Discussion of EPA's IRIS and the Health Effects of Trichloroethylene

Testimony of

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I am a University Distinguished Professor in the Department of Biostatistics, Bioinformatics and Epidemiology at the Medical University of South Carolina in Charleston. Prior to joining the university, I was employed for over twenty years at the National Institute of Environmental Health Sciences of the National Institutes of Health. There I was Director of the Division of Risk Assessment, and served for a time as Acting Scientific Director of the Intramural Research Program. I was a member of the Environmental Protection Agency's scientific panels for perchlorate and for trichloroethylene (TCE). I was a peer reviewer of the National Research Council's report on TCE.

The opinions I state today are my own.

I will comment on the general process used by EPA (e.g. IRIS) for calculating permissible dose levels of environmental carcinogens with a focus on the example of TCE. I will conclude with a few recommendations.

- EPA 2001 TCE Report

The EPA 2001 TCE risk assessment had a number of shortcomings that were pointed out by individual scientists and EPA's Scientific Advisory Board's TCE Advisory Panel. Although there were several health endpoints under consideration, cancer is the predominant outcome used for exposure standard setting. This is due in part to the target of one in a million lifetime cancer risk, and the assumption of a linear no threshold dose-response for carcinogens. It should be noted that the NRC report discussed this assumption and the need to validate it. The usual method for estimating cancer risk was applied to TCE. Basically, a few selected epidemiological studies and a few high dose rodent studies were individually fit to a linear dose response function in order to estimate the dose which would correspond to a lifetime risk of one in a million. Figure 1 is a reproduction of a graph of the results of this process taken from the EPA draft report, with Table 1 giving the numbers used in Figure 1.

First there is a question of the selection of epidemiological studies used for this process.

EPA used three studies: Henschler (1995) kidney cancers among workers in a German cardboard factory, Anttila (1995) Finnish workers who were monitored for TSE (kidney, liver and NHL) and an ecological study of drinking water in New Jersey (NHL).

The data from animal studies was also treated in a manner similar to human studies. Using kidney cancer as the primary example, EPA gave three dose estimates. They were derived from the rat study, the German worker study and the Finnish worker study. EPA calculated the dose estimates to be (see Table 1)

3.3×10^{-3} mg/kg-d (rat)
5×10^{-5} mg/kg-d (German)
5×10^{-7} mg/kg-d (Finnish).

This represents a range in estimated dose by a factor of almost 10,000, suggesting that the process is so variable as to be meaningless. It should be noted that the most extreme result produced by EPA was from the Finnish study, which was not statistically significant, and the workers had fewer kidney tumors than were expected. It is not clear why this study was included in the analysis.

Multiple studies are often quantitatively combined using meta analysis or joint data analysis techniques. A meta-analysis was carried out by EPA (Wartenberg et al. 2000), but not used in the calculating cancer risk. The specific TCE application has been criticized in the scientific literature and most recently by the NRC 2006 report. If done correctly, with consideration of exposure, as has been done with radiation and cancer (eg. Lubin and Boice 1997), one could avoid using selected studies and their less stable risk estimates. Further Bayesian statistical methods can adjust for exposure uncertainties which vary among studies. The NRC report gives very detailed recommendations concerning the meta analysis process.

I feel that without a considerably more sophisticated analysis, which does not selectively choose individual studies and treat them independently, the low-exposure cancer risk

estimates in EPA 2001 are unreliable and should not be used to set environmental standards.

- NRC 2006 TCE Report

The NRC (2006) report on TCE recommended that low dose cancer risk estimates be based on rodent bioassays and human data be used as validation of the rodent studies. This is a reasonable approach, which I support. The human epidemiological data is thought to be preferable but the very large uncertainty of exposures plus the confounding of other chemical exposures, as well as lifestyle issues, greatly decreases the value of the data for quantitative risk estimation.

Basic toxicological research focuses on a compound's mode of action (MOA); that is, how it and its metabolites affect the carcinogenesis process. Also, the use of physiologically based pharmacokinetic models (PBPK) to evaluate the relationship between routes of exposure and the formation of reactive metabolites of interest is critical to quantitative risk estimation. This information, although discussed, was not incorporated into the EPA cancer risk models. This PBPK model information, along with MOA understanding, is key to evaluating the validity of the predictability of rodent cancer effects to man. The NRC report discusses these important issues and makes specific research recommendations for improved TCE risk estimation.

An issue of increasing concern is the variability in response by various susceptible human subgroups. This is frequently discussed but rarely employed in evaluating the degree of sensitivity in subgroups. These subgroups include age, medical conditions and genetic variability. For example, Bronley-Delancey et al. (2007) measured the variability of TCE metabolism by genetic subgroups by using human hepatocytes. This basic type of human data provides guidance on possible adjustments of environmental exposure levels for genetic subgroups in the population.

All of this is important applied science which is essential to quality risk estimation, but it suffers from two problems.

First, the risk assessors are not integrating enough scientific information into their actual cancer risk estimates. There are modern statistical methods for accomplishing this. The ongoing effort in radiation carcinogenesis is one area where re-analysis is performed as new, better methods are developed, and it is a good example of scientific responsiveness to innovation.

