Perspectives on EPA's Draft "Trichloroethylene Health Risk Assessment: Synthesis and Characterization"

1. Historical

Trichloroethylene (TCE) is a chemical with a rich, if complex, toxicological database.

The Environmental Health Committee of EPA's Science Advisory Board (SAB) reviewed EPA's draft cancer risk assessment addendum to the Health Assessment Document in 1987/88. SAB disagreed with EPA's cancer classification of B2, indicating that it should be considered to lie "on the continuum between B2 and C". As a result of this opinion, EPA withdrew the cancer classification and cancer potency terms from the IRIS database and these remain undefined in the current IRIS listing for TCE. The final version of EPA's Synthesis document will be used to update cancer and non-cancer endpoint information in IRIS.

EPA began a collaborative approach to TCE cancer risk assessment in the mid-1990's with two "Williamsburg Workshops" that brought together scientists from state and federal government agencies, industry and academia. Several consensus positions were established. In 1995 EPA began the reassessment of the toxicity of TCE and, as a foundation, commissioned "state of the science" (SoS) chapters to be written by experts in a selected series of topics. These 16 chapters were published in a Supplement to Environmental Health Perspectives in May, 2000.

The first draft of EPA's Synthesis document was released to the SoS authors and members of the steering committee (the External Involvement Group) in August 1999. A review meeting was held in October 1999 with these groups participating. Substantial comments were made by the SoS authors regarding errors of logic (some easily testable), biased interpretation etc. None of these corrections have been made to date.

In September of 2001 EPA released an external review draft of the Synthesis document. Also in September, six of the nine non-EPA SoS authors sent a letter (copy attached) to EPA Administrator Whitman expressing serious concerns about the Synthesis document. The public comment period ended on January 18, 2002 and a substantial set of critical comments was filed.

The draft Synthesis document has been subjected to review by a panel created by extending the membership of the SAB Environmental Health Committee. The TCE Panel met in public session on June 18, 2002. Prior to this meeting, a group of SoS authors and scientists who had filed written comments sent a letter (copy attached) to EPA's Assistant Administrator for Research and Development, Dr P. Gilman, expressing the opinion that the draft was not suitable for consideration by the SAB Panel and recommending that one more round of revision would be necessary to make it so. The issues of concern were substantial and the authors of the letter considered that the

Synthesis document should be withdrawn pending revision. No reply was received from Dr Gilman and no opinion was expressed following a meeting to discuss the recommendation to withdraw the draft - the Panel meeting did take place. The final SAB Panel report and letter to Administrator Whitman were released in December 2002.

2. Selected Issues

2.1 Epidemiology

The Synthesis document relies heavily on the SoS review of published epidemiological information by Wartenberg et al. This particular SoS paper was criticized in several letters to the editor and a number of commenters on the Synthesis document have also raised concerns. Wartenberg et al have used a statistical treatment to calculate "average" SIRs and SMRs for cohort studies and it appears that kidney cancer is associated with high level TCE exposures. The particular method used is considered suitable for combining results that are statistically homogeneous - the TCE studies are not. Wartenberg et al also chose to include a small "cluster study" by Henschler et al that, itself, has been widely criticized. Perhaps the most incisive criticism of the Wartenberg approach was provided by D. Hoel, a member of the SAB Panel (available in written form upon request). M. Kelsh demonstrated in a public presentation at the Panel meeting that, with or without Henschler's data, a more appropriate statistical procedure showed that no relationship between TCE exposure and increased incidences of kidney cancer was demonstrable. The interpretation of epidemiology is critical in considering the weight of evidence for carcinogenicity classification and this can only be achieved in a critical review of individual studies with meta-analysis applied only where studies can be combined with validity. Certain epidemiology studies were also improperly used in calculations of cancer slope factors and this will be discussed below.

2.2 Exaggeration of Human Variability

EPA has used the known 50-fold variation in activity of the primary enzyme that metabolizes (and activates) TCE, namely CYP2E1, to justify additional concerns for "susceptible" individuals and those in whom the enzyme is likely to have been induced (alcohol drinkers, those taking certain pharmaceutical products, for example). This also is used, in part, to justify greater uncertainty factors in RfC and RfD calculations and to direct risk managers to the upper end of the range of cancer slope factors. This increased sensitivity in line with greater enzyme activity is a fallacy. It was clearly stated by SoS authors in October 1999 that the metabolism of TCE at typical human dose levels is "perfusion limited" and virtually independent of CYP2E1 activity. This could have been tested by simple PBPK calculations. The lack of influence of enzyme activity has now been elegantly demonstrated using TCE data by a group with an EPA lead author, and this has been displayed in an award-winning poster at the Society for Toxicology meeting in March.

2.3 Bias in Acceptance of Modes of Action

The revised EPA guidelines for cancer risk assessment have led to expectations that mode of action consideration will play a greater part in EPA's risk assessments. The Synthesis document does discuss modes of action, but the authors have chosen to reject modes of action that could be favorable to TCE, even when these are plausible, consistent with all experimental observations and reasonably well accepted. In contrast, highly speculative modes of action are uncritically presented leading to such improbable conclusions as that diabetics are at greater risk than normal subjects.

