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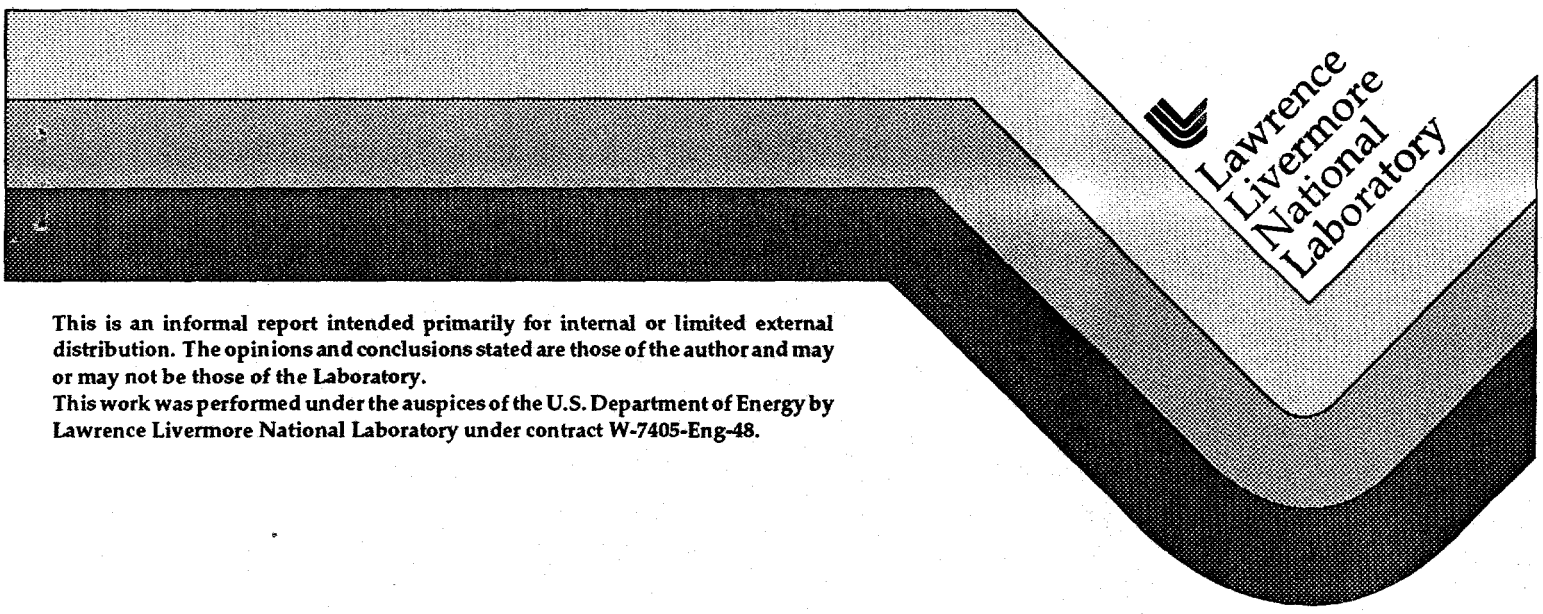

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Abstract

Scientific developments in the 1990's have important implications for the assessment of cancer risks posed by exposures to trichloroethylene (TCE). These new developments include: epidemiological studies; experimental studies of TCE carcinogenicity, metabolism and metabolite carcinogenicity; applications of new physiologically based pharmacokinetic (PBPK) models for TCE; and new pharmacodynamic data obtained for TCE and its metabolites. Following a review of previous assessments of TCE carcinogenicity, each of these new sets of developments is summarized. The new epidemiological data do not provide evidence of TCE carcinogenicity in humans, and the new pharmacodynamic data support the hypothesis that TCE carcinogenicity is caused by TCE-induced cytotoxicity, which is likely to have a threshold-like dose-response. Based on this information, PBPK-based estimates for likely no-adverse effect levels (NOAELs) for human exposures to TCE are calculated, using a 1000-fold safety factor, to be 0.090 μg/L (16 ppb) for TCE in air respired 24 hr/day, and 210 ppb for TCE in drinking water (assuming 2-L/d ingestion). Cancer risks of zero are predicted for TCE exposures below these calculated NOAELs. For comparison, hypothetical cancer risks posed by lifetime ingestive and multiroute household exposures to TCE in drinking water, at the currently enforced Maximum Contaminant Level (MCL) concentration of 5 ppb (e.g., present in ground water at or near a hazardous waste site), are extrapolated from animal bioassay data using a conservative, linear dose-response model, accounting quantitatively for several sources of uncertainty in cancer-potency estimation. These TCE-related risks are compared to corresponding ones associated with concentrations of chlorination by-products (CBP) in household water expected at the 80-ppb MCL for total trihalomethanes currently proposed by EPA. It is shown that, from the standpoint of comparative hypothetical cancer risks, based on conservative linear dose-response extrapolations, there would likely be no health benefit, and more likely a possible health detriment, associated with any switch from a household water supply containing <375 ppb TCE to one containing CBP at levels corresponding to the currently proposed 80-ppb MCL for total trihalomethanes. [This work was performed under the auspices of the U.S. Department of Energy at Lawrence Livermore National Laboratory under contract W-7405-ENG-48, with funding provided by Lawrence Berkeley Laboratory.]

Contents

Introduction

Scientific developments have occurred in the 1990's that have important implications for the assessment of cancer risks posed by exposures to trichloroethylene (TCE). These developments include: new epidemiological studies; new experimental studies of carcinogenicity, metabolism and metabolite carcinogenicity; applications of new physiologically based pharmacokinetic (PBPK) models for TCE; and new pharmacodynamic data obtained for TCE and its metabolites. The new epidemiological data do not provide evidence of TCE carcinogenicity in humans, and the new pharmacodynamic data support the hypothesis that TCE carcinogenicity is caused by TCE-induced cytotoxicity, which is likely to have a threshold-like dose-response. Based on this new information, PBPK-based estimates for likely no-adverse effect levels (NOAELs) for human exposures to TCE can now be calculated using relatively simple, steady-state analytic methods. Cancer risks of virtually zero would be predicted for TCE exposures below such calculated NOAELs.

For comparison, cancer risks posed by lifetime ingestive and multiroute household exposures to TCE in drinking water may also be extrapolated from animal bioassay data using a conservative, linear dose-response model. Such calculations can account quantitatively for several sources of uncertainty in cancer-potency estimation based on such bioassay data. TCE-related risks thus calculated may then be compared to corresponding ones associated, for example, with concentrations of chlorination by-products in household water derived from supplies that have been treated by

chlorination for disinfection purposes, as is commonly done with many surface-water supplies. After such analyses, the potential cancer risk of TCE in household water may be compared to that posed by other chemicals, such as chlorination by-products, that might be present in a substitute water supply used to replace one contaminated with trace amounts of TCE.

Previous assessments of TCE carcinogenicity are reviewed below in Section 1, followed by a summary of new developments in TCE-related epidemiology, carcinogenicity, and metabolite carcinogenicity, and related PBPK applications and pharmacodynamic data in Sections 2-5. Based on this new information, new PBPK-based NOAELs are obtained in Section 6 for human exposures to TCE. Finally, in Section 7, cancer risks of zero predicted for exposures below these calculated NOAELs are compared to hypothetical risks associated with lifetime ingestive and multiroute household exposures to TCE in drinking water, at the currently enforced Maximum Contaminant Level (MCL) concentration of 5 ppb (e.g., present in ground water at or near a hazardous waste site), extrapolated from animal bioassay data using a conservative, linear dose-response model, accounting quantitatively for several sources of uncertainty in estimated cancer potency. The calculated TCE-related risks are compared to corresponding ones associated with concentrations of chlorination by-products in household water expected at the 80-ppb MCL for total trihalomethanes currently proposed by EPA.

1. Previous (Pre-1990's) Studies of TCE Carcinogenicity

1.1. Human Epidemiology

Human epidemiological evidence for TCE carcinogenicity based on studies reported through 1990 have generally been interpreted as negative or as inadequate to assess human carcinogenicity of TCE (IARC, 1982,1988; EPA, 1995; Bogen et al., 1988; Fan, 1988; Brown et al., 1990). These studies include a study of 1424 men occupationally exposed to TCE (as demonstrated by urinary excretion of TCA, at <100 mg/L urine for 90% of those exposed) showed an overall deficit in total cancer mortality, but a significant excess of urogenital tract cancers (11 observed vs. 4.8 expected) and hematolymphatic malignancies (5 cases vs. 1.2 expected), which were not interpreted as exposure-related (Axelson, 1986). Two earlier studies, each involving similar groups (>2000 workers) potentially or actually (as confirmed by TCA in urine) exposed to TCE, failed to find greater than expected cancer mortality in those studied (Tola et al., 1980; Shindall and Ulrich, 1985), as did some smaller case-control studies that focused specifically on liver cancer (Novatna et al., 1979; Malek et al., 1979; Paddle, 1982; Hernberg et al., 1984). A possible association of TCE exposure and elevated incidence of hematolymphatic malignancies was suggested in four studies of workers (*e.g.*, laundry or dry cleaning workers) exposed to relatively high solvent concentrations in air; however, specific TCE exposure levels were not determined in any of these studies (Blair et al., 1979; Olsson and Brandt, 1980; Hardell et al., 1981; Katz and Jowett, 1981).

