Discussion of the Health Effects of Trichloroethylene and the Methods Used for Setting Safe Exposure Levels

Testimony of

David G. Hoel, Ph.D

Medical University of South Carolina
Charleston, South Carolina

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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 process used by EPA for calculating dose levels of environmental carcinogens, with a focus on TCE. I will comment specifically on the proposed legislation S-1911, the EPA 2001 report on TCE and the National Research Council (NRC) 2006 report on TCE. I will conclude with a few recommendations.

- S-1911

I have two comments concerning the proposed legislation.

1. 3-D – This section of the bill states that the NRC study reported that there is strong evidence in a dose-dependent manner that TCE is associated with kidney cancer and leukemia in humans. The NRC committee focused on kidney, liver and lung cancer, and stated that in the future, non-Hodgkin's lymphoma (NHL) and childhood leukemia should be reviewed. I question, therefore, the inclusion of leukemia. Some of the newer studies have reported on several other cancers possibly related to TCE exposure. I have attached a brief summary of some of the reported potential adverse health effects of TCE in human studies (Hoel 2004).

2. 7-1-B – This section states that IRIS should produce a reference concentration of TCE within 180 days. My opinion is that a scientifically defensible integrated risk analysis is likely to require more than 180 days. This opinion is based upon the

following comments on the manner in which cancer risk estimation is currently conducted.

- 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, seems foolish from a societal viewpoint.

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 and other governmental agencies should sponsor the development and refinement of risk assessment methodology in general. Also, they should support key laboratory studies directed at specific problems associated with any compound, such as TCE, that is under study.

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

Figure 1

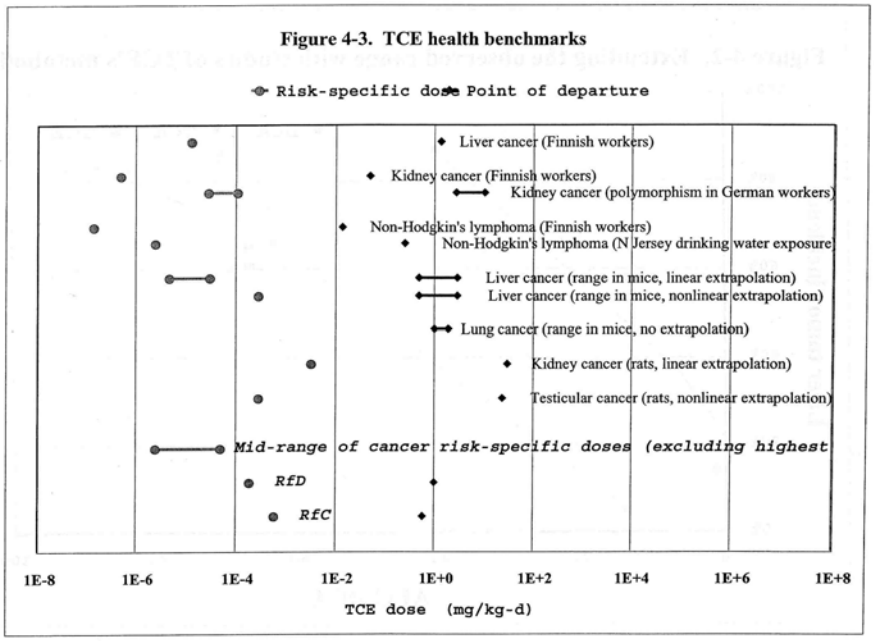

Table 1

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

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Human Exposure to TCE: Epidemiology Studies

David G. Hoel, Ph.D., Department of Biostatistics, Bioinformatics, and Epidemiology
Medical University of South Carolina

Trichloroethylene (TCE) is a common industrial solvent that is commonly found at low levels in drinking water. This compound has been well studied for its adverse health effects both in the laboratory and in human populations. The EPA is currently involved in reviewing their updated risk assessment analysis (1) with the likely outcome of further restricting the compound's permissible levels in drinking water.

TCE is a chemical that has been identified as being associated with or causing a wide range of adverse health effects in humans. These effects range from various cancers to neurological, developmental and autoimmune diseases as well as organ toxicities. Although there are a very wide variety of health effects from TCE, some have been more extensively studied than others. This is due in part to the specific disease interests of researchers and not necessarily due to the sensitivity of the various health endpoints in humans to TCE exposures. What follows is a summary of those health effects for which the epidemiological evidence is the strongest.

