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Evaluating the Risk of Liver Cancer in Humans Exposed to Trichloroethylene Using Physiological Models

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Trichloroethylene (TCE) is a widespread environmental pollutant. TCE is classified as a rodent carcinogen by the U.S. Environmental Protection Agency (EPA). Using the rodent cancer bioassay findings and estimates of metabolized dose, the EPA has estimated lifetime exposure cancer risks for humans that ingest TCE in drinking water or inhale TCE. In this study, a physiologically based pharmacokinetic (PB-PK) model for mice was used to simulate selected gavage and inhalation bioassays with TCE. Plausible dose-metrics thought to be linked with the mechanism of action for TCE carcinogenesis were selected. These dose-metrics, adjusted to reflect an average amount per day for a lifetime, were metabolism of TCE (AMET, mg/kg/day) and systemic concentration of TCA (AUCTCA, mg/L/day). These dose-metrics were then used in a linearized multistage model to estimate AMET and AUCTCA values that correspond to liver cancer risks of 1 in 1 million in mice. A human PB-PK model for TCE was then used to predict TCE concentrations in drinking water and air that would provide AMET and AUCTCA values equal to the predicted mice AMET and AUCTCA values that correspond to liver cancer risks of 1 in 1 million. For the dose-metrics, AMET and AUCTCA, the TCE concentrations in air were 10.0 and 0.1 ppb TCE (continuous exposure), respectively, and in water, 7 and 4 μg TCE/L, respectively.

KEY WORDS: Trichloroethylene; risk assessment; cancer; trichloroacetic acid; physiologically based pharmacokinetic modeling.

1. INTRODUCTION

Trichloroethylene (TCE) is a common and persistent environmental contaminant found in groundwater near most large cities and at Superfund landfill sites. Because of the widespread distribution of TCE in the environment, a significant fraction of the population may ingest or inhale TCE over an extended period of time. Typically, environmental concentrations of TCE are in the ppb range.[1] Health concerns for environmental exposure to TCE stem largely from positive outcomes in laboratory cancer bioassay studies with rodents.[2] Epidemiological evidence that TCE is a human carcinogen is equivocal.[2]

Several investigators have attempted to gain insights into the mechanisms by which TCE exerts its carcinogenic effects. TCE is a very weak mutagen,[3] and does not react appreciably with DNA,[4] which suggests that tumor formation is caused by an epigenetic mechanism. Recent studies with B6C3F1 mice have linked two metabolites of TCE, dichloroacetic acid (DCA) and trichloroacetic acid (TCA), with liver cancer.[5,6] Thus, metabolic activation is apparently required for TCE to exert its carcinogenic effect. TCE is metabolized by the cytochrome P450 system, yielding a transient epoxide which rapidly undergoes an intramolecular rearrangement to form trichloroacetaldehyde,[7] which is either oxidized to TCA or reduced to trichloroethanol. Other minor metabolites are formed via dechlorination reac-

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tions (oxalic acid, carbon dioxide, and DCA).[8] There is little evidence that trichloroethylene oxide acts as an electrophile and causes mutations in DNA or tissue damage,[9] even though an epoxide intermediate is often involved in carcinogenesis for other chemicals.[10] Bull and colleagues[5] have recently proposed that tumorigenesis of DCA involves stimulation of cell division and that tumorigenesis of TCA involves free radical formation.

The U.S. Environmental Protection Agency (EPA) has estimated the health risks of cancer for humans exposed chronically to low concentrations of TCE using data from rodent cancer bioassay studies.[2,11] Their risk analysis approach used a nonthreshold dose–response model (linearized multistage model) to estimate an excess cancer risk of 1 in 1 million in humans based on the surface-area-adjusted amounts of TCE metabolized in the cancer bioassay rodents. In the first EPA document,[2] cancer risk estimates for human exposure to TCE (ingestion and inhalation) were determined using rodent cancer bioassays in which rodents were gavaged with TCE. Various target organs and types of cancer were included in the cancer risk calculations. In a more recent draft document,[11] the EPA estimated human cancer risks for inhalation of TCE using TCE inhalation rodent cancer bioassay studies. Again, various target organs and types of cancer were used in the cancer risk calculations. In the latter EPA report, a classical first-order compartmental model for TCE was used to estimate the amount of TCE metabolized by the rodents exposed to TCE vapors.[11]

A shortcoming in the EPA TCE risk analysis methodology is that proper metabolic studies were not undertaken to quantitatively characterize the metabolism of TCE in rodents; that is, studies were not performed to determine metabolic rate constants for TCE. Instead, metabolism of TCE in rodents was characterized using published rodent metabolic studies on TCE that were not designed for quantitative analysis. Consequently, it is unclear if the TCE cancer risk estimates are based on reasonable estimates of metabolized dose.