1.2. Animal Studies

TCE is a rodent carcinogen in some standard bioassay studies, in which it has been found to elicit significant elevation of malignant and/or malignant+benign tumor incidence in male and female mice of multiple strains in lifetime corn-oil-gavage and/or inhalation bioassays, as well as increased incidences of tumors in male rats in lifetime

inhalation bioassays (see, e.g., Gold et al., 1984,1986,1987,1990,1993a; EPA, 1985). Positive tumorigenic responses observed in these studies include increased incidences of: hepatocellular carcinomas in male and female B6C3F1 mice dosed by gavage 5 day/wk in corn oil or 7 hr/day for 5 day/wk by inhalation (NCI, 1976; Bell et al., 1978; Fukuda et al., 1983; NTP, 1990), malignant lymphomas in female Han:NMRI mice dosed 6 hr/day for 5 day/wk by inhalation (Henschler et al., 1980), pulmonary tumors and/or malignant hepatomas in male Swiss and female B6C3F1 mice dosed 7 hr/day for 5 day/wk by inhalation (Maltoni et al., 1986), and Leydig cell (testicular) tumors in male Sprague-Dawley rats dosed 7 hr/day for 5 day/wk by inhalation and by gavage in corn oil (Maltoni et al., 1986). All of the NCI studies and some of the NTP studies used TCE with epichlorhydrin as a stabilizer; epichlorhydrin was later determined to be carcinogenic (see EPA, 1985; Bogen et al., 1988). In the Henschler et al. (1980) study, the TCE contained only 0.0015% triethanolamine as a stabilizer. In the study by NTP (1990), TCE without epichlorhydrin was found to induce significant increases in lung and liver tumor incidence in male and female B6C3F1 mice. Purified TCE specifically without epichlorhydrin (again containing only 0.0015% triethanolamine as a stabilizer), administered by gavage 5 day/wk in corn oil to 50 male and female Swiss (ICR/HA) mice at doses of ~2 g/kg, was not found to elicit tumors (Henschler et al., 1984). However, due to decreased survival observed in dosed animals in the NTP study, gavage was stopped for all groups during weeks 35-40, 65 and 69-78, and all doses were reduced by a factor of two from the 40th week. A number of other negative cancer bioassays for TCE have been reported as well, including a study in which TCE was administered in drinking water (reviewed in IARC, 1982,1988; Gold et al., 1984,1986,1987,1990,1993a; EPA, 1985; Bogen et al., 1988; Fan, 1988; Brown et al., 1990).

Based on limited rodent cancer-bioassay results involving elevated tumor incidences considered questionable or involving sites with high spontaneous incidence,

TCE generally has been considered either a possible human carcinogen or not possible to classify as to its human carcinogenicity (IARC, 1982,1988; EPA, 1985,1987). Until more recent applications of physiologically based pharmacokinetic (PBPK) models (discussed below) focusing on particular TCE metabolites, cancer potency assessments for TCE made for regulatory purposes generally have been based on estimates of tumorigenic response per unit low-level dose of either the parent compound TCE, or of the total metabolized TCE dose per unit body or target-organ weight (EPA, 1985,1987; Bogen, 1988; Bogen et al., 1988; Fan, 1988; Brown et al., 1990).

A summary of data derived from cancer bioassays for TCE, and of related information, appears in Table 1, based on information included in the Carcinogenic Potency Database (CPDB) (Gold et al., 1984,1986,1987,1990,1993a). Corresponding CPDB-based summaries of tumorigenic doses (of values of the "TD_{50}", or dose that halves the probability of remaining tumorless) found for TCE appear in Table 2. For comparison, Table 2 also includes tumorigenic doses for carcinogenic TCE metabolites and water-chlorination by-products, discussed below. The latter information was also obtained from the CPDB, or obtained using methods similar to those used to obtain published CPDB data, applied to three studies not included in published CPDB data (Herren-Freund, et al., 1987; DeAngelo et al., 1991; Daniel et al., 1992).

2. New Developments in Epidemiology Addressing TCE Carcinogenicity

New epidemiological studies have indicated some possible associations between environmental and occupational exposures to TCE and/or other chlorinated solvents and increased human cancer incidence. One of these studies addressed occupational exposures to TCE using a very large cohort of workers. However, none of these studies, summarized below, provide convincing evidence that environmental or occupational exposures to TCE, in particular, have caused cancer in humans.

An ecologic epidemiological analysis of leukemia incidence in 27 towns in New Jersey (>1 million residents in 1980, >95% of whom were served by public water supplies) revealed a significant elevation in standard incidence ratio (to 1.53, with 95% conf. limits of 1.02 - 2.21) for females in towns supplied with water containing the highest mean 1984-5 levels (ranging from 37 to 72 mg/L) of non-trihalomethane-related volatile organic compounds (non-THM VOCs), such as TCE and tetrachloroethylene (PCE) (Fagliano et al., 1990). Corresponding regression analyses for female leukemia incidence using town-specific exposure data yielded increasing positive coefficients for non-THM VOCs (0.0072 ± 0.0039), TCE (0.012 ± 0.0067), and PCE (0.035 ± 0.021), but none of these coefficients were significantly higher than zero at a $p < 0.05$ significance level. A corresponding analysis for males yielded negative results. None of these analyses controlled for socioeconomic status, medical X-ray exposures, and other potentially confounding factors for increased leukemia risk in humans.

Cancer maps for 1950-1979 showing areas of high male and female mortality from bladder cancer in several northwestern Illinois counties led to a more detailed study of eight counties involved (Mallin, 1990). For cases first diagnosed with bladder cancer in 1978-1985, age adjusted standardized incidence ratio (SIR) values [and corresponding 95% conf. limits] were calculated by county and zip code. While county

results revealed no excesses, zip-code results indicated two significantly elevated risks in one of the Winnebago County zip-code areas (males, SIR = 1.5 [1.1-1.9]; females, SIR = 1.9 [1.2-2.8]), particularly in one town in this zip code (males, SIR = 1.7 ; females, SIR = 2.6). Further investigation revealed that one of four public drinking water wells in the town had been closed due to contamination; two wells installed in 1955 were within a half mile (0.8 km) of a landfill site that had ceased operating in 1972. In 1982, tests of these two wells revealed traces of TCE, tetrachloroethylene (PCE) and other solvents. At this time, the more contaminated of these wells—which contained, *e.g.*, 2 to 15 ppb TCE, 5.1 ppb PCE, 27 ppb chloroform, and 12 ppb dibromochloromethane—was closed.

A retrospective cohort study of 14,457 aircraft-maintenance workers evaluated mortality associated with exposures to work-related solvents, particularly trichloroethylene (Spirtas et al., 1991a). The study group consisted of all civilian employees who worked for ≥1 year between 1952 and 1956 at Hill Air Force Base, Utah. Standard mortality ratio (SMR) values [and 95% confidence intervals] were calculated for Caucasian people based on the Utah Caucasian population adjusted for age, sex and calendar period. In the entire cohort, significant deficits occurred for mortality from all causes (SMR = 92 [90-95]), all malignant neoplasms (SMR = 90 [83-97]), ischaemic heart disease (SMR = 93 [88-98]), non-malignant respiratory disease (SMR = 87 [76-98]), and accidents (SMR = 61 [52-70]). Mortality was raised for multiple myeloma (MM) in women (SMR = 236 [87-514]), raised significantly for non-Hodgkin's lymphoma (NHL) in women (SMR 212 [102-390]), and raised significantly for cancer of the biliary passages and liver in men dying after 1980 (SMR 358 [116-836]).

A highly detailed exposure analysis was undertaken for employees holding 150,000 jobs at Hill Air Force Base between 1939 and 1982, including walkthrough surveys, interviews with long-term employees, and analysis of available industrial

hygiene data (Spirtas et al., 1991b). Frequency- and duration-of -use data were used to estimate peak and low-level indices for all workers exposed to TCE and to mixed solvents, in particular, who numbered 7,282 and 10,256, respectively (Spirtas et al., 1991b). It was not possible to estimate actual air-concentration levels in the exposure study, because monitoring data could not be linked to specific job titles, but rather only to specific shops onsite (Spirtas et al., 1991b). The 6929 employees occupationally exposed to TCE—the most widely used solvent at the base during the 1950s and 1960s (but not used after 1978)—did not show any significant or persuasive association between several measures of TCE exposure and any excess of cancer (Spirtas et al., 1991a). Women employed in departments in which fabric cleaning and parachute repair operations were performed had more deaths than expected from MM and NHL, but inconsistent mortality patterns and small numbers prevent definitive attribution of the excesses to any particular substance. This study did show substantially and significantly elevated multiple myeloma mortality among female employees studied who were exposed to 1,1,1-trichloroethane (SMR = 5660 [685-20,400]) or to tetrachloroethylene (SMR = 1705 [206-6159]), although both these results were based on only two observed cases (Spirtas et al., 1991a).

