

TCE Meeting Presentation: Supporting Material for M. Kelsh
Paul Dugard
to:
Marc Rigas
05/03/2010 09:09 PM
Please respond to Paul Dugard
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Dear Dr Rigas:

Please find material attached that M. Kelsh will use as the basis of his presentation on TCE epidemiology on May 10.

This analysis has been abstracted from the comments submitted by the Aerospace Industries Alliance during the public review of the IRIS draft. The original may be found in the docket but it is supplied "stand alone" for the convenience of the panel members.

Thank you.

Paul Dugard



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**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**

Summary:

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 dose-response 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 40% 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.”

Comments

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 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.

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., Henschler 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.

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 meta-analysis 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.

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.

Use of Epidemiologic Data for Quantitative Cancer Risk Assessment

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.

Specific Comments on Use of Charbotel et al. 2006 Study for Dose Response Modeling in EPA's External Review Draft of Trichloroethylene

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].

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:

- **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 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.

- **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 screw-cutting 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 hospital-based 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 is 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.

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 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)).

Specific Comments to EPA Meta-Analysis of Epidemiologic Studies

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.

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 meta-analysis 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 meta-analyses. Therefore, interpretation of meta-analysis findings should be done in consideration of the strengths and weakness of the underlying studies.

Specific Comments Pertaining to the EPA Report and Appendix C:

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. Kelsh et al. (2010) conducted a comprehensive meta-analysis of epidemiologic cohort and case-control studies of TCE exposure and kidney cancer. This comprehensive meta-analysis 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 dose-response by specific exposure metric. In addition, the methodological and analytical considerations of evaluating TCE and kidney cancer are fully discussed.
- 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).
- 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.

- 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.

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 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).

Liver Cancer

- 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.

References

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.

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.

Axelsson, 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.

Hill AB. The Environment and Disease: Association or Causation? *Proc R Soc Med* 1965; 58: 295-300.

Kelsh MA, Alexander DD, Mink PJ, Mandel JH. Occupational trichloroethylene exposure and kidney cancer: a meta-analysis. *Epidemiology*. 2010 Jan;21(1):95–102.

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.

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.

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

Weed DL. Weight of Evidence: A Review of Concept and Methods. *Risk Analysis*, Vol. 25, No. 6, 2005