Another shortcoming in the EPA risk methodology for TCE is that metabolism of TCE in humans was not critically evaluated. The estimates of the metabolized dose in the rodent bioassays were adjusted by a body-surface, dose-equivalence factor prior to use in the linearized multistage model. This adjustment factor was used for extrapolation of dose from rodents to humans.[2,11]

This paper demonstrates the application of physiologically based pharmacokinetic (PB-PK) modeling to account for metabolic differences between mice[12] and humans[13] for assessing the liver cancer risks in humans exposed to TCE over their lifetime. This risk assessment approach for TCE represents a refinement in the proposed EPA's risk assessment methodology for TCE.

2. METHODS

2.1. Risk Analysis Approach

The carcinogenic activity of TCE in human livers was estimated from rodent cancer bioassay studies. Two TCE cancer bioassays,[14,15] an inhalation study and a gavage study, were selected from numerous TCE cancer bioassays conducted with rats and mice.[2,11] These two cancer bioassays were selected for analysis because in both cancer bioassays liver tumors were produced in B6C3F1 mice, a sensitive rodent strain. In addition, dose–response relationships for two routes of exposure could be examined.

The guiding philosophy for this TCE risk analysis was that with the development of generic PB-PK models for TCE in mice and humans,[12,13] metabolism of TCE could be quantitatively characterized in both species and used in the assessment of liver cancer risks. In summary, to estimate the liver cancer risks for humans exposed to TCE, a PB-PK model for TCE in B6C3F1 mice was used to simulate the cancer bioassay mice exposures for oral ingestion and inhalation of TCE.[14,15] Plausible dose-metrics of exposure related to metabolism of TCE (e.g., amount of TCE metabolized) were determined and liver cancer incidence rates were then compared with the corresponding dose-metric values. After selection of the appropriate dose-metric(s), a linearized multistage model (LMS)[16] was used to predict excess cancer risks of 1 in 1 million for liver cancer in mice. These predicted dose-metric values then became the "internal target doses" that, given equal tissue response per lifetime for mice and humans, would produce excess cancer risks of 1 in 1 million in humans.

Descriptions of the four-compartment PB-PK model used to describe the kinetic behavior of TCE and the classical model used to describe the production and systemic clearance of TCA in mice and humans are presented elsewhere.[12,13] Simusolv (Dow Chemical Company) was used to simulate the TCE exposures for the mice cancer bioassays and the human TCE exposures.

2.2. Bioassay Simulations

PB-PK model parameters for the mouse and human are presented in Tables I and II. The PB-PK model structure is similar to the model structure for styrene.[17]

Table I. Physiological Model Parameters for Humans and Mice

	Female mice	Male mice	Human
Tissue group (fraction of body wt)			
Liver	0.04	0.04	0.026
Richly perfused	0.05	0.05	0.050
Slowly perfused	0.72	0.78	0.620
Fat	0.10	0.04	0.190
Flow (L/hr)			
Alveolar ventilation	$30 \cdot bW^{0.74}$	$30 \cdot bW^{0.74}$	$12.6 \cdot bW^{0.74}$
Cardiac output (CO)	$30 \cdot bW^{0.74}$	$30 \cdot bW^{0.74}$	$14.9 \cdot bW^{0.74}$
Tissue group (fraction of CO)			
Liver	0.24	0.24	0.26
Richly perfused	0.52	0.52	0.44
Slowly perfused	0.19	0.19	0.25
Fat	0.05	0.05	0.05

Table II. Kinetic Constants for Modeling TCE and TCA in Humans and Mice

	Female mice	Male mice	Human
Partition coefficients per tissue group			
Liver/blood	1.62	2.03	6.82
Richly perfused/blood	1.62	2.03	6.82
Slowly perfused/blood	0.48	1.00	2.35
Fat/blood	31.4	41.3	73.3
Blood/air	14.3	13.2	9.20
TCE metabolic rate constants			
V_{max_c} (mg/kg/hr)[a]	23.2	32.7	14.9
K_m (mg/L)	0.25	0.25	1.5
TCA kinetic constants			
Inhalation			
VDC (L/kg)	0.176	0.238	$0.34 - 0.0034 \cdot bW$
K_{el} (/hr)	0.104	0.043	0.029
PO[b] (unitless)	0.18 – 0.07	0.13 – 0.07	0.0336
Gavage			
VDC (L/kg)	0.176	0.238	
K_{el}[c] (/hr)	0.062 (0.003)	0.028 (0.002)	
PO (unitless)	0.09	0.06	
K_1[c] (/hr)	0.9 (0.110)	1.1 (0.071)	

[a] Scaled as $bW^{0.74}$.

[b] PO values determined for a range of TCE exposure concentrations.[12]

[c] The value in parentheses is the computer-generated standard deviation for the optimized parameter. K_{el} is the plasma elimination rate constant for TCA and K_1 is the "effective" TCE gastrointestinal uptake rate constant.

The NCI TCE gavage bioassay[14] dosing schedule and the Maltoni *et al.* TCE inhalation bioassay[15] exposure schedule were simulated for male and female B6C3F1 mice over a 7-day period. Animals in this gavage bioassay were dosed 5 days/week with weekends off and animals in the inhalation bioassay were exposed for 7 hr/day, 5 days/week, with weekends off. According to the model simulations, TCE cleared systemic circulation between each daily dosing or inhalation exposure and TCA accumulated during the week from daily TCE dosing or inhalation exposure and was then cleared from systemic circulation over the weekend.

