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Draft 2003 Report to Congress on the Costs and Benefits of Federal Regulations: Response to Request for Comments Relating to Chapter II, Under Section B (U.S. Approaches to Analysis and Management of Emerging Risks), 68Fed Reg 5492 (Feb 3, 2003)

The Example of EPA's Draft Health Risk Assessment for Trichloroethylene (TCE)

The Halogenated Solvents Industry Alliance, Inc. (HSIA) represents the producers and users of chlorinated solvents including trichloroethylene. HSIA welcomes the opportunity to present to OMB the example of US Environmental Protections Agency's Draft "Health Risk Assessment for Trichloroethylene: Synthesis and Characterization" dated August 2001 (hereafter "Health Risk Assessment"). Specifically, this EPA assessment provides an example of extreme conservatism applied at every stage in the risk assessment that leads to an unbalanced outcome. The report does not provide direct risk management guidance but leaves the risk manager with little choice but to use the most conservative options offered by EPA.

This commentary responds to OMB's request for input on:

- Ways in which "precaution" is embedded in current risk assessment procedures through "conservative" assumptions in estimation of risk, or through explicit "protective" measures in management decisions as required by statutory requirements as well as agency judgments.

and

- Examples of approaches in human and ecological risk assessment and management methods addressed by U.S. regulatory agencies (e.g., consumer

product safety, drug approval, pesticide registration, protection of endangered species) which appear unbalanced.

Background

A summary of the history of the development of EPA's risk assessment for trichloroethylene (TCE) and some of the issues of concern is provided in Attachment 1. EPA employed an unusual approach: Because of the wealth of toxicological and epidemiological information for TCE, and as an extension of an earlier consultative exercise, EPA appointed a group of scientists to write "state of the science" chapters. Each chapter, written by one or more recognized experts, addressed an issue considered significant for the cancer and non-cancer risk assessments for TCE. The chapters were subsequently published as a supplement to Environmental Health Perspectives (Vol. 108, Suppl. 2, May 2000). It is noteworthy that most of the non-EPA authors of these, scientists with a deep understanding of the properties of TCE, wrote to EPA Administrator Whitman to dissociate themselves from the conclusions reached by EPA in their risk assessment. The wording of that letter, dated September 24, 2001, is attached to the historical summary.

Application for the Health Risk Assessment

The TCE Health Risk Assessment document, once finalized, will provide information to be included in EPA's Integrated Risk Information System, the IRIS database. Therefore, the Health Risk Assessment will provide EPA's definitive opinions on such items as TCE cancer classification, cancer slope factor, oral and inhalation reference doses (RfD and RfC, respectively). These opinions will then be used by EPA in formal regulatory activities such as calculations of residual risk in relation to National Emission Standards for Hazardous Air Pollutants (NESHAPs) or for establishment of criteria for ground water remediation. State and local authorities are also known to use the IRIS database information in regulatory activities.

The situation for ground water is of special concern. At present, clean up levels are driven by the Safe Drinking Water Act, Maximum Concentration Limit (MCL) of 5 parts per billion (ppb). This level is set on the practical limits for analytical procedures, rather than calculations of risk *per se*. Historically, because of handling and disposal activities that were accepted practice and legal at the time, TCE is an extremely common ground water contaminant which is found at many Superfund and other sites undergoing remediation. There is an expectation on the part of many parties responsible for the remediation of such sites that the cancer slope factors identified in the Health Risk Assessment will drive the remediation targets below 5 ppb with 1 ppb being talked about as a possible new target. The costs of clean up, already high in reaching a difficult target of 5 ppb, rise dramatically in attempts to achieve levels below this concentration. There are also concerns that the cancer slope factors will be used in determining when levels achieved as a result of vapor intrusion require remedial action based on a calculated risk of 1 in 1,000,000. It is even anticipated that remediation sites that have been closed and become sites of new construction will have to be reactivated. These concerns are not

hypothetical, examples of the draft cancer slope values being used by EPA regional offices are detailed in supplementary comments filed by W. Caffey Norman III.

The result of EPA's extreme bias towards conservatism in the Health Risk Assessment carries enormous resource implications. It is anticipated that remediation costs for TCE based on the draft Health Risk Assessment would likely increase by many tens to hundreds of billions of dollars - the additional burden being carried by agencies such as Departments of Defense and Energy and many companies.