CANCER:

Traditionally and still today cancer remains the primary health endpoint used for environmental and occupational exposure standards. Epidemiological studies have shown a number of cancers to be increased from TCE and other solvent exposures including kidney, liver, non-Hodgkin's lymphoma (NHL), cervical, prostate and esophageal cancer. With these studies the major issue is separating the cancer effects of TCE from those of other solvents to which the subjects of the studies were often also exposed. Cohort and case-control studies have been carried out as well as ecological or population studies.

NHL and liver cancer are possibly the most convincing. Hansen et. al. (2) recently showed that among a cohort of male Danish workers exposed to TCE there was a statistically significant increase in NHL [SIR* = 3.5 (1.5-6.9)]. This study had good data on the exposure of the workers to TCE including both air and urine measurements of the major metabolite TCA taken since the beginning of the follow-up period. The other cohort study with actual TCA measurements was conducted by Antilla et al. (3). In this study of Finnish workers both males (2050) and females (1924) were followed from 1967 to 1992. After 10 years of exposure to TCE there was a nearly significant doubling of NHL [SIR = 2.17 (0.9-4.5)]. Of the occupational cohort studies these two have probably the most detailed information concerning the levels of TCE to which the workers were exposed. Other cohort studies reporting increases in NHL include Axelson et al. (4) [SIR = 1.6 (0.5-3.6)] and Blair et al. (5) [RR** = 2.0 (0.9-4.6)].

Case-control studies of NHL and TCE were carried out by (6) who reported a significant odds ratio [OR = 7.2 (1.3-42.0)] based on 105 cases. Also Persson et al. (7) observed an increased odds ratio of [OR=1.5 (0.6-3.7)].

For liver cancer which is the primary site of TCE metabolism Antilla et al. (3) observed a doubling of cases among the exposed [SIR = 2.3 (0.7-5.3)]. However, after 20 years of exposure this became a 6 fold increase [SIR = 6.1 (1.3-17.7)]. Also Axelson et al. (8) observed an increase [SIR = 1.4 (.4-3.6)] as did Blair et al. (9) [RR = 1.7 (0.2-16.2)]. The newer Hansen et al. (2) study reported a greater than 2 fold increase [SIR = 2.6 (0.8-6.0)]. Overall these studies all indicate an increased risk for liver cancer from TCE exposure.

Finally for women, cervical cancer is reported to be increased from TCE exposure. Hansen et al. (2) reports a significant [SIR = 3.8 (1.0-9.8)], Anttila et al. (3) found [SIR = 2.4 (1.1-4.8)], Blair et al. (9) [RR=1.8 (0.5-6.5)].

Wartenberg et al. (10) reviewed the current cancer studies and produced a meta analysis after first stratifying the studies into tiers defined by the quality and relevance of the individual studies.

* SIR = standard incidence rate. The estimate plus the 95% confidence interval is given.

** RR = relative risk.

A summary of the major cancer sites for the best cohort studies with the addition of two new studies (2), (11) is given in Table 1. It should be noticed that one site, namely kidney cancer, that has been used in risk estimation by both Cal EPA and the U.S.EPA, has only one positive study (12).

TABLE 1

Cancer Incidence Cohort Studies

SIR estimates and number of cases

Study	NHL	Liver	Kidney	Esoph.	Prostate	Cervical
Anttila	1.8 (8)	2.3 (5)	0.9 (6)		1.4 (13)	2.4* (8)
>10 yrs since exp.	2.2 (7)	3.0* (5)	1.0 (5)		1.4 (11)	1.3 (2)
Henschler			8.0* (5)			
Hansen#	3.5* (8)	2.6 (5)	0.9 (3)	4.2* (6)	0.6 (6)	3.8* (4)
Axelson	1.6 (5)	1.4 (4)	1.2 (6)		1.3 (26)	
Blair (male)	1.0 (7)	2.6 (3)	0.4 (2)		1.2 (56)	
Blair (female)	0.9 (2)		3.6 (2)			
Raaschou-Nielsen#	1.2* (96)	1.3 (34)	1.2 (76)	1.8* (23)	0.9 (163)	1.9* (62)

* $p<0.05$

new study not included in EPA's analysis.

Cancer Mortality Cohort Studies

SMR estimates and number of cases

Study	NHL	Liver	Kidney	Esoph.	Prostate	Cervical
Blair	2.0 (28)	1.7 (4)	1.6 (15)	5.6 (10) ?	1.1 (54)	1.8 (5)
Boice	1.2 (14)		1.0 (7)	0.8 (7)	1.0 (32)	
Henschler			3.3 (2)			
Morgan	1.0 (14)		1.3 (8)		1.2 (21)	
Ritz			0.7 (5)	1.2 (9)	1.4 (24)	

As with the rat model there may be an association with TCE exposure and renal cell carcinoma (RCC) with mutations in the von Hippel-Lindau (VHL) tumor suppressor gene. In a study by Brauch et al. (13) those RCC patients with high TCE exposures had a greater frequency of VHL mutations and especially a particular mutation (nucleotide 454) (see Table 2).