In B6C3F1 mice, the percent of metabolized TCE that is converted to TCA (PO) is dependent on the TCE vapor concentration.[12] To estimate a yield of TCA in B6C3F1 mice gavaged with TCE dissolved in corn oil was difficult because the kinetics of oral uptake of TCE into systemic circulation was more complex (see Results, Fig. 1) than the kinetics of inhaled TCE. The yield of TCA (PO) for the gavaged mice was simply estimated for each sex by fitting the simulated TCA plasma concentrations with the measured TCA plasma concentrations.

Potential dose-metrics or internal measures of dose, related to metabolism of TCE in B6C3F1 mice, were: (1) lifetime average daily total amount of TCE metabolized (AMET, mg/kg/day); (2) lifetime average daily amount of TCA formed (FTCA, mg/kg/day); and (3) lifetime average daily area-under-the-concentration-curve for TCA in plasma (AUCTCA, mg/L/day). The average daily dose-metric value was calculated by multiplying the cumulative 7-day dose-surrogate value by 1/7. The average daily dose-metric value was then multiplied by the fraction of lifetime exposure to TCE (78 weeks/104 weeks) to obtain the lifetime average value for the dose-metric on a per day basis.[2] Correspondence between dose-metric values and liver cancer incidence rates was investigated in each treatment group and appropriate dose-metric(s) selected for liver cancer risk analysis.

2.3. Linearized Multistage Model and Human PB-PK Model

A linearized multistage model[16] was used to estimate the lower bound of the 95% confidence interval for the selected dose-metric value that corresponded to an excess risk of 1 in 1 million risk for liver cancer. The LMS calculations were determined for extra risk using the Monte Carlo method. These calculations were performed with male and female mice for inhalation and oral ingestion of TCE. These dose-metric values in male and female mice then became "target" internal dose

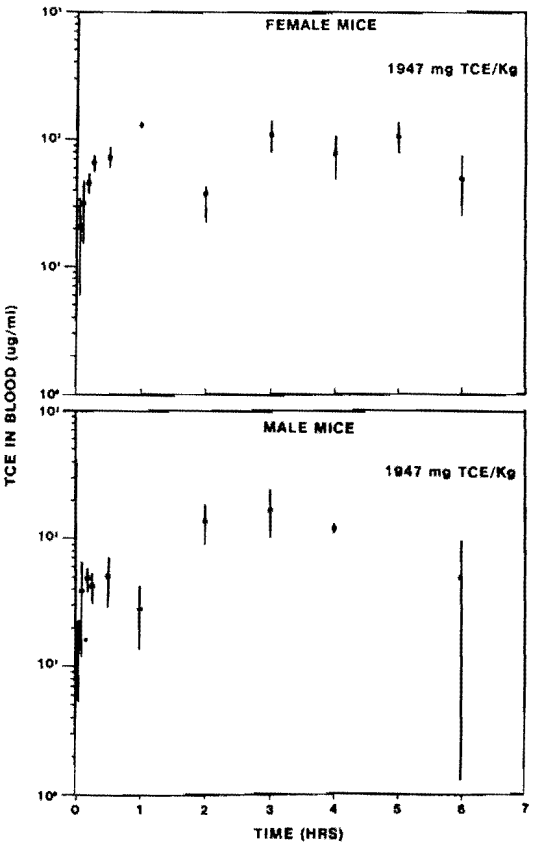

Fig. 1. Venous blood concentrations of TCE in male and female mice gavaged with 1947 mg TCE/kg body weight. Each vertical bar represents the standard deviation of the measured TCE blood concentration.

measures for assessing the risk of liver in humans exposed to TCE in drinking water and air.

To obtain the "target" internal dose-metric values for humans, a human PB-PK model[13] for TCE and TCA was exercised by varying the exposure concentration for inhalation of TCE vapors and for oral ingestion of TCE in water. Because human consumption of drinking water is variable, the drinking water exposure model was configured to simulate two drinking water scenarios, a single 2 L bolus ingestion of water per day or four equal bolus ingestions of water, totaling 2 L, over a 12 hr period per day (0.5 L per ingestion). For modeling purposes, the rate of gastrointestinal absorption of TCE dissolved in water was described as first order with a rate constant value of 5.5/hr.[12,18]

Dose-metric values for human exposure to TCE in drinking water were calculated on a per-day basis at steady state by simulating repeated daily TCE exposures which lasted for 44 and 45 days and determining the difference between the cumulative time-dependent dose-metric values. Oral ingestion of TCE was assumed to occur 7 days per week. For vapor exposure to TCE, two exposure conditions were considered; continuous exposure, 24 hr/day, 7 days/week, and an intermittent exposure, 7 hr/day, 5 days/week. Forty-four and 45 day repeated TCE exposures were simulated to determine an average daily dose-metric value at steady state for the continuous exposure scenario and 42 day and 49 day repeated TCE exposures for the intermittent exposure scenario. The average weekly dose-metric value for intermittent exposure was adjusted (multiplied by 1/7) to obtain an average daily dose-metric value.

