exposed to TCE as an anesthetic; (2) dry cleaning workers and members of the public using dry cleaning services; and (3) average members of the population exposed to TCE in indoor and outdoor air from miscellaneous sources.</p> <p>With regard to hospital exposures, Corbett et al. (1973) studied occupational levels of exposure to TCE in operating room personnel during operations when TCE was administered as an anesthetic. Mean TCE levels in the operating room were 1-4 ppm except for samples taken directly over the equipment valve (25 to 30 ppm on average). TCE levels in exhaled breath of three patients were measured directly after the operation and for a period up to 12 days later. TCE levels in exhaled breath after anesthesia varied from 100-300 ppm for these patients who received anesthesia for 30, 100, or 160 minutes. A reasonable estimate of patient exposure during anesthesia is 200 ppm (1,074,000 ug/m3) for 2 hours.</p> <p>Two anesthesiologists who administered TCE for 120 minutes or more had TCE levels in their breath of ~0.5 ppm, so it is reasonable to assume that they experienced exposure concentrations of at least 1-4 ppm for the duration of the operation, as did other operating room personnel. Since they were directly operating the anesthesiology equipment, the concentrations found around the equipment valve (25-30 ppm) may be more relevant estimates for them. From the Corbett et al. (1973) study, ARCADIS concludes that is reasonable to assume that hospital workers were exposed to ~13,425 ug/m3 daily for an approximate 20 year period when TCE was used as an anesthetic and anesthesiologists were exposed to ~134,250 ug/m3 for the same period of time.</p> <p>ARCADIS has not yet identified any literature that specifically measured the TCE exposure levels in dry cleaning facilities during the time period when TCE was in use as the solvent of choice for dry cleaning. According to Bakke et al. (2007), this period was approximately 1930-1945. Despite the fact that little to no exposure measurements are available for TCE dry cleaning facilities, there is considerable exposure information from more recent years for PCE dry cleaning facilities. Table</p>	

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>4 summarizes exposure measurements for PCE usage in dry cleaning. ARCADIS sees no reason why PCE concentration levels in areas where PCE was used as a dry cleaning solvent would not serve as conservative surrogate values for TCE concentration levels earlier in time before PCE had replaced TCE as a dry cleaning solvent of choice. If anything, exposure levels for PCE in more recent years would probably underestimate the TCE exposure levels because industrial hygiene practices improved in all industries when the practices of 1930 - 1945 are compared to the practices of the 1990's, when the PCE measurements were made. As noted in the table, average exposure levels vary considerably, but it is reasonable to assume that the average concentration of TCE to which dry cleaning operators were exposed during these years was >100,000 µg/m3. In addition, it is reasonable to assume that clerks and customers were exposed to >50,000 µg/m3.</p> <p>Exposures to average members of the population exposed to TCE in indoor air from miscellaneous sources can be estimated by summarizing various indoor air quality studies. ARCADIS has obtained and summarized many such studies and notes that most available indoor air quality studies have been performed in the last 20 years, as shown in Table 5.</p> <p>Given that TCE use has steadily declined since 1970, all studies performed in the 1990's and 2000's will underestimate the typical exposure levels experienced by the US population during the exposure period of interest for a validation exercise, which is 1930 -1980. Still, these data are informative. As shown in Table 5, average indoor air levels of 1-5 µg/m3 have been commonly reported in the 1990s and 2000s. The only citation that gives measurements from the 1970's is Shah and Singh (1988) and Shah and Heyerdahl (1988), who summarized data from the late 1970's and 1980's. The mean indoor air value reported in this study was 7 µg/m3. ARCADIS thus concludes that it is not unreasonable to assume that the average indoor TCE exposure in the period 1930-1980 was >>10 µg/m3.</p> <p>TCE spills and releases have affected soils and groundwater at numerous sites across the country. ARCADIS has not yet performed a literature search to determine what the indoor TCE concentrations have been in commercial and residential buildings affected by TCE in the subsurface media because of vapor intrusion. EPA (2009) described two such locations: Cortlandville, New York, where indoor levels ranged from 1-17 µg/m3, and Endicott, New York, where indoor levels ranged from 1-140 µg/m3. Clearly, people living and working in buildings affected by TCE vapor intrusion from historical spills and releases may have been exposed for many years to levels much higher than the average population. Additional research work could be performed to make a refined estimate of the exposures for this specific subpopulation.</p> <p>Exposure Assessment for Validation Exercise</p> <p>ARCADIS has not yet performed a comprehensive exposure assessment of individual population groups who were exposed to TCE in the past in industrial, commercial, or residential settings. However, in the above section, selected summaries of published studies are presented that demonstrate that considerable exposure information is available that would allow a retrospective population risk assessment of TCE, at least at the screening level. Such as assessment would serve as a validation exercise to test whether EPAs' proposed carcinogen classification and URF are reasonable given the known facts about the historical and current incidence of RCC, liver and biliary cancer, and NHL and their causes. Considerable work needs to be done to execute such an exercise in a robust fashion. The preliminary information is presented above for EPA's consideration, because ARCADIS is recommending that EPA should not issue a carcinogen classification and a URF for an important chemical such as TCE without assessing the implications of the action and validating the proposed action against the known facts.</p> <p>Number of Exposed Individuals</p> <p>To perform a historical population risk assessment, one needs estimates of the numbers of people at risk in each population group to be assessed. Many questions are raised by this task, including the following:</p> <ul style="list-style-type: none"> • How many people worked in jobs where they performed metal degreasing operations before 1980? • How many people worked in areas in which or adjacent to which metal degreasing operations occurred before 1980? 	

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<ul style="list-style-type: none"> • How many workers used or worked adjacent to someone who used TCE as a spot remover before 1980? • How many workers used or worked adjacent to someone who used TCE as a dry cleaning solvent before 1980? • How many workers or consumers used or worked or lived adjacent to someone who used TCE-containing paints, varnishes, lacquers, or paint strippers before 1980? • How many anesthesiologists used TCE as an anesthetic before 1980? • How many operating room staff members were exposed to TCE when used as an anesthetic before 1980? • How many members of the population were administered TCE as an anesthetic before 1980? • How many workers used or worked adjacent to people who used TCE-containing typewriter correction fluids before 1980? <p>To perform a comprehensive historical population risk assessment for TCE, many more such questions must be posed and answered. While the task may seem too difficult to undertake, the task is really not all that different from the task that human health risk assessors face every day when performing a prospective risk assessment. For example, a human health risk assessment of a Superfund site requires that complete exposure pathways be identified, receptors identified, exposure point concentrations estimated, and exposure doses estimated after making reasonable assumptions about exposure frequency and duration. It is common for site risk assessors to consult EPA risk assessment guidance documents, perform literature searches, and employ predictive models to make reasonable assumptions about “reasonable maximum exposures” and then make estimates of risk using standard EPA equations and key EPA-derived estimates of carcinogenic potency, such as URFs.</p> <p>When key information is not known with certainty, assumptions are made. For instance, no one really knows how many times a child may trespass onto private land and ingest the surface soil at any given site, but assumptions are made, and the assessment progresses.</p> <p>Much information about the sizes of exposed populations can be gleaned from historical records. As an example, employment in certain industries can be gleaned from US Department of Labor reports. The 1970 Employment and Wages report was consulted, and selected information is summarized below to demonstrate the type of workforce information that is available.</p> <p>In private industry alone, in 1970, over 14 million people were employed in industries where TCE could potentially have been used. Of course, not all of these workers had exposures because some of them were office workers who worked in locations where TCE was not used for any purpose. The above estimates of potentially exposed workers compares reasonably with the value of 3,500,000 reported by the National Institute of Occupational Health (NIOSH) in 1978 (NIOSH 1978). Twenty years later, the Agency for Toxic Substances and Disease Registry (ATSDR 1997) reported that 400,000 workers were exposed to TCE thirty years after the peak in US production. At that time, US production of TCE had dropped to about 25% of the 1970 level.</p> <p>Population Risk Estimation</p> <p>ARCADIS recommends that EPA make population risk estimates and compare them to the known incidence rates for the cancer sites of interest. With estimates of exposure for various populations who were exposed in the period 1930-1980, and using EPA’s standard risk assessment approaches as applied to prospective risk assessment activities in all EPA programs, the final risk characterization step is not difficult to calculate. Probabilistic techniques can be applied to large data sets to bound the uncertainty in the various required exposure estimates. Population risk estimates for known risk factors should also be undertaken.</p> <p>Time Course of Cancer Incidence Rates</p> <p>As noted in Figure 1, which summarizes historical US incidence rates of RCC, liver and biliary cancer, and NHL from the NCI SEER database, the incidence rates for all three tumor types has been increasing steadily for years. Given that TCE production and use in the US peaked in 1970, the observed time course of incidence rates is not consistent with TCE being a major cause of any of these cancers in the US population. Figure 1 also shows production statistics and shows the time points that are 20 years and 30 years after the peak in production. Given that any cancers caused by TCE would be expected to be observable in the national cancer incidence statistics</p>	

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>20-30 years after critical exposure events, one would expect that incidence rates would be decreasing, not increasing, if TCE were a major cause. Of course, decreases in the incidence rates of any TCE-caused cancers could be masked by increasing rates of cancers associated with other causal agents. Whether such masking is occurring or not, the conclusion is the same: the time courses of RCC, liver and biliary cancer, and NHL do not provide support for any hypothesis that TCE poses a great risk of cancer in the human population.</p> <p>Figure 1: US TCE production (1941-1998) and US incidence rates of RCC, liver and biliary cancer, and NHL (1973-2006). Lines at 1990 and 2000 indicate 20-year and 30-year latency periods, respectively, from peak TCE production in 1970. US production data from Bakke et al. (2007), IARC (1995), Doherty (2000), and EPA (2009). Incidence rates from SEER (2009 a,b,c).</p> <p>Conclusion</p> <p>ARCADIS finds EPA's proposed action to be deficient because the implications of the proposal were not discussed, and no validation exercise was performed to determine if cancer incidence predictions made with the proposed URF match the known incidence rates of RCC, liver and biliary cancer, and NHL in the context of the many well-characterized risk factors for these cancers. The preliminary information presented above is provided for EPA's consideration, because ARCADIS is recommending that EPA not issue a carcinogen classification and a URF for an important chemical such as TCE without assessing the implications of the action and validating the proposed action against the known facts.</p> <p>In addition, ARCADIS notes that the TCE concentration that poses a residential excess lifetime cancer risk of 1×10^{-6} is $0.25 \mu\text{g}/\text{m}^3$. According to the EPA's 1999 TO-15 method, the method detection limits for TCE in indoor air are $2.42 \mu\text{g}/\text{m}^3$, or $0.38 \mu\text{g}/\text{m}^3$ if Selective Ion Monitoring is used.</p>	

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics																																																																																																																																
7	163	EPA-HQ-ORD-2009-0791-0011.1	ARCADIS	[See Excerpt ID 162 for Excerpt Text-additional graphic presented in this Excerpt]	<p style="text-align: center;">TABLE 2 WORKPLACE EXPOSURE MEASUREMENTS, BAKKE ET AL. (2007)</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left;">Source of Exposure</th> <th style="text-align: center;">Year(s) of Measurement</th> <th style="text-align: center;">Arithmetic Mean (ppm)</th> <th style="text-align: center;">Maximum (ppm)</th> </tr> </thead> <tbody> <tr><td>Degreasing</td><td style="text-align: center;">1980–1989</td><td style="text-align: center;">33</td><td></td></tr> <tr><td>Degreasing</td><td style="text-align: center;">1947–1959</td><td style="text-align: center;">136</td><td></td></tr> <tr><td>Degreasing</td><td style="text-align: center;">1980–1989</td><td style="text-align: center;">0.9</td><td></td></tr> <tr><td>Degreasing</td><td style="text-align: center;">1970–1979</td><td style="text-align: center;">7.9</td><td></td></tr> <tr><td>Degreasing</td><td style="text-align: center;">1947–1959</td><td style="text-align: center;">34</td><td></td></tr> <tr><td>Vapor degreasing</td><td style="text-align: center;">1955</td><td style="text-align: center;">46</td><td style="text-align: center;">131</td></tr> <tr><td>Vapor degreasing</td><td style="text-align: center;">1955</td><td style="text-align: center;">56</td><td style="text-align: center;">225</td></tr> <tr><td>Vapor degreasing</td><td style="text-align: center;">1955</td><td style="text-align: center;">25</td><td style="text-align: center;">35</td></tr> <tr><td>Vapor degreasing</td><td style="text-align: center;">1955</td><td style="text-align: center;">35</td><td></td></tr> <tr><td>Vapor degreasing</td><td style="text-align: center;">1955</td><td style="text-align: center;">105</td><td style="text-align: center;">157</td></tr> <tr><td>Degreasing</td><td style="text-align: center;">1980</td><td></td><td></td></tr> <tr><td>Degreasing</td><td style="text-align: center;">1986</td><td></td><td style="text-align: center;">224</td></tr> <tr><td>Vapor degreasing</td><td style="text-align: center;">1988</td><td style="text-align: center;">5.1</td><td></td></tr> <tr><td>Vapor degreasing</td><td style="text-align: center;">1963</td><td style="text-align: center;">23</td><td style="text-align: center;">140</td></tr> <tr><td>Vapor degreasing</td><td style="text-align: center;">1963</td><td style="text-align: center;">7</td><td style="text-align: center;">80</td></tr> <tr><td>Vapor degreasing</td><td style="text-align: center;">1963</td><td style="text-align: center;">225</td><td style="text-align: center;">375</td></tr> <tr><td>Vapor degreasing</td><td style="text-align: center;">1963</td><td style="text-align: center;">50</td><td style="text-align: center;">400</td></tr> <tr><td>Vapor degreasing</td><td style="text-align: center;">1963</td><td style="text-align: center;">70</td><td style="text-align: center;">375</td></tr> <tr><td>Vapor degreasing</td><td style="text-align: center;">1963</td><td style="text-align: center;">36</td><td style="text-align: center;">415</td></tr> <tr><td>Vapor degreasing</td><td style="text-align: center;">1963</td><td style="text-align: center;">46</td><td style="text-align: center;">375</td></tr> <tr><td>Vapor degreasing</td><td style="text-align: center;">1963</td><td style="text-align: center;">32</td><td style="text-align: center;">375</td></tr> <tr><td>Degreasing</td><td style="text-align: center;">1986</td><td style="text-align: center;">3.4</td><td style="text-align: center;">5.1</td></tr> <tr><td>Degreasing</td><td style="text-align: center;">1984</td><td style="text-align: center;">34</td><td style="text-align: center;">68</td></tr> <tr><td>Degreasing</td><td style="text-align: center;">1984</td><td style="text-align: center;">94</td><td style="text-align: center;">214</td></tr> <tr><td>Degreasing</td><td style="text-align: center;">1984</td><td style="text-align: center;">85</td><td style="text-align: center;">426</td></tr> <tr><td>Degreasing</td><td style="text-align: center;">1984</td><td style="text-align: center;">86</td><td style="text-align: center;">274</td></tr> <tr><td>Degreasing</td><td style="text-align: center;">1990</td><td style="text-align: center;">92</td><td></td></tr> <tr><td>Degreasing</td><td style="text-align: center;">1990</td><td style="text-align: center;">2.2</td><td style="text-align: center;">5.3</td></tr> <tr><td>Degreasing</td><td style="text-align: center;">1990</td><td style="text-align: center;">4.9</td><td style="text-align: center;">5.2</td></tr> <tr><td>Degreasing</td><td style="text-align: center;">1989</td><td style="text-align: center;">10</td><td style="text-align: center;">11</td></tr> <tr><td>Degreasing</td><td style="text-align: center;">1986</td><td style="text-align: center;">120</td><td style="text-align: center;">137</td></tr> </tbody> </table> <p style="text-align: center;">[See Excerpt ID 162 for Excerpt References-additional graphic presented in this Excerpt]</p>	Source of Exposure	Year(s) of Measurement	Arithmetic Mean (ppm)	Maximum (ppm)	Degreasing	1980–1989	33		Degreasing	1947–1959	136		Degreasing	1980–1989	0.9		Degreasing	1970–1979	7.9		Degreasing	1947–1959	34		Vapor degreasing	1955	46	131	Vapor degreasing	1955	56	225	Vapor degreasing	1955	25	35	Vapor degreasing	1955	35		Vapor degreasing	1955	105	157	Degreasing	1980			Degreasing	1986		224	Vapor degreasing	1988	5.1		Vapor degreasing	1963	23	140	Vapor degreasing	1963	7	80	Vapor degreasing	1963	225	375	Vapor degreasing	1963	50	400	Vapor degreasing	1963	70	375	Vapor degreasing	1963	36	415	Vapor degreasing	1963	46	375	Vapor degreasing	1963	32	375	Degreasing	1986	3.4	5.1	Degreasing	1984	34	68	Degreasing	1984	94	214	Degreasing	1984	85	426	Degreasing	1984	86	274	Degreasing	1990	92		Degreasing	1990	2.2	5.3	Degreasing	1990	4.9	5.2	Degreasing	1989	10	11	Degreasing	1986	120	137
Source of Exposure	Year(s) of Measurement	Arithmetic Mean (ppm)	Maximum (ppm)																																																																																																																																		
Degreasing	1980–1989	33																																																																																																																																			
Degreasing	1947–1959	136																																																																																																																																			
Degreasing	1980–1989	0.9																																																																																																																																			
Degreasing	1970–1979	7.9																																																																																																																																			
Degreasing	1947–1959	34																																																																																																																																			
Vapor degreasing	1955	46	131																																																																																																																																		
Vapor degreasing	1955	56	225																																																																																																																																		
Vapor degreasing	1955	25	35																																																																																																																																		
Vapor degreasing	1955	35																																																																																																																																			
Vapor degreasing	1955	105	157																																																																																																																																		
Degreasing	1980																																																																																																																																				
Degreasing	1986		224																																																																																																																																		
Vapor degreasing	1988	5.1																																																																																																																																			
Vapor degreasing	1963	23	140																																																																																																																																		
Vapor degreasing	1963	7	80																																																																																																																																		
Vapor degreasing	1963	225	375																																																																																																																																		
Vapor degreasing	1963	50	400																																																																																																																																		
Vapor degreasing	1963	70	375																																																																																																																																		
Vapor degreasing	1963	36	415																																																																																																																																		
Vapor degreasing	1963	46	375																																																																																																																																		
Vapor degreasing	1963	32	375																																																																																																																																		
Degreasing	1986	3.4	5.1																																																																																																																																		
Degreasing	1984	34	68																																																																																																																																		
Degreasing	1984	94	214																																																																																																																																		
Degreasing	1984	85	426																																																																																																																																		
Degreasing	1984	86	274																																																																																																																																		
Degreasing	1990	92																																																																																																																																			
Degreasing	1990	2.2	5.3																																																																																																																																		
Degreasing	1990	4.9	5.2																																																																																																																																		
Degreasing	1989	10	11																																																																																																																																		
Degreasing	1986	120	137																																																																																																																																		

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics																																																																																																																																								
7	164	EPA-HQ-ORD-2009-0791-0011.1	ARCADIS	[See Excerpt ID 162 for Excerpt Text-additional graphic presented in this Excerpt]	<table border="1"> <thead> <tr> <th data-bbox="1623 180 1865 224">Source of Exposure</th> <th data-bbox="1873 180 2072 224">Year(s) of Measurement</th> <th data-bbox="2080 180 2287 224">Arithmetic Mean (ppm)</th> <th data-bbox="2295 180 2448 224">Maximum (ppm)</th> </tr> </thead> <tbody> <tr><td>Degreasing</td><td>1986</td><td>38</td><td>89</td></tr> <tr><td>Degreasing</td><td>1980</td><td><0.1</td><td></td></tr> <tr><td>Degreasing</td><td>1980</td><td>0.2</td><td>0.7</td></tr> <tr><td>Degreasing</td><td>1980</td><td><0.3</td><td></td></tr> <tr><td>Degreasing</td><td>1980</td><td>0.6</td><td></td></tr> <tr><td>Degreasing</td><td>1980-1989</td><td>7.9</td><td></td></tr> <tr><td>Degreasing</td><td>1960-1969</td><td>38</td><td></td></tr> <tr><td>Degreasing</td><td>1947-1959</td><td>24</td><td></td></tr> <tr><td>Degreasing</td><td>1990</td><td>19</td><td>50</td></tr> <tr><td>Degreasing</td><td>1990</td><td>4.1</td><td>11</td></tr> <tr><td>Degreasing</td><td>1982</td><td>0.7</td><td>1.1</td></tr> <tr><td>Degreasing</td><td>1982</td><td>5.3</td><td>23</td></tr> <tr><td>Degreasing</td><td>1982</td><td>62</td><td>234</td></tr> <tr><td>Degreasing</td><td>1982</td><td>4.1</td><td></td></tr> <tr><td>Degreasing</td><td>1982</td><td>5.7</td><td>39</td></tr> <tr><td>Degreasing</td><td>1983</td><td>7.8</td><td>25</td></tr> <tr><td>Degreasing</td><td>1981</td><td>1</td><td>3</td></tr> <tr><td>Degreasing</td><td>1981</td><td>1.2</td><td>1.7</td></tr> <tr><td>Degreasing</td><td>1988</td><td>28</td><td>64</td></tr> <tr><td>Degreasing</td><td>1988</td><td>25</td><td>33</td></tr> <tr><td>Degreasing</td><td>1981</td><td>1.4</td><td>1.7</td></tr> <tr><td>Degreasing</td><td>1940</td><td>134</td><td>342</td></tr> <tr><td>Vapor degreasing</td><td>1956</td><td>68</td><td>73</td></tr> <tr><td>Vapor degreasing</td><td>1956</td><td>398</td><td>423</td></tr> <tr><td>Vapor degreasing</td><td>1956</td><td>566</td><td>637</td></tr> <tr><td>Vapor degreasing</td><td>1974</td><td>57</td><td>65</td></tr> <tr><td>Vapor degreasing</td><td>1989</td><td>39</td><td>120</td></tr> <tr><td>Degreasing</td><td>1988-1999</td><td>5.1</td><td>27</td></tr> <tr><td>Spot remover</td><td>1997-1999</td><td></td><td>22</td></tr> <tr><td>Spot remover</td><td>1996</td><td>1.9</td><td>4.1</td></tr> <tr><td>Spot remover</td><td>1996</td><td>1.1</td><td>1.7</td></tr> <tr><td>Printing dyes</td><td>1980-1989</td><td>6.4</td><td></td></tr> <tr><td>Printing dyes</td><td>1960-1969</td><td>81</td><td></td></tr> </tbody> </table> <p data-bbox="1623 1386 2381 1409">[See Excerpt ID 162 for Excerpt References-additional graphic presented in this Excerpt]</p>	Source of Exposure	Year(s) of Measurement	Arithmetic Mean (ppm)	Maximum (ppm)	Degreasing	1986	38	89	Degreasing	1980	<0.1		Degreasing	1980	0.2	0.7	Degreasing	1980	<0.3		Degreasing	1980	0.6		Degreasing	1980-1989	7.9		Degreasing	1960-1969	38		Degreasing	1947-1959	24		Degreasing	1990	19	50	Degreasing	1990	4.1	11	Degreasing	1982	0.7	1.1	Degreasing	1982	5.3	23	Degreasing	1982	62	234	Degreasing	1982	4.1		Degreasing	1982	5.7	39	Degreasing	1983	7.8	25	Degreasing	1981	1	3	Degreasing	1981	1.2	1.7	Degreasing	1988	28	64	Degreasing	1988	25	33	Degreasing	1981	1.4	1.7	Degreasing	1940	134	342	Vapor degreasing	1956	68	73	Vapor degreasing	1956	398	423	Vapor degreasing	1956	566	637	Vapor degreasing	1974	57	65	Vapor degreasing	1989	39	120	Degreasing	1988-1999	5.1	27	Spot remover	1997-1999		22	Spot remover	1996	1.9	4.1	Spot remover	1996	1.1	1.7	Printing dyes	1980-1989	6.4		Printing dyes	1960-1969	81	
Source of Exposure	Year(s) of Measurement	Arithmetic Mean (ppm)	Maximum (ppm)																																																																																																																																										
Degreasing	1986	38	89																																																																																																																																										
Degreasing	1980	<0.1																																																																																																																																											
Degreasing	1980	0.2	0.7																																																																																																																																										
Degreasing	1980	<0.3																																																																																																																																											
Degreasing	1980	0.6																																																																																																																																											
Degreasing	1980-1989	7.9																																																																																																																																											
Degreasing	1960-1969	38																																																																																																																																											
Degreasing	1947-1959	24																																																																																																																																											
Degreasing	1990	19	50																																																																																																																																										
Degreasing	1990	4.1	11																																																																																																																																										
Degreasing	1982	0.7	1.1																																																																																																																																										
Degreasing	1982	5.3	23																																																																																																																																										
Degreasing	1982	62	234																																																																																																																																										
Degreasing	1982	4.1																																																																																																																																											
Degreasing	1982	5.7	39																																																																																																																																										
Degreasing	1983	7.8	25																																																																																																																																										
Degreasing	1981	1	3																																																																																																																																										
Degreasing	1981	1.2	1.7																																																																																																																																										
Degreasing	1988	28	64																																																																																																																																										
Degreasing	1988	25	33																																																																																																																																										
Degreasing	1981	1.4	1.7																																																																																																																																										
Degreasing	1940	134	342																																																																																																																																										
Vapor degreasing	1956	68	73																																																																																																																																										
Vapor degreasing	1956	398	423																																																																																																																																										
Vapor degreasing	1956	566	637																																																																																																																																										
Vapor degreasing	1974	57	65																																																																																																																																										
Vapor degreasing	1989	39	120																																																																																																																																										
Degreasing	1988-1999	5.1	27																																																																																																																																										
Spot remover	1997-1999		22																																																																																																																																										
Spot remover	1996	1.9	4.1																																																																																																																																										
Spot remover	1996	1.1	1.7																																																																																																																																										
Printing dyes	1980-1989	6.4																																																																																																																																											
Printing dyes	1960-1969	81																																																																																																																																											