The conclusions of the Synthesis document place great emphasis on the role of dichloroacetic acid (DCA), a metabolite, in toxicity of TCE. This appears to be based on pre-1998 information for formation of DCA from TCE in the mouse, information subsequently corrected by the investigators. It is now known that, even in the mouse, DCA is a very minor metabolite and unlikely to play a significant part in TCE effects. Even less, perhaps even no, DCA is generated from TCE in humans. This has been explained by SoS authors, including a member of EPA's staff, and others, but the greater concern regarding TCE if DCA is given prominence remains in the Synthesis document. The suggestion that DCA alone could be responsible for mouse liver tumors following TCE administration, as stated in the biologically based risk assessment, is highly improbable but the evidence supporting this conclusion cannot be evaluated (see section 2.4).

2.4 Lack of Transparency

This is a concern in relation to several parts of the Synthesis document such as the treatment that quantifies the range of uncertainty in PBPK calculations and selection of uncertainty factors for RfC and RfD, but becomes most extreme in relation to "biologically based" calculations of cancer slope factors. Such notables as K. Crump and S. Moolgavkar have attempted to reproduce EPA's calculations based on epidemiological data and have failed. Informal and formal (Freedom of Information Act) requests have not provided the needed data and EPA acknowledges that they are no longer available. One of the highest cancer slope factors is derived from unpublished data provided by the author of one of the older epidemiology studies (in the paper the result is negative for this particular endpoint). EPA does not have the unpublished data. The SAB Panel recognized the lack of transparency in the biologically based risk assessments and elsewhere.

2.5 Groundbreaking Approaches to Risk Assessment May not be Valid

EPA has attempted a number of new approaches in this document. These include: a) integration of multiple types of evidence, b) manner of addressing risks to children and susceptible individuals, c) cumulative risks, d) contribution of background exposures, e) quantitation of uncertainty, f) use of biologically based risk assessment, g) combination of multiple endpoints in deriving a single RfD or RfC, h) combination of cancer slope factors derived in a variety of ways and presented in a unified range of values. The SAB

Panel considers that several of these approaches involve considerable uncertainty and will be subject to evolution within EPA - there is a need for consistent policies to emerge. If this is the case, the question has to be asked whether the "bottom lines" in the Synthesis document, whether qualitative or quantitative, are suitable as bases for regulations. This is before concerns about the validity of interpretations of toxicological and epidemiological data come into play.

2.6 Biased Selection and Use Of Toxicity Information

Throughout the Synthesis document the most anti-TCE use of data has been selected. Positive results have been accepted uncritically with no evaluation of the quality of the study or strength of evidence overall. These concerns are particularly evident for the non-cancer end-point evaluation. Having totally rejected the SoS paper covering non-cancer end-points, it became incumbent upon EPA to present a balanced and comprehensive review of their own. Instead, positive findings have been taken without evaluation, without comparison with (or even any reference to) negative results and ignoring any potential modifiers such as extremely high dose levels or questionable relevance to man. Concern about the extent of bias has been a recurrent theme amongst reviewers.

2.7 Failure to Match Current Cancer Risk Assessment Guidelines

Until the guidelines become final, EPA has announced a policy decision that the Agency will follow the draft guidelines of 1999. The authors of the Synthesis document have had to cope with guidelines that have evolved as they have composed the report and deviations are not unexpected. There are many detailed examples of deviations from the guidelines of 1999. EPA has promised the SAB Panel that the final Synthesis document will meet the guidelines current at the time of completion. Technical details probably can be adjusted, but the dominant problem is that the Synthesis document does not meet the philosophical intentions of the new guidelines, indeed, the primary reason for developing the guidelines. This has been seen by the scientific community as leading to a deeper analysis of the available science, inclusion of modes of action, integration of human and animal data into the assessment. This might appear to be the case for TCE at first sight, but the analysis is so directed to conservative interpretations at every step, and exaggerated concerns regarding uncertainties, that the scientist can recognize that a grossly distorted risk assessment has resulted. The conclusion is that, if the guidelines are to be interpreted this way, gaining additional information on modes of action etc are likely to lead more severe assessments, if for no other reason than each piece of information will contribute to the cumulative uncertainty.

3. SAB Panel Opinions and Revision of the Synthesis Document

To their credit the SAB Panel has recognized several of the general issues described above. They have not been in a position to recognize the more specific distortions of the evidence that appear throughout the Synthesis document. This is because the Panel was composed of activists (whose objectives would not allow them to acknowledge overly-

conservative analyses) and those not familiar with the data for TCE who were thus forced to assume that EPA had produced a balanced review of the underlying studies.

The Panel's recommendations (see attached) do indicate that a substantial revision, both in quantity and quality, of the Synthesis document will be required. It is for the EPA Administrator or Office of R&D to request a review of the revised document, but this seems unlikely to happen spontaneously and the SAB Panel has not requested an opportunity for review. Thus there will be no check outside EPA that the revised document fully reflects the views of the SAB Panel. There will also be no process in which EPA's promise to take into account public comments and the views of SoS authors will be assessed before the document becomes final.

It appears inevitable that the overly conservative numerical conclusions in the current version will remain in the final Synthesis document. In that situation, it seems certain that further forceful challenges will occur at that time.

4. Resolution

One further round of external review involving those possessing knowledge of the toxicological properties of trichloroethylene would provide the best opportunity to avoid an undesirable public conflict at a later date. Such a review should allow the views of the SoS author's and others versed in TCE's properties to contribute to an assessment that achieves a scientific balance and is also protective of public health.

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