2.4. Experimental

The development of a PB-PK model for inhalation of TCE vapors in B6C3F1 mice has been previously reported.[12] The kinetics for gastrointestinal absorption of large doses of TCE dissolved in corn oil is described in Results. Each male and female B6C3F1 mouse (obtained from Charles River Breeding Laboratories, Kingston, New York) was given a bolus oral intubation of TCE dissolved in 3.3 ml corn oil/kg body weight. Each mouse was dosed with either 1947.0, 973.0, or 487.0 mg TCE/kg. Three or four mice were killed by carbon dioxide asphyxiation at selected time periods after dosing and blood collected from the inferior vena cava for analyses of TCE and TCA. TCE-blood and TCA-plasma concentrations were determined according to the methods of Fisher *et al.*[12,19]

3. RESULTS

3.1. Experimental

The oral uptake kinetics of TCE in corn oil was complex and could not be described by simple first-order kinetics (Fig. 1). Systemic uptake of TCE was prolonged over many hours and appeared to be episodic. Because of the complexity in the behavior of oral uptake of TCE, an "effective" first-order uptake rate constant (K_1) for TCE was determined for male and female mice (Table II) based on the production of TCA. This was accomplished by visually fitting the model predicted TCA plasma concentrations with the measured TCA plasma concentrations. K_1 was initially set to a value 1.0/hr for each dose group and sex of mouse. The plasma elimination rate constant value, K_{el} (/hr) was optimized for each

gavage dose group and sex and an average K_{el} value was calculated for each sex (Table II). Using the average K_{el} values for each sex, K_1 values were then refined by optimization for each dose group and sex and an average K_1 value was calculated for each sex (Table II).

In male mice, the peak measured plasma concentrations for the 487.0, 973.0, and 1947 mg/kg groups were 82.0, 91.0, and 94.0 μg TCA/ml, respectively, and in female mice, 69.0, 44.0, and 89.0 μg TCA/ml, respectively. Female mice cleared TCA from systemic circulation more quickly than male mice. The plasma elimination rate constants and volume of distribution values for TCA in mice are reported in Table II.

3.2. Bioassay Simulations

Tables III and IV display the dose-metric values corresponding to the inhalation and gavage TCE exposures of the cancer bioassays. Also shown are the liver cancer incidence rates observed in the TCE cancer bioassays.

The dose-metric values presented in Tables III and IV were visually compared to corresponding liver cancer incidences rates by sex, within and among treatment groups (gavage and inhalation). For each sex, the dose-metric, AMET, appeared to be consistent, in a qualitative fashion, with liver cancer rates for both the gavage and inhalation bioassays. That is, increases in AMET values were associated with increases in the liver cancer rates, although the correspondence was not one to one. When comparing AMET values across routes of exposure (gavage and inhalation), for both male and female mice, the gavage route resulted in lower AMET values than those from the high and middle inhalation concentrations, despite the fact that the gavage doses yielded higher liver cancer rates.

Table III. Dose-Metric Values for TCE Vapor Exposures in B6C3F1 Mice[15]

TCE exposure ppm	Liver cancer incidence[a]	Dose-metric AMET (mg/kg/day)	FTCA (mg/kg/day)	AUCTCA (mg/L/day)
Female mice (PO)				
600.0 (0.08)	9/87	285.7	28.4	553.0
300.0 (0.07)	4/89	249.7	21.7	422.8
100.0 (0.18)	3/90	111.5	25.0	485.5
0.0	2/90	—	—	—
Male mice				
600.0 (0.07)	6/88	355.9	31.0	1112.7
300.0 (0.13)	3/88	301.3	58.5	1740.9
100.0 (0.11)	1/86	108.4	14.8	530.0
0.0	1/85	—	—	—

[a] Hepatomas include all malignant tumors of hepatic cells. No statistically significant increases in hepatoma incidences were detected in male mice.[15] A large portion of these mice died during the bioassay.[15]

Table IV. Dose-Metric Values for B6C3F1 Mice Gavaged with TCE[14]

TCE dose (mg/kg)	Liver cancer incidence[a]	Dose-metric AMET (mg/kg/day)	FTCA (mg/kg/day)	AUCTCA (mg/L/day)
Male mice				
2339.0	31/48	211.4	15.8	857.2
1169.0	26/50	176.5	13.2	715.5
0.0	1/20	—	—	—
Female mice				
1739.0	11/47	196.2	21.0	695.6
869.0	4/50	158.7	17.7	562.7
0.0	0/20	—	—	—

[a] Hepatocellular carcinoma.

For the dose-metric related to the production of TCA (FTCA), there was little correspondence with liver cancer rates across routes of exposure (Table III).