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics																																																																																																																																								
7	165	EPA-HQ-ORD-2009-0791-0011.1	ARCADIS	[See Excerpt ID 162 for Excerpt Text-additional graphic presented in this Excerpt]	<table border="1"> <thead> <tr> <th data-bbox="1623 155 1865 215">Source of Exposure</th> <th data-bbox="1873 155 2072 215">Year(s) of Measurement</th> <th data-bbox="2080 155 2292 215">Arithmetic Mean (ppm)</th> <th data-bbox="2300 155 2448 215">Maximum (ppm)</th> </tr> </thead> <tbody> <tr><td>Degreasing</td><td>1986</td><td>38</td><td>89</td></tr> <tr><td>Degreasing</td><td>1980</td><td><0.1</td><td></td></tr> <tr><td>Degreasing</td><td>1980</td><td>0.2</td><td>0.7</td></tr> <tr><td>Degreasing</td><td>1980</td><td><0.3</td><td></td></tr> <tr><td>Degreasing</td><td>1980</td><td>0.6</td><td></td></tr> <tr><td>Degreasing</td><td>1980-1989</td><td>7.9</td><td></td></tr> <tr><td>Degreasing</td><td>1960-1969</td><td>38</td><td></td></tr> <tr><td>Degreasing</td><td>1947-1959</td><td>24</td><td></td></tr> <tr><td>Degreasing</td><td>1990</td><td>19</td><td>50</td></tr> <tr><td>Degreasing</td><td>1990</td><td>4.1</td><td>11</td></tr> <tr><td>Degreasing</td><td>1982</td><td>0.7</td><td>1.1</td></tr> <tr><td>Degreasing</td><td>1982</td><td>5.3</td><td>23</td></tr> <tr><td>Degreasing</td><td>1982</td><td>62</td><td>234</td></tr> <tr><td>Degreasing</td><td>1982</td><td>4.1</td><td></td></tr> <tr><td>Degreasing</td><td>1982</td><td>5.7</td><td>39</td></tr> <tr><td>Degreasing</td><td>1983</td><td>7.8</td><td>25</td></tr> <tr><td>Degreasing</td><td>1981</td><td>1</td><td>3</td></tr> <tr><td>Degreasing</td><td>1981</td><td>1.2</td><td>1.7</td></tr> <tr><td>Degreasing</td><td>1988</td><td>28</td><td>64</td></tr> <tr><td>Degreasing</td><td>1988</td><td>25</td><td>33</td></tr> <tr><td>Degreasing</td><td>1981</td><td>1.4</td><td>1.7</td></tr> <tr><td>Degreasing</td><td>1940</td><td>134</td><td>342</td></tr> <tr><td>Vapor degreasing</td><td>1956</td><td>68</td><td>73</td></tr> <tr><td>Vapor degreasing</td><td>1956</td><td>398</td><td>423</td></tr> <tr><td>Vapor degreasing</td><td>1956</td><td>566</td><td>637</td></tr> <tr><td>Vapor degreasing</td><td>1974</td><td>57</td><td>65</td></tr> <tr><td>Vapor degreasing</td><td>1989</td><td>39</td><td>120</td></tr> <tr><td>Degreasing</td><td>1988-1999</td><td>5.1</td><td>27</td></tr> <tr><td>Spot remover</td><td>1997-1999</td><td></td><td>22</td></tr> <tr><td>Spot remover</td><td>1996</td><td>1.9</td><td>4.1</td></tr> <tr><td>Spot remover</td><td>1996</td><td>1.1</td><td>1.7</td></tr> <tr><td>Printing dyes</td><td>1980-1989</td><td>6.4</td><td></td></tr> <tr><td>Printing dyes</td><td>1960-1969</td><td>81</td><td></td></tr> </tbody> </table> <p data-bbox="1623 1385 2381 1409">[See Excerpt ID 162 for Excerpt References-additional graphic presented in this Excerpt]</p>	Source of Exposure	Year(s) of Measurement	Arithmetic Mean (ppm)	Maximum (ppm)	Degreasing	1986	38	89	Degreasing	1980	<0.1		Degreasing	1980	0.2	0.7	Degreasing	1980	<0.3		Degreasing	1980	0.6		Degreasing	1980-1989	7.9		Degreasing	1960-1969	38		Degreasing	1947-1959	24		Degreasing	1990	19	50	Degreasing	1990	4.1	11	Degreasing	1982	0.7	1.1	Degreasing	1982	5.3	23	Degreasing	1982	62	234	Degreasing	1982	4.1		Degreasing	1982	5.7	39	Degreasing	1983	7.8	25	Degreasing	1981	1	3	Degreasing	1981	1.2	1.7	Degreasing	1988	28	64	Degreasing	1988	25	33	Degreasing	1981	1.4	1.7	Degreasing	1940	134	342	Vapor degreasing	1956	68	73	Vapor degreasing	1956	398	423	Vapor degreasing	1956	566	637	Vapor degreasing	1974	57	65	Vapor degreasing	1989	39	120	Degreasing	1988-1999	5.1	27	Spot remover	1997-1999		22	Spot remover	1996	1.9	4.1	Spot remover	1996	1.1	1.7	Printing dyes	1980-1989	6.4		Printing dyes	1960-1969	81	
Source of Exposure	Year(s) of Measurement	Arithmetic Mean (ppm)	Maximum (ppm)																																																																																																																																										
Degreasing	1986	38	89																																																																																																																																										
Degreasing	1980	<0.1																																																																																																																																											
Degreasing	1980	0.2	0.7																																																																																																																																										
Degreasing	1980	<0.3																																																																																																																																											
Degreasing	1980	0.6																																																																																																																																											
Degreasing	1980-1989	7.9																																																																																																																																											
Degreasing	1960-1969	38																																																																																																																																											
Degreasing	1947-1959	24																																																																																																																																											
Degreasing	1990	19	50																																																																																																																																										
Degreasing	1990	4.1	11																																																																																																																																										
Degreasing	1982	0.7	1.1																																																																																																																																										
Degreasing	1982	5.3	23																																																																																																																																										
Degreasing	1982	62	234																																																																																																																																										
Degreasing	1982	4.1																																																																																																																																											
Degreasing	1982	5.7	39																																																																																																																																										
Degreasing	1983	7.8	25																																																																																																																																										
Degreasing	1981	1	3																																																																																																																																										
Degreasing	1981	1.2	1.7																																																																																																																																										
Degreasing	1988	28	64																																																																																																																																										
Degreasing	1988	25	33																																																																																																																																										
Degreasing	1981	1.4	1.7																																																																																																																																										
Degreasing	1940	134	342																																																																																																																																										
Vapor degreasing	1956	68	73																																																																																																																																										
Vapor degreasing	1956	398	423																																																																																																																																										
Vapor degreasing	1956	566	637																																																																																																																																										
Vapor degreasing	1974	57	65																																																																																																																																										
Vapor degreasing	1989	39	120																																																																																																																																										
Degreasing	1988-1999	5.1	27																																																																																																																																										
Spot remover	1997-1999		22																																																																																																																																										
Spot remover	1996	1.9	4.1																																																																																																																																										
Spot remover	1996	1.1	1.7																																																																																																																																										
Printing dyes	1980-1989	6.4																																																																																																																																											
Printing dyes	1960-1969	81																																																																																																																																											

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics																																																																																																																																											
7	166	EPA-HQ-ORD-2009-0791-0011.1	ARCADIS	[See Excerpt ID 162 for Excerpt Text-additional graphic presented in this Excerpt]	<table border="1"> <thead> <tr> <th data-bbox="1623 188 1865 215">Source of Exposure</th> <th data-bbox="1900 164 2048 215">Year(s) of Measurement</th> <th data-bbox="2088 164 2279 215">Arithmetic Mean (ppm)</th> <th data-bbox="2314 164 2421 215">Maximum (ppm)</th> </tr> </thead> <tbody> <tr><td>NA</td><td>1982</td><td>1</td><td>1.3</td></tr> <tr><td>NA</td><td>1976</td><td>2.8</td><td>3.6</td></tr> <tr><td>NA</td><td>1976</td><td>2.8</td><td>4.3</td></tr> <tr><td>Adhesives</td><td>1989</td><td>0.1</td><td></td></tr> <tr><td>NA</td><td>1977</td><td>0.4</td><td></td></tr> <tr><td>NA</td><td>1977</td><td>8.6</td><td>17</td></tr> <tr><td>Adhesives</td><td>1980</td><td>0.2</td><td>0.5</td></tr> <tr><td>Adhesives</td><td>1981</td><td>0.5</td><td>0.1</td></tr> <tr><td>Adhesives</td><td>1980-1989</td><td>3.8</td><td></td></tr> <tr><td>Adhesives</td><td>1947-1959</td><td>29</td><td></td></tr> <tr><td>Mold release agent</td><td>1957</td><td></td><td>425</td></tr> <tr><td>Mold release agent</td><td>1957</td><td></td><td>200</td></tr> <tr><td>Mold release agent</td><td>1957</td><td></td><td>300</td></tr> <tr><td>Mold release agent</td><td>1957</td><td></td><td>50</td></tr> <tr><td>NA</td><td>1977</td><td>46</td><td>290</td></tr> <tr><td>Adhesives/paints</td><td>1977</td><td>63</td><td>79</td></tr> <tr><td>NA</td><td>1980</td><td>2.7</td><td>27</td></tr> <tr><td>NA</td><td>1980</td><td>2.5</td><td>40</td></tr> <tr><td>Lacquer</td><td>1993</td><td>0.04</td><td>0.05</td></tr> <tr><td>Lacquer</td><td>1993</td><td>0.04</td><td>0.04</td></tr> <tr><td>Adhesives</td><td>1990</td><td>9</td><td>21</td></tr> <tr><td>Wastewater</td><td>1983</td><td>0.002</td><td>0.04</td></tr> <tr><td>Wastewater</td><td>1981</td><td>2</td><td>7</td></tr> <tr><td>Wastewater</td><td>1981</td><td>0.5</td><td>0.7</td></tr> <tr><td>Wastewater</td><td>1981</td><td>3.2</td><td>7.6</td></tr> <tr><td>Wastewater</td><td>1981</td><td>6.3</td><td>11</td></tr> <tr><td>Spot remover</td><td>1980-1989</td><td>4.2</td><td></td></tr> <tr><td>Spot remover</td><td>1970-1979</td><td>4</td><td></td></tr> <tr><td>Spot remover</td><td>1960-1969</td><td>35</td><td></td></tr> <tr><td>Spot remover</td><td>1947-1959</td><td>95</td><td></td></tr> <tr><td>NA</td><td>1983</td><td>0.2</td><td></td></tr> <tr><td>NA</td><td>1983</td><td>3.1</td><td></td></tr> <tr><td>Lacquer</td><td>1983</td><td>0.3</td><td></td></tr> </tbody> </table> <p data-bbox="1623 1377 2381 1398">[See Excerpt ID 162 for Excerpt References-additional graphic presented in this Excerpt]</p>				Source of Exposure	Year(s) of Measurement	Arithmetic Mean (ppm)	Maximum (ppm)	NA	1982	1	1.3	NA	1976	2.8	3.6	NA	1976	2.8	4.3	Adhesives	1989	0.1		NA	1977	0.4		NA	1977	8.6	17	Adhesives	1980	0.2	0.5	Adhesives	1981	0.5	0.1	Adhesives	1980-1989	3.8		Adhesives	1947-1959	29		Mold release agent	1957		425	Mold release agent	1957		200	Mold release agent	1957		300	Mold release agent	1957		50	NA	1977	46	290	Adhesives/paints	1977	63	79	NA	1980	2.7	27	NA	1980	2.5	40	Lacquer	1993	0.04	0.05	Lacquer	1993	0.04	0.04	Adhesives	1990	9	21	Wastewater	1983	0.002	0.04	Wastewater	1981	2	7	Wastewater	1981	0.5	0.7	Wastewater	1981	3.2	7.6	Wastewater	1981	6.3	11	Spot remover	1980-1989	4.2		Spot remover	1970-1979	4		Spot remover	1960-1969	35		Spot remover	1947-1959	95		NA	1983	0.2		NA	1983	3.1		Lacquer	1983	0.3	
Source of Exposure	Year(s) of Measurement	Arithmetic Mean (ppm)	Maximum (ppm)																																																																																																																																													
NA	1982	1	1.3																																																																																																																																													
NA	1976	2.8	3.6																																																																																																																																													
NA	1976	2.8	4.3																																																																																																																																													
Adhesives	1989	0.1																																																																																																																																														
NA	1977	0.4																																																																																																																																														
NA	1977	8.6	17																																																																																																																																													
Adhesives	1980	0.2	0.5																																																																																																																																													
Adhesives	1981	0.5	0.1																																																																																																																																													
Adhesives	1980-1989	3.8																																																																																																																																														
Adhesives	1947-1959	29																																																																																																																																														
Mold release agent	1957		425																																																																																																																																													
Mold release agent	1957		200																																																																																																																																													
Mold release agent	1957		300																																																																																																																																													
Mold release agent	1957		50																																																																																																																																													
NA	1977	46	290																																																																																																																																													
Adhesives/paints	1977	63	79																																																																																																																																													
NA	1980	2.7	27																																																																																																																																													
NA	1980	2.5	40																																																																																																																																													
Lacquer	1993	0.04	0.05																																																																																																																																													
Lacquer	1993	0.04	0.04																																																																																																																																													
Adhesives	1990	9	21																																																																																																																																													
Wastewater	1983	0.002	0.04																																																																																																																																													
Wastewater	1981	2	7																																																																																																																																													
Wastewater	1981	0.5	0.7																																																																																																																																													
Wastewater	1981	3.2	7.6																																																																																																																																													
Wastewater	1981	6.3	11																																																																																																																																													
Spot remover	1980-1989	4.2																																																																																																																																														
Spot remover	1970-1979	4																																																																																																																																														
Spot remover	1960-1969	35																																																																																																																																														
Spot remover	1947-1959	95																																																																																																																																														
NA	1983	0.2																																																																																																																																														
NA	1983	3.1																																																																																																																																														
Lacquer	1983	0.3																																																																																																																																														

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics																																																								
7	167	EPA-HQ-ORD-2009-0791-0011.1	ARCADIS	[See Excerpt ID 162 for Excerpt Text-additional graphic presented in this Excerpt]	<table border="1"> <thead> <tr> <th>Source of Exposure</th> <th>Year(s) of Measurement</th> <th>Arithmetic Mean (ppm)</th> <th>Maximum (ppm)</th> </tr> </thead> <tbody> <tr> <td>Skin degreasing</td> <td>1983</td> <td>3</td> <td></td> </tr> <tr> <td>Anesthetics</td> <td>1973</td> <td></td> <td>103</td> </tr> <tr> <td>Anesthetics</td> <td>1973</td> <td></td> <td>1.5</td> </tr> <tr> <td>Anesthetics</td> <td>1974</td> <td></td> <td>50</td> </tr> <tr> <td>Adhesives</td> <td>1981</td> <td>135</td> <td></td> </tr> <tr> <td>Smoke bomb</td> <td>1987</td> <td>0.2</td> <td>3.2</td> </tr> <tr> <td>Smoke bomb</td> <td>1987</td> <td></td> <td>0.7</td> </tr> <tr> <td>Solvent</td> <td>1982</td> <td>0.2</td> <td></td> </tr> <tr> <td>Waste</td> <td>1982</td> <td>0.002</td> <td></td> </tr> <tr> <td>NA</td> <td>1951</td> <td>13</td> <td></td> </tr> <tr> <td>NA</td> <td>1951</td> <td>179</td> <td>240</td> </tr> <tr> <td>NA</td> <td>1989</td> <td>0.04 (median)</td> <td></td> </tr> <tr> <td>Lab chemical</td> <td>1989</td> <td>0.01 (median)</td> <td>0.02</td> </tr> </tbody> </table> <p>-</p> <p>[See Excerpt ID 162 for Excerpt References-additional graphic presented in this Excerpt]</p>	Source of Exposure	Year(s) of Measurement	Arithmetic Mean (ppm)	Maximum (ppm)	Skin degreasing	1983	3		Anesthetics	1973		103	Anesthetics	1973		1.5	Anesthetics	1974		50	Adhesives	1981	135		Smoke bomb	1987	0.2	3.2	Smoke bomb	1987		0.7	Solvent	1982	0.2		Waste	1982	0.002		NA	1951	13		NA	1951	179	240	NA	1989	0.04 (median)		Lab chemical	1989	0.01 (median)	0.02
Source of Exposure	Year(s) of Measurement	Arithmetic Mean (ppm)	Maximum (ppm)																																																										
Skin degreasing	1983	3																																																											
Anesthetics	1973		103																																																										
Anesthetics	1973		1.5																																																										
Anesthetics	1974		50																																																										
Adhesives	1981	135																																																											
Smoke bomb	1987	0.2	3.2																																																										
Smoke bomb	1987		0.7																																																										
Solvent	1982	0.2																																																											
Waste	1982	0.002																																																											
NA	1951	13																																																											
NA	1951	179	240																																																										
NA	1989	0.04 (median)																																																											
Lab chemical	1989	0.01 (median)	0.02																																																										
7	168	EPA-HQ-ORD-2009-0791-0011.1	ARCADIS	[See Excerpt ID 162 for Excerpt Text-additional graphic presented in this Excerpt]	<p style="text-align: center;">TABLE 3 SUMMARY OF WORK PLACE EXPOSURE MEASUREMENTS, BAKKE et al. (2007)</p> <table border="1"> <thead> <tr> <th>Source of Exposure</th> <th>Lowest and Highest Reported Average Concentration of TCE (µg/m³)</th> </tr> </thead> <tbody> <tr> <td>Degreasing, Vapor Degreasing</td> <td><537 – 3,039,420</td> </tr> <tr> <td>Spot Removing</td> <td>5,907 – 510,150</td> </tr> <tr> <td>Printing Dyes</td> <td>34,368 – 434,970</td> </tr> <tr> <td>Adhesives</td> <td>537 – 724,950</td> </tr> <tr> <td>Lacquers</td> <td>215 – 1,611</td> </tr> <tr> <td>Anesthetics</td> <td>128,880</td> </tr> </tbody> </table> <p>-</p> <p>[See Excerpt ID 162 for Excerpt References-additional graphic presented in this Excerpt]</p>	Source of Exposure	Lowest and Highest Reported Average Concentration of TCE (µg/m ³)	Degreasing, Vapor Degreasing	<537 – 3,039,420	Spot Removing	5,907 – 510,150	Printing Dyes	34,368 – 434,970	Adhesives	537 – 724,950	Lacquers	215 – 1,611	Anesthetics	128,880																																										
Source of Exposure	Lowest and Highest Reported Average Concentration of TCE (µg/m ³)																																																												
Degreasing, Vapor Degreasing	<537 – 3,039,420																																																												
Spot Removing	5,907 – 510,150																																																												
Printing Dyes	34,368 – 434,970																																																												
Adhesives	537 – 724,950																																																												
Lacquers	215 – 1,611																																																												
Anesthetics	128,880																																																												

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics																																																																																				
7	169	EPA-HQ-ORD-2009-0791-0011.1	ARCADIS	[See Excerpt ID 162 for Excerpt Text-additional graphic presented in this Excerpt]	<p style="text-align: center;">TABLE 4 PCE CONCENTRATIONS IN DRY CLEANING FACILITIES (µg/m³)</p> <table border="1" data-bbox="1623 212 2467 829"> <thead> <tr> <th>Study</th> <th>Notes</th> <th>Mean</th> <th>Maximum</th> </tr> </thead> <tbody> <tr> <td>Aggazzotti et al. (1994a)</td> <td>Maxima in Small Dry Cleaning Facilities (n=28)</td> <td>5,000</td> <td>308,000</td> </tr> <tr> <td>Aggazzotti et al. (1994b)</td> <td>Medians In Small Dry Cleaning Facilities (n=28)</td> <td>600-75,000 (median)</td> <td></td> </tr> <tr> <td>Cai et al. (1992)</td> <td></td> <td>68,000</td> <td>136,000</td> </tr> <tr> <td>Cavalleri et al. (1994)</td> <td></td> <td>42,364</td> <td></td> </tr> <tr> <td>Earnest (1996)</td> <td>Operators</td> <td>88,000</td> <td>130,000</td> </tr> <tr> <td>Echeverria et al. (1995)</td> <td></td> <td>248,240</td> <td></td> </tr> <tr> <td>Ferroni et al. (1992)</td> <td></td> <td>102,060</td> <td></td> </tr> <tr> <td>Gobba et al. (1997)</td> <td></td> <td>57,000</td> <td></td> </tr> <tr> <td>Gobba et al. (1998)</td> <td>Shops</td> <td>30,000</td> <td></td> </tr> <tr> <td>Gulyas and Hemmerling (1990)</td> <td>Coin-operated establishments</td> <td>55,000</td> <td></td> </tr> <tr> <td>Kawauchi and Nishiyama (1989)</td> <td>Shops (n=11)</td> <td></td> <td>4,813</td> </tr> <tr> <td>Kawauchi and Nishiyama (1989)</td> <td>Shops (n=11)</td> <td></td> <td>1,649</td> </tr> <tr> <td>Keen et al. (1996)</td> <td>Operators</td> <td>21,000; 242,000; 324,000</td> <td></td> </tr> <tr> <td>Ludwig et al. (1983)</td> <td>Operators</td> <td>211,000</td> <td></td> </tr> <tr> <td>Ludwig et al. (1983)</td> <td>Non-operators</td> <td>41,000</td> <td></td> </tr> <tr> <td>Ludwig et al. (1983)</td> <td>Clerks</td> <td>40,000</td> <td></td> </tr> <tr> <td>Materna et al. (1985)</td> <td>Operators</td> <td>590,000</td> <td></td> </tr> <tr> <td>Moschandreas and O'Dea (1995)</td> <td>Shops</td> <td>34,000</td> <td>112,000</td> </tr> <tr> <td>Pellizari et al. (1984)</td> <td>Shops</td> <td>10,000</td> <td></td> </tr> <tr> <td>Raisanen et al. (2001)</td> <td>Operators</td> <td>28,000; 32,000</td> <td></td> </tr> </tbody> </table> <p data-bbox="1623 873 2381 898">[See Excerpt ID 162 for Excerpt References-additional graphic presented in this Excerpt]</p>	Study	Notes	Mean	Maximum	Aggazzotti et al. (1994a)	Maxima in Small Dry Cleaning Facilities (n=28)	5,000	308,000	Aggazzotti et al. (1994b)	Medians In Small Dry Cleaning Facilities (n=28)	600-75,000 (median)		Cai et al. (1992)		68,000	136,000	Cavalleri et al. (1994)		42,364		Earnest (1996)	Operators	88,000	130,000	Echeverria et al. (1995)		248,240		Ferroni et al. (1992)		102,060		Gobba et al. (1997)		57,000		Gobba et al. (1998)	Shops	30,000		Gulyas and Hemmerling (1990)	Coin-operated establishments	55,000		Kawauchi and Nishiyama (1989)	Shops (n=11)		4,813	Kawauchi and Nishiyama (1989)	Shops (n=11)		1,649	Keen et al. (1996)	Operators	21,000; 242,000; 324,000		Ludwig et al. (1983)	Operators	211,000		Ludwig et al. (1983)	Non-operators	41,000		Ludwig et al. (1983)	Clerks	40,000		Materna et al. (1985)	Operators	590,000		Moschandreas and O'Dea (1995)	Shops	34,000	112,000	Pellizari et al. (1984)	Shops	10,000		Raisanen et al. (2001)	Operators	28,000; 32,000	
Study	Notes	Mean	Maximum																																																																																						
Aggazzotti et al. (1994a)	Maxima in Small Dry Cleaning Facilities (n=28)	5,000	308,000																																																																																						
Aggazzotti et al. (1994b)	Medians In Small Dry Cleaning Facilities (n=28)	600-75,000 (median)																																																																																							
Cai et al. (1992)		68,000	136,000																																																																																						
Cavalleri et al. (1994)		42,364																																																																																							
Earnest (1996)	Operators	88,000	130,000																																																																																						
Echeverria et al. (1995)		248,240																																																																																							
Ferroni et al. (1992)		102,060																																																																																							
Gobba et al. (1997)		57,000																																																																																							
Gobba et al. (1998)	Shops	30,000																																																																																							
Gulyas and Hemmerling (1990)	Coin-operated establishments	55,000																																																																																							
Kawauchi and Nishiyama (1989)	Shops (n=11)		4,813																																																																																						
Kawauchi and Nishiyama (1989)	Shops (n=11)		1,649																																																																																						
Keen et al. (1996)	Operators	21,000; 242,000; 324,000																																																																																							
Ludwig et al. (1983)	Operators	211,000																																																																																							
Ludwig et al. (1983)	Non-operators	41,000																																																																																							
Ludwig et al. (1983)	Clerks	40,000																																																																																							
Materna et al. (1985)	Operators	590,000																																																																																							
Moschandreas and O'Dea (1995)	Shops	34,000	112,000																																																																																						
Pellizari et al. (1984)	Shops	10,000																																																																																							
Raisanen et al. (2001)	Operators	28,000; 32,000																																																																																							
7	170	EPA-HQ-ORD-2009-0791-0011.1	ARCADIS	[See Excerpt ID 162 for Excerpt Text-additional graphic presented in this Excerpt]	<table border="1" data-bbox="1623 932 2467 1110"> <thead> <tr> <th>Study</th> <th>Notes</th> <th>Mean</th> <th>Maximum</th> </tr> </thead> <tbody> <tr> <td>Raisanen et al. (2001)</td> <td>Pressers</td> <td>3,400; 7,700</td> <td></td> </tr> <tr> <td>Raisanen et al. (2001)</td> <td>Clerks</td> <td>800</td> <td></td> </tr> <tr> <td>Solet et al. (1990)</td> <td>Non-operators</td> <td>87,000</td> <td></td> </tr> <tr> <td>Solet et al. (1990)</td> <td>Clerks</td> <td>79,000</td> <td></td> </tr> <tr> <td>WHO EHC (1984)</td> <td>Shops</td> <td>4,000,000; 1,000,000; 251,000; 200,000</td> <td></td> </tr> </tbody> </table> <p data-bbox="1623 1115 2429 1154">*Note: As stated in the text, PCE concentrations from the 1990's are proposed as surrogate values for TCE concentrations in dry cleaning facilities were TCE was in use in the 1930's and 1940's.</p> <p data-bbox="1623 1190 2381 1214">[See Excerpt ID 162 for Excerpt References-additional graphic presented in this Excerpt]</p>	Study	Notes	Mean	Maximum	Raisanen et al. (2001)	Pressers	3,400; 7,700		Raisanen et al. (2001)	Clerks	800		Solet et al. (1990)	Non-operators	87,000		Solet et al. (1990)	Clerks	79,000		WHO EHC (1984)	Shops	4,000,000; 1,000,000; 251,000; 200,000																																																													
Study	Notes	Mean	Maximum																																																																																						
Raisanen et al. (2001)	Pressers	3,400; 7,700																																																																																							
Raisanen et al. (2001)	Clerks	800																																																																																							
Solet et al. (1990)	Non-operators	87,000																																																																																							
Solet et al. (1990)	Clerks	79,000																																																																																							
WHO EHC (1984)	Shops	4,000,000; 1,000,000; 251,000; 200,000																																																																																							

