HSIA halogenated solvents industry alliance, inc.

Toxicological Review of Trichloroethylene (TCE) in Support of the IRIS Database (draft of October 2009)

Comments Submitted by HSIA for Consideration by the EPA Chartered Science Advisory Board in Connection with the Quality Review (December 15, 2010) of the TCE Panel's Draft Review of the Draft IRIS Toxicological Assessment

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Topic: Numerical Outcomes of the Draft IRIS Assessment

The Halogenated Solvents Industry Alliance, Inc. (HSIA) submits the following comments for consideration by the Chartered Science Advisory Board (SAB) in connection with its quality review of an SAB draft review of EPA's draft IRIS assessment of trichloroethylene (TCE) to take place on December 15. HSIA provides these comments in addition to those addressing cancer classification submitted in a separate document. This analysis addresses issues that relate directly to the numerical outcomes of the IRIS assessment – RfC, RfD and unit risks for cancer. These values will factor into major regulations and play a part in determining where, and to what extent, cleanup of TCE contamination will be required. It is important that the most reliable basis for deriving these values be established.

Kidney Toxicity, Glutathione Conjugation and Extrapolation from Rodents to Humans

The Panel considers that the products of TCE metabolism via the glutathione (GSH) conjugation pathway may play a part in both cancer and non-cancer responses in the rodent kidney. Ideally, PBPK modeling of this pathway would provide a means of quantitative extrapolation from rodents to man. There are, however, substantial uncertainties regarding the production of DCVG from TCE (an early stage in the route to the generation of biologically active products in the kidney) in the human. This is discussed in detail by the Panel in a response to Charge Question 3. Non-Cancer Hazard Assessment, Section 3b. *The Kidney*. The key concern is that a poor analytical technique employed by Lash et al (1999) to assess DCVG in the blood of human volunteers indicated production of DCVG to be many fold greater in man than rodents. Studies *in vitro* employing sophisticated analytical procedures (Green et al 1997) indicated a much lower rate of production in human liver (primary location for DCVG production). The concern regarding the Lash et al. HPLC approach is one of correctly identifying a small

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peak amongst many much larger peaks (discussed by Prof. Wolfgang Dekant in public comments on the draft IRIS assessment submitted to EPA by HSIA in January 2010). The choice of the extent to which humans generate DCVG has a dramatic effect on the outcome of the quantitative extrapolation of kidney effects from rodents to man. This is recognized by the Panel and the Lash versus Green problem is referred to in responses to Charge Question 5. Role of Metabolism on TCE Toxicity. Section 5c. *Role of GSH-Conjugation Pathway on TCE-Induced Kidney Effects,* Charge Question 6. Mode of Action, Section 6a. *Hazard Assessment and Mode of Action,* Charge Question 8. Non-Cancer Dose Response, Section 8c. *The Selected PBPK-based dose metrics for inter-species, intra-species, and route-to-route extrapolation, including the use of body weight to the ¾ power scaling for some dose metrics* and Section 8c (relating to choice of studies) The issue is also fundamental in the response to Charge Question 9. Cancer Dose-Response Assessment in which the Panel expresses a strong preference for calculations based on epidemiology rather than kidney tumor incidence in rats.

The Panel in response 5c, with reference to the DCVG production uncertainties, states: "Given the difficult task of drawing conclusions from such different results, the conservative approach the EPA has taken is defensible from a public safety policy perspective. From a strictly scientific perspective however, at a minimum, such large literature disparities call for a more complete discussion of the strengths and limitations of the analytical methodologies used than what is described in the review." The recommendation that follows is: "The discussion of how each of the in vitro and in vivo data sets were used to estimate DCVG formation parameters for the PBPK model should be more transparent indicating strengths and weaknesses in the database." The recommendation for "A more complete discussion of the strengths and limitations of the analytical methodologies used should be provided to address the large discrepancies in estimates of DCVG formation." carries over to the Executive Summary.

Comment: The Panel should have recognized that more evidence than simply the contrast between analytical techniques can be called upon to assess whether the Lash et al or Green et al data set is more reliable. Because of the importance of the extent of formation of DCVG, the recommendation should have required a full evaluation by EPA taking into account biological and biochemical evidence and the advice that good science should govern which data are used in PBPK modeling if one set of information is clearly more reliable.