The most compelling relationship observed was the correlation of female mice AUCTCA values for the inhalation and gavage TCE exposures with corresponding liver cancer rates (Fig. 3). The linear regression correlation coefficient was 0.95 when extra liver cancer rates (which account for cancer rates in control mice) were regressed on AUCTCA values for the two routes of exposure. Another observation was that the AUCTCA dose-metric values for male and female mice were consistent with liver cancer rates across sex in the gavage studies; the AUCTCA values associated with the male gavage exposures were greater than those associated with the female gavage exposures, as were the observed cancer rates (Table IV). This was not true for the inhalation studies. There was poor correspondence between AUCTCA values and cancer rates in the male mice exposed via inhalation.

3.3. Dose-Metric Selection

The gavage bioassay mice were used to estimate liver cancer risks for ingestion of TCE in drinking water and the inhalation bioassay mice were used to estimate liver cancer risks for inhalation of TCE vapors. AMET was selected as one plausible dose-metric for estimating human liver cancer risks because the AMET values were, in general, consistent with liver cancer rates within the

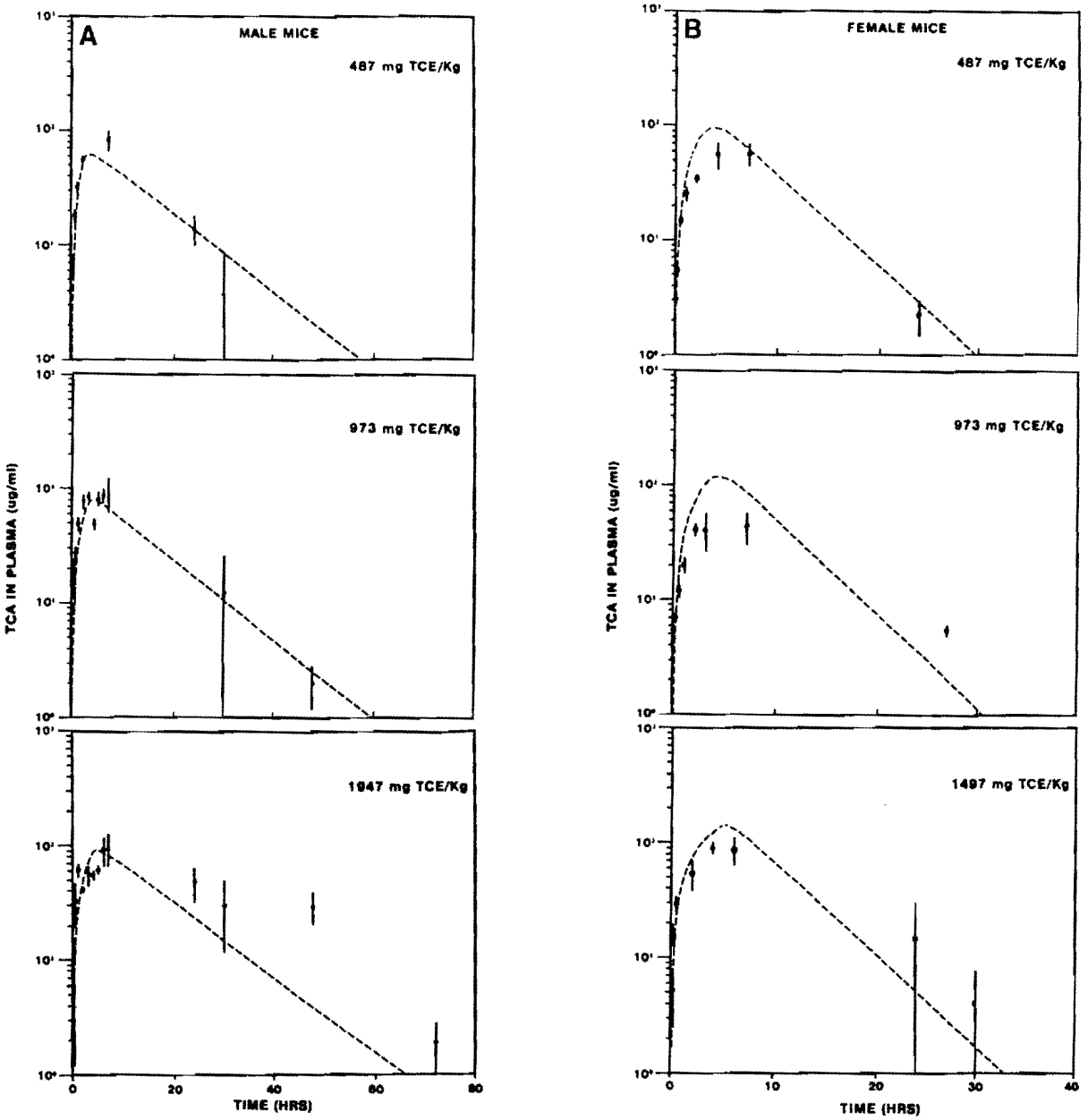

Fig. 2. Venous plasma concentrations of TCA in male (A) and female (B) mice gavaged with either 487, 973, and 1947 mg TCE/kg body weight. Each vertical bar represents the standard deviation of the measured TCA plasma concentrations. The dotted line depicts the computer-simulated TCA plasma concentration.

four data sets (Tables III and IV), although the relationship was not linear. Additionally, the EPA used this dose-metric in their TCE risk assessment approach.[2,11] AUCTCA was selected as a complimentary dose-metric for liver cancer risk analysis because of its strong correlation with liver cancer rates in female mice across both routes of exposure (Fig. 3).