In the context of evaluating epidemiological evidence concerning cancer risk posed by constituents (such as TCE) associated with hazardous waste sites, a relevant consideration would be similar evidence concerning health risks posed by alternative remediation or exposure-mitigation measures that might be taken. To the extent that mitigation measures might include switching a water supply to one that contains chlorination by-products or trace levels of chlorinated solvents, it would be reasonable to consider competing cancer risks potentially associated with such an alternative water supply. The studies by Fagliano et al. (1990) and Mallin (1990), mentioned above, provide recent epidemiological data bearing on potential cancer risks associated with

domestic exposure to water containing such compounds. Remediation of hazardous waste sites may also involve operations expected to result in physical injury or death. Mar et al. (1993) assessed transportation risks associated with removal of contaminated soils at a Superfund cleanup site near a copper smelting plant in Ruston, Washington. Using a scenario involving the greatest soil-removal operation considered, it was estimated that about 1 fatality, 4 disabling injuries and 15 potentially disabling injuries would arise from accidents during transport of contaminated soil to an approved hazardous waste disposal site, compared to predicted increased lifetime risks of 0.002 for arsenic-related skin cancers in potentially exposed persons (Mar et al., 1993).

A recent ecologic epidemiological study indicates that drinking water mutagenicity correlates significantly with gastrointestinal and urinary-tract cancers in Finland (Koivusalo et al., 1994). In this study, predicted mutagenicity levels in drinking water were not found to be significantly correlated with estimated chlorinated-solvent (e.g., TCE) or trihalomethane levels, but were predicted to correlate with the presence of other chlorination by-products such as chlorinated 5-methyl-5-hydroxyfuranones.

3. Developments in Experimental TCE Carcinogenicity, TCE Metabolism, and TCE Metabolite Carcinogenicity

TCE itself is a relatively unreactive compound, but TCE is thought to be metabolized initially to a reactive epoxide, which decomposes in the microsomal environment to chloral hydrate (CH), and in a relatively aqueous cytosolic environment to dichloroacetic acid (DCA), *N*-(hydroxyacetyl)-aminoethanol (HAAE), glyoxylic acid, formic acid and/or carbon monoxide; CH in turn is oxidatively metabolized in rodents and humans principally to the metabolites trichloroacetic acid (TCA) and trichloroethanol (TCEL), where TCA has the longest half-life in circulated blood (Dekant et al., 1984; EPA, 1985; Rouisse and Chakrabarti, 1986; Davidson and Beliles,

1991; Larson and Bull; 1992a; Templin et al., 1993). The metabolites are then subject to further spontaneous degradation, enzyme-mediated oxidative and/or reductive metabolism, and/or glutathione- or glucuranide-conjugation (Davidson and Beliles, 1991; Larson and Bull; 1992a; Templin et al., 1993). In rodents and humans, TCA partitions to extracellular water and is very tightly and extensively bound to plasma protein, and roughly 50-80% of metabolized TCE is excreted as urinary TCA and free plus glucuranide-conjugated urinary TCEL (see Bogen et al., 1988; Davidson and Beliles, 1991). In both rats and mice, TCA has been shown to be metabolized (probably oxidatively) to DCA (Larson and Bull; 1992a), and DCA appears as a relatively small percentage (1-2%) of urinary metabolites measured (Hathway, 1980; Dekant et al., 1984; Green and Prout, 1985; Larson and Bull; 1992a). Contrary to the data summary indicated by Davidson and Beliles (1991), DCA was not measured as a urinary or other TCE metabolite in humans by Hathway (1980), Dekant et al. (1984), or Green and Prout (1985), and its formation in humans has not yet been confirmed. TCE-epoxide degradation to DCA and/or other non-CH-metabolites in TCE-exposed humans is currently estimated to be 5% of the total amount of TCE metabolized (Allen and Fisher, 1993; see Section 4).

Acute and chronic TCE-induced cytotoxicity primarily occurs in the liver, which is the principal site of TCE metabolism. TCE-related acute toxicity is best correlated with the amount of TCE metabolized, indicating that the major forms of TCE-induced chronic cytotoxicity are almost certainly caused by metabolism or metabolites of this compound, rather than the parent TCE compound itself (Buben and O'Flaherty, 1985; Prout et al., 1985; EPA, 1985,1987; Rouisse and Chakrabarti, 1986; Davidson and Beliles, 1991). The data of Buben and O'Flaherty (1985), in particular, show clearly in Swiss-Cox mice that a single dose of (from 100 to 3200 mg/kg) TCE given by gavage in corn oil induces hepatotoxicity (as elevated liver-to-body-weight ratio or glucose-6-phosphate

dehydrogenase inhibition) that is directly proportional to the extent of TCE metabolism. In this study, some elevated liver trigliceride and serum SGPT activity levels indicative of mild liver damage were also observed in TCE-treated mice, but only at one or two of the highest doses tested. Histopathologic examination of mice given 400 or 1600 mg/kg TCE revealed hepatocellular swelling, nuclear disintegration (karyorrhexis, indicative of cell killing, and some central lobular necrosis and polyploidy (indicative of regeneration) (Buben and O'Flaherty, 1985). As many (e.g., Buben and O'Flaherty, 1985; Prout et al., 1985; Rouisse and Chakrabarti, 1986; Barton, 1994) have noted, this type of evidence indicates the possibility that such cytotoxicity may partly or fully explain TCE-induced cancers observed in rodent bioassays.

The major TCE metabolites (chloral hydrate, TCA and DCA) have all been shown to be rodent carcinogens when administered in buffered drinking water (Herren-Freund et al., 1987; Bull et al., 1990; DeAngelo and Daniel, 1990; DeAngelo et al., 1991; Daniel et al., 1992). In particular, Herren-Freund et al. (1987) observed that 5 g/L NaCl-buffered DCA administered in drinking water for 61 wk was roughly 4 times as potent a carcinogen for male B6C3F1 mice than an equal exposure to buffered TCA, where both doses were roughly equivalent to 1000 mg/kg-day. Hepatocarcinoma incidences in DCA- and TCA-dosed animals were 7*/22 (32%) and 21*/26 (81%), respectively, compared to 0/22 in NaCl-dosed control animals (where * here indicates $p<.01$ by Fisher's exact test for comparison with controls). In the study by DeAngelo et al. (1991), incidence of hyperplastic nodules and of carcinomas and/or adenomas were observed to be significantly increased over control levels in 30 male B6C3F1 mice administered NaCl-buffered DCA in drinking water for 60 or 75 wk at concentrations of 3.5 and 5 g/L (at which the incidences ranged from ~60 to 100%), but not at either 0.05 or 0.5 g/L. However, Daniel et al. (1992) observed significantly elevated levels of hepatocellular necrosis, hyperplasia and (a 63% incidence of) hepatocellular carcinoma in 24 male

B6C3F1 mice administered 0.5 g/L (93 mg/kg-day) of DCA in drinking water for 104 wk (*i.e.*, for about twice as long as in the study by DeAngelo et al., 1991), compared to control animals. Results from a full-lifetime bioassay using a similarly low (e.g., 0.5 - 1 g/L) concentration of TCA in drinking water are not yet available. Based on the results obtained for DCA by Daniel et al. (1992), however, it might be expected that concentrations of TCA in drinking water substantially less than 5 g/L may cause increased liver cancer observable in 20-25 mice exposed over their complete lifetimes. NTP bioassays of chloral hydrate carcinogenicity in mice and rats are currently in progress.

Consistent with the finding reported in the Herren-Freund et al. (1987) study, Bull et al. (1990) found that the incidence of total tumors per liver in mice, treated with DCA for 52 wk at 2 g/L (2×10^6 ppb) in drinking water, was roughly 3 times higher than that in mice similarly dosed with TCA (3 vs. 7 tumors per liver in 11 animals exposed to 1 g/L, and 92 vs. 30 lesions in 24 animals exposed to 2 g/L, respectively; with 2 tumors per liver found in 35 control animals). Bull et al. (1990) noted that this incidence pattern was approximately linear in dose for TCA, but significantly nonlinear and increasing with dose for DCA. Based on this observation, plus the fact that dose-related accumulation of lipofucin (indicative of lipid peroxidation such as that induced by carbon tetrachloride) was found to be much greater in TCA- vs. DCA-exposed mice, Bull et al. (1990) hypothesized a different mechanism of carcinogenic action for these two TCE metabolites. However, the pattern of neoplastic-lesion incidence observed in this study is also consistent with an approximately constant potency ratio for DCA to TCA in the range of 2 to 4, indicating the possibility of similar mechanisms of action for ultimately carcinogenic metabolite(s) produced (in relatively different amounts) by both compounds.

Bull et al. (1990) concluded that DCA was only somewhat more efficient than TCA for increasing the incidence of hepatocellular carcinomas, in particular, in mice treated via drinking water at the highest concentration tested (2 g/L, or 2×10^6 ppb). At drinking water concentrations of 1 and 2 g/L, the incidences in DCA-exposed mice were 0/11 (0%) and 6*/24 (25%), while those in TCA-exposed mice were 2/11 (18%) and 4*/24 (17%), respectively (compared to 0/35 in controls; * here indicates $p<0.05$ by Fisher's exact test for comparison with controls). In this study, however, DCA was observed to elicit substantially more liver-weight gain and liver histopathology than TCA, and was additionally found to induce liver lesions (uniform cytomegaly throughout the organ, basophilic hepatoproliferative foci) not observed in any of the TCA-dosed animals. This finding is consistent with that of Maher et al. (1990), who found that DCA given to Sprague-Dawley rats in drinking water caused more marked signs of systemic toxicity (decreased body weight, increased relative liver weight and liver cytopathology) than did similar concentrations of TCA. Significant kidney weight changes were not observed either with DCA or TCA treatment in this study.