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics																																																																																																												
7	171	EPA-HQ-ORD-2009-0791-0011.1	ARCADIS	[See Excerpt ID 162 for Excerpt Text-additional graphic presented in this Excerpt]	<p style="text-align: center;">TABLE 5 BACKGROUND LEVELS OF TCE IN INDOOR AIR</p> <table border="1"> <thead> <tr> <th>Study</th> <th>Location</th> <th>Date</th> <th>Fixed Loc./ Breathing Zone*</th> <th>n</th> <th>50th%</th> <th>75th%</th> <th>90th%</th> <th>95th%</th> <th>mean</th> </tr> </thead> <tbody> <tr> <td>Adgate et al. (2004)</td> <td rowspan="2">Urban and Rural Minnesota</td> <td rowspan="2">1997</td> <td rowspan="2">FL</td> <td rowspan="2">101</td> <td></td> <td>0.7</td> <td></td> <td>1.1</td> <td>0.6</td> </tr> <tr> <td>Intensive-phase</td> <td>0.6</td> <td></td> <td></td> </tr> <tr> <td>Adgate et al. (2004)</td> <td rowspan="2">Urban and Rural Minnesota</td> <td rowspan="2">1997</td> <td rowspan="2">BZ</td> <td rowspan="2">72</td> <td></td> <td>0.8</td> <td></td> <td>1.9</td> <td>0.8</td> </tr> <tr> <td>Intensive-phase</td> <td>0.6</td> <td></td> <td></td> </tr> <tr> <td>Bonanno (2001)</td> <td>Six mid-western states</td> <td>1995-1997</td> <td>FL</td> <td>248</td> <td></td> <td></td> <td></td> <td></td> <td>2.1</td> </tr> <tr> <td>CDC NCHS NHANES (2000)</td> <td>Various US Locations</td> <td>1999-2000</td> <td>FL</td> <td>635</td> <td>0.33</td> <td>0.5</td> <td>1.25</td> <td>7.26</td> <td>4.42</td> </tr> <tr> <td>Chan et al. (1990)</td> <td>Canada</td> <td>1990</td> <td>FL</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>1.6</td> </tr> <tr> <td>Clayton (1999)</td> <td>Six midwestern states</td> <td>1995-1997</td> <td>FL</td> <td>402</td> <td></td> <td></td> <td>2.3</td> <td></td> <td></td> </tr> <tr> <td>De Bortoli et al. (1986)</td> <td>Italy</td> <td>1983</td> <td>FL</td> <td>14</td> <td></td> <td></td> <td></td> <td></td> <td>18</td> </tr> <tr> <td>Dodson et al. (2007)</td> <td>Boston</td> <td>2004-2005</td> <td>FL</td> <td>83</td> <td></td> <td></td> <td></td> <td></td> <td>0.61</td> </tr> <tr> <td>Foster (2002)</td> <td>Denver</td> <td>1996-2001</td> <td>FL</td> <td>427</td> <td></td> <td></td> <td></td> <td></td> <td>1.4</td> </tr> </tbody> </table> <p>-</p> <p>[See Excerpt ID 162 for Excerpt References-additional graphic presented in this Excerpt]</p>	Study	Location	Date	Fixed Loc./ Breathing Zone*	n	50th%	75th%	90th%	95th%	mean	Adgate et al. (2004)	Urban and Rural Minnesota	1997	FL	101		0.7		1.1	0.6	Intensive-phase	0.6			Adgate et al. (2004)	Urban and Rural Minnesota	1997	BZ	72		0.8		1.9	0.8	Intensive-phase	0.6			Bonanno (2001)	Six mid-western states	1995-1997	FL	248					2.1	CDC NCHS NHANES (2000)	Various US Locations	1999-2000	FL	635	0.33	0.5	1.25	7.26	4.42	Chan et al. (1990)	Canada	1990	FL						1.6	Clayton (1999)	Six midwestern states	1995-1997	FL	402			2.3			De Bortoli et al. (1986)	Italy	1983	FL	14					18	Dodson et al. (2007)	Boston	2004-2005	FL	83					0.61	Foster (2002)	Denver	1996-2001	FL	427					1.4
Study	Location	Date	Fixed Loc./ Breathing Zone*	n	50th%	75th%	90th%	95th%	mean																																																																																																								
Adgate et al. (2004)	Urban and Rural Minnesota	1997	FL	101		0.7		1.1	0.6																																																																																																								
Intensive-phase					0.6																																																																																																												
Adgate et al. (2004)	Urban and Rural Minnesota	1997	BZ	72		0.8		1.9	0.8																																																																																																								
Intensive-phase					0.6																																																																																																												
Bonanno (2001)	Six mid-western states	1995-1997	FL	248					2.1																																																																																																								
CDC NCHS NHANES (2000)	Various US Locations	1999-2000	FL	635	0.33	0.5	1.25	7.26	4.42																																																																																																								
Chan et al. (1990)	Canada	1990	FL						1.6																																																																																																								
Clayton (1999)	Six midwestern states	1995-1997	FL	402			2.3																																																																																																										
De Bortoli et al. (1986)	Italy	1983	FL	14					18																																																																																																								
Dodson et al. (2007)	Boston	2004-2005	FL	83					0.61																																																																																																								
Foster (2002)	Denver	1996-2001	FL	427					1.4																																																																																																								

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics																																																																																																																																																																																															
7	172	EPA-HQ-ORD-2009-0791-0011.1	ARCADIS	[See Excerpt ID 162 for Excerpt Text-additional graphic presented in this Excerpt]	<table border="1"> <thead> <tr> <th>Study</th> <th>Location</th> <th>Date</th> <th>Fixed Loc./ Breathing Zone*</th> <th>n</th> <th>50th%</th> <th>75th%</th> <th>90th%</th> <th>95th%</th> <th>mean</th> </tr> </thead> <tbody> <tr> <td>Heavner (1995)</td> <td>Columbus, OH (non-smoking residences)</td> <td>1991</td> <td>FL</td> <td>24</td> <td></td> <td></td> <td></td> <td></td> <td>1.8</td> </tr> <tr> <td>Heavner (1995)</td> <td>Columbus, OH (smoking residences)</td> <td>1991</td> <td>FL</td> <td>25</td> <td></td> <td></td> <td></td> <td></td> <td>0.7</td> </tr> <tr> <td>Heavner et al. (1996)</td> <td>NJ, PA (smoking workplaces)</td> <td>1992</td> <td>FL</td> <td>29</td> <td></td> <td></td> <td></td> <td></td> <td>6.4</td> </tr> <tr> <td>Heavner et al. (1996)</td> <td>NJ, PA (non-smoking workplaces)</td> <td>1992</td> <td>FL</td> <td>51</td> <td></td> <td></td> <td></td> <td></td> <td>4.5</td> </tr> <tr> <td>Heavner et al. (1996)</td> <td>New Jersey (smoking residence)</td> <td>1992</td> <td>FL</td> <td>32</td> <td></td> <td></td> <td></td> <td></td> <td>0.9</td> </tr> <tr> <td>Heavner et al. (1996)</td> <td>New Jersey (non-smoking residence)</td> <td>1992</td> <td>FL</td> <td>61</td> <td></td> <td></td> <td></td> <td></td> <td>0.8</td> </tr> <tr> <td>Jia et al. (2007)</td> <td>Southeast Michigan</td> <td>2004/2005</td> <td>FL</td> <td>252</td> <td>0.03</td> <td></td> <td></td> <td></td> <td>0.06</td> </tr> <tr> <td>Kinney et al. (2005)</td> <td>New York City</td> <td>1999</td> <td>FL</td> <td>80</td> <td>0.26</td> <td>0.53</td> <td>1</td> <td>1.4</td> <td>0.64</td> </tr> <tr> <td>Kinney et al. (2005)</td> <td>New York City</td> <td>1999</td> <td>BZ</td> <td>72</td> <td>0.34</td> <td>0.56</td> <td>1.1</td> <td>2.3</td> <td>1.35</td> </tr> <tr> <td>Kurtz (2002)</td> <td>Denver</td> <td>1998-2001</td> <td>FL</td> <td>282</td> <td></td> <td></td> <td>0.3</td> <td>0.7</td> <td></td> </tr> <tr> <td>NYSDOH (1997)</td> <td>New York City</td> <td>1989-1996</td> <td>FL</td> <td>125</td> <td></td> <td></td> <td><10</td> <td></td> <td>2.2</td> </tr> <tr> <td>NYSDOH (2003)</td> <td>New York City</td> <td>1997-2003</td> <td>FL</td> <td>400</td> <td></td> <td></td> <td>0.5</td> <td></td> <td>0.4</td> </tr> <tr> <td>NYSDOH (2006)</td> <td>Albany, NY</td> <td>1997-2003</td> <td>FL</td> <td>400</td> <td></td> <td></td> <td>0.5</td> <td>0.8</td> <td>0.4</td> </tr> <tr> <td>Sax et al. (2004)</td> <td>New York City</td> <td>Winter 1999</td> <td>FL</td> <td>36</td> <td>0.4</td> <td></td> <td></td> <td></td> <td>1.1</td> </tr> <tr> <td>Sax et al. (2004)</td> <td>New York City</td> <td>Summer 1999</td> <td>FL</td> <td>30</td> <td>0.1</td> <td></td> <td></td> <td></td> <td>0.3</td> </tr> <tr> <td>Sax et al. (2004)</td> <td>Los Angeles</td> <td>Winter 2000</td> <td>FL</td> <td>40</td> <td>0.2</td> <td></td> <td></td> <td></td> <td>0.2</td> </tr> <tr> <td>Sax et al. (2004)</td> <td>Los Angeles</td> <td>Fall 2000</td> <td>FL</td> <td>32</td> <td>0.1</td> <td></td> <td></td> <td></td> <td>0.2</td> </tr> <tr> <td>Sax et al. (2006)</td> <td>New York City</td> <td>1999</td> <td>FL</td> <td>41</td> <td>0.33</td> <td></td> <td></td> <td></td> <td>0.9</td> </tr> </tbody> </table>	Study	Location	Date	Fixed Loc./ Breathing Zone*	n	50th%	75th%	90th%	95th%	mean	Heavner (1995)	Columbus, OH (non-smoking residences)	1991	FL	24					1.8	Heavner (1995)	Columbus, OH (smoking residences)	1991	FL	25					0.7	Heavner et al. (1996)	NJ, PA (smoking workplaces)	1992	FL	29					6.4	Heavner et al. (1996)	NJ, PA (non-smoking workplaces)	1992	FL	51					4.5	Heavner et al. (1996)	New Jersey (smoking residence)	1992	FL	32					0.9	Heavner et al. (1996)	New Jersey (non-smoking residence)	1992	FL	61					0.8	Jia et al. (2007)	Southeast Michigan	2004/2005	FL	252	0.03				0.06	Kinney et al. (2005)	New York City	1999	FL	80	0.26	0.53	1	1.4	0.64	Kinney et al. (2005)	New York City	1999	BZ	72	0.34	0.56	1.1	2.3	1.35	Kurtz (2002)	Denver	1998-2001	FL	282			0.3	0.7		NYSDOH (1997)	New York City	1989-1996	FL	125			<10		2.2	NYSDOH (2003)	New York City	1997-2003	FL	400			0.5		0.4	NYSDOH (2006)	Albany, NY	1997-2003	FL	400			0.5	0.8	0.4	Sax et al. (2004)	New York City	Winter 1999	FL	36	0.4				1.1	Sax et al. (2004)	New York City	Summer 1999	FL	30	0.1				0.3	Sax et al. (2004)	Los Angeles	Winter 2000	FL	40	0.2				0.2	Sax et al. (2004)	Los Angeles	Fall 2000	FL	32	0.1				0.2	Sax et al. (2006)	New York City	1999	FL	41	0.33				0.9	[See Excerpt ID 162 for Excerpt References-additional graphic presented in this Excerpt]
Study	Location	Date	Fixed Loc./ Breathing Zone*	n	50th%	75th%	90th%	95th%	mean																																																																																																																																																																																											
Heavner (1995)	Columbus, OH (non-smoking residences)	1991	FL	24					1.8																																																																																																																																																																																											
Heavner (1995)	Columbus, OH (smoking residences)	1991	FL	25					0.7																																																																																																																																																																																											
Heavner et al. (1996)	NJ, PA (smoking workplaces)	1992	FL	29					6.4																																																																																																																																																																																											
Heavner et al. (1996)	NJ, PA (non-smoking workplaces)	1992	FL	51					4.5																																																																																																																																																																																											
Heavner et al. (1996)	New Jersey (smoking residence)	1992	FL	32					0.9																																																																																																																																																																																											
Heavner et al. (1996)	New Jersey (non-smoking residence)	1992	FL	61					0.8																																																																																																																																																																																											
Jia et al. (2007)	Southeast Michigan	2004/2005	FL	252	0.03				0.06																																																																																																																																																																																											
Kinney et al. (2005)	New York City	1999	FL	80	0.26	0.53	1	1.4	0.64																																																																																																																																																																																											
Kinney et al. (2005)	New York City	1999	BZ	72	0.34	0.56	1.1	2.3	1.35																																																																																																																																																																																											
Kurtz (2002)	Denver	1998-2001	FL	282			0.3	0.7																																																																																																																																																																																												
NYSDOH (1997)	New York City	1989-1996	FL	125			<10		2.2																																																																																																																																																																																											
NYSDOH (2003)	New York City	1997-2003	FL	400			0.5		0.4																																																																																																																																																																																											
NYSDOH (2006)	Albany, NY	1997-2003	FL	400			0.5	0.8	0.4																																																																																																																																																																																											
Sax et al. (2004)	New York City	Winter 1999	FL	36	0.4				1.1																																																																																																																																																																																											
Sax et al. (2004)	New York City	Summer 1999	FL	30	0.1				0.3																																																																																																																																																																																											
Sax et al. (2004)	Los Angeles	Winter 2000	FL	40	0.2				0.2																																																																																																																																																																																											
Sax et al. (2004)	Los Angeles	Fall 2000	FL	32	0.1				0.2																																																																																																																																																																																											
Sax et al. (2006)	New York City	1999	FL	41	0.33				0.9																																																																																																																																																																																											

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics																																																																																																																																																																										
7	173	EPA-HQ-ORD-2009-0791-0011.1	ARCADIS	[See Excerpt ID 162 for Excerpt Text-additional graphic presented in this Excerpt]	<table border="1"> <thead> <tr> <th>Study</th> <th>Location</th> <th>Date</th> <th>Fixed Loc./ Breathing Zone*</th> <th>n</th> <th>50th%</th> <th>75th%</th> <th>90th%</th> <th>95th%</th> <th>mean</th> </tr> </thead> <tbody> <tr> <td>Sax et al. (2006)</td> <td>Los Angeles</td> <td>2000</td> <td>FL</td> <td>40</td> <td>0.18</td> <td></td> <td></td> <td></td> <td>0.22</td> </tr> <tr> <td>Sexton et al. (2004)</td> <td>Urban Minnesota</td> <td>Spring, Summer, Fall 1999</td> <td>FL</td> <td>292</td> <td>0.2</td> <td></td> <td>0.8</td> <td></td> <td>0.5</td> </tr> <tr> <td>Sexton et al. (2004)</td> <td>Urban Minnesota</td> <td>Spring, Summer, Fall 1999</td> <td>BZ</td> <td>288</td> <td>0.2</td> <td></td> <td>1.4</td> <td></td> <td>1</td> </tr> <tr> <td>Sexton et al. (2007)</td> <td>Minneapolis/St. Paul</td> <td>1999</td> <td>FL</td> <td>333</td> <td></td> <td></td> <td>1.8</td> <td></td> <td>1</td> </tr> <tr> <td>Shah and Singh (1988); Shah, J.J. and Heyerdahl (1988)</td> <td>Various US Locations</td> <td>1970-1987</td> <td>FL</td> <td>2,132</td> <td></td> <td>4.5</td> <td></td> <td></td> <td>7.3</td> </tr> <tr> <td>Sheldon (1991)</td> <td>California</td> <td>1990</td> <td>FL</td> <td>125</td> <td></td> <td></td> <td>1.9</td> <td></td> <td>0.7</td> </tr> <tr> <td>EPA (1987)</td> <td>Bayonne and Elizabeth, NJ</td> <td>1981-1982</td> <td>FL</td> <td>NA</td> <td></td> <td></td> <td>9.8</td> <td></td> <td>3.86</td> </tr> <tr> <td>EPA (1987)</td> <td>Los Angeles</td> <td>1984</td> <td>FL</td> <td>NA</td> <td></td> <td></td> <td>4.7</td> <td></td> <td>0.7</td> </tr> <tr> <td>EPA (1987)</td> <td>Contra Costa, CA</td> <td>1984</td> <td>FL</td> <td>NA</td> <td></td> <td></td> <td>2.1</td> <td></td> <td>0.3</td> </tr> <tr> <td>EPA (2001)</td> <td>Various US Locations</td> <td>1994-1996</td> <td>FL</td> <td>100</td> <td></td> <td>1.2</td> <td>4.2</td> <td>6.5</td> <td>2.6</td> </tr> <tr> <td>EPA NHEXAS (2008)</td> <td>Six midwestern states</td> <td>1995-1997</td> <td>FL</td> <td>387</td> <td>0.48</td> <td>1.17</td> <td>2.07</td> <td>3.24</td> <td>3.46</td> </tr> <tr> <td>EPA NHEXAS (2008)</td> <td>Six midwestern states</td> <td>1995-1997</td> <td>BZ</td> <td>362</td> <td>0.53</td> <td>1.48</td> <td>3.1</td> <td>6.53</td> <td>2.89</td> </tr> <tr> <td>Van Winkle (2001)</td> <td>Chicago</td> <td>1994-1995</td> <td>FL</td> <td>48</td> <td></td> <td></td> <td>1.1</td> <td></td> <td>0.5</td> </tr> <tr> <td>Weisel et al. (2005)</td> <td>LA, Elizabeth (NJ), Houston</td> <td>1999-2001</td> <td>FL</td> <td>554</td> <td></td> <td></td> <td></td> <td>1.4</td> <td>0.5</td> </tr> <tr> <td>Weisel (2006)</td> <td>New Jersey</td> <td>1999-2001</td> <td>FL</td> <td>100</td> <td></td> <td></td> <td>1.35</td> <td>2.74</td> <td></td> </tr> <tr> <td>Zhu et al. (2005)</td> <td>Ottawa, Canada</td> <td>2002-2003</td> <td>FL</td> <td>75</td> <td>0.01</td> <td>0.08</td> <td>0.19</td> <td></td> <td>0.06</td> </tr> </tbody> </table> <p>FL = Fixed Location; BZ = Breathing Zone</p> <p>Given that TCE use has steadily declined since 1970, all studies performed in the 1990's and 2000's will underestimate the typical exposure levels experienced by the US population during the</p> <p>[See Excerpt ID 162 for Excerpt References-additional graphic presented in this Excerpt]</p>	Study	Location	Date	Fixed Loc./ Breathing Zone*	n	50th%	75th%	90th%	95th%	mean	Sax et al. (2006)	Los Angeles	2000	FL	40	0.18				0.22	Sexton et al. (2004)	Urban Minnesota	Spring, Summer, Fall 1999	FL	292	0.2		0.8		0.5	Sexton et al. (2004)	Urban Minnesota	Spring, Summer, Fall 1999	BZ	288	0.2		1.4		1	Sexton et al. (2007)	Minneapolis/St. Paul	1999	FL	333			1.8		1	Shah and Singh (1988); Shah, J.J. and Heyerdahl (1988)	Various US Locations	1970-1987	FL	2,132		4.5			7.3	Sheldon (1991)	California	1990	FL	125			1.9		0.7	EPA (1987)	Bayonne and Elizabeth, NJ	1981-1982	FL	NA			9.8		3.86	EPA (1987)	Los Angeles	1984	FL	NA			4.7		0.7	EPA (1987)	Contra Costa, CA	1984	FL	NA			2.1		0.3	EPA (2001)	Various US Locations	1994-1996	FL	100		1.2	4.2	6.5	2.6	EPA NHEXAS (2008)	Six midwestern states	1995-1997	FL	387	0.48	1.17	2.07	3.24	3.46	EPA NHEXAS (2008)	Six midwestern states	1995-1997	BZ	362	0.53	1.48	3.1	6.53	2.89	Van Winkle (2001)	Chicago	1994-1995	FL	48			1.1		0.5	Weisel et al. (2005)	LA, Elizabeth (NJ), Houston	1999-2001	FL	554				1.4	0.5	Weisel (2006)	New Jersey	1999-2001	FL	100			1.35	2.74		Zhu et al. (2005)	Ottawa, Canada	2002-2003	FL	75	0.01	0.08	0.19		0.06
Study	Location	Date	Fixed Loc./ Breathing Zone*	n	50th%	75th%	90th%	95th%	mean																																																																																																																																																																						
Sax et al. (2006)	Los Angeles	2000	FL	40	0.18				0.22																																																																																																																																																																						
Sexton et al. (2004)	Urban Minnesota	Spring, Summer, Fall 1999	FL	292	0.2		0.8		0.5																																																																																																																																																																						
Sexton et al. (2004)	Urban Minnesota	Spring, Summer, Fall 1999	BZ	288	0.2		1.4		1																																																																																																																																																																						
Sexton et al. (2007)	Minneapolis/St. Paul	1999	FL	333			1.8		1																																																																																																																																																																						
Shah and Singh (1988); Shah, J.J. and Heyerdahl (1988)	Various US Locations	1970-1987	FL	2,132		4.5			7.3																																																																																																																																																																						
Sheldon (1991)	California	1990	FL	125			1.9		0.7																																																																																																																																																																						
EPA (1987)	Bayonne and Elizabeth, NJ	1981-1982	FL	NA			9.8		3.86																																																																																																																																																																						
EPA (1987)	Los Angeles	1984	FL	NA			4.7		0.7																																																																																																																																																																						
EPA (1987)	Contra Costa, CA	1984	FL	NA			2.1		0.3																																																																																																																																																																						
EPA (2001)	Various US Locations	1994-1996	FL	100		1.2	4.2	6.5	2.6																																																																																																																																																																						
EPA NHEXAS (2008)	Six midwestern states	1995-1997	FL	387	0.48	1.17	2.07	3.24	3.46																																																																																																																																																																						
EPA NHEXAS (2008)	Six midwestern states	1995-1997	BZ	362	0.53	1.48	3.1	6.53	2.89																																																																																																																																																																						
Van Winkle (2001)	Chicago	1994-1995	FL	48			1.1		0.5																																																																																																																																																																						
Weisel et al. (2005)	LA, Elizabeth (NJ), Houston	1999-2001	FL	554				1.4	0.5																																																																																																																																																																						
Weisel (2006)	New Jersey	1999-2001	FL	100			1.35	2.74																																																																																																																																																																							
Zhu et al. (2005)	Ottawa, Canada	2002-2003	FL	75	0.01	0.08	0.19		0.06																																																																																																																																																																						