3.4. Dose–Response Modeling and Human Cancer Risks

Table V reports the 95% lower bounds on dose-metrics, AMET and AUCTCA, for a risk level of 1 in 1 million. The dose-metric AUCTCA provided greater

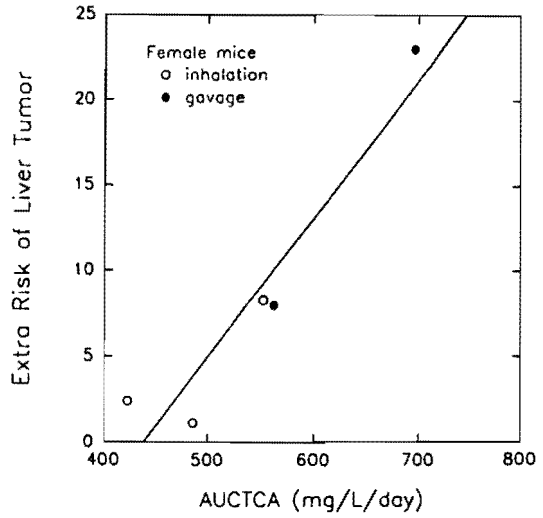

Fig. 3. Linear regression analysis (R^2 = 0.95) of the dose-metric AUCTCA and extra liver tumor risk for female cancer bioassay mice exposed to TCE via gavage and inhalation.

$$\text{Extra risk} = \frac{P(d) - P(o)}{1 - P(o)}$$

where $P(d)$ is the liver cancer incidence at dose d and $P(o)$ is the observed control (background) liver cancer incidence.

Table V. Linearized Multistage Modeling with AMET and AUCTCA

Route of exposure	Sex of mice	95% lower bound on dose-metrics at 1.0E-6 risk (mg/kg/day) AMET	AUCTCA
Inhalation			
	Male	5.200E-3	
	Female	3.223E-3	8.081E-3
Gavage			
	Male	1.875E-4	
	Female	1.024E-3	3.632E-3

human liver cancer risk estimates than AMET (Table VI).

For continuously inhaled TCE vapors, the concentrations estimated to produce an excess risk of liver cancer in humans equal to 1 in 1 million for the dose-metrics, AMET and AUCTCA, were 10–15 ppb and 0.1 ppb, respectively. For the intermittent inhalation exposures, like those encountered in occupational settings, the estimated concentrations were 42–69 ppb and 0.2 ppb, respectively, for the AMET and AUCTCA dose-metrics (Table VI).

Table VI. TCE Concentrations in Drinking Water and Air

	Human TCE exposures for 1.0E-6 risk		
	Male mice	Female mice	
Route of exposure	AMET	AMET	AUCTCA
Inhalation (ppb)			
Continuous	15.0	10.0	0.1
Intermittent	69.0	42.0	0.2
Drinking water (μg/L)	7.0	39.0	0.004

For ingestion of drinking water containing TCE, the one drink per day (2 L bolus ingestion) and four drinks per day (0.5 L bolus ingestions) simulations did not differ significantly with respect to predicted dose-metrics or liver cancer risks (data not shown). The TCE drinking water concentrations estimated to produce an excess risk of liver cancer equal to 1 in 1 million in humans were 7–39 μg TCE/L and 4.0 ng TCE/L for the AMET and AUCTCA dose-metrics, respectively (Table VI).

4. DISCUSSION

4.1. Cancer in Rodents

The primary cancer findings for TCE in rats are renal adenocarcinoma, leukemia, and leydig cell tumors.[2] Negative findings have been reported as well in rats. In mice, lung and liver tumors represent the most significant positive findings.[2,11] For risk assessment purposes, the lung and liver of the B6C3F1 mouse represent the most sensitive organs in the TCE cancer bioassays.

Considering the stage of development of the dosimetry model for TCE and TCA and the current understanding of TCE-induced liver cancer, AMET and AUCTCA were selected as appropriate metrics for liver cancer risk analysis, despite the divergent outcomes in risk (Table VI). An implicit assumption for these dose-metrics is that on a per weight or volume basis, the human liver is less sensitive than the mouse liver. From a research perspective, the dose-metrics, AMET and AUCTCA provide focus for further research investigations. The general correspondence between the amount of TCE metabolized (AMET) and liver cancer rates and the strong correlation between TCA plasma concentrations (AUCTCA) and liver cancer rates in the female

mice (Fig. 3), both suggest that metabolism of TCE and the production of one of its stable metabolites, TCA, are important events linked to TCE-induced liver cancer.