Use of Charbotel et al (2006) for Cancer Dose-Response Assessment and Unit Risks from Animal Data

A. Charbotel et al (2006)

In response to Charge Question 9. Cancer Dose-Response Assessment, Section 9a. *Estimation of Unit Risks for Renal Cell Carcinoma*, the Panel makes some pertinent observations and recommendations regarding the specifics of using data from the Charbotel et al (2006) case control study. These concerns notwithstanding, the Panel supported the use of data from this study for calculating unit risk values. The Charbotel et al study appears to provide a dose response relationship for calculation of unit risk for human renal cancer with numerical estimates of exposure. It is the reliability of these estimates of exposure that are of concern. The NAS Committee that reviewed the draft IRIS assessment released in 2001 stated firmly in a report released in 2006 that none of the epidemiology studies available at that time should be used for the calculation of unit risk values. The primary concern was the uncertainty of exposure classification and assessment. At first sight, the Charbotel et al (2006) study and its companion paper describing methods used to assess exposure (Fevotte et al, 2006) appear to offer a greatly improved exposure assessment. Unfortunately, the exposure assessment is not as robust as it might seem:

1. The study was not designed to provide data for a calculation of unit risk, only to provide bands of exposure levels for use within the epidemiology study.
2. The exposure assessment was based on questionnaires and expert judgment, not direct measures of exposure. Standard assumptions were applied to the nature of the equipment used.
3. The main exposed workers were "screw cutters" and the criteria were clearly defined for estimating exposure. However, the highest exposure group included a significant number of other occupations and the criteria applied are not clear and thus the reliability of the assessment is unknown.
4. Expert reviewers of the original draft report (incorporating material reported in Fevotte et al and Charbotel et al plus some additional information on exposures) expressed concern about the unjustified precision in the exposure estimates. The report and subsequent papers were not amended.
5. The authors concluded that the study "…shows a possible link between high levels of exposure and increased renal cell carcinoma…" or "….suggests an association….", which do not indicate the existence of a robust relationship for dose-response assessment.
6. Charbotel et al found evidence of confounding from cutting fluid exposure. Unfortunately, TCE and cutting oil were co-exposures that could not be disaggregated and

the majority of the TCE exposed population, the screw cutters, could be expected to experience similar patterns of exposure for both TCE and cutting fluids (probably in aerosol form). Thus the apparent dose response relationship for TCE could be wholly, or in part, the result of exposure to cutting fluids.

7. EPA, in the current draft assessment, acknowledges that the incidence versus dose data from Charbotel et al is "imprecise" and restricts the dose-response to a linear regression.

Comment: The Panel clearly had some concerns regarding the use of Charbotel et al data and the manner of calculating unit risks from them. The recommendations made are a step in the right direction but the use of this study must be rigorously justified by EPA before it can be considered sufficiently robust to drive the type of regulations and decisions based on unit risk. The evidence shows that this study should not be used as the source of a "preferred" unit risk. The opinion of the NAS committee in 2006 continues to apply and unit risks for TCE based on epidemiology should only be used for comparisons with those derived from animal studies.

B. Unit Risks from Animal Data

If Charbotel et al is rejected as the source of preferred unit risks, additional concerns arise from the estimates of unit risk based on animal data. The worst case animal-based estimate predicts a risk of almost 1 in 10 for a lifetime exposure of 1 ppm. This is plainly absurd in view of occupational experience. The problems with this value are that it is based on Maltoni (Ramazzini Laboratory) studies combined with the assumed extremely high conversion of TCE to DCVG in humans. We acknowledge that EPA has not focused on this worst case. If Charbotel et al, upon further review, is considered unsuitable for development of unit risk values, the calculations based on animal studies must be revised: The Maltoni studies were poorly managed and conducted following a unique protocol; a formal petition has been filed requesting that these studies not be relied upon for TCE. In addition, the Lash versus Green assessment plays directly into the animal study-derived values involving kidney tumor incidence and unit risk should be shown for both levels of DCVG production unless one is to be preferred on scientific grounds.

Comment: Recommending that studies from the Ramazzini Laboratory be excluded from consideration may be beyond the standard SAB review process at this stage and EPA has appeared to accord their results less weight in the calculation of unit risk. Nevertheless, it would be appropriate for such calculations to be excluded completely. Any calculation of unit risk must reflect the most appropriate dose metric for calculations based on kidney tumor incidence. This is a corollary of the concerns expressed by the Panel regarding the

uncertainty of the extent of DCVG formation in humans. The options are: to show separate calculations based on Green or Lash estimates of DCVG formation with equal weight, select either Lash or Green based on a scientific assessment of reliability, or abandon DCVG/DCVC-based extrapolation and employ either total metabolism or even administered dose. It should be a matter of transparent scientific evaluation as to which of these should be adopted.

References:

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