Consistent with the finding of more TCE-related tumors in mice than in rats, the peak blood concentrations of TCA and DCA observed following administration of TCE in water consumed by B6C3F1 mice were greater than those resulting from similar doses to F344 rats (Larson and Bull, 1992b). Larson and Bull (1992a) also investigated the liver production of thiobarbituric-acid-reactive substances (TBARS, indicative of lipoperoxidative-stress-induced cell killing in liver, similar to that induced by CCl_4) after administration of single oral doses of NaOH-buffered TCA or DCA (or CCl_4, as a positive control) in water to male B6C3F1 mice and Fisher 344 rats. TBARS were elevated above the control level in mice given 300, 1000 and 2000 (but not when given 100) mg/kg TCA, and in mice given 300 and 1000 (but not 100) mg/kg DCA. Significantly elevated liver TBARS levels in DCA-dosed mice were roughly 2-fold

higher than those in TCA-dosed mice. Results for rats were similar to those observed for mice, except that 300 mg/kg TCA failed to yield significantly elevated liver TBARS in rats. TBARS production in mice did not increase proportional to, and in rats decreased with, DCA dose over 300 mg/kg. The fact that TBARS were not elevated in mice administered 100 mg/kg DCA in this study contrasts sharply with the observation by Daniel et al. (1992) of hepatocellular toxicity and increased liver cancer in male B6C3F1 mice exposed for 104 wk to 0.5 g/L DCA in drinking water, estimated to be equivalent to 93 mg/kg-day (discussed earlier in this section). This contrast indicates clearly that chronically administered DCA is more hepatotoxic than a single, acute DCA dose, highlighting the critical important need for additional data on the effect of dose rate on hepatotoxicity for TCE and its major metabolites.

In light of TCE metabolism to both TCA and DCA, the TBARS results obtained by Larson and Bull (1992a) correspond with results obtained by Rouisse and Chakrabarti, 1986) concerning elevation in serum transaminase (SGPT, SGOT) levels (indicative of liver-cell toxicity and killing) 24 hr after single i.p. administration of 0, 0.25, 0.50, 0.75, 1.0 and 2.0 mL/kg TCE in corn oil to male Sprague-Dawley rats. In the earlier study, these serum levels were observed to increase markedly above control levels with all doses tested but the lowest (equivalent to 370 mg/kg), at which serum enzyme levels were not elevated above control levels. Based on these findings, Larson and Bull (1992a) concluded (in contrast to Bull et al., 1990) that TBARS production from both DCA and TCA in mice and rats was evidence of parallel reductive metabolic pathways for these compounds—with both pathways capable of inducing free-radical production, consequent lipoperoxidation-mediated cytotoxicity, and possibly also tumor formation. Larson and Bull (1992a) found that DCA was more extensively (~98%) metabolized than TCA (~50%), based on relative recoveries of the two parent

compounds in urine; this was noted as being consistent with earlier observations of greater carcinogenic potency of DCA compared to TCA in mice.

Templin et al. (1993) also studied metabolite pharmacokinetics in male B6C3F1 mice given single gavage doses of TCE in 2% aqueous Tween 80. In male B6C3F1 mice administered approximately 2000 mg/kg (15 mmol/kg) TCE in 1-2% aqueous Tween 80, the measured area under the blood-concentration-times-time curve (AUC) for DCA was approximately 30-fold smaller than that for TCA (Larson and Bull, 1992b; Templin et al., 1993). Peak blood concentrations of DCA in male B6C3F1 mice administered TCE doses did not show appreciable change with TCE doses increasing from 100 to 2000 mg/kg, and the AUC for DCA appeared to increase only slightly, albeit roughly linearly, over this dose range; both peak and AUC values for TCA increased substantially and linearly over this TCE dose range (Templin et al., 1993). The peak and AUC values for DCA and TCA at a carcinogenic TCE dose of 15 mmol/kg (2000 mg/kg) were noted by Templin et al. (1993) as being similar to those reported by Larson and Bull (1992a) that arose from direct administration of 100 mg/kg DCA, which in turn was approximately the dose used by Daniel et al., (1992) to demonstrate that DCA is carcinogenic to male B6C3F1 mice. Based on this reasoning, Templin et al. (1993) concluded that DCA and TCA production kinetics were consistent with the hypothesis that TCE-induced mouse-liver cancers may be caused by either DCA or TCA or both. However, the apparent relative insensitivity of DCA levels produced as a function of administered TCE doses ranging from 100 to 2000 mg/kg in mice (Templin et al., 1993), as well as the similarity of relatively low yields of DCA as a urinary TCE metabolite in rats (in which TCE has not been found to be hepatocarcinogenic) vs. mice (in which TCE is clearly hepatocarcinogenic), indicate that DCA is unlikely to explain a substantial fraction of rodent cancers induced by TCE.

4. Physiologically Based Pharmacokinetic Models for TCE

Recent assessments of TCE's cancer potency for regulatory purposes have been based on the assumption that the parent compound is not the proximate cause of increased tumor incidence observed in bioassays, and on physiologically based pharmacokinetic (PBPK) models of TCE metabolism in rodents and humans (EPA 1985,1987; Bogen, 1988; Bogen et al., 1988). Table 3 lists carcinogenic potency estimates for TCE based on the "linearized multistage" extrapolation model, taking into account TCE metabolism (assuming, e.g., that the biologically effective carcinogenic dose is total TCE metabolized per kg body wt. per day). Because TCE is subject to appreciable metabolism in both humans and rodents, even at relatively high exposure levels, direct extrapolations of carcinogenic potency as a function of administered TCE dose do not differ greatly from extrapolations based on corresponding effective doses estimated from metabolic data and/or PBPK models, as are the values listed in Table 3. Nevertheless, pharmacokinetic considerations addressing species-specific differences in TCE metabolism have been claimed to explain observed differences in results obtained for TCE-induced carcinogenicity in rodent bioassays, and to provide the basis for more rational assessment of human cancer risks posed by chlorinated solvents like TCE (Green, 1990).

Subsequent PBPK models describing TCE metabolism and metabolite disposition in rodents (Koizumi et al., 1989; Dallas et al., 1990; Fisher et al., 1990a-b,1991) and in humans (Allen and Fisher, 1993) have focused on TCA, in particular, as an hypothesized proximate carcinogen of primary concern for low-dose risk extrapolation. This assumption appears to have been based primarily on conclusions made by Bull et al. (1990), discussed above, concerning different hypothesized toxic mechanisms of TCA vs. DCA, but perhaps also on the relative amounts of TCA vs. DCA estimated to be formed in humans. The fraction of TCE-epoxide degradation to DCA plus other

products in humans exposed to TCE was estimated by to be 5% of the total amount of TCE metabolized, based on optimization of PBPK-model parameters to yield predictions most consistent with blood and plasma concentrations of TCE and TCA and urinary TCA excretion observed in several previous human studies (Allen and Fisher, 1993). The fact that *N*-(hydroxyacetyl)-aminoethanol was detected as a TCE metabolite in humans exposed by inhalation of 600 ppm TCE for 6 hr, while DCA was not (Dekant et al., 1984), also supports the hypothesis that DCA may be a relatively minor TCE metabolite in humans.

Based on a PBPK model of TCA production and excretion in TCE-exposed mice (Fisher et al., 1991), and corresponding bioassay data on hepatocarcinogenicity of TCE in the same strain of male and female mice dosed by gavage and inhalation (NCI, 1976; Maltoni et al., 1986), Fisher and Allen (1993) calculated new estimates of effective dose corresponding to administered TCE doses resulting in elevated liver cancer in mice. They analyzed the correlation between observed and linearized-multistage-model-predicted tumor incidence at these estimated effective dose levels using three different plausible metrics of effective TCE-related carcinogenic dose: (1) total TCE metabolized (AMET), (2) total TCA formed, and (3) average blood concentration of TCA (AUCTCA). It was noted that the AMET and AUCTCA metrics yielded plausible dose-response correlations, and that AUCTCA in particular—when used with combined bioassay results for female mice dosed by gavage and inhalation—yielded the best dose-response correlation ($R^2 = 0.95$).

Based on the latter modeling results, Fisher and Allen (1993) calculated corresponding new estimates of ingestive and respiratory TCE exposure for humans corresponding to a hypothetical 10^{-6} risk, using AMET for male and female mice and AUCTCA for female mice. For ingestive exposures, these calculated "virtually safe

dose" (VSD) estimates correspond to TCE potencies of 0.0050, 0.00090 and 8.75 (mg/kg-d)$^{-1}$ using the AMET-male, AMET-female and AUCTCA-female metrics, respectively. For continuous respiratory exposures (assuming a reference inhalation rate of 20 m^3/d), the virtually safe doses calculated correspond to TCE potencies of 0.000043, 0.000064 and 0.0064 (mg/kg-d)$^{-1}$ using the AMET-male, AMET-female and AUCTCA-female metrics, respectively (see Table 3). Fisher (1993) reported PBPK-based lung-cancer risk estimates for TCE, which were similar to those obtained by Fisher and Allen (1993) for liver cancer using AMET-related dose metrics.