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics																																				
7	174	EPA-HQ-ORD-2009-0791-0011.1	ARCADIS	[See Excerpt ID 162 for Excerpt Text-additional graphic presented in this Excerpt]	<p style="text-align: center;">TABLE 6 AVERAGE CALENDAR YEAR 1970 EMPLOYMENT, WORKERS IN PRIVATE INDUSTRY COVERED BY STATE UI LAWS</p> <table border="1" data-bbox="1634 235 2451 846"> <thead> <tr> <th>Industrial Code and Title</th> <th>Average Employment</th> <th>Potential TCE Exposures</th> </tr> </thead> <tbody> <tr> <td>172: Construction: Special and Trade Contractors, Painting Paper Hanging and Decorating</td> <td>114,673</td> <td>Paints, varnishes, lacquers, paint strippers, paint thinners</td> </tr> <tr> <td>19: Manufacturing: Ordnance and Accessories</td> <td>241,829</td> <td>Metal degreasing</td> </tr> <tr> <td>20: Manufacturing: Food and Kindred Products</td> <td>1,797,636</td> <td>Extraction solvent for animal and plant fats, caffeine extractant</td> </tr> <tr> <td>22: Manufacturing: Textile Mill Products</td> <td>16,565</td> <td>Textile cleaning</td> </tr> <tr> <td>23: Manufacturing: Apparel and Other Finished Products Made From Fabrics and Other Similar Materials</td> <td>1,398,087</td> <td>Textile cleaning</td> </tr> <tr> <td>27: Manufacturing: Printing Publishing and Allied Industries</td> <td>1,079,734</td> <td>Printing inks</td> </tr> <tr> <td>28: Manufacturing: Chemicals and Allied Products</td> <td>1,054,878</td> <td>Chemical manufacturing, elastomers, lubricants, adhesives</td> </tr> <tr> <td>34: Manufacturing: Fabricated Metal Products, Except Ordnance, Machinery and Transportation Equipment</td> <td>1,382,797</td> <td>Metal degreasing, lubricants</td> </tr> <tr> <td>35: Manufacturing: Machinery, Except Electrical</td> <td>1,977,243</td> <td>Metal degreasing, lubricants</td> </tr> <tr> <td>36: Manufacturing: Electrical Machinery, Equipment and Supplies</td> <td>1,926,791</td> <td>Metal degreasing, lubricants</td> </tr> <tr> <td>37: Manufacturing: Transportation Equipment</td> <td>1,820,102</td> <td>Metal degreasing, lubricants</td> </tr> </tbody> </table> <p>[See Excerpt ID 162 for Excerpt References-additional graphic presented in this Excerpt]</p>	Industrial Code and Title	Average Employment	Potential TCE Exposures	172: Construction: Special and Trade Contractors, Painting Paper Hanging and Decorating	114,673	Paints, varnishes, lacquers, paint strippers, paint thinners	19: Manufacturing: Ordnance and Accessories	241,829	Metal degreasing	20: Manufacturing: Food and Kindred Products	1,797,636	Extraction solvent for animal and plant fats, caffeine extractant	22: Manufacturing: Textile Mill Products	16,565	Textile cleaning	23: Manufacturing: Apparel and Other Finished Products Made From Fabrics and Other Similar Materials	1,398,087	Textile cleaning	27: Manufacturing: Printing Publishing and Allied Industries	1,079,734	Printing inks	28: Manufacturing: Chemicals and Allied Products	1,054,878	Chemical manufacturing, elastomers, lubricants, adhesives	34: Manufacturing: Fabricated Metal Products, Except Ordnance, Machinery and Transportation Equipment	1,382,797	Metal degreasing, lubricants	35: Manufacturing: Machinery, Except Electrical	1,977,243	Metal degreasing, lubricants	36: Manufacturing: Electrical Machinery, Equipment and Supplies	1,926,791	Metal degreasing, lubricants	37: Manufacturing: Transportation Equipment	1,820,102	Metal degreasing, lubricants
Industrial Code and Title	Average Employment	Potential TCE Exposures																																							
172: Construction: Special and Trade Contractors, Painting Paper Hanging and Decorating	114,673	Paints, varnishes, lacquers, paint strippers, paint thinners																																							
19: Manufacturing: Ordnance and Accessories	241,829	Metal degreasing																																							
20: Manufacturing: Food and Kindred Products	1,797,636	Extraction solvent for animal and plant fats, caffeine extractant																																							
22: Manufacturing: Textile Mill Products	16,565	Textile cleaning																																							
23: Manufacturing: Apparel and Other Finished Products Made From Fabrics and Other Similar Materials	1,398,087	Textile cleaning																																							
27: Manufacturing: Printing Publishing and Allied Industries	1,079,734	Printing inks																																							
28: Manufacturing: Chemicals and Allied Products	1,054,878	Chemical manufacturing, elastomers, lubricants, adhesives																																							
34: Manufacturing: Fabricated Metal Products, Except Ordnance, Machinery and Transportation Equipment	1,382,797	Metal degreasing, lubricants																																							
35: Manufacturing: Machinery, Except Electrical	1,977,243	Metal degreasing, lubricants																																							
36: Manufacturing: Electrical Machinery, Equipment and Supplies	1,926,791	Metal degreasing, lubricants																																							
37: Manufacturing: Transportation Equipment	1,820,102	Metal degreasing, lubricants																																							
7	175	EPA-HQ-ORD-2009-0791-0011.1	ARCADIS	[See Excerpt ID 162 for Excerpt Text-additional graphic presented in this Excerpt]	<table border="1" data-bbox="1634 954 2451 1305"> <thead> <tr> <th>Industrial Code and Title</th> <th>Average Employment</th> <th>Potential TCE Exposures</th> </tr> </thead> <tbody> <tr> <td>38: Manufacturing: Professional, Scientific, and Controlling Instruments, Photographic and Optical Goods, Watches and Clocks</td> <td>469,032</td> <td>Metal degreasing, lubricants, optical lense cleaning</td> </tr> <tr> <td>39: Manufacturing: Miscellaneous Manufacturing Industries</td> <td>427,069</td> <td>Metal degreasing, lubricants</td> </tr> <tr> <td>721: Services: Laundries, Laundry Services, and Cleaning and Dyeing Plants</td> <td>482,832</td> <td>Textile cleaning</td> </tr> <tr> <td>727: Services: Pressing, Alteration, and Garment Repair</td> <td>20,931</td> <td>Textile cleaning</td> </tr> <tr> <td>801: Medical and Health Services: Offices of Physicians and Surgeons</td> <td>318,283</td> <td>Anesthetic, surgical instrument cleaner</td> </tr> <tr> <td>806: Medical and Health Services: Hospitals</td> <td>209,968</td> <td>Anesthetic, surgical instrument cleaner</td> </tr> </tbody> </table> <p>Source: U.S. Department of Labor (1972)</p> <p>[See Excerpt ID 162 for Excerpt References-additional graphic presented in this Excerpt]</p>	Industrial Code and Title	Average Employment	Potential TCE Exposures	38: Manufacturing: Professional, Scientific, and Controlling Instruments, Photographic and Optical Goods, Watches and Clocks	469,032	Metal degreasing, lubricants, optical lense cleaning	39: Manufacturing: Miscellaneous Manufacturing Industries	427,069	Metal degreasing, lubricants	721: Services: Laundries, Laundry Services, and Cleaning and Dyeing Plants	482,832	Textile cleaning	727: Services: Pressing, Alteration, and Garment Repair	20,931	Textile cleaning	801: Medical and Health Services: Offices of Physicians and Surgeons	318,283	Anesthetic, surgical instrument cleaner	806: Medical and Health Services: Hospitals	209,968	Anesthetic, surgical instrument cleaner															
Industrial Code and Title	Average Employment	Potential TCE Exposures																																							
38: Manufacturing: Professional, Scientific, and Controlling Instruments, Photographic and Optical Goods, Watches and Clocks	469,032	Metal degreasing, lubricants, optical lense cleaning																																							
39: Manufacturing: Miscellaneous Manufacturing Industries	427,069	Metal degreasing, lubricants																																							
721: Services: Laundries, Laundry Services, and Cleaning and Dyeing Plants	482,832	Textile cleaning																																							
727: Services: Pressing, Alteration, and Garment Repair	20,931	Textile cleaning																																							
801: Medical and Health Services: Offices of Physicians and Surgeons	318,283	Anesthetic, surgical instrument cleaner																																							
806: Medical and Health Services: Hospitals	209,968	Anesthetic, surgical instrument cleaner																																							
7	58	EPA-HQ-ORD-2009-0791-	Natural Resources Defense	A very recent study titled, "Association between Residential Proximity to PERC [PCE] Dry Cleaning Establishments and Kidney Cancer in New York City" reports on an exposure-dependent increase of 10 to 27% in kidney cancers (based on hospital discharges for kidney or renal cancer) associated with proximity to dry	- 6 Ma J, Lessner L, Carpenter D, Schreiber J. 2010. Association between Residential Proximity to PERC Dry Cleaning Establishments and Kidney Cancer in New York City. Journal of Environmental and																																				

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
		0007.1	Council (NRDC) and Supoprters	cleaners, as determined by NYC zip code after accounting for population density, socioeconomic strata and other variables. ⁶ Despite some limitations in the study design (an ecological study looking at large groups of people, not individuals) the authors report highly significant 'p-values' indicating that the results were very unlikely to occur by chance. ⁷ These data are highly relevant because PCE (perchloroethylene) dry cleaning fluid and TCE are both related chlorinated solvents and are often co-contaminants in soil and water. PCE and TCE are chemically very similar and are both metabolized to the same cancer-causing metabolite, trichloroacetic acid (TCA). ⁸	Public Health, Volume 2009 (2009), Article ID 183920, 7 pages. Available at http://www.hindawi.com/journals/jep/2009/183920.abs.html 7 Ma et al, 2009. The rate of kidney cancer hospital discharges is positively associated with increasing exposure levels 2, 4, and 5, with rate ratios (RR) of 1.14, 1.17, and 1.15, respectively, and with P-values of .01, .006, and .03, respectively. 8 Agency for Toxic Substances and Disease Registry (ATSDR). 1997. Toxicological profile for Trichloroethylene (TCE). Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. Complete profile available at http://www.atsdr.cdc.gov/toxprofiles/tp19.html
7	74	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	This notion of a high proportion of TCE being metabolized via the glutathione conjugation pathway is based upon the work of Lash and co-workers which depended upon a questionable analytical technique. If EPA had employed a critical evaluation of the evidence, the substantial and credible information from three other laboratories (Dekant, Green and Kim/Rusyn and co-workers) that indicate a very low level of metabolism of TCE via the glutathione conjugation pathway would have been preferred. The extent of metabolism of TCE via the glutathione conjugation pathway (and DCVC activation) in humans is lower than the already low levels in rodents.	AUTHOR: Paul H. Dugard, Halogenated Solvents Industry Alliance, Inc. -
7	87	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	2.4 MoA of TCA Hepatocarcinogenicity and Implications for Human Exposure to TCE: At the time of writing, release of the report of an NRC committee review of the draft IRIS support document for perchloroethylene is imminent. The issue of TCA MoA is expected to be addressed in that review. The evidence strongly indicates a PPAR ALPHA-related MoA for the induction of mouse liver tumors by TCA and thus also by TCE. This would leave the issue of the implications of such a MoA for human exposures to TCE. At this time EPA's NCEA Washington Office is becoming increasingly isolated in its opinion that PPAR ALPHA-related rodent liver tumors remain fully relevant to man and that linear dose-response extrapolations are appropriate. This isolation is apparent within EPA as well as from other regulatory federal agencies in the US and around the world. It remains to be seen how this debate plays out, but the majority opinion among respected scientists seems to support a diminished concern regarding rodent liver tumors associated with a PPAR ALPHA-related MoA.	AUTHOR: Paul H. Dugard, Halogenated Solvents Industry Alliance, Inc. -
7	94	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	A number of inconsistent datasets questions the reliability of the "Reed-method" to determine DCVG and DCVC: - In a study assessing DCVG and DCVC formation in rodents after high oral doses of TCE, DCVG-concentrations reported in blood were high, but did not show dose or time-dependence (Lash et al., 2006). In addition, the study reports high concentrations of DCVC excreted in urine. EPA calls the results of this study "aberrant", but apparently did not further assess reliability. Others have reported a very low rate of DCVC-formation in vivo (Dekant et al., 1990; Kim et al., 2009) and DCVC has not been reported as urinary metabolite of TCE using either mass spectrometry or HPLC which radiochemical detection after administration of 14C-TCE (Dekant et al., 1986a). - The "Reed-method" has also been used to determine DCVG-formation from TCE in subcellular fractions from liver and kidney of rats, mice, and humans. Again, high rates of formation of DCVG were reported (table 1). In contrast, using C-TCE and radioactivity detection, much lower reaction rates were observed in other studies (table 1). In addition, isolated glutathione, S-transferases also have a very low capacity to metabolize TCE to DCVG (Hissink et al., 2002) and the application of the "Reed-method" to study formation of S-(1,2,2-trichlorovinyl)glutathione (TCVG) from perchloroethylene (PERC) in subcellular fractions also gave much higher rates of formation (Lash et al., 1998) when compared with methods using 14C-perchloroethylene and HPLC with radioactivity detection (Dekant et al., 1987; Green et al., 1990; Dekant et al., 1998). Therefore, DCVG concentrations determined by the "Reed-method" may be greatly overestimated. The more reliable and consistent data support a very low extent of DCVG formation in rodents:	AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany Lash, L. H., Putt, D. A., and Parker, J. C. (2006). Metabolism and tissue distribution of orally administered trichloroethylene in male and female rats: identification of glutathione- and cytochrome P-450-derived metabolites in liver, kidney, blood, and urine. <i>J Toxicol Environ Health A</i> 69, 1285-1309. Dekant, W., Schulz, A., Metzler, M., and Henschler, D. (1986a). Absorption, elimination and metabolism of trichloroethylene: a quantitative comparison between rats and mice. <i>Xenobiotica</i> 16, 143-152. Dekant, W., Koob, M., and Henschler, D. (1990). Metabolism of trichloroethene - in vivo and in vitro evidence for activation by glutathione conjugation. <i>Chemico-Biological Interactions</i> 73, 89-101. Kim, S., Kim, D., Pollack, G. M., Collins, L. B., and Rusyn, I. (2009). 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. <i>Toxicol Appl Pharmacol</i> 238, 90-99. Hissink, E. M., Bogaards, J. J. P., Freidig, A. P., Commandeur, J. N. M., Vermeulen, N. P. E., and van Bladeren, P. J. (2002). The use of in vitro metabolic parameters and physiologically based pharmacokinetic (PBPK) modeling to explore the risk assessment of trichloroethylene. <i>Environmental Toxicology and Pharmacology</i> 11, 259-271.

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>- Very low rates of formation of DCVG in rodent liver subcellular fractions are consistent with very low blood levels of DCVG in mice (Kim et al., 2009) and a very low biliary elimination of DCVG in rats after oral administration of doses > 2 000 mg TCE/kg bw (Dekant et al., 1990). In mice, DCVG concentrations were several thousand-fold lower than those of the oxidative metabolite trichloroacetic acid (TCA) (Kim et al., 2009). In rats, biliary elimination of DCVG within seven hours after oral administration was 2 microg and therefore accounted for << 0.01 % of administered dose (Dekant et al., 1990). Due to its molecular weight (> 350 D) and the presence of effective transport systems for glutathione S-conjugates in the canalicular membrane, most of the DCVG formed in rat liver is expected to be excreted in bile. Therefore, the low concentrations of DCVG in blood of mice and the low recovery of DCVG in bile of rats after TCE-administration well support very low rates of DCVG formation.</p>	<p>Lash, L. H., Qian, W., Putt, D. A., Desai, K., Elfarra, A. A., Sicuri, A. R., and Parker, J. C. (1998). Glutathione conjugation of perchloroethylene in rats and mice in vitro: sex-, species-, and tissue-dependent differences. <i>Toxicol Appl Pharmacol</i> 150, 49-57.</p> <p>Dekant, W., Martens, G., Vamvakas, S., Metzler, M., and Henschler, D. (1987). Bioactivation of tetrachloroethylene. Role of glutathione S-transferase-catalyzed conjugation versus cytochrome P-450-dependent phospholipid alkylation. <i>Drug Metab Dispos</i> 15, 702-709.</p> <p>Dekant, W., Birner, G., Werner, M., and Parker, J. (1998). Glutathione conjugation of perchloroethene in subcellular fractions from rodent and human liver and kidney. <i>Chem Biol Interact</i> 116, 31-43.</p> <p>Green, T., Odum, J., Nash, J. A., and Foster, J. R. (1990). Perchloroethylene-induced rat kidney tumors: an investigation of the mechanisms involved and their relevance to humans. <i>Toxicol. Appl. Pharmacol.</i> 103, 77-89.</p>
7	95	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>* Kinetic studies on acetylation, and β-lyase-mediated metabolism of DCVC support a low flux through β-lyase activation since the relative flux through the N-acetylation pathway (detoxication) is one to two orders of magnitude higher than through β-lyase activation (Green et al., 1997a). In addition, a low flux through β-lyase is indicated by the recovery of most of a low intravenous dose of DCVC isomers in urine as mercapturic acids in rats (Birner et al., 1997), the weak nephrotoxicity of DCVC (Green et al., 1997a) and observations with PERC, which is also metabolized by glutathione S-conjugate formation and β-lyase. The PERC metabolite S-(1,2,2-trichlorovinyl)-L-cysteine is cleaved by β-lyase to dichloroacetic acid (DCA) which, when formed in the kidney, is excreted with urine. While DCA is a metabolite of PERC in rats, this compound is not excreted as a PERC metabolite in humans (Völkel et al., 1998). In addition, dichloroacetylated proteins were detected both in rat kidney proteins and rat blood proteins after PERC inhalation. Such protein modifications were not detected in blood proteins from humans after identical exposures (Pähler et al., 1999). These observations indicate that flux through β-lyase in humans is even lower than in rodents.</p> <p>* Chloroacetic acid is formed by β-lyase from DCVC (Dekant et al., 1988). In rodents, chloroacetic acid and its metabolites (Green and Hathway, 1975; Green and Hathway, 1977) are not significant metabolites of TCE (< 0.1 % of radioactivity in urine) (Dekant et al., 1984; Dekant et al., 1986a). If the β-lyase pathway is more relevant, such metabolites should be present in urine in higher concentrations. Other metabolites indicative of alternative processing of DCVC have also not been detected in humans exposed to TCE (Bloemen et al., 2001).</p>	<p>AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany</p> <p>Green, T., Dow, J., Ellis, M. K., Foster, J. R., and Odum, J. (1997a). The role of glutathione conjugation in the development of kidney tumours in rats exposed to trichloroethylene. <i>Chemico-Biological Interactions</i> 105, 99-117.</p> <p>Birner, G., Bernauer, U., Werner, M., and Dekant, W. (1997). Biotransformation, excretion and nephrotoxicity of haloalkene-derived cysteine S-conjugates. <i>Arch Toxicol</i> 72, 1-8.</p> <p>Völkel, W., Friedewald, M., Lederer, E., Pähler, A., Parker, J., and Dekant, W. (1998). Biotransformation of perchloroethene: dose-dependent excretion of trichloroacetic acid, dichloroacetic acid and N-acetyl-S-(trichlorovinyl)-L-cysteine in rats and humans after inhalation. <i>Toxicology and Applied Pharmacology</i> 153, 20-27.</p> <p>Dekant, W., Berthold, K., Vamvakas, S., Henschler, D., and Anders, M. W. (1988). Thioacylating intermediates as metabolites of S-(1,2-dichlorovinyl)-L-cysteine and S-(1,2,2-trichlorovinyl)-L-cysteine formed by cysteine conjugate β-lyase. <i>Chemical Research in Toxicology</i> 1, 175-178.</p> <p>Green, T., and Hathway, D. E. (1975). The biological fate in rats of vinyl chloride in relation to its oncogenicity. <i>Chem Biol Interact</i> 11, 545-562.</p> <p>Green, T., and Hathway, D. E. (1977). The chemistry and biogenesis of the S-containing metabolites of vinyl chloride in rats. <i>Chem Biol Interact</i> 17, 137-150.</p> <p>Dekant, W., Metzler, M., and Henschler, D. (1984). Novel metabolites of trichloroethylene through dechlorination reactions in rats, mice and humans. <i>Biochem. Pharmacol.</i> 33, 2021-2027.</p> <p>Dekant, W., Schulz, A., Metzler, M., and Henschler, D. (1986a). Absorption, elimination and metabolism of trichloroethylene: a quantitative comparison between rats and mice. <i>Xenobiotica</i> 16, 143-152.</p> <p>Bloemen, L. J., Monster, A. C., Kezic, S., Commandeur, J. N., Veulemans, H., Vermeulen, N. P., and Wilmer, J. W. (2001). Study on the cytochrome P-450- and glutathione-dependent biotransformation of trichloroethylene in humans. <i>Int Arch Occup Environ Health</i> 74, 102-108.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics																																																																																																				
7	100	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	Table 1: [SEE FOLLOWING PAGE] Reported rates of formation of DCVC from Trichloroethene (TCE) in rat, mouse and human subcellular fractions. The concentration of TCE in the incubation is based on the amount added. N.d. = not determined	<table border="1"> <thead> <tr> <th>Tissue</th> <th>Species</th> <th>TCE Conc (mM)</th> <th>Rate of DCVC formation (pmol/minxmg)</th> <th>Analytical method to determine DCVG</th> <th>Reference</th> </tr> </thead> <tbody> <tr> <td rowspan="3">Liver cytosol</td> <td>Rat</td> <td>1.4 (¹⁴C)</td> <td>0.54 (non-enzymatic reaction rates subtracted)</td> <td rowspan="12">HPLC with radiochemical detection, peak identity confirmed by LC/MS</td> <td rowspan="12">(Green <i>et al.</i>, 1997b)</td> </tr> <tr> <td>Mouse</td> <td>1.9 (¹⁴C)</td> <td>0.35</td> </tr> <tr> <td>Human</td> <td>1.9 – 2.5 (¹⁴C)</td> <td>0.012 – 0.055</td> </tr> <tr> <td rowspan="3">Liver microsomes</td> <td>Rat</td> <td>1.4 (¹⁴C)</td> <td>Not different from non-enzymatic reaction</td> </tr> <tr> <td>Mouse</td> <td>1.9 (¹⁴C)</td> <td>n.d.</td> </tr> <tr> <td>Human</td> <td>1.9 – 2.5 (¹⁴C)</td> <td>n.d.</td> </tr> <tr> <td rowspan="3">Kidney cytosol</td> <td>Rat</td> <td>1.4 (¹⁴C)</td> <td>Not different from non-enzymatic reaction</td> </tr> <tr> <td>Mouse</td> <td>n.d.</td> <td></td> </tr> <tr> <td>Human</td> <td>n.d.</td> <td></td> </tr> <tr> <td rowspan="3">Kidney microsomes</td> <td>Rat</td> <td>1.4 (¹⁴C)</td> <td>Not different from non-enzymatic reaction</td> </tr> <tr> <td>Mouse</td> <td>n.d.</td> <td></td> </tr> <tr> <td>Human</td> <td>n.d.</td> <td></td> </tr> <tr> <td>Liver cytosol</td> <td>Rat</td> <td>4 (¹⁴C)</td> <td>< 2</td> <td rowspan="2">HPLC with radioactivity detection, peak identity confirmed by GC/MS after hydrolysis</td> <td rowspan="2">(Dekant <i>et al.</i>, 1990)</td> </tr> <tr> <td>Liver microsomes</td> <td>Rat</td> <td>4 (¹⁴C)</td> <td>2</td> </tr> <tr> <td rowspan="3">Liver cytosol</td> <td>Rat</td> <td>2</td> <td>121 (males) 81 (females)</td> <td rowspan="12">Derivatization and ion exchange HPLC ("Reed-method")</td> <td rowspan="12">(Lash <i>et al.</i>, 1999a)</td> </tr> <tr> <td>Mouse</td> <td>2</td> <td>408 (males) 361 (females)</td> </tr> <tr> <td>Human</td> <td>1</td> <td>1 700 – 4 180</td> </tr> <tr> <td rowspan="3">Liver microsomes</td> <td>Rat</td> <td>2</td> <td>171 (males) 120 (females)</td> </tr> <tr> <td>Mouse</td> <td>2</td> <td>666 (males) 426 (females)</td> </tr> <tr> <td>Human</td> <td>1</td> <td>495 – 3 245</td> </tr> <tr> <td rowspan="3">Kidney cytosol</td> <td>Rat</td> <td>2</td> <td>7.5 (males) 5.3 (females)</td> </tr> <tr> <td>Mouse</td> <td>2</td> <td>93 (males) 61 (females)</td> </tr> <tr> <td>Human</td> <td>na</td> <td>810 (vmax)</td> </tr> <tr> <td rowspan="3">Kidney microsomes</td> <td>Rat</td> <td>2</td> <td>Nd (males) 1.0 (females)</td> </tr> <tr> <td>Mouse</td> <td>2</td> <td>91 (males) 278 (females)</td> </tr> <tr> <td>Human</td> <td>na</td> <td>6 290 (vmax)</td> </tr> </tbody> </table> <p>AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany</p>	Tissue	Species	TCE Conc (mM)	Rate of DCVC formation (pmol/minxmg)	Analytical method to determine DCVG	Reference	Liver cytosol	Rat	1.4 (¹⁴ C)	0.54 (non-enzymatic reaction rates subtracted)	HPLC with radiochemical detection, peak identity confirmed by LC/MS	(Green <i>et al.</i> , 1997b)	Mouse	1.9 (¹⁴ C)	0.35	Human	1.9 – 2.5 (¹⁴ C)	0.012 – 0.055	Liver microsomes	Rat	1.4 (¹⁴ C)	Not different from non-enzymatic reaction	Mouse	1.9 (¹⁴ C)	n.d.	Human	1.9 – 2.5 (¹⁴ C)	n.d.	Kidney cytosol	Rat	1.4 (¹⁴ C)	Not different from non-enzymatic reaction	Mouse	n.d.		Human	n.d.		Kidney microsomes	Rat	1.4 (¹⁴ C)	Not different from non-enzymatic reaction	Mouse	n.d.		Human	n.d.		Liver cytosol	Rat	4 (¹⁴ C)	< 2	HPLC with radioactivity detection, peak identity confirmed by GC/MS after hydrolysis	(Dekant <i>et al.</i> , 1990)	Liver microsomes	Rat	4 (¹⁴ C)	2	Liver cytosol	Rat	2	121 (males) 81 (females)	Derivatization and ion exchange HPLC ("Reed-method")	(Lash <i>et al.</i> , 1999a)	Mouse	2	408 (males) 361 (females)	Human	1	1 700 – 4 180	Liver microsomes	Rat	2	171 (males) 120 (females)	Mouse	2	666 (males) 426 (females)	Human	1	495 – 3 245	Kidney cytosol	Rat	2	7.5 (males) 5.3 (females)	Mouse	2	93 (males) 61 (females)	Human	na	810 (vmax)	Kidney microsomes	Rat	2	Nd (males) 1.0 (females)	Mouse	2	91 (males) 278 (females)	Human	na	6 290 (vmax)
Tissue	Species	TCE Conc (mM)	Rate of DCVC formation (pmol/minxmg)	Analytical method to determine DCVG	Reference																																																																																																				
Liver cytosol	Rat	1.4 (¹⁴ C)	0.54 (non-enzymatic reaction rates subtracted)	HPLC with radiochemical detection, peak identity confirmed by LC/MS	(Green <i>et al.</i> , 1997b)																																																																																																				
	Mouse	1.9 (¹⁴ C)	0.35																																																																																																						
	Human	1.9 – 2.5 (¹⁴ C)	0.012 – 0.055																																																																																																						
Liver microsomes	Rat	1.4 (¹⁴ C)	Not different from non-enzymatic reaction																																																																																																						
	Mouse	1.9 (¹⁴ C)	n.d.																																																																																																						
	Human	1.9 – 2.5 (¹⁴ C)	n.d.																																																																																																						
Kidney cytosol	Rat	1.4 (¹⁴ C)	Not different from non-enzymatic reaction																																																																																																						
	Mouse	n.d.																																																																																																							
	Human	n.d.																																																																																																							
Kidney microsomes	Rat	1.4 (¹⁴ C)	Not different from non-enzymatic reaction																																																																																																						
	Mouse	n.d.																																																																																																							
	Human	n.d.																																																																																																							
Liver cytosol	Rat	4 (¹⁴ C)	< 2	HPLC with radioactivity detection, peak identity confirmed by GC/MS after hydrolysis	(Dekant <i>et al.</i> , 1990)																																																																																																				
Liver microsomes	Rat	4 (¹⁴ C)	2																																																																																																						
Liver cytosol	Rat	2	121 (males) 81 (females)	Derivatization and ion exchange HPLC ("Reed-method")	(Lash <i>et al.</i> , 1999a)																																																																																																				
	Mouse	2	408 (males) 361 (females)																																																																																																						
	Human	1	1 700 – 4 180																																																																																																						
Liver microsomes	Rat	2	171 (males) 120 (females)																																																																																																						
	Mouse	2	666 (males) 426 (females)																																																																																																						
	Human	1	495 – 3 245																																																																																																						
Kidney cytosol	Rat	2	7.5 (males) 5.3 (females)																																																																																																						
	Mouse	2	93 (males) 61 (females)																																																																																																						
	Human	na	810 (vmax)																																																																																																						
Kidney microsomes	Rat	2	Nd (males) 1.0 (females)																																																																																																						
	Mouse	2	91 (males) 278 (females)																																																																																																						
	Human	na	6 290 (vmax)																																																																																																						
7	109	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	Support for a cytotoxic MoA regarding the mouse lung tumors induced by TCE can also be derived from observations with other chemicals. The consequences of Clara cell specific cytotoxicity for tumor induction has been assessed with a number of other chemicals and the very high capacity of the mouse lung Clara cell for biotransformation is also the basis for the mouse-specific lung toxicity. The assessment therefore should integrate this information. * Styrene, naphthalene, and coumarin induce lung tumors in mice and chronic damage of Clara cells including	<p>AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany</p> <p>Green, T., Mainwaring, G. W., and Foster, J. R. (1997b). Trichloroethylene induced mouse lung tumours: studies of the mode of action and comparisons between species. <i>Fundamental and Applied Toxicology</i> 37, 125-130.</p> <p>Villaschi, S., Giovanetti, A., Lombardi, C. C., Nicolai, G., Garbati, M., and Andreozzi, U. (1991).</p>																																																																																																				