4.2. Liver Cancer Risks in Humans

The EPA health assessment document on TCE[2] reports a 1 in 1 million excess risk of liver cancer in humans for a lifetime ingestion of water containing 3.1 μg TCE/L water and for a lifetime continuous inhalation of 0.14 ppb TCE vapors. These TCE concentrations are based on the geometric mean of potency calculations (1.3×10^{-2} mg/kg/day) for liver cancer from two gavage cancer bioassays using B6C3F1 mice, including the NCI, 1976 cancer bioassay[14] used in this liver cancer risk analysis. The EPA-derived TCE concentrations for drinking water and air that correspond to a lifetime excess cancer risk of 1 in 1 million are less than the PB-PK-derived TCE concentrations using AMET by a factor of 2 for ingestion of TCE in drinking water (using gavage dosed male mice, Table VI) and a factor of 71 for continuous inhalation of TCE (using vapor exposed female mice, Table VI). The PB-PK-derived TCE concentrations corresponding to an excess risk of liver cancer of 1 in 1 million using AUCTCA are less than the EPA-derived TCE concentrations by a factor of 775 for ingestion of TCE in drinking water and a factor of 1.4 for continuous inhalation of TCE vapors (Table VI).

In a more recent draft addendum to the Health Assessment Document on TCE,[11] the EPA, using a classical compartmental model for vapor exposure to TCE estimated that a continuous lifetime vapor exposure of 0.21 ppb of TCE would correspond to an excess liver cancer risk of 1 in 1 million. This TCE exposure concentration is based on the geometric mean of 2 potency calculations (8.7×10^{-3} mg/kg/day) of liver cancer from two strains of mice.[11] The EPA-derived TCE concentration that corresponds to a lifetime excess cancer risk of 1 in 1 million is 48 times lower than the PB-PK-derived TCE concentration (using vapor exposed female mice, Table VI) using the dose-metric, AMET, and is 2.1 times higher using the dose-metric, AUCTCA.

PB-PK modeling is a useful tool for the chemical risk assessment process. PB-PK-based cancer risk assessments have been conducted for methylene chloride,[20] 1,4-dioxane,[21] chloroform,[22] and perchloroethylene (for a review, see Ref. 23). The key issue for PB-PK-based risk assessments, however, is selection of a tissue dose measure which correlates well with the observed toxicity or tumorigenicity, and which can be plausibly linked with the mechanism of action. We concluded that the dose-metrics, AUCTCA and AMET, correlated with some, but not all of the observed cancer rates. The lack of consistent correspondence of either the TCA dose-metrics (FTCA and AUCTCA) for all data sets analyzed or the amount of TCE metabolized (AMET) with liver cancer rates observed in the bioassays suggests that further investigation into the mechanism of TCE carcinogenicity is needed to identify an effective dose-metric before further refinements in liver cancer risks can be undertaken.

An understanding of the mechanism of action by which TCE induces liver cancer in mice is needed to ascertain the cancer risks TCE poses to humans. Laboratory studies examining the role DCA plays in the cancer process may be useful. DCA can be formed by dechlorination of TCA and is more toxic than TCA.[24] The next generation risk assessment for TCE should include a quantitative mechanistically or biologically based approach for assessing the cancer risks of TCE,[25] thus replacing the linearized nonthreshold model (LMS).

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REFERENCES

1. W. E. Coleman, R. D. Lingg, R. G. Melton, and F. C. Kopfler, "The Occurrence of Volatile Organics in Five Drinking Water Supplies Using Gas Chromatography/Mass Spectrometry," in L. H. Keith (ed.), *Identification and Analysis of Organic Pollutants of Water* (Ann Arbor Science Pub., Ann Arbor, Michigan, 1976), pp. 305–327.
2. U.S. Environmental Protection Agency, "Heath Assessment Document for Trichloroethylene" (Office of Health and Environmental Assessment, Washington, D.C., EPA/600/8-82/006F, PB-249696, 1985).
3. C. R. Elcombe, "Species Differences in Carcinogenicity and Peroxisome Proliferation Due to Trichloroethylene: A Biochemical Human Hazard Assessment," *Archives of Toxicology Supplement* **8**, 6–17 (1985).
4. W. T. Stott, J. F. Quast, and P. G. Watanabe, "The Pharmacokinetics and Molecular Interactions of Trichloroethylene in Mice and Rats," *Toxicology and Applied Pharmacology* **62**, 137–151 (1982).