In comparing their potency estimates with those of EPA (1985,1987), Fisher and Allen (1993) noted (among other things) that their AUCTCA-based VSD estimates were substantially lower (and their corresponding potency estimates were thus substantially higher) than those obtained by EPA (1985,1987) using PBPK models under the assumption that total metabolized TCE was the effective dose. As mentioned above, Fisher and Allen (1993) highlighted that the AUCTCA metric they used gave the best dose-response correlation with increased risk of tumor incidence (assuming independence from background rates) in female mice dosed by gavage and inhalation. They failed to note, however, that the excellent correlation they observed was for data involving only the dosed animals. In fact, the fit they obtained corresponded to a (quite good) linear regression that had an unrealistically negative 0-intercept (predicting an increased risk in control animals of about -25). Thus, this fit grossly contradicts the linearized multistage model upon which they based their analysis. The fit clearly is much more consistent with a threshold or quasi-threshold (*e.g.*, log-normal) dose-response, such as that suggested by results for TBARS production and tumor induction associated with exposure to TCE or its metabolites in rodents (Rouisse and Chakrabarti, 1986; DeAngelo et al., 1991; Larson and Bull, 1992a).

It is noteworthy that in their PBPK-based risk analysis, Fisher and Allen (1993) failed to consider dose metrics that are plausibly related to oxidative-stress-related hepatocellular toxicity of the type observed upon administration of TCE or its metabolites TCA and DCA (*e.g.*, Rouisse and Chakrabarti, 1986; Bull et al., 1990; Larson and Bull, 1992a). The metric most logically related to this type of toxicity, as indicated by an analysis regarding somewhat similar toxicity induced by carbon tetrachloride (Bogen, 1990), would be peak (as opposed to average or time-integrated) blood concentration of TCA and/or DCA, or simply the corresponding amounts of dose-induced elevation in TBARS or serum liver enzymes (such as SGOT or SGPT). Calculation of effective dose as daily peak TCA concentration in blood, for example, is straightforward using the PBPK model of Fisher et al., (1991) and Allen and Fisher (1993). Figure 1 illustrates this calculation for female B6C3F1 mice administered 1739 mg/kg of trichloroethylene (TCE) by gavage in corn oil, once per day for five days, which was the high dose rate used in the NCI (1976) bioassay involving this exposure route and mouse strain. This approach was used for the present report to estimate daily peak TCA concentration in blood in the female B6C3F1 mice used in the NCI (1976) gavage and the Maltoni et al. (1986) inhalation bioassays of TCE carcinogenicity in mice. The increased tumor risks as functions of estimated effective doses for these two bioassays, plotted in Figure 2, shows that—as with effective dose assumed to be total metabolized TCE (see above)—increased tumor risk is for each bioassay a rather nonlinear function of effective dose as daily peak TCA concentration in blood. Notably, Figure 2 shows that when the latter dose metric is used, the two bioassays involving female B6C3F1 mice appear to reveal a marked difference in dose-response. This difference might, for example, indicate an approximate five-fold leftward shift in a nonlinear (concave) dose-response function for TCE administered in corn oil by gavage compared with that associated with TCE administered by inhalation, which in turn might be interpreted as being the consequence of enhanced hepatotoxicity of TCE

administered via the former route compared to the latter. Such an interpretation is highly plausible in light of clear evidence of substantially enhanced hepatotoxicity and hepatocarcinogenicity of another chlorinated lipophilic solvent, chloroform, when administered by gavage in corn oil instead of in drinking water (Jorgenson et al., 1985; Larson et al., 1994). By definition, such a route-specific difference in hepatotoxicity/hepatocarcinogenicity of specified effective doses indicates an inappropriately defined effective dose. It may be, for example, that TCE-induced toxicity is largely explained by metabolism to TCA, but that neither TWA nor peak TCA concentrations in blood are good predictors of (for example) peak TCA concentration in liver when TCE is administered in a corn oil vehicle. This poor predictivity would arise if the lipophilic parent compound, TCE, contained in oil droplets transported to liver present a much higher effective concentration of TCE to liver cells involved in oil-droplet metabolism than is predicted by PBPK models (e.g., Fisher et al., 1991; Allen and Fisher, 1993) that consider only distribution of TCE dissolved uniformly in perfusing blood.

5. New Pharmacodynamic Data Concerning TCE & Metabolites

TCE-related tumorigenesis has been observed to be correlated with toxicity associated with its metabolism, particularly with the metabolites TCA and DCA (Buben and O'Flaherty, 1985; Rouisse and Chakrabarti, 1986; Larson and Bull, 1992a-b; Templin et al., 1993). Based on this type of information, current cancer-potency assessments for TCE based on linear extrapolation of tumor response in rodent bioassays have been questioned, in light of evidence indicating that TCE's mechanism of carcinogenic action involves animal strains with high spontaneous (particularly liver) cancer incidence, and involves metabolite-related toxicity likely to have a quasi-threshold-type dose-response (in contrast to genotoxic mechanisms which might

plausibly have a linear low-dose dose-response) (Abelson, 1993; Steinberg and DeSesso, 1993; Barton, 1994). Steinberg (1993) recently made a similar point regarding chloral hydrate (CH). As noted above, CH is a primary TCE metabolite that is carcinogenic and that is metabolized to both TCA and DCA. Noting that CH is a widely used sedative in both adults and children, Steinberg (1993) argued that a threshold model is appropriate for evaluation of cancer risks posed by medical uses of CH in humans because: the rodent-cancer bioassay dose-response relationships for CH and its breakdown products TCA and DCA are "nonlinear"; these bioassays all involved high, necrogenic doses which appear necessary for tumor induction for these TCE metabolites; and epidemiologic data on people exposed to substantial amounts of TCE do not demonstrate exposure-related increased mortality or cancers.

Marked peroxisome proliferation (measured as peroxisomal percentage of cytoplasmic volume), significantly above control levels, was observed in centrilobular hepatocytes of both male Swiss (Alderly Park) and male B6C3F1 mice administered doses of 500, 1000 or 1500 mg/kg of TCE by gavage in corn oil per day for 10 days (Elcombe et al., 1985), as well as in both male Swiss mice and male Wistar-derived rats administered 50, 100 or 200 mg/kg TCA per day for 10 days (Elcombe, 1985). Hepatocellular peroxisome proliferation was only slightly (and not significantly) elevated in male Wistar-derived and Osborne-Mendel rats administered 1000 or 1500 mg/kg TCE by gavage in corn oil per day for 10 days (Elcombe, 1985; Elcombe et al., 1985). This differential response observed in mice vs. rats has been considered evidence that differential peroxisome proliferation may explain differences in TCE-induced hepatocarcinogenicity in mice vs. rats (Elcombe, 1985; Elcombe et al., 1985; McClain, 1994). Furthermore, these findings have been used as the basis of an hypothesis that TCE is unlikely to induce liver cancer in humans, because monkey and human hepatocytes are much less susceptible to induction of peroxisome proliferation than

rodent hepatocytes (Elcombe, 1985; Eacho et al., 1986; McClain, 1994). However, this argument fails to explain why, for example, TCA causes peroxisome induction but not preneoplastic liver lesions in rats (see Larson and Bull, 1992b).

Certain alterations in cell proliferation kinetics are also capable of increasing cancer risk (Armitage and Doll, 1957; Moolgavkar and Knudson, 1981; Moolgavkar, 1983; Moolgavkar et al., 1988; Bogen, 1989; Ames and Gold, 1990; Cohen and Ellwein, 1990,1991; Preston-Martin, 1990; Monticello and Morgan, 1994). With some chemicals, such as certain chlorinated solvents that incapacitate liver cells through oxidative stress, this increased risk is both expected and observed to be substantially nonlinear, or quasi-threshold-like, as a function of dose (Bogen, 1990; Larson et al., 1994). Subchronic administration of TCE in corn oil by gavage to mice has been shown to induce significantly increased hepatocellular proliferation (Mirsalis et al., 1985; Dees and Travis, 1993). In the more recent study by Dees and Travis (1993), liver toxicity, hepatocellular proliferation and hepatocellular apoptosis were assessed in male and female B6C3F1 mice given 0, 100, 250, 500 and 1000 mg/kg TCE in corn oil by gavage for 10 days and 100 μCi/kg [^{3}H]thymidine 6 hr prior to sacrifice. All treated mice appeared clinically ill. [^{3}H]thymidine incorporation was determined by autoradiography and reported as positive cells per 100 200×-power fields examined (*i.e.*, not as an estimated percentage of cells examined, which is the more standard method for reporting such results). Histopathologic changes seen in treated animal livers were increased eosinophilic staining of hepatocytes located near central veins, accompanied by loss of cytoplasmic vacuolization. Increased apoptosis was observed only in mice receiving the highest dose (1000 mg/kg), and increased lipofuscin was not observed in any of the treated animals. [^{3}H]thymidine-labeled hepatocytes counted, and hepatocytes counted per μg DNA, were "significantly" increased in both male and female mice in all treated groups; similar changes were not observed in peri-sinusoidal

cells counted (Dees and Travis, 1993), although statistical test results were not reported. The increased [^{3}H]thymidine-incorporation levels in hepatocytes appeared to saturate at approximately 2-fold higher than background, for treated animals in the 250-, 500- and 1000-mg/kg dose groups. Incorporation at the 100- and 250-mg/kg levels appeared to increase in linear proportion to dose (Dees and Travis, 1993). However, the numbers of hepatocytes counted per μg DNA reported for males and females dosed with 100 mg/kg TCE, together with the corresponding reported standard deviations, indicate that the incorporations of [^{3}H]thymidine observed in these animals were not statistically significantly elevated over the reported control levels (by T-tests, $p > 0.18$). Again, corresponding statistical test results were not reported by Dees and Travis (1993).