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>hyperplasia, often with a time- and dose-related increase in bronchiolar hyperplasia in terminal bronchioles. As with TCE, lung lesions are induced by short term administration, recess after repeated exposures and reappear after continuing exposures. None of these chemical induced lung tumors or histopathologic changes in rat lung (Cruzan et al., 1998; Cruzan et al., 2001).</p> <p>* Major species differences in lung tumor induction and lung anatomy are one likely basis for the selective tumorigenicity of these chemicals in mice. Lung tumors occur spontaneously in several mouse strains and the incidences of benign lung tumors in control mice are often very high. In general, murine lung tumors are mostly adenomas originating from bronchiolar Clara cells. The adenomas may progress to adenocarcinomas. (Witschi, 1991).</p> <p>* Clara cells are the major site of xenobiotic metabolism in the mouse lung (Chichester et al., 1991; Buckpitt et al., 1995). In addition to marked species differences in metabolic capacity of Clara cells in different species, species differences in Clara cell abundance and function may contribute to selective pulmonary toxicity in mice. Clara cell number is significantly higher within the terminal bronchioles of mice relative to rats and humans (Plopper et al., 1980; Lumsden et al., 1984). Clara cells represent approximately 5 % of all cell types and are distributed throughout the airways in mice. In humans, only very few Clara cells are present and are localized in specific regions. Moreover, Clara cells differ morphologically among species, with human cells containing little smooth endoplasmic reticulum.</p> <p>* TCE and the other chemicals inducing selective lung damage and lung tumors in mice require biotransformation by pulmonary CYP2F and CYP2E1 (Green et al., 1997b; Shultz et al., 1999; Shultz et al., 2001; Born et al., 2002; West et al., 2002; Forkert et al., 2005).</p> <p>* In mice, both CYP2E1 and CYP2F1 are preferentially localized in Clara cells (Forkert et al., 1989; Buckpitt et al., 1995; Forkert, 1995; Shultz et al., 2001). In rat lung, the expression of CYP2F4, an ortholog of mouse CYP2F2 (Baldwin et al., 2004) is app. 30-fold lower consistent with a much lower turnover of CYP2F substrates in rat. Evidence for the presence of the human ortholog CYP2F1 in human lung is lacking. In rhesus monkeys, CYP2F1 was not detected in the respiratory tract except in the nasal epithelium (Ding and Kaminsky, 2003; Baldwin et al., 2004). CYP2E1 catalytic activity is present in human lung with an activity app. 100-fold lower than in human liver (Bernauer et al., 2006).</p> <p>In summary, the available information on the presence and catalytic activities of CYP2E1 and CYP2F enzymes in the lung of different species suggest a much higher activity of these enzymes in the mouse, the species susceptible to the pneumotoxicity. Studies directly quantifying relevant metabolite formation from the different pneumotoxic compounds show that mice consistently have a much higher capacity for oxidation as compared to rats and humans. The available data on the mode-of-action for induction of lung tumors share many common features with regard to the induction of Clara cell lesions in the mouse and a number of observations support a non-genotoxic mode-of-action: Glutathione depletion is a major determinant of the toxic responses in the mouse Clara toxicity (West et al., 2000a; West et al., 2000b; Plopper et al., 2001; Phimister et al., 2004; Turner et al., 2005). Glutathione-depletion induced cell death induced by mouse specific Clara cell toxicants initiates extensive cell replication and subsequent hyperplasia which are considered important steps in the multi-step progression to tumor development (Gadberry et al., 1996; Green et al., 1997b; Green et al., 2001).</p>	<p>Damage and repair of mouse bronchial epithelium following acute inhalation of trichloroethylene. Exp Lung Res 17, 601-614.</p> <p>Cruzan, G., Cushman, J. R., Andrews, L. S., Granville, G. C., Johnson, K. A., Bevan, C., Hardy, C. J., Coombs, D. W., Mullins, P. A., and Brown, W. R. (2001). Chronic toxicity/oncogenicity study of styrene in CD-1 mice by inhalation exposure for 104 weeks. J Appl Toxicol 21, 185-198.</p> <p>Cruzan, G., Cushman, J. R., Andrews, L. S., Granville, G. C., Johnson, K. A., Hardy, C. J., Coombs, D. W., Mullins, P. A., and Brown, W. R. (1998). Chronic toxicity/oncogenicity study of styrene in CD rats by inhalation exposure for 104 weeks. Toxicol Sci 46, 266-281.</p> <p>Witschi, H. (1991). Lung tumor susceptibility in mice: an overview. Exp Lung Res 17, 281-282.</p> <p>Chichester, C. H., Philpot, R. M., Weir, A. J., Buckpitt, A. R., and Plopper, C. G. (1991). Characterization of the cytochrome P-450 monooxygenase system in nonciliated bronchiolar epithelial (Clara) cells isolated from mouse lung. Am J Respir Cell Mol Biol 4, 179-186.</p> <p>Buckpitt, A., Chang, A. M., Weir, A., Van Winkle, L., Duan, X., Philpot, R., and Plopper, C. (1995). Relationship of cytochrome P450 activity to Clara cell cytotoxicity. IV. Metabolism of naphthalene and naphthalene oxide in microdissected airways from mice, rats, and hamsters. Mol Pharmacol 47, 74-81.</p> <p>Plopper, C. G., Mariassy, A. T., and Hill, L. H. (1980). Ultrastructure of the nonciliated bronchiolar epithelial (Clara) cell of mammalian lung: I. A comparison of rabbit, guinea pig, rat, hamster, and mouse. Exp Lung Res 1, 139-154.</p> <p>Lumsden, A. B., McLean, A., and Lamb, D. (1984). Goblet and Clara cells of human distal airways: evidence for smoking induced changes in their numbers. Thorax 39, 844-849.</p> <p>Shultz, M. A., Choudary, P. V., and Buckpitt, A. R. (1999). Role of murine cytochrome P-450 2F2 in metabolic activation of naphthalene and metabolism of other xenobiotics. J Pharmacol Exp Ther 290, 281-288.</p> <p>Shultz, M. A., Morin, D., Chang, A. M., and Buckpitt, A. (2001). Metabolic capabilities of CYP2F2 with various pulmonary toxicants and its relative abundance in mouse lung subcompartments. J Pharmacol Exp Ther 296, 510-519.</p> <p>Born, S. L., Caudill, D., Fliter, K. L., and Purdon, M. P. (2002). Identification of the cytochromes P450 that catalyze coumarin 3,4-epoxidation and 3-hydroxylation. Drug Metab Dispos 30, 483-487.</p> <p>West, J. A., Williams, K. J., Toskala, E., Nishio, S. J., Fleschner, C. A., Forman, H. J., Buckpitt, A. R., and Plopper, C. G. (2002). Induction of tolerance to naphthalene in Clara cells is dependent on a stable phenotypic adaptation favoring maintenance of the glutathione pool. Am J Pathol 160, 1115-1127.</p> <p>Forkert, P. G., Baldwin, R. M., Millen, B., Lash, L. H., Putt, D. A., Shultz, M. A., and Collins, K. S. (2005). Pulmonary bioactivation of trichloroethylene to chloral hydrate: relative contributions of CYP2E1, CYP2F, and CYP2B1. Drug Metab Dispos 33, 1429-1437.</p> <p>Forkert, P. G., Vessey, M. L., Park, S. S., Gelboin, H. V., and Cole, S. P. (1989). Cytochromes P-450 in murine lung. An immunohistochemical study with monoclonal antibodies. Drug Metab Dispos 17, 551-555.</p> <p>Forkert, P. G. (1995). CYP2E1 is preferentially expressed in Clara cells of murine lung: localization by in situ hybridization and immunohistochemical methods. Am J Respir Cell Mol Biol 12, 589-596.</p> <p>Baldwin, R. M., Jewell, W. T., Fanucchi, M. V., Plopper, C. G., and Buckpitt, A. R. (2004).</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
					<p>Comparison of pulmonary/nasal CYP2F expression levels in rodents and rhesus macaque. <i>J Pharmacol Exp Ther</i> 309, 127-136.</p> <p>Ding, X., and Kaminsky, L. S. (2003). Human extrahepatic cytochromes P450: function in xenobiotic metabolism and tissue-selective chemical toxicity in the respiratory and gastrointestinal tracts. <i>Annu Rev Pharmacol Toxicol</i> 43, 149-173.</p> <p>Bernauer, U., Heinrich-Hirsch, B., Tonnie, M., Peter-Matthias, W., and Gundert-Remy, U. (2006). Characterisation of the xenobiotic-metabolizing Cytochrome P450 expression pattern in human lung tissue by immunochemical and activity determination. <i>Toxicol Lett</i> 164, 278-288.</p> <p>West, J. A., Buckpitt, A. R., and Plopper, C. G. (2000a). Elevated airway GSH resynthesis confers protection to Clara cells from naphthalene injury in mice made tolerant by repeated exposures. <i>J Pharmacol Exp Ther</i> 294, 516-523.</p> <p>West, J. A., Chichester, C. H., Buckpitt, A. R., Tyler, N. K., Brennan, P., Helton, C., and Plopper, C. G. (2000b). Heterogeneity of clara cell glutathione. A possible basis for differences in cellular responses to pulmonary cytotoxicants. <i>Am J Respir Cell Mol Biol</i> 23, 27-36.</p> <p>Plopper, C. G., Van Winkle, L. S., Fanucchi, M. V., Malburg, S. R., Nishio, S. J., Chang, A., and Buckpitt, A. R. (2001). Early events in naphthalene-induced acute Clara cell toxicity. II. Comparison of glutathione depletion and histopathology by airway location. <i>Am J Respir Cell Mol Biol</i> 24, 272-281.</p> <p>Phimister, A. J., Lee, M. G., Morin, D., Buckpitt, A. R., and Plopper, C. G. (2004). Glutathione depletion is a major determinant of inhaled naphthalene respiratory toxicity and naphthalene metabolism in mice. <i>Toxicol Sci</i> 82, 268-278.</p> <p>Turner, M., Mantick, N. A., and Carlson, G. P. (2005). Comparison of the depletion of glutathione in mouse liver and lung following administration of styrene and its metabolites styrene oxide and 4-vinylphenol. <i>Toxicology</i> 206, 383-388.</p> <p>Gadberry, M. G., DeNicola, D. B., and Carlson, G. P. (1996). Pneumotoxicity and hepatotoxicity of styrene and styrene oxide. <i>J Toxicol Environ Health</i> 48, 273-294.</p> <p>Green, T., Toghiani, A., and Foster, J. R. (2001). The role of cytochromes P-450 in styrene induced pulmonary toxicity and carcinogenicity. <i>Toxicology</i> 169, 107-117.</p>
7	119	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	Page 3-35: Metabolite recovery data in male and female human beings are available. In addition, metabolite excretion in humans and rats exposed to TCE by inhalation under identical conditions are available (Bernauer et al., 1996).	<p>AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany</p> <p>Bernauer, U., Birner, G., Dekant, W., and Henschler, D. (1996). Biotransformation of trichloroethene: dose-dependent excretion of 2,2,2-trichloro-metabolites and mercapturic acids in rats and humans after inhalation. <i>Arch Toxicol</i> 70, 338-346.</p>
7	121	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	Page 3-44: Table 3-23 should include additional data on GSH-conjugation of TCE (Dekant et al., 1990; Green et al., 1997a).	<p>AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany</p> <p>Dekant, W., Koob, M., and Henschler, D. (1990). Metabolism of trichloroethene - in vivo and in vitro evidence for activation by glutathione conjugation. <i>Chemico-Biological Interactions</i> 73, 89-101.</p> <p>Green, T., Dow, J., Ellis, M. K., Foster, J. R., and Odum, J. (1997a). The role of glutathione conjugation in the development of kidney tumours in rats exposed to trichloroethylene. <i>Chemico-Biological Interactions</i> 105, 99-117.</p>
7	123	EPA-HQ-ORD-2009-	Halogenated Solvents	Page 3-46: Information on β -lyase catalyzed metabolism of DCVC is available (Green et al., 1997a).	<p>AUTHOR: Prof. Dr. Wolfgang Dekant, University of Wurzburg, Germany</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
		0791-0018.1	Industry Alliance, Inc.		Green, T., Dow, J., Ellis, M. K., Foster, J. R., and Odum, J. (1997a). The role of glutathione conjugation in the development of kidney tumours in rats exposed to trichloroethylene. <i>Chemico-Biological Interactions</i> 105, 99-117.
7	207	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>EPA's assessment of TCE uses data on heart defects as a major endpoint for setting the RfD and RfC. The data selected to support this decision are from studies that are poorly designed and flawed. Furthermore, EPA neither incorporates nor accounts for more robust data from guideline- and GLP- compliant studies that show no increase in congenital heart defects.</p> <p>Two additional GLP- and guideline-compliant studies showing no effect on heart development were conducted by Fisher et al. (2001) and Carney et al. (2006).</p>	<p>AUTHORS: Carole A. Kimmel, PhD; Gary L. Kimmel, PhD; John M. DeSesso, PhD from Exponent</p> <p>Carney, E.W., B.A. Thorsrud, P.H. Dugard, and C.L. Zablony. 2006. Developmental toxicity studies in CrI:CD (SD) rats following inhalation exposure to trichloroethylene and perchloroethylene. <i>Birth Defects Research, Part B: Developmental and Reproductive Toxicology</i> 77:405-412.</p> <p>Fisher JW, Channell SR, Eggers JS, Johnson PD, MacMahon IKL, Goodyear CD, Sudberry GL, Warren DA, Latendresse JR, Graeter IJ. Trichloroethylene, trichloroacetic acid, and dichloroacetic acid: Do they affect fetal rat heart development? <i>Int J Toxicol.</i> 2001; 20:257-67.</p>
7	210	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>* The draft assessment is not a "weight of evidence" evaluation but a "strength of evidence" evaluation (NRC, 1994). All the focus is on those studies that found a compound-related effect and no attention was given to the strengths and weaknesses of those studies that found no compound-related effects. Data from GLP-compliant animal studies that were carefully designed to probe the existence of potential links between TCE or its metabolites and heart or eye defects have shown no associations at exposure levels that are several orders of magnitude higher than those expected in environmental or occupational settings.</p> <p>- Fisher et al. (2001) specifically investigated the cardiac teratogenic potential of TCE, TCA, and DCA in groups of 19 -20 pregnant Sprague-Dawley rats. The rats received oral bolus doses of TCE (500 mg/kg/day, in soybean oil), TCA (300 mg/kg/day, in water) or DCA (300 mg/kg/day, in water) on gestational days 6 -15. On gestational day 21, fetuses were removed by laparohysterectomy and hearts were examined and microdissected under a stereomicroscope by an investigator experienced in the procedure (Dr. Paula Johnson, author of Johnson et al. (2003)). The rates of cardiac malformations among treated animals did not differ from control rates. Also, TCE caused no change in the weight of fetuses and did not inhibit maternal weight gain at the high dose level [FOOTNOTE 1] used in this study.</p> <p>- An inhalation study of TCE in pregnant Charles River CD IGS rats (Carney et al., 2001; 2006) exposed groups of 27 animals to filtered air or to atmospheric concentrations of TCE up to and including the limit dose (600 ppm) for 6 hours/day on each of gestational days 6 -20. Although maternal toxicity (decreased body weight gain) was elicited at the highest dose, TCE exposure caused no increase in gross, skeletal, or visceral (including heart and eye) malformations at any of the concentrations tested.</p> <p>- Some early studies of TCA and DCA in pregnant Long-Evans rats (Smith et al., 1989, 1992) reported ocular malformations. In a follow-up to the Fisher et al. (2001) study, Warren et al. (2006) reported that examination of the heads showed that none of the chemicals used in the Fisher et al. (2001) study elicited gross ocular malformations. Morphometric analysis of the lens area, globe area and interocular distances revealed reductions of these parameters only in the TCA- and DCA-treated fetuses, but the overall smaller sizes of the fetuses in those groups were sufficient to explain the reductions.</p> <p>* Weight of evidence clearly must consider all of the data, both positive and no effect data. When the majority of the positive data are derived from clearly flawed studies using methods that give results that are not replicable in other laboratories, it is difficult to understand how the Agency can justify using only these data as the basis for a regulatory assessment.</p>	<p>FOOTNOTE 1: For purposes of estimating the comparability of the dosages in the Fisher and Johnson studies, the following rough estimates can be made, in the Johnson drinking water study, the high dose was 1100 ppm TCE in the water. If the rats drank 20 mL/day, they received ~22 mg TCE/day. In the Fisher gavage study, the rats were administered 500 mg/kg/day. If the rats weighed 350 g, they received ~175 mg TCE/day.</p> <p>AUTHORS: Carole A. Kimmel, PhD; Gary L. Kimmel, PhD; John M. DeSesso, PhD from Exponent NRC (1994). <i>Science and Judgment in Risk Assessment</i>. National Research Council; National Academy Press, Washington, DC; 1994.</p> <p>Fisher JW, Channell SR, Eggers JS, Johnson PD, MacMahon IKL, Goodyear CD, Sudberry GL, Warren DA, Latendresse JR, Graeter IJ. Trichloroethylene, trichloroacetic acid, and dichloroacetic acid: Do they affect fetal rat heart development? <i>Int J Toxicol.</i> 2001; 20:257-67.</p> <p>Johnson PD, Goldberg SJ, Mays MZ, Dawson BV. Threshold of trichloroethylene contamination in maternal drinking waters affecting fetal heart development in the rat. <i>Environ Health Perspect.</i> 2003; 111:289-92.</p> <p>Carney EW, Zablony CL, Clements CM. Trichloroethylene: inhalation developmental toxicity. The Dow Chemical Company, Study ID: 981129. Midland, Michigan; 2001.</p> <p>Carney, E.W., B.A. Thorsrud, P.H. Dugard, and C.L. Zablony. 2006. Developmental toxicity studies in CrI:CD (SD) rats following inhalation exposure to trichloroethylene and perchloroethylene. <i>Birth Defects Research, Part B: Developmental and Reproductive Toxicology</i> 77:405-412.</p> <p>Smith MK, Randall JL, Read EJ, Stober JA. Teratogenic activity of trichloroacetic acid in the rat. <i>Teratology</i> 1989; 40:445-51.</p> <p>Smith MK, Randall JL, Read EF, Stober JA. Developmental toxicity of dichloroacetate in the rat. <i>Teratology</i> 1992; 46(3):217-23.</p>
7	213	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	* The NRC (2009) report updated the conclusions of the IOM (2003) report and concluded that "there continues to be inadequate/insufficient evidence" for a link between TCE and congenital malformations in humans.	<p>AUTHORS: Carole A. Kimmel, PhD; Gary L. Kimmel, PhD; John M. DeSesso, PhD from Exponent</p> <p>IOM (2003). <i>Gulf War and Health, Vol. 2, Insecticides and Solvents</i>. Washington, DC: National Academies Press.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
					NRC (2009). Contaminated Water Supplies at Camp LeJeune: Assessing Potential Health Effects. National Research Council: National Academies Press, Washington, DC.
7	228	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	Data that could potentially improve the estimation of PBPK model parameters, including some of the highly uncertain parameters, are currently available. Some of these data were clearly available to EPA at the time of model development; other data were more recently published, but should certainly be considered at this time to improve the models as described in the IRIS draft and published, peer-reviewed versions of the model (Chiu et al., 2009; Evans et al., 2009).	AUTHOR: Lisa M. Sweeney, Ph.D., DABT Chiu WA; Okino MS, Evans MV. Characterizing uncertainty and population variability in the toxicokinetics of trichloroethylene and metabolites in mice, rats, and humans using an updated database, physiologically based pharmacokinetic (PBPK) model, and Bayesian approach. Toxicol Appl Pharmacol. 2009; 241 (1):36-60. Evans MV, Chiu WA, Okino MS, Caldwell JC. Development of an updated PBPK model for trichloroethylene and metabolites in mice, and its application to discern the role of oxidative metabolism in TCE-induced hepatomegaly. Toxicol Appl Pharmacol. 2009; 236(3):329-40.
7	229	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	Other model structures could be considered by EPA. The performance of the GSH-related metrics in the rodent models could potentially be improved by consideration of the Kim et al (2009) mouse DCVC blood data and the rat DCVC data of Birner et al. (1997).	AUTHOR: Lisa M. Sweeney, Ph.D., DABT Kim S, Kim D, Pollack GM, Colhns 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. 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.
7	253	EPA-HQ-ORD-2009-0791-0012.1	McKenna, Long & Aldrige, LLP	Quote from Charbotel et al 2006 “The results of the present study do not agree with the negative results obtained by a number of large cohort studies. ... Although this study shows a possible link between high levels of exposure to TCE and increased risk of RCC, further epidemiological studies are necessary to assess the effect of lower levels of exposure.”	- -
7	284	EPA-HQ-ORD-2009-0791-0014.1	Exponent Health Services	Because “dose-response” is an important consideration in the evaluation of epidemiologic studies for causality, we evaluated exposure-response data to the extent possible in our published meta-analyses and observed no clear pattern of increasing cancer risk with increasing exposure level or duration (Kelsh et al 2010; Mandel et al 2006; Alexander et al. 2007; Alexander et al., 2006). Such an analysis by EPA would provide helpful information in the consideration of potential relationships between TCE and cancer.	- Alexander DD, Wagner ME. Benzene exposure and Non-Hodgkin Lymphoma: A meta-analysis of epidemiologic studies. J Occup Environ Med 2009, in press. Alexander DD, Mink PJ, Mandel JH, Kelsh M. A meta-analysis of occupational trichloroethylene exposure and multiple myeloma or leukemia. Occup Med (Lond) 2006; 56(7):485-493. Kelsh MA, Alexander DD, Mink PJ, Mandel JH. Occupational trichloroethylene exposure and kidney cancer: a meta-analysis. Epidemiology. 2010 Jan;21(1):95-102. Mandel JH, Kelsh MA, Mink P, Alexander DD. Occupational trichloroethylene exposure and non-Hodgkin's lymphoma: a meta-analysis and review. Occup. Environ. Med. 2006;63:597-607.
7	291	EPA-HQ-ORD-2009-0791-0014.1	Exponent Health Services	Kidney Cancer · On page 4-170 of the external report, EPA discusses the 2006 NRC deliberations on the epidemiology surrounding TCE. Wartenberg et al. 2000 and Kelsh et al. 2005 are discussed. This discussion needs to be updated with a discussion of Kelsh et al. 2010, which includes studies that were published after the Kelsh et al. 2005 report/presentation.	- Anttila, A; Pukkala, E; Sallmén, M; et al. (1995) Cancer incidence among Finnish workers exposed to halogenated hydrocarbons. J Occup Environ Med 37:797-806. Axelson, O; Selden, A; Andersson, K; et al. (1994) Updated and expanded 1 Swedish cohort study on trichloroethylene and cancer risk. J Occup Med 36:556-562.