5. R. J. Bull, I. M. Sanchez, M. A. Nelson, J. L. Larson, and A. J. Lansing, "Liver Tumor Induction in B6C3F1 Mice by Dichloroacetate and Trichloroacetate," *Toxicology* **63**, 341–359 (1990).
6. S. L. Herren-Freund, M. A. Pereira, M. D. Khoury, and G. Olson, "The Carcinogenicity of Trichloroethylene and Its Metabolites, Trichloroacetic Acid and Dichloroacetic Acid, in Mouse Liver," *Toxicology and Applied Pharmacology* **90**, 183–189 (1987).
7. J. W. Daniel, "The Metabolism of ^{36}Cl-Labelled Trichloroethylene and Tetrachloroethylene in the Rat," *Biochemical Pharmacology* **12**, 795–802 (1963).
8. W. DeKant, A. Schultz, M. Metzler, and D. Henschler, "Absorption, Elimination, and Metabolism of Trichloroethylene: A Quantitative Comparison Between Rats and Mice," *Xenobiotica* **16**, 143–152 (1986).
9. T. Green and M. S. Prout, "Species Differences in Response to Trichloroethylene. II. Biotransformation in Rats and Mice," *Toxicology and Applied Pharmacology* **79**, 401–411 (1985).
10. D. Henschler, "Metabolism and Mutagenicity of Halogenated Olefins: A Comparison of Structure and Activity," *Environmental Health Perspectives* **21**, 61–64 (1977).
11. U.S. Environmental Protection Agency, "Addendum to the Health Assessment Document for Trichloroethylene: Updated Carcinogenicity Assessment for Trichloroethylene, draft" (Office of Health and Environmental Assessment, Washington, D.C., EPA/600/8-82/006FA, 1987).
12. J. W. Fisher, M. L. Gargas, B. C. Allen, and M. E. Andersen, "Physiologically Based Pharmacokinetic Modeling with Trichloroethylene and Its Metabolite, Trichloroacetic Acid, in the Rat and Mouse," *Toxicology and Applied Pharmacology* **109**, 183–195 (1991).
13. B. C. Allen and J. W. Fisher, "Pharmacokinetic Modeling of Trichloroethylene and Trichloroacetic Acid in Humans," *Risk Analysis* **13**, 71–86 (1993).
14. National Cancer Institute, "Carcinogenesis Bioassay of Trichloroethylene" (CAS no. 79-01-6, DHEW Publ. no. (NIH) 76-802, 1976).
15. C. Maltoni, G. Lefemine, and G. Cotti, "Experimental Research on Trichloroethylene Carcinogenesis," in C. Maltoni and M. A. Mehlman (eds.), *Archives of Research on Industrial Carcinogenesis* (Princeton Scientific, Princeton, 1986).
16. R. B. Howe and C. Van Landingham, "Global86" (Clement Associates, Ruston, Louisiana, 1986).
17. J. C. Ramsey and M. E. Andersen, "A Physiologically Based Description of the Inhaled Pharmacokinetics of Styrene Monomer in Rats and Humans," *Toxicology and Applied Pharmacology* **73**, 159–175 (1984).
18. J. W. Fisher and M. E. Andersen, "Using Inhalation Kinetic Data in the Development of Physiological Models for Oral Absorption: A Case Study with Trichloroethylene," in T. R. Gerrity and C. J. Henry (eds.), *Principles of Route-to-Route Extrapolation for Risk Assessment* (olsevier Science Publishing Co., New York, 1990), pp. 297–311.
19. J. W. Fisher, T. A. Whittaker, D. H. Taylor, H. J. Clewell, III, and M. E. Andersen, "Physiologically Based Pharmacokinetic Modeling of the Pregnant Rat: A Multiroute Exposure Model for Trichloroethylene and Its Metabolite Trichloroacetic Acid," *Toxicology and Applied Pharmacology* **99**, 395–414 (1989).
20. M. E. Andersen, H. J. Clewell, III, M. L. Gargas, F. A. Smith, and R. H. Reitz, "Physiologically Based Pharmacokinetics and the Risk Assessment Process for Methylene Chloride," *Toxicology and Applied Pharmacology* **87**, 185–205 (1987).
21. R. H. Reitz, P. S. McCroskey, C. N. Park, M. E. Andersen, and M. L. Gargas, "Development of a Physiologically Based Pharmacokinetic Model for Risk Assessment with 1,4-Dioxane," *Toxicology and Applied Pharmacology* **105**, 37–54 (1990).
22. R. H. Reitz, A. L. Mendrala, R. A. Corley, J. F. Quast, M. L. Gargas, M. E. Andersen, D. Staats, and R. B. Conolly, "Estimating the Risk of Liver Cancer Associated with Human Exposures to Chloroform Using Physiologically Based Pharmacokinetic Modeling," *Toxicology and Applied Pharmacology* **105**, 443–459 (1990).
23. D. Hattis, P. White, L. Marmorstein, and P. Koch, "Uncertainties in Pharmacokinetic Modeling for Perchloroethylene. I. Comparison of Model Structure, Parameters, and Predictions for Low-Dose Metabolism Rates for Models by Different Authors," *Risk Analysis* **10**, 449–457 (1990).
24. H. K. Bhat, M. F. Kanz, G. A. Campbell, and G. A. S. Ansari, "Ninety Day Toxicity Study of Chloroacetic Acids in Rats," *Fundamental and Applied Toxicology* **17**, 240–253 (1991).
25. R. B. Conolly and M. E. Andersen, "Biologically Based Pharmacodynamic Models: Tools for Toxicological Research and Risk Assessment," *Annual Review of Pharmacology and Toxicology* **31**, 503–523 (1991).