More detailed studies, currently underway, are addressing TCE-induced alterations in liver-cell proliferation/apoptosis kinetics over a much larger range of doses and dosing periods than has been investigated previously (Barton, 1994). Results from these studies are not expected until late 1994 or early 1995 (Barton, 1994). However, the correlation of hepatocellular toxicity with liver-tumor induction by TCE, TCA and DCA, together with the observed nonlinear kinetics of hepatocellular toxicity induction by these compounds (Larson and Bull, 1992a; Templin et al., 1993), suggest that TCE may present virtually zero cancer risk (*i.e.*, $<<10^{-8}$) for lifetime exposures to ambient concentrations in the ppb range. An adequate test of this hypothesis would require definitive mechanistic studies, demonstrating lack of elevated incidence (or size) of either cancers or related proliferative (precursor) lesions at the highest TCE dose levels consistent with generally normal rates of hepatocellular proliferation and apoptosis.

6. A PBPK-Based NOAEL for TCE in Humans

Based on the information reviewed in Sections 3-5 above, it appears likely that TCE-induced carcinogenesis observed in rodents may be caused indirectly by cytotoxic effects of further metabolism of TCE's primary reactive metabolites, TCA and DCA. As noted in Sections 3 and 4, TCA is likely to be the predominant cytotoxic metabolite produced in humans exposed to TCE. Assuming such cytotoxic effects involve simultaneous failure of multiple intracellular targets similar to that arising from oxidative stress, these effects are likely to have a threshold or quasi-threshold (e.g., log-normal) type dose-response relationship (Bogen, 1990). Protective standard-setting for this type of expected dose-response has traditionally involved the application of safety factors to an experimentally observed or estimated no-adverse-effect-level (NOAEL) (Dourson and Stara, 1983). NOAEL-based exposure standards can readily incorporate PBPK considerations, and so improve the basis for inter-route and interspecies extrapolation of such calculated levels (Bogen and Hall, 1989). Below, a PBPK-based NOAEL for TCE in humans is calculated, using data on TCE metabolism and metabolite toxicity reviewed above, related PBPK models, and some convenient steady-state PBPK methods (Bogen, 1988).

Hepatotoxicity appears to be the most sensitive cytotoxic response observed upon acute administration of TCE or its metabolites. As noted above, TCA-induced TBARS production in B6C3F1 mice administered single doses of TCA by gavage was elevated above control levels in mice given 300, 1000 and 2000 mg/kg TCA, but not 100 mg/kg TCA (Larson and Bull, 1992a). Therefore, 100 mg/kg TCA represents a NOAEL for acute, gavage administration of TCA in these mice. For chlorinated solvents such as carbon tetrachloride and chloroform, peak chemical concentration in blood is known to correlate very well with oxidative-damage-mediated hepatotoxicity (Bogen, 1990). Here, it shall be assumed that peak TCA concentration in blood is a good predictor of

TCA-mediated tissue toxicity. An administered dose of 100 mg/kg TCA corresponds to a measured peak concentration of TCA in mouse blood of approximately 790 μmol/L (130 mg/L) (Larson and Bull, 1992a). The PBPK model of Fisher et al. (1991), Allen and Fisher (1993), and Fisher and Allen (1993) describes metabolism of TCE to TCA in humans, and so may be used to predict, e.g., ingestive or respiratory human exposures to TCE resulting in a peak blood concentration of 130 mg/L of TCA. These exposure levels may then be divided by appropriate "uncertainty" or safety factors to derive acceptable, route-specific intake rates (Dourson and Stara, 1983). Here, three factors of 10 shall be used, reflecting (1) uncertainty in extrapolating from acute to chronic concentrations sufficient to induce hepatotoxicity in mice, (2) uncertainty in extrapolating from mice to humans, and (3) human interindividual variability in susceptibility to TCA-induced cytotoxicity.

From the PBPK model described by Allen and Fisher (1993), rate of change in blood concentration, $C_{TCA}(t)$, of TCA in humans at time t is given by

$$\frac{dC_{TCA}(t)}{dt} = \frac{P}{V}\left(\frac{B(t)V_{max}}{B(t)+K_m}\right)\frac{MW_{TCA}}{MW_{TCE}} - kC_{TCA}(t) \quad , \qquad (1)$$

where the variates used in Eq. (1) (and the corresponding values used by Allen and Fisher, 1993) are: the net fraction of metabolized TCE converted to TCA (P = 0.33); the apparent (largely blood) volume of TCA distribution (V = 7.1 L, for a reference 70-kg person); venous blood concentration of TCE exiting liver ($B(t)$); maximum rate of TCE metabolism (V_{max} = 345.6 mg/hr); the Michaelis constant, or value of B at which the rate of TCE metabolism is half V_{max} (K_m = 1.5 mg/L); the apparent first-order rate constant governing TCA elimination (k = 0.00783 hr^{-1}); and molecular weight (MW = 131.4 and 163.4 g/mol for TCE and TCA respectively). Substituting the appropriate values, Eq. (1) may be rewritten

$$\frac{dC_{TCA}(t)}{dt} = 0.0578\,L^{-1}\left(\frac{B(t)V_{max}}{B(t)+K_m}\right) - 0.00783\,hr^{-1}C_{TCA}(t) \quad . \tag{2}$$

The parenthesized quantity in Eqs. (1-2) is simply the rate of TCE metabolism conditional on $B(t)$. After a long-term, continuous respiratory exposure to a TCE concentration of C_{in} in air, $B(t)$ attains a virtual steady-state value $B(\infty)$ that corresponds to a rate of TCE metabolism equal to $Q_a C_{in} f_{mr}$, where Q_a is the alveolar ventilation rate taken by Allen and Fisher (1993) to be 292.2 L/hr for a reference 70kg person, and where f_{mr} is the steady-state fraction of respired TCE dose that is metabolized. For PBPK models of the type used by Allen and Fisher (1993), it has been shown by Bogen (1988) that

$$f_{mr} = \left[1 + \frac{Q_a}{P_b}\left(\frac{K_m}{V_{max}} + Q^{-1}\right)\right]^{-1} \quad , \tag{3}$$

in which Q is blood flow rate to liver and P_b is the blood/air partition coefficient for TCE, taken by Allen and Fisher (1993) to be 89.9 L/hr and 9.2, respectively. Thus, for TCE, f_{mr} is estimated to be 0.671. The steady-state solution to Eq. (2), using three significant digits, is therefore

$$\begin{aligned} C_{TCA}(\infty) &= 7.38\,hr\,L^{-1}Q_a C_{in} f_{mr} \\ &= 1450\,C_{in} \quad , \end{aligned} \tag{4}$$

whereupon substituting the NOAEL TCA concentration of 130 mg/L for $C_{TCA}(\infty)$ and applying a 1000-fold safety factor yields a corresponding acceptable concentration of 0.090 μg/L (or 16 ppb) for TCE in continuously respired air.

Eq. (2) also implies that continuous ingestive TCE intake at a rate R (mg/hr) corresponds to a steady-state TCA concentration in blood of

$$C_{TCA}(\infty) = \frac{0.0578}{k\,L} R f_{mo} \quad , \tag{5}$$

in which f_{mo} is the steady-state fraction of ingested TCE dose that is metabolized. For PBPK models of the type used by Allen and Fisher (1993), it has been shown by Bogen (1988) that

$$f_{mo} = \left[1 + \frac{K_m}{V_{max}}\left(\frac{P_b}{Q_a} + Q^{-1}\right)^{-1}\right]^{-1} \quad , \tag{6}$$

which corresponds to a value of $f_{mo} = 0.908$ for TCE using the parameter values given above. Brief daily infusions into a first-order system such as that described by Eq. (2) result in multiple dosing kinetics characterized by a "sawtooth" approach to dynamic-equilibrium oscillation between a maximum and relative minimum values (see, e.g., Wiegand et al., 1963). It is easily shown that after a sufficiently lengthy regime of multiple dosing, peak concentrations at virtual dynamic-equilibrium all equal a fraction f_{deq} of the steady-state concentration that would be achieved if system input were continuous, where

$$\begin{aligned} f_{deq} &= \frac{1-e^{-kt}}{1-e^{-kt_p}} \\ &\approx \frac{kt}{1-e^{-kt_p}} \qquad \text{for } kt << 1 \end{aligned} \tag{7}$$

in which t is the assumed approximate duration of daily infusions arising from ingestion, t_p is exposure/non-exposure period (t_p = 24 hr), and k is the rate constant

governing system loss defined above for TCA. Substituting Eq. (7) and the value of f_{mo} into Eq. (5), and using three significant figures, yields

$$\text{Max}[C_{TCA}(\infty)] = 0.306 L^{-1} Rt \quad , \tag{8}$$

The corresponding daily input mass Rt (in mg) of TCE required to achieve a peak TCA concentration in blood of 130 mg/L at dynamic equilibrium is thus approximately 425 mg. Assuming a daily ingestion of 2 L, and again applying a safety factor of 1000, the latter mass corresponds to an acceptable concentration of 210 ppb for TCE in drinking water.