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>Kelsh et al. (2010) conducted a comprehensive meta-analysis of epidemiologic cohort and case-control studies of TCE exposure and kidney cancer. This comprehensive metaanalysis evaluates workers with any TCE exposure, sub-cohorts of workers more likely exposed to TCE, and examines summary associations by important characteristics, such as study design, type of exposure ascertainment method (e.g., biomonitoring), and doseresponse by specific exposure metric. In addition, the methodological and analytical considerations of evaluating TCE and kidney cancer are fully discussed.</p> <p>· Because accurate and valid exposure assessment is instrumental to any evaluation of a factor and disease outcome, EPA should have identified and analyzed in a separate analysis the three cohort studies (i.e., Anttila 1995; Axelson 1994; Hansen 2001) for which biomonitoring of TCE exposure was conducted. When we evaluated the summary association across the biomonitoring studies of TCE and kidney cancer, no effect was apparent (SRRE = 1.02, 95% CI: 0.59-1.77) (Kelsh et al. 2010).</p>	<p>Hansen, J; Raaschou-Nielsen, O; Christensen, JM; et al. (2001) Cancer incidence among Danish workers exposed to trichloroethylene. J Occup Environ Med 43:133–139.</p> <p>Kelsh MA, Alexander DD, Mink PJ, Mandel JH. Occupational trichloroethylene exposure and kidney cancer: a meta-analysis. Epidemiology. 2010 Jan;21(1):95–102.</p>
8	39	EPA-HQ-ORD-2009-0791-0011.1	ARCADIS	<p>Scope of Work for Validation Exercise</p> <p>EPA has provided no validation exercises of their proposals about the potential for TCE to cause cancer in the human population. ARCADIS recommends that an historical population risk assessment of RCC, liver and biliary cancer, and NHL in the US due to historical TCE exposure would provide useful information to validate EPA’s proposed classification and URF derivation. The purpose of the historical population risk assessment would be to compare the actual number of such tumors in the US population to the level of TCE-caused tumors that would be predicted to be caused by TCE by standard human health risk assessment methods if EPA’s proposed URF were an accurate predictor of human health risk.</p> <p>The first step in such an historical population risk assessment would involve calculating the number of the specified tumors in the US population predicted to be related solely to TCE exposure, assuming that EPA’s proposed URF is a true estimator of human risk. TCE is ubiquitous in the environment, and there has been widespread exposure to the entire human population for almost a century. Several scenarios would be selected to represent the types of exposures individuals in the US population have typically experienced. Scenarios that would be considered for the exposure assessment include the following:</p> <ul style="list-style-type: none"> • Workers exposed to TCE in dry cleaning operations in the 1930’s to 1950’s when TCE was in widespread use. • Members of the public exposed to TCE by visiting dry cleaning operations in the 1930’s to 1950’s and storing and wearing TCE-cleaned garments. • Workers exposed to TCE in metal cleaning and degreasing operations. • Members of the public exposed to TCE by using consumer products, such as paint removers, cleaning products, typewriter correction fluid, etc. • Hospital workers and patients exposed to TCE when TCE was in use as an anesthetic. • Members of the public exposed to TCE in indoor air from the use of TCE-contaminated water or vapor intrusion near historical or ongoing TCE releases. • Members of the public exposed to TCE in outdoor ambient air from various miscellaneous releases. <p>ARCADIS is in the process of performing an historical population risk assessment of TCE of the type that EPA should have presented in External Review Draft: Toxicological Review of Trichloroethylene. Because the risk assessment is not yet completed, ARCADIS outlines here a scoping exercise for such a validation exercise for EPA’s consideration. When the risk assessment is completed, ARCADIS would be pleased to submit it to EPA to add to the body of information in its TCE files.</p>	-
8	285	EPA-HQ-ORD-2009-0791-0014.1	Exponent Health Services	<p>Because “dose-response” is an important consideration in the evaluation of epidemiologic studies for causality, we evaluated exposure-response data to the extent possible in our published meta-analyses and observed no clear pattern of increasing cancer risk with increasing exposure level or duration (Kelsh et al 2010; Mandel et al 2006; Alexander et al. 2007; Alexander et al., 2006). Such an analysis by EPA would provide helpful information in the consideration of potential relationships between TCE and cancer.</p>	<p>-</p> <p>Alexander DD, Wagner ME. Benzene exposure and Non-Hodgkin Lymphoma: A meta-analysis of epidemiologic studies. J Occup Environ Med 2009, in press.</p> <p>Alexander DD, Mink PJ, Mandel JH, Kelsh M. A meta-analysis of occupational trichloroethylene exposure and multiple myeloma or leukemia. Occup Med (Lond) 2006; 56(7):485–493.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
					<p>Kelsh MA, Alexander DD, Mink PJ, Mandel JH. Occupational trichloroethylene exposure and kidney cancer: a meta-analysis. <i>Epidemiology</i>. 2010 Jan;21(1):95–102.</p> <p>Mandel JH, Kelsh MA, Mink P, Alexander DD. Occupational trichloroethylene exposure and non-Hodgkin's lymphoma: a meta-analysis and review. <i>Occup. Environ. Med.</i> 2006;63:597–607.</p>
APPENDIX A	134	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>There is considerable uncertainty in the proposed RfC of 0.001 ppm for TCE, particularly related to potential uncertainty in the Physiologically Based Pharmacokinetic (PBPK) modeling of the DCVC dose metric in humans, and the relationship of that dose metric with increased kidney weight.</p>	<p>AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp. -</p>
APPENDIX A	136	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>The allowance for inter-human PK variability double counts and misconstrues the nature of the dose-response curve.</p> <p>There are two questions about the allowance for human variability in metabolic activation. The first, addressed elsewhere in these comments, is whether the extent of variability has been reliably estimated. The second, addressed here, is how allowance for variability has been entered in to the RfD/C calculations. It would appear that allowance for human variability has been double-counted because inter-individual variability is built in to the tolerance distribution-based dose-response curve.</p> <p>The method employed in the document is to set a point of departure (PoD) on the animal-based dose-response curve, using central estimates of "standard rat" internal doses as the dose measure. That is, inter-individual PK variation among rats, even though it exists, was not estimated and not considered in the dose-response curve estimation. For non-cancer endpoints, the dose-response curve is interpreted as a tolerance distribution – as the cumulative distribution of individual sensitivity variation. The reason that some animals respond at a given (externally applied) dose and others do not is that some have their individual tolerances exceeded while others do not, and higher doses exceed the individual tolerances of a greater fraction of the variable population, thereby yielding higher disease incidences.</p> <p>Some of this variation is in PK, and so to some extent, the rats that respond do so because they are more vulnerable owing to their individual PK variation that makes them have a higher proportionality of internal to external dose. The contribution of this effect is captured in the fitted dose-response curve, which also reflects variation in sensitivity for other, non-PK reasons, but the contributions of PK variation are already incorporated, and are not readily split out without some attempt to characterize PK variation among individual rats.</p> <p>The rat dose-response curve is then used to determine a PoD by finding a dose that yields a low predicted response, say 1%. Because the dose scale is measured in average internal dose among the rats, the dose associated with a 1% response level is the average internal dose for rats such that 1% of them are expected to have their individual tolerances exceeded. For the sake of argument, if we hypothetically say that there is absolutely no inter-rat variation in PK, then all the rats in a hypothetical experiment at the 1% response dose will have the same internal dose, and which rats respond and which do not will be ruled entirely by variation in pharmacodynamic (PD) sensitivity to this fixed internal dose. But, if one instead hypothesizes that variation in sensitivity is entirely ruled by PK variation (with no contribution of PD variability) then the 1% of rats responding are that same 1% that are most sensitive owing to their PK variation – that is, they are the 99th percentile of the internal dose distribution.</p> <p>The reality is somewhere in between, with both PK and PD variability contributing to variation in ability to tolerate the dose. But without characterization of PK variation among individual rats, we have no way to split the components out (though there is the conventional split between PK and PD that we apply to Uncertainty Factors).</p> <p>Staying with the hypothetical case that sensitivity variation is all in PK, then the only reason to make further allowance for human PK variation is if variation in PK among humans is greater than variation among rats, and even then the correction should only be for the degree to which it is greater – that is, the ratio of the 99th percentile in humans versus the 99th percentile in rats rather than the ratio of the 99th to the 50th percentile in</p>	<p>AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp. -</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>humans.</p> <p>The hypothetical case of pure PK dependence of sensitivity variation is made to clarify the argument, but in the real case of contributions from both PK and PD, the principle illustrated still applies. There is some mix of influence of PK- and PD-based sensitivity among the responding rats, and the effect of this is captured in the fitted dose-response curve, for which the dose variable is the average internal dose. That internal dose is likely higher on average among the 1% of rats responding, because of the contribution of PK to their sensitivity; but, since this is unmeasured, all the analysis can say is that when a group of rats is dosed at a given external level, the average internal dose among them has some level estimated by the rat PBPK model. In view of the (unknown) contribution of PK to sensitivity and the (unknown) degree to which PK varies among rats, there is some (unknown) degree to which some rats have higher-than-average internal doses and thereby have an increased response probability (which is dictated by PD sensitivity to internal dose levels).</p> <p>When the rat PoD is extrapolated to a human PoD based on average PK in the two species, it implicitly assumes that the mix of PK and PD, and the extent of inter-individual variation in PK, are the same in humans as in the rats. If one then makes a correction for the difference between the 50th percentile of PK in humans and the 99th percentile (as the draft reassessment does) it essentially implicitly assumes that all of the variation in sensitivity reflected in the dose-response curve is attributable to PK alone.</p> <p>If one assumes that the mix of PK and PD influence is similar across species, then the correct correction is the ratio of 99th percentiles across species, but since the 99th percentile in rats is not estimated, this cannot be calculated. If one cannot assume that the mix of PK and PD is the same, then it is doubly impossible to calculate a correction.</p> <p>The method that has been employed in the draft reassessment seems to implicitly assume that all of the dose-response in rats is attributable to PD (and this drives the PoD down as far as possible in internal-dose terms) and that all of the dose-response in humans is attributable to PK (and this drives the sensitive human allowance down as far as possible). The net result is to yield an RfC that is overcorrected for human inter-individual variation to a degree that is not possible to know with the analyses available.</p>	
APPENDIX A	140	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>Transparency means more than just showing all the calculations in large appendices; there is a critical need for effective communication about the impact of choices and judgments that are made, about the basis for those judgments, and about the impacts of those judgments vis-à-vis possible alternatives on the final outcome.</p> <p>For example, it should be made clear that the chief impact on changing the RfD/C from what they would be under default procedures (and from how they were previously characterized) is the invocation of much greater flux through the conjugative metabolic pathway in humans than had previously been estimated. As discussed further elsewhere in these comments, this result is the chief reason that an internal-dose basis for an RfC based on kidney toxicity comes out much lower than if the RfC were based on other endpoints or on applied dose, though this conclusion is not obvious without deep reading of the document and detailed tracing of the calculations. There are reasons to question whether this finding of high human flux through the conjugative pathway is correct (as discussed elsewhere), but any discussion of that question and any documentation of the basis for that conclusion is far removed from its application in a later chapter. The discussion of what pathway, and what measure of that pathway's activity, is best used as an internal dose metric for kidney toxicity is in yet another place, and these conclusions can also be questioned. But again, that discussion (to the extent it exists anywhere) is far removed from its place of application.</p>	AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp. -
APPENDIX A	143	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>It is not clear that DCVC constitutes an appropriate basis for an internal dose metric for kidney non-cancer toxicity.</p> <p>The kidney is seen as a sensitive target, and low RfC values drive the consideration of an overall RfC. The incorporation of internal doses makes the calculated RfC much lower than it would be if based on administered doses. It is therefore critically important that the internal-dose basis of kidney toxicity characterization be correct and reliable. The changes in non-cancer toxicity standards implied by the analyses in the Draft Reassessment hinge largely on assumptions about the PK of internal doses in kidney in rats and humans; and, if these assumptions are wrong, the basis for lowering the RfC is lost.</p>	AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp. Lash, LH; Parker, JC; Scott, CS. 2000. "Modes of action of trichloroethylene for kidney tumorigenesis." Environ. Health Perspect. 108(Suppl. 2):225-240.

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>This being said, there are many questions about the PK assumptions that have been employed. First is the choice of DCVC as the basis for the dose metric. Just because DCVC is used for kidney cancer evaluation does not mean that the same dose measure is appropriate for non-cancer toxicity. Indeed, Lash et al. (2000) describe formic acid as a potential mode of action (MOA) for kidney damage for TCE, distinguishing the case of cancer and non-cancer kidney effects, stating, "Hence, although formic acid formation may contribute to TCE-induced renal damage, this is not likely to be a significant MOA in TCE-induced kidney carcinogenesis" (emphasis added). While the beta-lyase pathway may play a predominant role in kidney carcinogenesis, the possible roles of other chemical actors (formic acid and trichloroethanol) are not adequately addressed. The PBPK modeling effort focuses solely on the products of the beta-lyase pathway and apparently ignores these other possibilities. The conclusions are accordingly dependent on this being the correct dose metric. If alternative pathways could be addressed via the model, this could either provide some support for US EPA's position that they are not relevant or it could show that a different dose metric is warranted. The current argument, i.e., that there are differences in kidney histopathology between TCE- and trichloroethanol-treated rats, and that this indicates a different MOA, is not particularly compelling.</p>	
APPENDIX A	147	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>The document's conclusion that humans have high flux through the conjugative pathway is at odds with previous assessments, and is not well supported by evidence; yet, this assumption markedly lowers RfC/D values compared to those using traditional applied-dose approaches.</p> <p>The consensus of scientific opinion had been that humans have low flux through the conjugative pathway, which would lead to low internal doses to the kidney. It was also the consensus that it is difficult to pin down the extent of flux through this pathway for experimental reasons. The draft reassessment document indicates that the human flux through the conjugation pathway can be concluded to be much greater than in rats. In view of the importance of this judgment to the eventual RfD/C, it must be clearly explained why this altered conclusion is warranted.</p> <p>As stated on page 3-128, the PBPK model reports one to two orders of magnitude more glutathione (GSH) conjugation and DCVC bioactivation in humans relative to rats. US EPA acknowledges that the 95% confidence intervals of the predicted population means for the two species overlap but there is little discussion of how this result is inconsistent with much of the previous data on TCE metabolism and TCE health effects in both humans and animals. For example, Lash et al. (2000) state that metabolic studies of PCE and Compound A indicate greater flux through the beta-lyase pathway in rats compared to humans (i.e., several fold higher in rodents). It would be unusual if TCE were somehow different from these structurally similar compounds such that the flux in humans was many times higher than in rats. Along similar lines, Lash et al. (2007) state that the flux of tetrachloroethylene (PCE) through the GSH pathway is approximately fivefold faster in rodents than that of TCE. They also indicate that the reactive intermediates derived via the beta-lyase pathway from PCE are more reactive than those derived from TCE. This would suggest that PCE should be a much stronger kidney toxicant than TCE in the rat; yet, to our knowledge, neither chemical could be regarded as a very potent nephrotoxicant. For example, in the National Toxicology Program (NTP) and National Institute of Health (NIH) oral bioassays (NTP, 1990; NIH, 1977) toxic nephrosis was observed in rats treated with either chemical and at similar doses. In human studies, neither chemical is consistently shown to be a potent nephrotoxicant (if anything, studies such as that by Henschler et al. (1995) would suggest TCE is more potent). This line of reasoning argues against the primary role of the beta-lyase pathway in PCE/TCE nephrotoxicity, and should be discussed in the document.</p> <p>The basis for finding such large human flux through the conjugative pathway is also questionable. The result comes from the hierarchical Bayesian analysis of the PBPK model. The US EPA PBPK model yields good fits to the rat and human urinary DCVC excretion data and also to S-dichlorovinyl glutathione (DCVG) measured in human blood. We would suggest caution, however, in assuming that just because the model, as formulated and parameterized, fits the available DCVC/DCVG data, that highly quantitative predictions can then be made concerning the mean and variation of the various model parameters. This is particularly of concern given the huge changes resulting from the Bayesian updating of the DCVC bioactivation constants (i.e., from 0.14 to 0.0087 in the rat and from 0.0021 to 0.023 in the human). The basis for the prior is not clear, but what is evident is that something other than direct experimental characterization is driving the updated DCVC bioactivation result, and some direct confirmation that such large flux actually occurs would seem critical to using this result in</p>	<p>AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp.</p> <p>Lash, LH; Parker, JC; Scott, CS. 2000. "Modes of action of trichloroethylene for kidney tumorigenesis." Environ. Health Perspect. 108(Suppl. 2):225-240.</p> <p>National Toxicology Program (NTP). 1990. "Carcinogenesis studies of trichloroethylene (without epichlorohydrin) (CAS No. 79-01-6) in F344/N rats and B6C3F1 mice (gavage studies)." Research Triangle Park, NC. National Institutes of Health. NTP TR 243; NIH Publication No. 90-1779. 174p., May.</p> <p>National Institute of Health (NIH). 1977. "Bioassay of tetrachloroethylene for possible carcinogenicity." Bethesda, MD. National Technical Information Service (NTIS), Springfield, VA. NCI-CG-TR-13; NIH 77-813.</p> <p>Lash, LH; Putt, DA; Huang, P; Hueni, SE; Parker, JC. 2007. "Modulation of hepatic and renal metabolism and toxicity of trichloroethylene and perchloroethylene by alterations in status of cytochrome P450 and glutathione." Toxicology 235(1-2):11-26.</p> <p>Henschler, D; Vamvakas, S; Lammert, M; Dekant, W; Kraus, B; Thomas, B; Ulm, K. 1995. "Increased incidence of renal cell tumors in a cohort of cardboard workers exposed to trichloroethene." Arch. Toxicol. 69(5):291-299.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>so influential a manner.</p> <p>Given the disparity between the model results and prior general scientific opinion about rat vs. human differences in GSH conjugation towards TCE, it would be valuable to use the model to predict what possible DCVC target organ doses would be for some of the key epidemiology studies. The reported prevalence of kidney damage could then be compared across studies for logical consistency with estimated DCVC concentrations. This would serve as a useful "reality check" for a model that is making novel claims regarding chemical toxicity. In any case, a clear and convincing case must be made as to why the previous scientific consensus about human DCVC activation and its estimation is being overturned.</p>	
APPENDIX A	150	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>Reliable estimates of the extent of variability among humans in DCVC activation have not been established, yet this factor is very influential in lowering the RfC/D.</p> <p>It is not only the high estimate of the average amount of human DCVC activation via flux through the conjugative pathway that results in markedly lowered reference values, it is also the calculation of the impact of estimated variability among humans in this rate. Elsewhere in these comments it is argued that the method for considering the impact of inter-human variability is flawed; but, in addition, there is the question of how reliably its extent has been estimated. In the previous comment it was noted that the soundness of the basis for estimating a much-changed average DCVC activation is unclear in view of widely acknowledged experimental difficulties and the evident influence of the Bayesian updating procedure. This concern applies even more to the characterization of variation among individuals, and great care must be taken to avoid attributing to genuine inter-individual variability differences that are really just due to experimental error, which can have marked effects for measurements on single individuals.</p> <p>US EPA notes that the variability in the renal GSH conjugation and bioactivation of DCVC is substantial due to the data set of Lash et al. (1999, as cited in the assessment). The Lash et al. data set, consisting of eight males and eight females in the 100-ppm dose group and five individuals (three males, two females) in the 50-ppm dose group is indeed very limited for characterizing such an important parameter in the model. The stability of any variance estimate drawn from such a small sample size (when developing a model meant to characterize the whole human population) should be viewed as tentative. This has fairly important implications when attempting to use the PBPK model for RfC calculations in ways meant to protect large fractions (i.e., 99%) of the human population. It would also be helpful to show the model predictions as compared to Lash et al.'s results for the 50-ppm dose group (Figure 3-10 only shows the 100-ppm group) to get a better sense of the model's predictive ability at lower exposure concentrations.</p>	AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp. -
APPENDIX A	156	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>There is uncertainty in the PBPK model reflecting a higher DCVC bioactivation in humans than in rodents.</p> <p>In addition, the one p-cRfC that was based on an inhalation study (Woolhiser et al., 2006) was 400-fold lower than the cRfC derived from the applied dose default methodology from the same study. US EPA discusses how this difference is due to a 30- to 100-fold difference between rats and humans in DCVC bioactivation that is reflected in the PBPK modeling, with humans having a higher level of DCVC bioactivation in the model. As discussed above, there is uncertainty in this difference that needs careful consideration before placing such emphasis on this model as the basis of an inhalation RfC. Given that the Woolhiser et al. (2006) study is the only inhalation study in this narrow lower end of the range, this study inherently provides more weight to the proposed RfC than the other four oral studies, and is discussed in more detail below.</p>	AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp. -
APPENDIX A	161	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>Although derivation and consideration of a range of RfCs is a sound approach to deriving an RfC, choosing the lowest range of RfCs (without a sufficient weight-of-evidence evaluation of the RfCs in that range), reflected by only one inhalation study for which the effect of increased kidney weight is questionable, is not strongly supported by the scientific evidence for TCE non-cancer effects. This is based on: (1) the fact that the significance of the observed effect in the Woolhiser study was weak and based on a small sample size; (2) uncertainty in the oral to inhalation route-to-route extrapolation for the five other RfCs in the range; (3) uncertainty in the PBPK model reflecting a higher DCVC bioactivation in humans than in rodents that was used for three of these RfCs; (4) uncertainty in the relevance of increased kidney weight as a critical effect for non-cancer effects of TCE; and finally, (5) the fact that there is another narrow range of six RfCs (from 0.013 to 0.12 ppm) that are all based on inhalation studies and for which, had a level of confidence in those RfCs been presented, might in fact reflect a more robust set of RfCs, base on a weight-of-evidence analysis of those</p>	AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp. -