TABLE 2

Drinking Water Contamination and Incidence of Leukemia and NHL

Population Study of 75 New Jersey Towns

Total Leukemia	**Cases**		**RR (95%CI)**	
TCE ppb	**Male**	**Female**	**Male**	**Female**
<0.1	438	315	1	1
0.1-5.0	162	156	0.85 (0.71-1.02)	1.13 (0.93-1.37)
>5.0	63	56	1.10 (0.84-1.43)	1.43 (1.07-1.90)

NHL	**Cases**		**RR (95%CI)**	
TCE ppb	**Male**	**Female**	**Male**	**Female**
<0.1	491	504	1	1
0.1-5.0	272	226	1.28 (1.10-1.48)	1.02 (0.87-1.20)
>5.0	78	87	1.20 (0.94-1.52)	**1.36 (1.08-1.70)**

ALL	**Cases**		**RR (95%CI)**	
TCE ppb	**Male**	**Female**	**Male**	**Female**
<0.1	45	25	1	1
0.1-5.0	16	22	0.91 (0.53-1.57)	1.85 (1.03-3.70)
>5.0	3	7	0.54 (0.17-1.70)	2.36 (1.03-5.45)

NHL high grade	**Cases**		**RR (95%CI)**	
TCE ppb	**Male**	**Female**	**Male**	**Female**
<0.1	15	15	1	1
0.1-5.0	7	3	1.26 (0.51-3.09)	0.53 (0.15-1.82)
>5.0	2	9	0.61 (0.14-2.65)	2.74 (1.20-6.26)

non-Burkitt's Lymphoma

From: Cohen et al. 1994 EHP 102:556-61

In summary, these cancer epidemiology studies and others coupled with the induction of cancer in laboratory animals give a convincing argument that TCE is a human carcinogen capable of inducing cancer at several organ sites. Table 4 gives the meta-analysis estimates developed by Wartenberg et al. (10) for the cancer sites believed to be associated with TCE exposures.

TABLE 3

Association of TCE levels and mutations in the von Hippel-Lindau tumor suppressor gene among HCC patients.

			Number of patients (%) with VHL mutations		
Exposure	**Number**	**Nucleotide**	**Number of mutations**		
Level	**Patients**	**#454 mut.**	**zero**	**one**	**two or more**
+++	17	7 (41%)	2 (11%)	4 (24%)	11 (65%)
++	24	6 (25%)	6 (25%)	15 (63%)	3 (13%)
+	3	0	3 (100%)	0	0
-	107	0	31/73(42%)	42/73 (58%)	0/73 (0%)

from: Brauch H. et al. JNCI 91:854-860 (1999)

TABLE 4

Meta Analysis of TCE Cancer Studies

SIR/SMR values with total number of cases

	Tier 1		**Tier 2**	
Cancer Site	**Incidence**	**Mortality**	**Incidence**	**Mortality**
Cervix	2.4* (8)	1.8 (5)	1.1 (1)	1.2 (13)
Esophagus		1.1 (26)		1.1 (32)
Hodgkin's	1.5 (4)	2.0* (16)		0.8 (13)
Kidney	1.7* (21)	1.2 (37)	3.7* (6)	1.3 (41)
Liver	1.9* (12)	1.7 (4)		2.0* (15)
NHL	1.5 (22)	1.2 (56)		0.9 (20)
Prostate	1.3* (95)	1.2* (131)	1.6 (7)	0.9 (72)

* $p<0.05$

from: Wartenberg et al. 2000 EHP 108 suppl.2 161-176

POPULATION CANCER STUDIES

Prompted by the well-known Woburn Study that linked childhood acute lymphocytic leukemia (ALL) with drinking water contamination by TCE and PCE, (14) studied towns in N.J. with increased TCE drinking water levels and possible associations with leukemia and lymphoma rates. Table 3 shows the results for total leukemia and NHL in general. Specific leukemia types as well as NHL stage were also analyzed. It appears that for NHL there were effects in females at the high dose group and increases but no dose response in males. A population down-stream from a contaminated industrial site was studied in Taiwan (15). Liver cancer relative risks in males were observed to be [RR = 2.57 (1.21-5.46)] with a linear trend over time for the affected areas.