7. Preliminary Comparative Risk Assessment for TCE vs. Typical Concentrations of Chlorination Byproducts in Household Water

A commonly used approach to mitigate possible cancer risk associated with use of domestic water contaminated with trace amounts of chlorinated solvents, such as TCE from groundwater passing through a hazardous waste site, is to switch the household water supply to an "uncontaminated" source. Such an alternative source might include a (typically surface) water supply that has been chlorinated for purposes of disinfection. However, while such an alternative supply may not contain a particular contaminant of concern such as TCE, chlorinated water is known to contain an array of chlorination by-products (CBP), including the 11 rodent carcinogens besides TCE listed in Table 2. These 11 CBP compounds consist of four trihalomethane (THM) compounds (primarily chloroform, but also bromoform, dichlorobromomethane and dibromochloromethane), two haloacetic acid (HAA) compounds (DCA and TCA), two aldehydes (formaldehyde and acetaldehyde), chloral hydrate (CH), and a chlorophenol

(Table 2). As indicated in Table 2, at least some rodent cancer bioassay data exist for all 11 of these compounds indicating exposure-related increases in tumor incidence. Epidemiological evidence linking increased exposure to CBP in chlorinated drinking water with elevated risk of certain cancers is suggestive but not conclusive (EPA, 1994). In particular, a recent meta-analysis of results from 10 ecologic studies investigating possible cancer risk associated with CBP exposure (albeit without controlling for diet) found that pooled data from seven of these studies indicated a CBP-related increased risk of cancer of the bladder (RR = 1.21, 95% conf. interv. = 1.09, 1.34) and rectum (RR = 1.38, 95% conf. interv. = 1.01, 1.87) (Morris et al., 1992). Coincidentally, as discussed above (Section 3), three of these CBP compounds (CH, TCA and DCA) are themselves TCE metabolites, and therefore human exposure to these compounds may occurs either by TCE metabolism, or by exposure to CBP in household water, or both.

The occurrence of a number of carcinogenic disinfection by-products in chlorinated U.S. drinking water supplies (in particular, the 10 CBP compounds besides chloroacetaldehyde listed in Table 2) is now well documented, and their average concentrations are known to be very well correlated with total THM (TTHM) concentrations, which in turn are dominated by chloroform (Krasner et al., 1989; EPA, 1994). The median of measured averages of TTHM concentrations for large U.S. water utilities (with >10,000 connections) lies in an approximate range of 30 to 50 μg/L (i.e., 30 to 50 ppb) (Krasner et al., 1989; EPA, 1994). A survey of TTHM concentrations during the period 1984-1989 in large public drinking water utilities in California revealed that, among 279 systems in all 32 counties, all (i.e., 100% of) systems in 7 (i.e., 22% of) the counties had ≥1 4-quarter running average TTHM concentration exceeding 50 ppb, and that 50 ppb was likewise exceeded in ≥80% of all systems in 11 (i.e., 34% of all) counties (CDHS, 1994). Due to their widespread occurrence and the potential health impact of CBP concentrations in U.S. water supplies, the U.S. Environmental Protection Agency (EPA) recently proposed a reduction in the Maximum Contaminant Level (MCL) for

TTHM from 100 to 80 ppb, and establishment of a 60-ppb MCL for HAA compounds (including TCA and DCA) for large water-treatment utilities with >10,000 connections (EPA, 1994). The proposed 80-ppb MCL for TTHM is at approximately the 90th percentile of measured average TTHM concentrations for water-treatment utilities serving >10,000 people (EPA, 1994).

These data on CBP occurrence and levels in U.S. water supplies indicate that water, particularly chlorinated surface water, used to replace another water supply (e.g., because the latter contains trace amounts of an organic solvent of concern, such as TCE) is quite likely itself to contain a number of other chemicals that are also rodent carcinogens. If this were the case, the 10 CBP compounds referred to above might present a hypothetical increase in aggregate cancer risk that equals or exceeds that posed by the contaminant of concern in the original water supply. In such a case, there could be no health-risk-based rationale for switching to a new water supply that contains CBP because chlorination was used to reduce the very certain risk of acute microbial infections. A quantitative comparative risk analysis is required to assess the relevance of such a scenario involving "competing risks" posed by water contaminants present in different supplies, for example, to decisions involving the selection of hazardous-waste-site remediation strategies. Therefore, such an analysis was made specifically to compare a hypothetical increase in cancer risk calculated for household exposure to TCE in domestic water at 5 ppb, the current California and U.S./EPA MCL for this compound in drinking water; California (1994), to that associated with household exposure to the 10 CBP mentioned above in domestic water at concentrations corresponding to an average TTHM level of 80 ppb, the MCL newly proposed by (EPA, 1994). The methods used for this analysis are described below, followed by a summary of the results obtained.

7.1 Methods

Total Multiroute Exposures to TCE and CBP

To compare hypothetical risks posed by TCE at 5 ppb in domestic water to the total risk posed by CBP corresponding to water-borne CBP levels corresponding to a TTHM level of 80 ppb, methods were selected to estimate CBP levels expected to correspond to a TTHM level of 80 ppb, and to estimate total household exposure from all relevant exposure routes (ingestion + inhalation + dermal). To estimate CBP levels expected to correspond to a TTHM level of 80 ppb, water concentrations of the 10 CBP of interest were scaled to a TTHM concentration of 80 ppb based on the ratio of average of four quarterly median concentrations for each CBP to that of TTHM reported by Krasner et al. (1989) for water sampled from 35 water treatment utilities during 1988-1989.

The relevant measure of multiroute exposure selected to extrapolate potential cancer risk from animal cancer-bioassay data was lifetime time-weighted average (TWA) intake per unit body weight (mg/kg-day) (Anderson et al., 1983; Gold et al., 1984). Oral TCE and CBP doses were estimated directly from the stated assumptions concerning TCE and CBP concentrations in household water, assuming an average U.S. daily fluid-ingestion rate of 1.36 L and a lifetime TWA body weight of 62 kg (CEPA, 1993). Household respiratory exposure was estimated using the CalTOX multimedia total-exposure model, and corresponding physical-chemical constants for TCE supplied with the CalTOX exposure assessment computer program (CEPA, 1993). The respiratory component of this model is based on the household respiratory model of McKone (1987,1989). Corresponding constants for the compounds chloroform, acetaldehyde, bromodichloromethane, CH, chlorodibromomethane, DCA, formaldehyde, tribromomethane (bromoform), TCA, and 2,4,6-trichlorophenol were obtained and/or estimated (using vapor-pressure and solubility data obtained) from the

literature (Korenman and Selmanscchuck, 1983; Budavari, 1989; Howard, 1990; Lide, 1994; Yaws, 1994). The CalTOX model for dermal exposure to water-based chemicals is similar to an approach recently proposed by EPA (1992a), which has been shown by Bogen (1994) to involve substantial underpredictions of "effective" dermal permeability, K_p^{eff} (in cm/hr; defined as the average volume of constant aqueous solution cleared per unit exposed dermal surface area—see McKone, 1993), estimated from *in vivo* (mostly human) data on uptake of organic chemicals from dilute aqueous solution. In contrast, the alternative model,

$$\log_{10} K_p^{eff} = -0.812 - 0.0104MW + 0.616\log_{10}K_{ow} , \qquad (9)$$

in which MW (mol/g, unitless) is molecular weight and K_{ow} (unitless) is the octanol/water partition coefficient, provides good predictions of the logs of *in vivo* K_p^{eff} measures for nine organic chemicals in dilute aqueous concentrations, including chloroform (the primary CBP) and TCE ($R^2 = 0.98$, $p = 3 \cdot 10^{-6}$) (Bogen, 1994a).

Using K_p^{eff} thus defined, the corresponding ingestive-equivalent volume, E_d, due to dermal uptake from shower/bathing water can be estimated as

$$E_d = (3.6 \text{ L hr/cm}) K_p^{eff} (1-[K/2]) , \qquad (10)$$

where K is the volatilized fraction of chemical contained in shower water volatilized during a typical shower, here assumed to last 0.2 hr (Bogen, 1994a). Values of K experimentally measured for carbon tetrachloride, tetrachloroethylene, TCE, chloroform, 1,2,3-trichloropropane (Tancrede et al., 1992), and estimated for 1,2-dibromo-3-chloropropane (McKone, 1987,1989,1992; Little, 1992), are predicted fairly well by the model

$$K = 1 - 0.2905 H^{-0.197} \qquad \text{for } H \geq 0.005 \qquad (11)$$

in which H is the dimensionless Henry's law constant (i.e., inverse Ostwald coefficient) ($R^2 = 0.99$, $p = 10^{-4}$), as illustrated in Figure 3. Eq. (11) was used to evaluate Eq. (10) for purposes of estimating dermal exposure to TCE and CBP in household water.

Cancer Potencies of TCE and CBP

Cumulative probability distributions (cdfs) characterizing some of the uncertainty in carcinogenic potencies of lifetime TWA human exposures to TCE and 10 CBP compounds were calculated using TD_{50}-related data from Table 2, obtained from the Carinogenic Potency Database (CPDB) or from similar analyses of bioassay data on CBP not yet included in the CPDB (Herren-Freund, et al., 1987; DeAngelo et al., 1991; Daniel et al., 1992). The cdfs calculated reflect uncertainty in estimated potency for nonnegative studies arising from: (1) statistical potency-estimation error conditional on the CPDB one-hit time-to-tumor dose-response extrapolation model (Gold et al., 1984); (2) interspecies potency extrapolation using body-weight- and body-surface-area-based methods, which were averaged assuming equal likelihood (AAEL); (3) maximum site-specific potencies estimated from multiple studies or routes involving the same species/strain/sex (AAEL); (4) multiple averaged strain/sex-specific potencies pertaining to the same species (AAEL); (5) averaged species-specific potencies pertaining to multiple species (AAEL); and (6) the presence, conditional on estimated potency being significantly less than the lowest significant potency among all non-"-" studies pertaining to the same species, of negative study/species/strain/sex-specific results (here defined as those for which $p > 0.05$ or designated "-", and assumed to reflect a potency of 0 AAEL with those from nonnegative studies).