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				endpoints.	
APPENDIX A	187	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	Lack of sensitivity analyses to identify key data sets and assumptions in models and numerical derivations. The key risk outcomes of the assessment are based on multiple assumptions and data sets. AIA agrees with DOD and NASA that sensitivity analyses are needed to test the effects of these assumptions and to enable evaluation of the most important assumptions.	AUTHOR: Lisa Goldberg -
APPENDIX A	215	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>Lisa M. Sweeney, Ph.D., DABT Toxicology Excellence for Risk Assessment</p> <p>The extensive use of complex modeling in the trichloroethylene (TCE) assessment presents a formidable challenge to scientific peer review. EPA should facilitate peer review by providing an analysis of the most influential assumptions (commonly referred to as a "sensitivity analysis"). Such an analysis would not have to be complex itself, or delay the review of tile draft excessively. However, a sensitivity analysis is necessary to provide a sufficient review of this document.</p> <p>Some key assumptions in the physiologically based pharmacokinetic (PBPK) and dose response modeling in the assessment provide an example of why such an analysis is needed. For example, the assumption of glutathione (GSH) conjugation rate differences between humans and rodents apparently has a several hundred fold effect on the derived values for the inhalation reference concentrations. This assumption appears to be only weakly supported by the weight of the evidence; EPA's own statistical analysis of the related dose metrics also casts doubt on its validity. EPA should use other data in the literature to improve this parameter estimate.</p> <p>Other examples that show tile value of a sensitivity analysis are presented. Please consider the value of providing such an analysis to the Scientific Advisory Board reviewers and provide them with the information they need to conduct a full and scientifically robust peer review of this document.</p>	AUTHOR: Lisa M. Sweeney, Ph.D., DABT -
APPENDIX A	218	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	The comments provided below focus on physiologically based pharmacokinetic (PBPK) modeling, its role in the Agency's assessment of TCE, and the uncertainty regarding the model. Clearly, the Agency has devoted a great deal of effort to developing and applying PBPK models in the TCE risk assessment. The use of Bayesian analysis to integrate a large number of kinetic studies of TCE and its key metabolites, conducted in three species, is a very impressive accomplishment. As the precedents for use of these approaches for PBPK model development and application in risk assessment are limited, it is important that key assumptions and criteria for use in the risk assessment be clearly articulated so that the scientific community can evaluate the modeling of TCE and how it was applied. To that end, we identify the need for sensitivity analyses to identify these key assumptions, such that they may be subjected to proper scrutiny.	AUTHOR: Lisa M. Sweeney, Ph.D., DABT -
APPENDIX A	220	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>WHY IS SCRUTINY OF THE TCE PBPK MODEL IMPORTANT?</p> <p>The use of PBPK model-derived estimates of GSH metabolism as a metric (rather than applied dose) for kidney toxicity had a 300- to 400-fold impact on the cRfC and RID (p. 5-51), after taking into account dose-response and interspecies differences. The use of internal dose metrics is generally preferred over applied dose when the data are sufficient, support the choice of dose metric, and tie the dose metric to the endpoint of interest, because such internal dose metrics are more predictive of the observed toxicity. Although there is not necessarily an inherent problem with dose metrics that differ markedly from applied dose measures, such barge differences call for greater scrutiny of the reasons for the differences, and increase the importance of the consideration of the implications of uncertainties. The use of GSH metabolism (calculated using the PBPK model) as the dose metric for the kidney resulted in kidney effects being identified as one of the key noncancer effects. Intuitively, the 300 to 400-fold difference in the calculated cRfC and cRfD must somehow be related to the values of the parameters in the PBPK model, most likely those pertaining to GSH metabolism, but it is not necessarily clear which parameters arc the key drivers, and whether large interspecies differences in these parameters are supportable based on the available data.</p>	AUTHOR: Lisa M. Sweeney, Ph.D., DABT -
APPENDIX A	223	EPA-HQ-ORD-2009-0791-	Aerospace Industries Association	CONSIDERATION OF CONFIDENCE AND UNCERTAINTIES IN THE CURRENT PBPK MODEL PARAMETER ESTIMATES	AUTHOR: Lisa M. Sweeney, Ph.D., DABT -

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
		0009.1	(AIA)	<p>GSH conjugation pathway rate estimates</p> <p>The extremely broad posterior distributions of the mouse GSH pathway parameters resulting from the Bayesian model optimization (e.g. 2.5% and 97.5% values of 0.1 l and 3,700,000 mg/L, a range exceeding 7 orders of magnitude, for the Km for hepatic TCE GSH conjugation) (p. 3-93) indicate that the parameterization is highly uncertain. The extremely large differences in optimized, posterior estimates of Km for hepatic GSH conjugation in humans vs. rats or mice (approximately 1000-fold difference, based on median values) are contrary to the understanding that similar enzymes are involved in TCE conjugation across species. Since no mouse or rat S-dichlorovinyl glutathione (DCVG) data were used for model calibration and the differences between rodent and human Kms for DCVG production seem implausible, we conclude that the parameterization of the GSH pathway is highly suspect.</p>	
APPENDIX A	225	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>Partition coefficients</p> <p>Data in the literature do not generally support extensive interindividual variability in partition coefficients. For example, when the blood:air partition coefficient of 1,3-butadiene was measured in vitro for 24 human subjects, the values ranged from 1.22 to 1.84, with a mean +/- standard deviation of 1.57 +/- 0.14 (Lin et al., 2002). In contrast, in some cases the posterior distributions of partition coefficients developed in EPA's analyses of TCE and its metabolites cover very wide ranges (p. 3-90). For example, the posterior estimate of the free trichloroacetic acid (TCA) body:blood partition coefficient in the rat had a median value of 0.77 with 2.5th percentile and 97.5 percentile estimates of 0.24 and 2.7, suggesting greater than 10-fold differences to cover 95% of the population. It is unlikely that this parameter is truly this variable, particularly in a standard rat colony, in light of the typically small variability in rats and in the more variable human population. If the posterior distributions of the partitioning parameters are allowed to be more variable than is realistic, it is likely that the optimization process shifted the variability away from other parameters (which could truly be more uncertain and/or variable) in order to create best-fit parameter distributions. As a result, these other parameters could appear more narrowly distributed than they would in the absence of high partition coefficient variability.</p>	AUTHOR: Lisa M. Sweeney, Ph.D., DABT 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.
APPENDIX A	227	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>Oral Absorption Rates</p> <p>The distributions for absorption parameters for corn oil and water gavage (p. 3-92) were highly variable -the ratio of the 97.5% and 2.5% values frequently exceeds 100,000-fold. A likely contributor was inappropriately lumping absorption rate from both cam oil and water into a single distribution, rather than separate distributions.</p> <p>Uncertainty in Calculated Dose Metrics</p> <p>The uncertainty in the parameter values produces uncertainty in the calculated dose metrics. Specifically, the EPA analyses considered dichlorovinyl cysteine (DCVC) bioactivation as a metric for rat kidney effects, while the analyses for mouse kidney effects relied on the dose metric of total GSH produced, due to lack of data on DCVG and DCVC in the mouse. The 95% confidence limits for the population median estimates of the fraction of intake that is conjugated with GSH cover a very large range of values; spanning over 3 orders of magnitude at concentrations and doses of toxicological interest in mice, and spanning about 1.5 orders of magnitude in rats. As noted by EPA, this range reflects only uncertainty, not variability. The DCVC bioactivation estimates in rats are highly uncertain, with the 95% confidence limits on the median spanning a range of 2 orders of magnitude. EPA acknowledges that the predictions related to GSH conjugation for rats and mice "remain more uncertain" than the human predictions (p. 3-131), but then states that GSH metabolism dose metrics were fairly well- characterized in rats (p. 3-138, line 4.). This large uncertainty in the dose metric necessarily translates to uncertainty in the corresponding cRfC and cRfD.</p> <p>The uncertainty of the estimate of "other" liver oxidation is also quite substantial (95% confidence limits approaching a 100-fold range). This uncertainty does not have a substantial impact on the risk assessment because this metric was not used to derive any reference values or slope factors.</p> <p>MODEL PARAMETER ESTIMATES COULD (AND SHOULD) BE IMPROVED USING CURRENTLY</p>	<p>AUTHOR: Lisa M. Sweeney, Ph.D., DABT</p> <p>Chiu WA; Okino MS, Evans MV. Characterizing uncertainty and population variability in the toxicokinetics of trichloroethylene and metabolites in mice, rats, and humans using an updated database, physiologically based pharmacokinetic (PBPK) model, and Bayesian approach. Toxicol Appl Pharmacol. 2009; 241 (1):36-60.</p> <p>Evans MV, Chiu WA, Okino MS, Caldwell JC. Development of an updated PBPK model for trichloroethylene and metabolites in mice, and its application to discern the role of oxidative metabolism in TCE-induced hepatomegaly. Toxicol Appl Pharmacol. 2009; 236(3):329-40.</p> <p>Kim S, Kim D, Pollack GM, Colhns 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.</p> <p>Sweeney LM, Kirman CR, Gargas ML, Dugard PH. Contribution of trichloroacetic acid to liver tumors observed in perchloroethylene (pert)-exposed mice. Toxicology. 2009; 260(1-3):77-83.</p> <p>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.</p> <p>Liao KH, Tan YM, Clewell HJ 3rd. Development of a screening approach to interpret human biomonitoring data on volatile organic compounds: reverse dosimetry of biomonitoring data for trichloroethylene. Risk Anal. 2007; 27(5):1223-36.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>AVAILABLE DATA</p> <p>Data that could potentially improve the estimation of PBPK model parameters, including some of the highly uncertain parameters, are currently available. Some of these data were clearly available to EPA at the time of model development; other data were more recently published, but should certainly be considered at this time to improve the models as described in the IRIS draft and published, peer-reviewed versions of the model (Chiu et al., 2009; Evans et al., 2009).</p> <p>EPA has compared the predictions of the models they used to the following recently published data sets for mice and reported their findings (Appendix A, Section A.6 and linked files).</p> <p>Kiln et al. (2009) provide blood DCVG and DCVC time course data for mice dosed with 2000 mg TCE/kg BW (corn oil gavage). The model (as used in the assessment) consistently underpredicted the blood DCVG data. (DCVC is not currently considered in the model structure.) Best fit parameters for the Kim et al. (2009) study were then developed. These new parameters were then used to estimate the fractional flux through the GSH pathway for mice continuously exposed to TCE via ingestion. It was found that the new, best-fit parameters resulted in a substantially lower fraction of ingested TCE being predicted to be metabolized by the GSH pathway in mice (three-fold lower). Hence, for any oral studies in mice, the potency of any GSH metabolite was likely overestimated by 3-fold, with corresponding underestimates in human cRfDs based on these dose metrics. While EPA may consider the parameters used in the assessment to be "reasonably consistent with the Kiln et al. (2009) data" (p. A-75, line 9); a potential three-fold change in candidate RfDs for a key endpoint deserves to be followed up.</p> <p>EPA also compares the model used in the assessment to additional mouse TCA kinetic data from Kim et al (2009) and data collected by Green (2003) and Mahle et al (2001) that were reported by Sweeney et al. (2009). Some large discrepancies were observed, especially at higher dosages and for females. EPA attributes these discrepancies in part to liver metabolism (assumed negligible in the Sweeney et al. (2009) model); but first pass metabolism does not explain the less-than linear increases in blood TCA observed for increasing drinking water concentration of TCA (Mahle et al., 2001). If anything, the impact of first pass metabolism should decrease with increasing drinking water concentration of TCA.</p> <p>Other model structures could be considered by EPA. The performance of the GSH-related metrics in the rodent models could potentially be improved by consideration of the Kim et al (2009) mouse DCVC blood data and the rat DCVC data of Birner et al. (1997).</p> <p>Another example of how it might be helpful to consider alternate model structures concerns the human data of Chiu et al. (2007). It is disconcerting that the greatest discrepancies between the model and the tested human database were for the Chiu et al. (2007) data. This data set is particularly important because the study involved volunteers exposed to 1 ppm TCE. In contrast, the bulk of the human calibration and validation data were for much higher exposures (40 ppm- 160 ppm). Since the Chiu et al. (2007) exposures were at levels most relevant to current environmental or occupational exposures, it would be desirable for the model to fit the data, and the lack of fit is a concern. It is our assumption that the residual error statistics reported in Appendix A (e.g., Table A-14 on p. A-73 for humans) reflect the discrepancies between the data and the predictions generated from the group-specific distributions of parameters. As such, the group-specific parameter distributions reflect an interpretation of the fit between the data and the model that should provide the least discrepancy -a comparison between the data and the population-based parameters would yield a greater residual error. Clearly, based on a review of both the individual-specific and population-based predictions, the "fit" is worse when the population-based parameters are used instead of the individual-specific parameter values. Despite the ability to generate individual-specific parameter distributions, the discrepancies for the Chiu et al. (2007) data exceed 2.0 (a cut-off value used by EPA to indicate a concern -p. 3-99) for 3 out of 7 measures (highest value was 2.9 for CVen). Chiu et al. (2007) is the only group that had residual error >2 for any measurement. For 5 out of 7 measures, the Chiu et al. (2007) study had the highest residual error. There does not appear to be any reason to exclude the Chiu et al. (2007) data; rather, as previously noted, fit to this study is of particular interest, since it is the only study with measurements in the low-exposure range of interest for environmental and occupational exposures. EPA has also not tested the model against biomonitoring data, which would also test the model at low doses/concentrations.</p>	<p>U.S. Environmental Protection Agency (EPA). (2006) Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment. National Center for Environmental Assessment, Washington, DC; EPA/600/R- 05/043F. Available from: National Technical Information Service, Springfield, VA, and online at http://epa.gov/ncea.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>We recommend that EPA explore the possibility of different model structures that might improve the fit to the Chiu et al. (2007) data without necessarily compromising the fit to the other data. While it does not seem likely that the volunteers in the Chiu et al. (2007) study would be physiologically dramatically different from those in the other 6 groups, some generalizations can be made from the individual specific parameters found in the linked human file for A.5.1. Compared to other individuals/groups, the individuals in the Chiu et al. (2007) study had lower optimized ventilation/perfusion ratios, low blood:air partition coefficients, and low blood flow to slowly perfused tissue but high blood flow to fat and widely scattered values for the slowly perfused tissues: blood partition coefficient. With respect to the biomonitoring data, EPA should consider how the updated model performs with respect to predictions of blood TCE (NHANES data) for the population, given what is known about general populations' exposure to TCE. The approach used could be similar to that used by Liao et al. (2007).</p> <p>MODEL SENSITIVITY ANALYSES THAT COULD (AND SHOULD) BE PERFORMED ON THE EPA TCE PBPK MODEL</p> <p>EPA has not provided any sensitivity analyses of the updated TCE PBPK model. As noted in EPA (2006), "it is important to carry out sensitivity analyses under conditions reflecting the studies providing data for model calibration (i.e., pharmacokinetic studies), under conditions appropriate for estimating dose metrics in critical studies, and finally under conditions appropriate to the risk assessment." To paraphrase, sensitivity analyses are particularly helpful for the following aspects of model evaluation: (1) parameter identifiability, (2) identification of key parameter values with respect to dose metric prediction in test species and (3) identification of key parameter values with respect to dose metric prediction in humans at the toxicity reference value. With respect to (1), parameter identifiability, sensitivity analyses for predictions of experimentally determined dose measures in pharmacokinetic studies indicate whether the available data were in fact useful for "identifying" a parameter value. That is, if no experimentally determined dose measure is sufficiently sensitive to a parameter's value, the data cannot then be said to have contributed to the identification of that parameter's value. Specifically; it is unclear whether the data used in model development allow for unambiguous determination of parameter values for the GSH pathway in mice and rats, in light of the wide confidence limits of the posterior distributions noted above. With respect to (2) and (3), sensitivity analyses of dose metrics used as internal points of departure (iPODs) in rodents and the same metrics in humans help to focus the critical evaluation of the reliability of key parameter estimates that drive the derivation of the toxicity reference values. These analyses are inter-related. The analyses for the iPODs 2 and 3 above can identify which parameters are key in determining the risk values. These risk values are the major conclusions of the report, and understanding the key determinants of uncertainty in the risk values (and the degree of uncertainty in those key determinants) is critical to the credibility and transparency of the calculated risk values. Given the large number of parameters in the model, it is impractical for reviewers to be able to scrutinize all of the parameters or to intuitively know which are "key". Once these "key" parameters are enumerated, the subsequent task is to evaluate whether one is confident that the numerical values of these parameters are reasonably well identified. While the general literature may be consulted for evaluation of anatomical/physiological parameter values, chemical-specific pharmacokinetic parameters are typically inferred from model fit. Hence, the ability to uniquely and conclusively "identify" these parameter values (#1 above) based on the studies available for fitting is necessary for overall confidence in the risk values identified using the models.</p> <p>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.</p> <p>Regarding 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, RID, and a chosen cancer risk level (e.g., 1 in 10⁵) under conditions of continuous exposure. We recommend that these analyses be conducted for the key endpoints (i.e., those from which the risk values were derived) and the candidate RfCs and RIDs that are within approximately 3-fold of the final RfC and</p>	