Scientific Issues

The draft TCE Health Risk Assessment was made available for public review by EPA and comments (substantial in number, quantity and quality) critical of EPA's analyses were filed by the deadline of January 18, 2002. Attachment 2 is the commentary filed by HSIA. The overview addresses scientific issues, data quality concerns, and deviations from EPA's draft guidelines for carcinogen risk assessment. Contributions from a number of experts in relevant fields form attachments to the overview. Comments filed by other organizations and individuals are available from EPA's National Center for Environmental Assessment (or from HSIA, upon request). Certain issues that are pertinent to OMB's request are discussed below:

1. Epidemiology: Cancer Classification and Calculation of Cancer Slope Factors

Unlike the products of most of the state of the science authors, EPA was happy to rely on a very broad review of TCE epidemiology by Wartenberg et al (2000), one of the three authors is an EPA staff member. Even before EPA employed the Wartenberg et al treatment in the Health Risk Assessment, the methods used to combine studies numerically had been criticized in letters to the editor. The selection of one cohort study (Henschler et al 1995) for combination with other studies drew particularly strong attacks. EPA was well aware of these concerns before releasing the draft Health Risk Assessment and chose not to address them in any way. Giving credence to the Henschler study has marked effects on the outcome of EPA's analyses. Concerns are these:

i) The Henschler study focuses on the relationship between renal cell carcinoma and TCE exposures in a German cardboard factory. It is a small study involving 50 deaths in an "exposed" group of 169 workers. There were two deaths due to kidney cancer and five kidney cancers cases in the exposed group. The incidence appeared statistically significantly elevated relative to Danish Cancer Registry or the East German Cancer Registry. The fundamental problem is that the renal cell cancer cases in this cohort study included those that were a pre-recognized cluster in the factory; this reduces the study to no more than "hypothesis setting". There are many other concerns regarding this study detailed in the attached comments. The conclusion is that the findings in this study cannot be used in the way that the results of much larger, well conducted occupational cohort studies can.

ii) Despite the weaknesses of the Henschler study, Wartenberg et al chose to include the SMR and SIR from that study in statistical treatments for kidney cancer in their partial meta-analysis for TCE. To use these values in any form of meta-analysis is inappropriate and even more undesirable in the methodology used by Wartenberg et al. The particular statistical treatment is suitable only for studies that are "homogeneous" in the statistical sense and does not weight studies for their size. Thus the result of the tiny Henschler study is sufficient to overcome the results of a number of larger, more robust, cohort studies to suggest a statistically significant relationship between TCE and kidney cancer. Removal of the Henschler study greatly reduces the concerns regarding kidney cancer. Even if the Henschler results are included in a calculation that takes into account the size of the studies, the outcome does not support a relationship between TCE and kidney cancer.

iii) In the draft Health Risk Assessment EPA provides the risk manager with a range of cancer slope factors (CSF) of 0.02 - 0.4 per mg/kg-day. This range is based on a mix of values derived animal studies and three epidemiology studies. Outlying values, both higher and lower than the range were excluded.

One of the epidemiology studies employed to yield a CSF within the range was the Henschler study. Clearly this was inappropriate, and particularly since the levels and duration of TCE exposure could only be guessed.

The second epidemiology study employed was that of Anttila et al (1995). One problem is that EPA used data supplied by Anttila that do not appear in the publication. EPA has sent the data back to the author and thus calculations cannot be reproduced. This is probably the most egregious example of "lack of transparency" in the Health Risk Assessment which suffers generally from this problem. Although Anttila et al appear to provide urinary monitoring information for assessing exposure levels, only one to, at most, three determinations per worker were made and it is questionable as to whether these are representative (of earlier in careers when exposures were likely to be higher, for example). Taking a study with a relatively small number of tumors (in this case. liver) makes an unreliable base for calculations.

The third epidemiology study used, Cohn et al (1994), gives the highest value in EPA's range of CSFs. This study is particularly unsuitable. Although an apparent statistically significant relationship between TCE in drinking water and non-Hodgkins lymphoma (NHL) was found for women, the "ecologic" (population) study design leaves many uncertainties in terms of exposure (use of drinking water, duration of residence in area, other exposures correlated with TCE, other confounders). Given the uncertainties, a relative risk of 1.4 is very close to the null. The dose factor in the calculation of a CSF is completely unknown. Overall, this study is completely unsuitable for the calculation of a

CSF and yet it is the value derived from this study that is being used by EPA regional offices to determine remediation targets.