The second issue is that there are no longer effective government programs directed at solving these issues through academic research. This work is too applied for NIH (i.e. NIH's toxicology grant study section no longer exists) and other agencies are not focused on these issues. Considering the cost of inappropriate risk estimates, in either dollars or health effects, this seems foolish from a societal viewpoint.

Finally, EPA's IRIS process involves both risk estimation and risk management. EPA should consider using outside scientific experts to carryout the risk estimation. This is done successfully by WHO's IARC for qualitative risk assessment of chemical carcinogens and by the NRC for quantitative risk estimation of various radiation types. Through the use of independent scientific experts and a rigorous peer review process these risk estimates are considered authoritative. Some 30 years ago EPA had the NRC develop quantitative cancer risk estimates for chemical contaminants in drinking water. The Agency could then use exposure levels and the NRC risk estimates to establish standards based upon risks and benefits.

Conclusions and Recommendations

- EPA must develop cancer risk estimates for TCE using an integrated approach following the advice of the SAB Panel and the NRC Committee. Further, it should focus on the best estimate of risk, including an estimated uncertainty. EPA should also seriously consider the NRC's recommendation of developing the risk estimates based upon the animal and laboratory studies and using the human studies as validation of their risk models.

- While developing risk estimates, EPA should consider obtaining quality outside scientific advice before and during the process, instead of waiting until the document is completed. EPA should consider having risk assessment, but not risk management, for the more important chemicals carried out by a committee of outside experts. The National Academies' NRC is well suited for this purpose.

- EPA and other governmental agencies should sponsor extramurally the development and refinement of risk assessment methodology in general. Also, they should support key laboratory and human studies directed at specific problems associated with any major chemical problem, such as TCE.

- Greater attention must be given to potentially sensitive subgroups and to adverse health outcomes other than cancer.

Figure 1

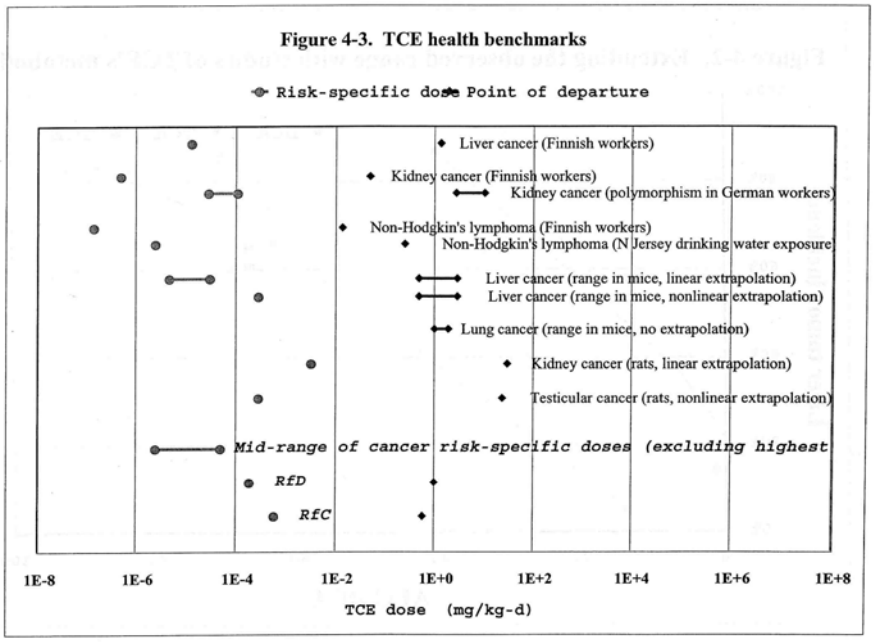

Table 1

Table 4-9. Compilation of cancer estimates

	Point of departure (mg/kg-d)	Slope factor $(mg/kg\text{-}d)^{-1}$	Risk-specific dose[a] (mg/kg-d)
Cancer estimates based on human studies			
Liver cancer			
Finnish cohort[b]	1.4[c]	7×10^{-2}	1.4×10^{-5}
Kidney cancer			
Finnish cohort[b]	0.05[c]	2×10^{0}	5×10^{-7}
German cohort	5[c]	2×10^{-2}	5×10^{-5}
Non-Hodgkin's lymphoma			
Finnish cohort[b]	0.014[c]	7×10^{0}	1.4×10^{-7}
New Jersey cohort	0.25[c]	4×10^{-1}	2.5×10^{-6}
Cancer estimates based on mouse studies			
Liver cancer			
Mechanism-based model[d]	Not applicable	8×10^{-4}	1.25×10^{-3}
Mechanism-based model[e]	Not applicable	8×10^{-2}	1.25×10^{-5}
Linear extrapolation	0.5–3.1	3×10^{-2}–2×10^{-1}	$0.5\text{–}3.1\times10^{-5}$
Nonlinear extrapolation	0.5–3.1	Not applicable	(3×10^{-4})[f]
Lung cancer[g]	1.7–4.8	Not applicable	(Not calculable)[f]
Cancer estimates based on rat studies			
Kidney cancer	33[h]	3×10^{-4}	3.3×10^{-3}
Testicular cancer	25	Not indicated	(8×10^{-4})[f]

From: EPA 2001 TCE report

References

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