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>RfD.</p> <p>Without conducting the sensitivity analyses, it is difficult to fully anticipate what the results would be, and how that would change the risk assessment. We can speculate, however, that GSH-pathway-related metrics will likely be sensitive to the Vmax and Km for this particular pathway; and may also be sensitive to the rates for competing pathways. If it is found that none of the metrics in the experimental studies (e.g., chamber TCE concentration, blood TCA concentration) are sensitive to the values used for the GSH pathway, it must then be concluded that the parameters for the GSH pathway are not well identified in rodents, so no reliable estimates of these metrics can be used for the derivation of human equivalent concentrations or human equivalent doses. If that is the case, other risk-relevant intenal doses or a default approach should be used.</p>	
APPENDIX A	235	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>An important consideration, especially when PBPK modeling is to be used, is the choice of dose metric. Assumptions/beliefs about the mode of action are embedded within the choice of dose metric used for dose-response analyses and route-to-route or interspecies extrapolations. Considerations include the use of parent compound vs. total metabolites generated vs. concentrations of specific metabolites, and opting to use peak values, time-weighted average (TWA) values; or cumulative values. For example, why did EPA use TCA produced rather than TWA liver TCA concentration to evaluate the potential dose-response relationship between TCE administration and liver weight increases in mice (Section 4.5)? Until the relationship between TCA and hepatomegaly is properly analyzed, it is premature to assert that TCA is insufficient to account for the rodent liver tumors.</p>	<p>AUTHOR: Lisa M. Sweeney, Ph.D., DABT</p> <p>-</p>
APPENDIX A	247	EPA-HQ-ORD-2009-0791-0012.1	McKenna, Long & Aldrige, LLP	<p>New policy: EPA is...</p> <p>*Using PbPk modeling so extensively has the effect of new policy by the sheer magnitude of its influence in the assessment.</p>	<p>-</p> <p>-</p>
APPENDIX A	257	EPA-HQ-ORD-2009-0791-0012.1	McKenna, Long & Aldrige, LLP	<p>Main messages: Non-cancer findings</p> <p>The new inhalation reference concentrations depend too heavily on assumptions in the PbPk and dose-response modeling</p>	<p>-</p> <p>-</p>
APPENDIX A	258	EPA-HQ-ORD-2009-0791-0012.1	McKenna, Long & Aldrige, LLP	<p>Main messages: Non-cancer findings</p> <p>Assuming higher human production of DCVC is a critical part of the complicated analysis of RfC, RfD, and cancer dose response</p> <p>– It is disputed science and EPA’s analysis appears to show that it does not fit the modeling well</p>	<p>-</p> <p>-</p>
APPENDIX A	267	EPA-HQ-ORD-2009-0791-0012.1	McKenna, Long & Aldrige, LLP	<p>EPA needs to show the effect of their assumptions and modeling choices</p> <p>- The inter-related PbPk and dose-response modeling for multiple endpoints and dose metrics is so complex that even experts have trouble sifting through it.</p> <p>- Even a simple narrative of the most influential assumptions and data sets (and their support) would be helpful.</p> <p>– The narrative does not have to be exhaustive and time consuming.</p> <p>– Scientists at EPA may already know the most sensitive parameters.</p>	<p>-</p> <p>-</p>
APPENDIX B	5	EPA-HQ-ORD-2009-0791-0010.1	ARCADIS on behalf of Deltrex Corporation	<p>The U.S. EPA has stated ...”TCE is characterized as “Carcinogenic to 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 U.S. EPA further states that “the evidence is ‘compelling’ for lymphoma and limited for liver and biliary tract cancers.” This conclusion overstates the results of the meta-analysis. Meta-analysis can be used in a systematic review of epidemiologic data regarding exposure and potential harm. Elements of this analysis should include a clearly stated purpose, careful literature searches, explicit inclusion and exclusion criteria, assessments of study validity and thus bias, and well-articulated definitions and rules of inference for selected causal criteria. The U.S. EPA has made a good attempt to follow these guidelines (Weed 2000; Blair et al. 1995) for the meta-analysis contained in their document, but the discussion in Appendix B is not clear about the U.S. EPA’s criteria</p>	<p>-</p> <p>-</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				for choosing the specific literature. It is equally important for the U.S. EPA to explain the hypothesis under investigation in the meta-analysis. In other words, what is the specific scientific study question to be answered? The U.S. EPA provides a sizable body of literature that may be complete, but the document lacks clarity. Choice of literature must support the basic study question, and criteria to use or exclude specific studies can have a profound effect on the results of the risk assessment. This may be a contributing factor in the U.S. EPA's overreaching interpretation of the data and conclusions.	
APPENDIX C	1	EPA-HQ-ORD-2009-0791-0010.1	ARCADIS on behalf of Deltrex Corporation	To improve the clarity and transparency of the meta-analysis description in this document, a number of basic epidemiology terms need to be defined and their relevance to the meta-analysis provided. At the very least, a glossary of terms should be added with definitions for terms such as case-control study, cohort study, odds ratio, relative risk, causation, strength of association, etc. This is very important because the U.S. EPA's use of epidemiology tools in toxicological reviews is limited, and this document assumes the reader already has a good working knowledge of epidemiology.	- -
APPENDIX C	28	EPA-HQ-ORD-2009-0791-0010.1	ARCADIS on behalf of Deltrex Corporation	The human epidemiology studies reviewed in this assessment exhibit external inconsistency relative to each other and internal inconsistencies relative to their own study subgroups. While meta-analysis provides a more formal statistical approach to the criterion of consistency, both internal consistency and external consistency are important. For instance, Do the increases in risk occur in the categories of exposure when expected and in all the subgroups where expected? Or do the results of the various studies provide the same or consistent results? The same or similar results in several studies add support to arguments concerning causality. However, the strength of each study should be individually taken into account. Often negative studies do not get published, so several studies suggesting a weak association do not automatically lead to acceptance of causation.	- -
APPENDIX C	280	EPA-HQ-ORD-2009-0791-0014.1	Exponent Health Services	<p>EPA's meta-analysis methods and summaries, for the most part, are consistent with recent published summaries of this literature – however, EPA's interpretation of the meta-analysis findings is not consistent with the general approaches used in evaluating causality from epidemiologic research study evaluation. Epidemiologic causal evaluation considers not only the presence of a statistical association, but also the strength of that association, whether exposure response trends are present, the consistency of study findings, biologic plausibility, coherence, and other factors (Hill 1965; Weed 2005). Although EPA considers these factors, their conclusions are not supported once these factors are applied to the epidemiologic literature. The epidemiologic literature on TCE exposure and cancer cannot be categorized as “strong” or “robust” or of sufficient quality to provide definitive evidence of a causal association between TCE exposure and cancer. The observed summary relative risk estimates from the meta-analyses of kidney cancer, liver cancer, and non-Hodgkin's lymphoma (NHL) are not sufficiently strong to be able to rule out other potential explanations such as bias due to confounding, exposure misclassification, or other factors (e.g. selection bias in case control studies). The consistency of the findings is not as robust as characterized in the EPA review. For example, in the kidney cancer analyses, the evaluation of cohorts defined from biomonitoring data, a source of exposure information considered more accurate than other exposure assessment characterizations, found no association with kidney cancer. Although these studies were small, these results merit consideration. In addition, several large cohort studies of aerospace/aircraft maintenance workers (e.g. Radican et al. 2008; Boice et al. 1999) reported no association between TCE exposure and kidney cancer. The EPA review recognizes the significant limitations of several German studies of TCE exposure and kidney cancer (e.g., Henchler et al., Vamvakas et al.) and did not include them in their meta-analysis summaries; a decision consistent with a recently published meta-analysis of TCE and kidney cancer (Kelsh et al., 2010). In summary, it is important to emphasize that the magnitude of the summary estimate in the EPA meta-analysis of kidney cancer was modest (relative risk =1.25). Furthermore given the range and imprecision of the individual study findings, with many studies reporting no increased risks, it is more accurate to report the study results as “mixed” rather than consistent or robust.</p> <p>In the latest EPA Toxicological Review of TCE, it is apparent that many of the issues and concerns raised in the methodological review of the inter-agency draft with respect to the metaanalysis of epidemiologic studies of TCE exposure and cancer of have been addressed. However, some important matters remain, particularly regarding the interpretation of the currently available epidemiologic evidence. In the widely read textbook Modern Epidemiology (Rothman, Greenland and Lash 2008), Greenland and O'Rourke describe the two main goals of meta-analysis: to estimate differences among study-specific effects (analytic goal) and/or to estimate an average effect across studies (synthetic goal). They further remind readers that “a sound meta-analysis needs to assess each study's limitations as well as gaps in the entire literature being assessed.” Thus, while a meta-analysis may serve as a valuable tool for analyzing data across a large body of scientific studies to produce a</p>	<p>-</p> <p>Boice JD, Jr. et al. Mortality among aircraft manufacturing workers. <i>Occup. Environ. Med.</i> 1999;56:581-97.</p> <p>Hill AB. The Environment and Disease: Association or Causation? <i>Proc R Soc Med</i> 1965; 58:295-300.</p> <p>Kelsh MA, Alexander DD, Mink PJ, Mandel JH. Occupational trichloroethylene exposure and kidney cancer: a meta-analysis. <i>Epidemiology.</i> 2010 Jan;21(1):95–102.</p> <p>Lash TL. Bias analysis applied to Agricultural Health Study publications to estimate non-random sources of uncertainty. <i>J Occup Med Toxicol.</i> 2007 Nov 26;2:15.</p> <p>Radican L, Blair A, Stewart P, Wartenberg D. Mortality of aircraft maintenance workers exposed to trichloroethylene and other hydrocarbons and chemicals: An extended follow-up. <i>J Occup Environ Med</i> 2008; 50(11): 1306–19.</p> <p>Weed DL. Weight of Evidence: A Review of Concept and Methods. <i>Risk Analysis</i>, Vol. 25, No. 6, 2005.</p> <p>Alexander DD, Wagner ME. Benzene exposure and Non-Hodgkin Lymphoma: A meta-analysis of epidemiologic studies. <i>J Occup Environ Med</i> 2009, in press.</p> <p>Alexander DD, Mink PJ, Mandel JH, Kelsh M. A meta-analysis of occupational trichloroethylene exposure and multiple myeloma or leukemia. <i>Occup Med (Lond)</i> 2006; 56(7):485–493.</p> <p>Kelsh MA, Alexander DD, Mink PJ, Mandel JH. Occupational trichloroethylene exposure and kidney cancer: a meta-analysis. <i>Epidemiology.</i> 2010 Jan;21(1):95–102.</p> <p>Mandel JH Kelsh MA, Mink P, Alexander DD. Occupational trichloroethylene exposure and non-Hodgkin's lymphoma: a meta-analysis and review. <i>Occup. Environ. Med.</i> 2006;63:597–607.</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>more precise estimate of relative risk, interpretation of summary findings should be made in consideration of several important methodological factors (e.g. exposure misclassification, confounding and selection bias) and guidelines for evaluation of causality based on epidemiologic data (Hill 1965; Weed 2005). Indeed, meta-analysis and causal inference are separate endeavours with different methods.</p> <p>Most epidemiologic studies of TCE exposure and cancer observed associations that were not statistically significant and most studies lacked quantitative exposure assessments. Across epidemiologic studies, different exposure metrics were used, exposure-response patterns were inconsistently observed, and uncontrolled (or incompletely controlled) confounding and other sources of systematic error likely influenced effect estimates. EPA conducted various sensitivity analyses (excluding individual studies to assess their impact on summary relative risk estimates); however, important evaluations such as summarization by sub-group characteristics, study design differences, or findings by exposure measurement method were not presented or fully considered. It is unfortunate that EPA did not conduct exposure-response analyses by specific exposure metrics, such as cumulative dose or years of exposure. Because “dose-response” is an important consideration in the evaluation of epidemiologic studies for causality, we evaluated exposure-response data to the extent possible in our published meta-analyses and observed no clear pattern of increasing cancer risk with increasing exposure level or duration (Kelsh et al 2010; Mandel et al 2006; Alexander et al. 2007; Alexander et al., 2006). Such an analysis by EPA would provide helpful information in the consideration of potential relationships between TCE and cancer. In summary, although EPA conducted a comprehensive meta-analysis and examined many issues in the epidemiologic data, EPA’s conclusions regarding the carcinogenicity of TCE are not supported by the studies they cite.</p>	
APPENDIX C	290	EPA-HQ-ORD-2009-0791-0014.1	Exponent Health Services	<p>Specific Comments to EPA Meta-Analysis of Epidemiologic Studies</p> <p>A meta-analysis is a systematic methodological and statistical technique for combining results data across individual studies to produce a more precise “weighted” estimate of relative risk. An equally important function of a meta-analysis is in evaluating potential heterogeneity. Heterogeneity reflects unexplained variation between study results, and a meta-analysis that has significant heterogeneity may not be a valid quantitative summarization of studies (Greenland). Heterogeneity may be the result of differences in study design, measurement techniques, patterns of associations by exposure level or occupational group, underlying differences in health susceptibility in the study populations, or other characteristics. A single meta-analysis model will not indicate the exact source of heterogeneity; rather, it is necessary to conduct a variety of sensitivity analyses by important factors such as intensity or duration of exposure, where applicable. Moreover, even if statistical heterogeneity is not indicated by p-value testing, between-study variability may be present. Thus, relying upon a p-value for heterogeneity in a meta-analysis may provide a false sense of consistency across the literature. To prevent this, sub-group analyses by similar exposure characteristics or other factors should be examined.</p> <p>A meta-analysis cannot answer all facets of causality between an exposure and disease, nor is it intended to do so, but it can clarify or augment the existing literature on any potential associations between an exposure and outcome. As such, a meta-analysis can be considered a type of weight-of-evidence approach to evaluate a body of literature (Weed 2005). A metaanalysis of epidemiologic observational data is subject to the inherent biases and methodological limitations from the original studies that gave rise to the summary associations observed in metaanalyses.</p> <p>Therefore, interpretation of meta-analysis findings should be done in consideration of the strengths and weakness of the underlying studies.</p>	<p>- Weed DL. Weight of Evidence: A Review of Concept and Methods. Risk Analysis, Vol. 25, No. 6, 2005</p>
APPENDIX C	293	EPA-HQ-ORD-2009-0791-0014.1	Exponent Health Services	<p>The p-values for heterogeneity are not presented across the meta-analyses in Appendix C. It is indicated that no heterogeneity was observed, however, the specific quantitative information is not presented for the reader. These data should be reported.</p>	<p>- -</p>
0	47	EPA-HQ-ORD-2009-0791-0007.1	Natural Resources Defense Council	<p>February 1, 2010</p> <p>Comments from the Natural Resources Defense Council and supporters on the Draft Toxicological Review of Trichloroethylene: In Support of the Summary Information in the Integrated Risk Information System (IRIS)</p>	<p>- -</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
			(NRDC) and Supoprters	<p>(External Review Draft, EPA/635/R-09/011A) Docket ID No. EPA-HQ-ORD-2009-0791</p> <p>These comments supported by:</p> <p>Sarah Anker, Executive Director, Community Health and Environment Coalition Mt. Sinai, NY Terrie Barrie, Founding Member Alliance of Nuclear Worker Advocacy Groups, Craig, CO Mike Belliveau, Executive Director, Environmental Health Strategy Center Kathleen Burns, Ph.D. Sciencecorps Lexington, MA Chris Borello – President, Concerned Citizens of Lake Twp. (CCLT)/ Uniontown IEL Superfund Site, Ohio Judy Braiman, President, RAMP perc (Rochesterians Against the Misuse of Pesticides) John G. Buddy Andrade, Old Bedford Village Development, Inc., New Bedford, MA Stephen Brittle, Don't Waste Arizona, Phoenix, AZ Kathleen A. Curtis, LPN, Policy Director, Clean New York Jim Davis, President, Veterans-For-Change Ken and Regina Deschere, Ithaca South Hill Industrial Pollution, Ithaca, NY</p> <p>J. M. Ensminger, ATSDR, Camp Lejeune Community Assistance Panel member Amanda Evans, Victims of TCE Exposure...A Lasting Legacy, Hillsboro, Oregon Neil Fischbein, The TCE Blog Jon Goodman, People for clean Air and Water, Collegeville, PA Debra Hall, Founder, Hopewell Junction Citizens for Clean Water, Hopewell Junction, NY Eugene J. Halus, Jr. Ph.D., Professor, Immaculata University and Resident of Perkiomen Township, Montgomery County, PA Rick Hind, Greenpeace USA Dona Hippert, Oregon Toxics Alliance Lin Kaatz Chary, PhD, MPH, Indiana Toxics Action, Gary, IN Pam Miller, Alaska Community Action on Toxics, AK Mark A. Mitchell M.D., MPH, President, Connecticut Coalition for Environmental Justice Robert J. O'Dowd, El Toro Marine Veterans Devawn Oberlender, Citizen-North Indian Bend Wash superfund cite in Scottsdale AZ Gail Shephard, Representing Injured Workers From exposure at the former NASA/Boeing Industrial Plant, Downey, CA Lenny Siegel, Center for Public Environmental Oversight Lynn Thorpe, Clean Water Action Mike Wright, Director, United Steelworkers, Health, Safety & Environment Dept</p>	
0	48	EPA-HQ-ORD-2009-0791-0007.1	Natural Resources Defense Council (NRDC) and Supoprters	<p>EPA announced the release of its draft Toxicological Review of Trichloroethylene (FR Notice, Nov 3, 2009), for public comment. EPA provided the following background information on its website: “The draft Toxicological Review of Trichloroethylene (TCE) provides scientific support and rationale for the hazard and dose-response assessment pertaining to chronic exposure to TCE. TCE is a chlorinated solvent that has been widely used as a metal degreaser, as a chemical intermediate and extractant, and as a component of some consumer products. TCE is designated as a Hazardous Air Pollutant, is a common groundwater contaminant, and has been found at more than 1,500 hazardous waste sites. TCE enters the atmosphere from vapor degreasing operations or volatilization from contaminated soils, surface waters via direct discharges, and groundwater through leaching from disposal operations and hazardous waste sites. In addition, TCE can be released to indoor air from the use of TCE-containing consumer products, volatilization from water supplies, and vapor intrusion through walls and floors from contaminated soil and groundwater.”¹</p>	<p>-</p> <p>1. EPA NCEA. IRIS Toxicological Review of Trichloroethylene. http://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=215006</p>
0	64	EPA-HQ-ORD-2009-0791-0018.1	Halogenated Solvents Industry Alliance, Inc.	<p>EPA is to be congratulated for comprehensively covering the extensive literature relating to trichloroethylene (TCE) epidemiology and toxicology. Unfortunately, the review of the large amount information has, too often, been unbalanced with study results selected to support an EPA position without due consideration of contradictory evidence. In all cases where the end-point is significant, EPA should give equal weight to evidence, pro and con. What follows are comments on several of the more significant endpoints with detailed comments provided by Prof. W. Dekant. A separate submission includes a version of the draft IRIS document showing annotations by Prof. Dekant. Dr . Rhomberg provides a series of concerns, both general and specific, regarding the derivation of RfC and RfD values.</p> <p>One approach that EPA could have used to organize and analyze data to aid interpretation would have been to employ the type of framework recommended by IPCS and ILSI. The framework approach is ideal for assessing mode of action, but other complex issues can often be addressed in this manner also.</p>	<p>AUTHOR: Paul H. Dugard, Halogenated Solvents Industry Alliance, Inc.</p> <p>-</p>
0	129	EPA-HQ-ORD-2009-0791-	Halogenated Solvents Industry	<p>Public Comments on US EPA</p> <p>Draft Trichloroethylene Assessment</p>	<p>AUTHOR: Lorenz Rhomberg, PhD, FATS, Gradient Corp.</p> <p>-</p>

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
		0018.1	Alliance, Inc.	<p>Docket ID No. EPA-HQ-ORD-0791</p> <p>Prepared by: Lorenz R. Rhomberg, Ph.D., FATS</p> <p>1 February 2010</p> <p>Submitted via Email to ORD.Docket.epa.gov</p> <p>Re: Docket ID No. EPA-HQ-ORD-2009-0791; Public Comments on US EPA Draft Trichloroethylene Assessment</p> <p>In accordance with the announcement in 74FR56834, I am pleased to present the following public comments on the United States Environmental Protection Agency (US EPA) "Draft Toxicological Review of Trichloroethylene: In Support of the Summary Information in the Integrated Risk Information System (IRIS)" [EPA/635/R-09/011A, dated October 2009]. I am writing as a Principal at Gradco LLC d/b/a Gradient, an environmental sciences consulting firm headquartered in Cambridge, MA. My comments are my own, but the effort to compile them was supported by the DuPont Corporate Remediation Group. These comments are intended for Docket ID No. EPA-HQ-ORD-2009-0791.</p> <p>I write as a former US EPA employee who has worked on earlier assessments of this chemical while at the agency, and as a former academic who did dose-response analysis on trichloroethylene (TCE) animal bioassay data under contract to US EPA. I have also presented public comments on earlier assessment documents on behalf of a variety of clients.</p>	
0	180	EPA-HQ-ORD-2009-0791-0017.1	Michael Partain	<p>I applaud the EPA's proposal to classify TCE as a known human carcinogen but I temper my concern with what I and many others feel is a questionable review process which is open to subversion by special interest. Our EPA is a holder of the public trust. We in the general public do not have the scientific training and knowledge to discern what substances may or may not be hazardous to our health. Instead we rely on our EPA to intercede and protect us from hidden dangerous in our environment.</p> <p>One of our concerns is the inclusion of nominees to the EPA's SAB who have ties to special interest and or industry. Tougher EPA requirements on TCE will translate into increased fiscal responsibility for the polluters and users to clean up and address their liabilities to the environment and people harmed by TCE. This fact is a significant motivator for special interest to block, manipulate and obfuscate any science or attempts to regulate TCE. The EPA must be extra vigilant to weed out any and all attempts to subvert their work or delay it to the point of harm to the general public.</p> <p>As we all know, TCE and other VOCs are contaminants found all over the country, especially in our groundwater. In many instances, as in my case, our exposures go unnoticed and in essence we become a ticking biological time bomb. In my case, my "time bomb" exploded in 2007 after I was diagnosed with male breast cancer at the age of 39.</p> <p>The debate over TCE has been elongated for over 30 years now, for example "In November 1979 the EPA stated that long term exposures to mice to TCE produced carcinogenic effects in both male and female animals. In addition to the carcinogenic effect, TCE has been reported to be mutagenic.</p> <p>The purpose of the listening session is to allow members of the public to comment on the EPA's work. I note that in the meeting today industry and users of TCE are well represented. My question to the EPA is why are these meetings limited to Washington DC? Why not provide travel in lodging for members of the public or spread them out in key regions of the country? As you can see, industry does not appear to have such problems. We the public do not have the luxury of a centralized office in DC or funding to fly in to DC for our presentations.</p> <p>One thing I wish to point out to the EPA concerning their work on chemicals such as TCE. Your risk assessments are based on adult exposures. What about the children? What about in-utero babies such as myself.</p>	-

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>Why isn't the EPA assessing exposures at the most critical phase of a person's development?</p> <p>I believe unusual cancers such as male breast cancer are our warning that we are affecting the environment through past and present improper use and disposal of chemicals such as trichloroethylene. What are we doing to ourselves and our future generations? What legacy will we leave for our children?</p>	
0	181	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	<p>The Aerospace Industries Association (AIA) represents the nation's leading manufacturers and suppliers of civil, military, and business aircraft, helicopters, unmanned aerial vehicles, space systems, aircraft engines, missiles, materiel, and related components, equipment, services and information technology. AIA represents more than 275 member companies. Many of our members were engaged in degreasing operations that employed the solvent trichloroethylene (TCE) at their facilities. Due to their past usage of TCE, AIA members have a significant interest in ensuring that the Environmental Protection Agency's Integrated Risk Information (IRIS) assessment of TCE reflects a comprehensive assessment of the relevant science....</p> <p>...We request the agency revise the draft IRIS TCE assessment to reflect these comments.</p> <p>We appreciate your consideration of our comments. If you have any questions regarding these comments, please contact me either by phone (703) 358-1050, or e-mail (lisa.goldberg@aia-aerospace.org). Lisa Goldberg, Director, Environment, Safety and Health Aerospace Industries Association</p>	AUTHOR: Lisa Goldberg -
0	189	EPA-HQ-ORD-2009-0791-0009.1	Aerospace Industries Association (AIA)	Pages 3 through 18, "EPA Toxicological Review of TCE: Comments on Epidemiology -Draft February 1,2010" see comment EPA-HQ-ORD-2009-0791-0014.1 for coding.	- -
0	237	EPA-HQ-ORD-2009-0791-0016.1	Jerome M. Ensminger	<p>Statement of Jerome M. Ensminger 61 Hunter's Run Elizabethtown, N. C. 28337</p> <p>Good morning, my name is Jerry Ensminger and I spent 24 and a half years serving our nation in the United States Marine Corps. I want to take this opportunity to thank the EPA for holding this listening session concerning the selection of members to your SAB to review the latest version of your risk assessment of the chemical trichloroethylene (TCE).</p> <p>I, as well as many other victims of the chemical TCE, have a personal interest in the selection process. Our drinking water at Camp Lejeune was contaminated with documented levels of TCE at 1,400 ppb. There was a recent report released by the National Research Council which for the most part stated that we were not harmed by our exposure to TCE even at these high levels. If this situation wasn't such a serious issue, I would find it almost comical that there are two signatories of that NAS/NRC report now under consideration to serve on the TCE SAB. How can that be possible? These two individuals have recently placed their names on a report that basically said that fetal and child exposures to 1,400 ppb of TCE weren't harmful. You have several other nominees for this TCE SAB who have for many years made a very comfortable living opposing reports and studies conducted by regulatory agencies and public health organizations. What has happened to the conflict of interest policies in our world of science? IARC recognized that their panels/committees were being infiltrated by representative of special interest groups which was severely damaging the reputation and work product of that organization. IARC in turn took drastic and sweeping steps to strengthen their conflict of interest polices and reclaim their strong reputation. Isn't it time for the USEPA and the National Academy of Sciences to follow suit? The mere fact that several of the special interest nominees are still on the list as candidates to serve on this TCE SAB is testimony in itself that EPA has yet to correct this problem.</p> <p>My daughter Janey was the only one of my four children to have been conceived and/or carried while being exposed to this contaminant at Camp Lejeune. When Janey was six years old, she was diagnosed with ALL and while she fought a valiant battle against her malignancy she ultimately lost the war. Janey died shortly after her ninth birthday on 24 September 1985, she suffered greatly!</p> <p>You will undoubtedly hear from many representatives of special interest groups throughout this process. Their</p>	- -

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
				<p>message will be the same, "you can't prove that these chemicals are harmful, therefore we shouldn't strengthen the regulatory standards for them." I constantly hear these claims from the special interest representatives but I will wager that not one of them making that claim would want 1 ppb of this chemical in their personal tap water or that of those closest to them.</p> <p>This listening process isn't fair. It heavily favors special interests with the financial means to travel to Washington, or who can hire a lawyer with an office on K Street. What about the citizens who can't afford to come to Washington every week? How is the process fair to us?</p>	
0	242	EPA-HQ-ORD-2009-0791-0019.2	Patton Boggs LLP	<p>"Contaminated Water Supplies at Camp Lejeune: Assessing Potential Health Effects"</p> <p>This document is not available in Regulations.gov since it is a copyrighted publication and may not be reproduced without consent of the copyright holder.</p> <p>Contact the EPA Docket Center, Public Reading Room to view or receive a copy of this document. Requests for copies may be made as follows:</p> <p>In person/writing: Environmental Protection Agency, Docket Center 1301 Constitution Ave NW, 2822T, Room 3334 Washington, DC. 20004</p> <p>Telephone: 202-566-1744 Fax: 202-566-9744 Email: docket-customerservice@epa.gov</p>	-
0	244	EPA-HQ-ORD-2009-0791-0012.1	McKenna, Long & Aldrige, LLP	<p>TCE is a flagship EPA regulatory toxicity assessment</p> <p>The assessment is considered "flagship" in the sense that it presents cutting edge approaches to regulatory risk assessment and policy.</p> <p>However, *It is a complex mix of new data and policy that are difficult to tease apart. *It takes on too much at once and, therefore, it may not stand the test of time. *Specific changes are needed to make it last.</p>	-
0	250	EPA-HQ-ORD-2009-0791-0012.1	McKenna, Long & Aldrige, LLP	<p>Main messages: Cancer findings</p> <p>*To be lasting the TCE assessment should be reviewed as carefully as EPA policy in a policy-review setting.</p>	-
0	270	EPA-HQ-ORD-2009-0791-0012.1	McKenna, Long & Aldrige, LLP	<p>Please...</p> <p>to make... this assessment a lasting one</p> <p>... Give the SAB ample time to hear and consider science comments from experts.</p> <p>– Five minutes per expert is not enough for a sufficient and transparent review of something this complex.</p> <p>... Help SAB sort through the complexity. Provide a road map that identifies influential data and model assumptions that drive the conclusions.</p> <p>... Clearly separate the review of science by scientists from the review of new policy in this assessment.</p> <p>... For transparency and to prevent process objections:</p> <p>– Show how last year's interagency science comments were addressed.</p> <p>– Let the National Academy of Sciences' National Research Council committee respond to EPA's response to their 2006 report.</p>	-

TCE Chapter	Excerpt ID	Submission ID	Organization	Excerpt	Excerpt Notes, References, and/or Graphics
0	302	EPA-HQ-ORD-2009-0791-0013.1	Environmental Protection Bureau, New York State Office of the Attorney General	Ma, Jing, Lawrence Lessner, Judith Schreiber, and David Carpenter. "Association between Residential Proximity to PERC Dry Cleaning." Journal of Environmental and Public Health. 2009. (2009): 7. Print.	- -