DEVELOPMENTAL TOXICITY

Women exposed to TCE shortly before and during their first trimester of pregnancy have shown to have an increased incidence of malformations in their offspring. In particular congenital cardiac malformations are increased. Goldberg et al. (16) studied the specific cardiac malformations observed in the Tucson Valley where about 8% of the people were exposed to well water with excess levels of TCE. A statistically significant 3-fold increase in congenital heart disease was observed among those exposed to the TCE contamination. Importantly this increase did not persist after the contaminated wells were closed. It should also be noted that no other contaminant in excess of drinking water guidelines was identified other than TCE or its by products. Also in laboratory studies cardiac defects have been induced in chick embryos and rat fetuses by TCE exposures (17).

In an analysis of the Baltimore-Washington Infant Study Wilson et al. (18) a relative risk of RR=3.4 was observed for solvent/degreaser exposure and occurrence of hypoplastic left heart. This contaminant was present in the public drinking water and the authors did not specify what the specific chemical or chemicals in the solvent grouping were likely to be the cause of the malformations.

A second type of malformation has been observed also from TCE drinking water exposures. In a study Bove et al. (19) of drinking water contamination in 75 towns in Northern New Jersey increased odds ratios greater than 1.5 were found for TCE and central nervous system defects, neural tube defects and oral cleft defects. For levels greater than 10ppb the odds ratios were 1.7, 2.5 and 1.3, respectively. In a case control study in Finland of oral clefts it was observed that solvents were a risk factor Holmberg et al. (20-21).

These ecological studies are very suggestive of the teratogenic potential of TCE at drinking water contamination levels. It is further strengthened by the fact that in the Arizona study once the contaminated wells were closed the increased rate of malformations ceased and that animal studies have replicated the effect.

NEUROTOXICITY

TCE is well established as a neurotoxin. The State of California (22) has used the study by Vandervort et al. (23) to determine a reference standard for non-cancer chronic effects. This study of TCE exposed workers showed non-specific neurotoxicological endpoints (e.g. eye irritation, drowsiness, dizziness etc.). A drinking water and TCE study was carried out by White et al. (24). The study involved neurological testing of individuals in 3 areas with high levels of TCE present in their drinking water (Mass., Ohio and Minn.). These examinations resulted in the authors' observation that "chronic environmental exposures to solvents at surprisingly low levels (parts per billion) can be associated with significant behavioral deficits as measured by neuropsychological tests." Further the data suggested that the exposures affect the CNS and the younger individuals showed a greater range of neurological deficits. In animal studies Isaacson et al. (25) it has been shown that TCE produces a loss of myelin in the brain stem and the sheaths in the spinal cord.

HEPATOTOXICITY

TCE is metabolized primarily in the liver and as such the liver will be exposed to relatively high levels of TCE metabolites. In a study of workers exposed to TCE Chia et

al. (26) observed a disruption of peripheral endocrine function which could be the result of TCE-induced liver malfunction. The researchers also observed an effect on serum insulin levels that depended on the duration of TCE exposure Goh et al. (27). In a second study Driscoll et al. (28) of TCE exposed workers the researchers showed increased levels of plasma bile acid concentrations in the exposed workers. This effect has also been shown in laboratory rats in a dose response manner. The bile acid concentrations are likely to be a more sensitive indicator of hepatic effects of solvents than the usual liver function tests. Finally in a worker study by Nagaya et al. (29) it was suggested that exposure to low-level TCE influences hepatic functions affecting cholesterol metabolism. The U.S. EPA used the exposure values in these studies (26-27) to support their development of an RfC (reference concentration) for TCE for use in exposure stand setting.

CONNECTIVE TISSUE DISEASES

TCE has been reported to be associated with various connective diseases. A few epidemiological studies have weakly linked solvent exposures and TCE with systemic sclerosis and undifferentiated connective tissue disease (30). There has been a lack of observed dose response and also there needs to be study replication. In a case-control study of scleroderma (178 cases and 200 controls) Nietert et al. (31) found a significant odds ratio of 2.9 for solvent exposure for both cumulative exposure and high maximum intensity exposure and comparing high maximum intensity of TCE exposure the odds ratio was 3.3 (1.0-10.3). In a large case-control study of scleroderma (660 cases and 2.227 controls) Garabrant et al. (32) found increased risk in women from solvent exposures but the risk did not increase with duration of exposure. TCE exposures increased the scleroderma risk but not significantly so.

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