2. Animal Data in Relation to Carcinogenicity

The animal responses of interest are liver tumors and lung tumors in mice, and kidney tumors in rats. Benign testicular tumors in rats have also been reported. All these responses display species and strain specificity and many studies have been conducted at dose levels above the maximum tolerated dose. TCE is considered to be non-genotoxic, or at most, weakly so. The only hypothesized, potentially genotoxic, mechanism involves the rat kidney tumors and depends on a TCE metabolite (DCVC) that, itself, forms reactive metabolites in the kidney under the action of the enzyme, β-lyase. The problem with this hypothesis is that so little DCVC is formed from TCE in rats that a response of any kind in the kidney is improbable, man produces even less DCVC from a given dose of TCE than occurs in the rat. The quantitative element arguing against the DCVC mode of action has been ignored by EPA.

There is a wealth of data regarding the mode of action of TCE in the induction of mouse lung and liver tumors that reduce concern of these findings for man. The evidence suggests that the murine tumors have no relevance for man, particularly at levels of exposure generally experienced by humans. The scientific community anticipated that "mode of action" considerations for TCE would be used, either to support a "lack of relevance" determination, or to permit a non-linear dose response assumption for mouse liver tumors. In the event, EPA has applied a linear treatment to mouse liver tumors. This has been exacerbated by EPA's treatments of uncertainty (particularly as manipulated mathematically by Bois, 2000): The boundaries of uncertainty seem to widen with increasing amounts of relevant information because each individual study carries uncertainty and this accumulates upon combination in EPA's methodology. Although it is far from clear exactly what was done, EPA appears to use a conservative outer bound on the range of uncertainty.

Overall, the treatment of TCE is little different from that of vinyl chloride (VC). In contrast to TCE, VC is a known human and multiple animal species carcinogen acting via a common genotoxic mechanism. The outcome of EPA's calculation of cancer slope factors is that, based on predictions of risk for a given dose, TCE is of similar or greater concern than VC - a conclusion that most toxicologists would find highly improbable and unacceptable.

3. Sensitive Individuals

In the draft Health Risk Assessment EPA addresses different classes of sensitive individual and also refers to the sensitive individual in a broad generic sense.

i) It is generally accepted that, for most toxicity end-points, metabolites of

TCE are the active agent. The principle enzyme for TCE metabolism is CYP2E1 whose activity in human liver is known to vary and to be inducible. A fifty fold range of CYP2E1 activity is believed to exist in humans and EPA assumes that those possessing higher activity will be proportionately more sensitive to TCE. At lower doses this is not the case because delivery of TCE to the enzyme limits the production of the active metabolites and enzyme activity has only a small effect. This factor was explained to EPA in a review meeting involving state of the science authors in October 1999 which addressed a preliminary draft of the Health Risk Assessment and could have been explored with PBPK calculations. EPA chose to ignore these well-found recommendations. As a result, those classes of humans such as diabetics and alcohol drinkers known to possess high levels of CYP2E1 activity have been erroneously identified as especially sensitive.

ii) As required, the possible sensitivity of children to TCE was reviewed by EPA. No definitive information exists and thus much of the discussion was speculative. Every factor discussed by EPA was put in terms of an increased response in children, this despite the fact that some could clearly reduce responses. For example, the higher respiratory intake relative to bodyweight, child versus adult, was deemed to increase dose absorbed. In some cases such as following oral intake or cessation of intake by inhalation, the clearance of TCE by exhalation will be more rapid in children. Since CYP2E1 levels are low at birth and build up over the first two year's of life, it is possible that the infant could be considered less sensitive.

iii) The generic statement that has a direct effect on risk management decisions is EPA's indication that the high end of the range of cancer slope factors should be used to account for the sensitive individual. There is no scientific justification given for this recommendation. In reality, this statement leaves the risk manager using a CSF to calculate risk no option but to use the upper value in the CSF range or else be charged with failing to take into account the sensitive individual.

General Comment

The draft Health Risk Assessment is remarkable because every interpretation is pushed to the most extreme conservative position possible, often without even mentioning contrary evidence or interpretations. There is no attempt to identify "central tendencies", or "most likely human responses" before applying conservative treatments. There is also no caveat that the cancer slope factors represent a conservative upper bound, that the true risks could be lower than those derived using the CSF range and could even be zero. The caveat is certainly appropriate for TCE. The outcome is extremely unbalanced and will lead to wasting substantial resources with negligible benefit and is thus a compelling example of an unduly conservative approach.

We have been pleased to have the opportunity to raise this example for OMB to consider. The evidence is complex and this analysis is brief. Reference to the comments sent to EPA during the public review phase would provide more detailed information but analysis of these would be a daunting task. If OMB staff wishes to explore any aspects of HSIA's concerns about the TCE Health Health Risk Assessment, please contact me by telephone at 703-741-5781 or via e-mail at "pdugard@hsia.org".

Yours sincerely,

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