Specifically, to estimate potency cdfs for each chemical, input data sets (data rows) were selected from CPDB-related data (Table 2) for each study/species/sex/strain/route (SSSSR) combination. Each of these data sets has 11

elements: study, species, sex, strain, route, tissue, tumor, $\hat{q}_1$, q_1^*, p-value for positive dose-response (p), and "opinion" (see Table 2). Here, $\hat{q}_1$ and q_1^* represent CPDB-estimated values of q_1 (cancer potency in kg-d/mg) and its upper 99.5th percentile, respectively, where potency is here interpreted as $\log_e(2)/TD_{50}$ and where q_1^* reflects uncertainty with respect only to parameter-estimation error conditional on the CPDB one-hit dose-response model. Each SSSSR-specific data set used contains either the maximum (and here, incidentally, the most significant) value of $\hat{q}_1 | (p \leq 0.05)$, or the most significant value of $\hat{q}_1 | (p > 0.05)$, among all corresponding tumor-type-specific data sets listed for that SSSSR in Table 2. (The data set used appears as the corresponding nonparenthesized data row in Table 2.) Each data set was assumed to reflect a "positive" study (PS), here defined as one for which $p \leq 0.05$ and opinion $\neq$ '-', or a "true negative" study (NS), defined as any non-PS except one for which Prob$\{q_1 \geq \hat{q}_1^+] <= 0.05$ (as assessed by a 1-tailed Gaussian test of difference between two means), where $\hat{q}_1^+$ is any $\hat{q}_1$ for a PS involving the same species. For each PS and for each NS involving a species with ≥1 PS, a corresponding 2-point, skewed, mean-preserving, probability mass function (Bogen, 1994b) was used as a crude, but efficient, approximation of uncertainty in q_1 arising from parameter-estimation error. Each corresponding cumulative mass function (cmf) included the q_1-values q_{lo} and q_{hi}, such that $\hat{q}_1 = (q_{lo} + q_{hi})/2$, where q_{hi} is the expected value of the upper 5% tail of a Gaussian variate whose mean is $\hat{q}_1$ and whose 99.5th percentile is q_1^*. Any non-PS also a non-NS was ignored, and it was assumed that $q_1 = 0$ for all NS. All species/sex/strain-specific (SSSS) cmfs for both PS and NS were AAEL. For each cmf thus obtained, a corresponding function (cmf_{SA}) was obtained using the former's abscissa values multiplied by $(70/BW)^{(1/3)}$, where BW is the species/sex-specific body weight assumed by Gold et al. (1984). Thus, each cmf_{SA} reflects animal-to-human cancer-potency extrapolation assuming cancer-potency equivalence of lifetime dose expressed as TWA daily chemical mass per unit body surface area, rather than per unit body weight. All

such resulting SSSS cmfs (and all corresponding cmf_{SA}s) pertaining to a given chemical/species were AAEL, to reflect the corresponding intraspecific q_1 range exhibited, where $q_1 = 0$ was assumed for any species with NS but no PS. All resulting species-specific cmfs (and all corresponding cmf_{SA}s) were AAEL, to reflect an assumed equal plausibility that q_1 exhibited in any particular animal species predicts q_1 in humans. Finally, the resulting cmf and corresponding cmf_{SA} were AAEL, reflecting an assumed equal plausibility of animal-to-human potency-extrapolation methods based on body weight and surface area, which has some empirical support (Allen et al., 1988; Crump, 1989; EPA, 1992b).

It is emphasized that the resulting characterizations of uncertainty in carcinogenic potency ***do not*** reflect the (perhaps substantial) likelihood that the low-dose potency of TCE and/or of any or all CBP may actually be zero (or virtually zero), and that the positive bioassay results obtained at relatively high doses relied on for low-dose potency extrapolation may actually be irrelevant to such extrapolation, due to possible involvement of biological mechanisms that may not be induced at typically low environmental concentrations, such as those considered here (Moolgavkar, 1983; Moolgavkar et al., 1988; Bogen, 1989; Ames and Gold, 1990; Cohen and Ellwein, 1990,1991; Preston-Martin, 1990; Monticello and Morgan, 1994). Thus, uncertainty analysis was undertaken conditional on the applicability of CPDB-type dose-response models for low-dose dose-response extrapolation, which is often assumed for environmental regulatory purposes (Anderson et al., 1983; EPA, 1986).

Note also that potency and corresponding risk estimates were obtained here without consideration of pharmacokinetic factors expected to affect dose- and route-related inter- and intra-species differences in relations between exposure levels, corresponding applied doses, and biologically effective doses in target tissues. Thus, in

this analysis, uncertainties in cancer potency arising from unaccounted-for pharmacokinetic considerations were effectively assumed to be negligible compared to those arising from uncertainty sources that were considered quantitatively. This assumption was tested to some degree by a separate comparison of cdfs characterizing variability in upper one-tail 95% confidence limits on the $\log_{10}$ value of TCE's BW-based carcinogenic potency in mice, as calculated from CPDB data on 9 nonnegative mouse studies without regard to pharmacokinetics (Table 2), and from the 11 potency estimates that took into account TCE pharmacokinetics for mouse studies listed in Table 3.

For the ingestion route alone, and for all exposure routes combined, increased cancer risk for each chemical was calculated as the product of (uncertain) potency and lifetime TWA ingested dose, and as the product of (uncertain) potency and the sum of route-specific lifetime TWA doses, respectively. All doses were treated deterministically, in accordance with an assumption that all uncertainties in the exposures associated with the routes and representative exposure scenario considered are small relative to those associated with estimated cancer potencies. Uncertainty in aggregate CBP-related risk was calculated by Monte Carlo methods as the stochastic sum of chemical specific risks (NRC, 1994). All exposure and potency calculations were performed on Apple Quadra® and PowerPC® workstations using the computer programs CalTOX (CEPA, 1993), *RiskQ* (Bogen, 1992) and *Mathematica* 2.1 (Wolfram, 1991). Monte Carlo calculations employed 11 vectors, each containing 500 independent values of each distributed variate involved, all obtained by systematic Latin-Hypercube sampling using the method of Iman and Connover (1982) to obtain sample-vector ranks that were not significantly correlated by the Jennrich (1970) test ($\chi^2 = 5.24$, df = 54, $p \approx 1$).

7.2 Results

Table 4 lists the ingestive-equivalent intake volumes due to household respiratory and dermal exposures for TCE and the 10 CBP compounds considered, as predicted by the CalTOX and the dermal models described above, respectively. The corresponding chemical-specific cmfs calculated to reflect uncertainty in carcinogenic potency as described above are shown in Figure 4. For ingested chemicals, and for chemicals absorbed by all household exposure routes (ingestion + respiratory + dermal), Figure 5 compares cmfs calculated to reflect uncertainty in cancer risk posed by TCE at 5 ppb in household water and by CBP in household water corresponding to water-borne CBP levels expected at a TTHM level of 80 ppb. The expected and approximate maximum values of TCE-related ingestive risk are 2.9 and 63×10^{-7}, respectively, whereas the corresponding CBP-related risks are 8.0 and 56×10^{-5} (i.e., ~280 and ~90 times higher), respectively. Expected and approximate maximum values of TCE-related multiroute risk are 8.1 and 180×10^{-7}, respectively, whereas the corresponding CBP-related risks are 1.8 and 13×10^{-4} (i.e., ~220 and ~75 times higher), respectively.

Figure 5 compares two cmfs characterizing variability in estimates of TCE's carcinogenic potency in mice calculated from CPDB data without regard to pharmacokinetics, vs. estimates that sought to account for pharmacokinetic considerations. Both mice and humans are expected to metabolize virtually all (or a major portion) of any very low applied TCE dose arising from ingestive (or respiratory or dermal) exposure (Bogen, 1988). The two curves thus reflect comparable potency measures, yet do not reflect a substantial difference in estimated potencies (2-tail T-test, $p > 0.35$), even if the two smallest pharmacokinetic-based values are not considered (2-tail T-test, $p > 0.16$). The impact of pharmacokinetic considerations on potency

estimation for CBP may also be relatively small compared to the other sources considered quantitatively here, to the extent that CBP are structurally related to and/or metabolically processed similarly to TCE (see Section 3). To this extent, the comparison shown in Figure 5 supports the hypothesis that the pharmacokinetics may not be a substantial source of uncertainty in estimated cancer potency, compared to the other sources treated quantitatively here, for all the chemicals considered.

Taken together, these results indicate that, from the standpoint of comparative potential cancer risks (all calculated using a conservative linear dose-response extrapolation model), there would likely be no health benefit, and more likely a possible health detriment, associated with a switch from a household water supply containing 5 ppb (or, indeed, any concentration <375 ppb) TCE to one containing CBP at levels expected to correspond to a TTHM level of 80 ppb.

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Table 1
Summary of Cancer Bioassay Results and Related Information for TCE, Based on the Carcinogenic Potency Database[a]

CAS#: 79-01-6, NCI/NTP#: c04547

Salmonella mutagenicity	- [equivocal]

Positivity by any route[b]	MR	FR	MM	FM
	+	-	+	+
Number of species positive/number tested	2/3			
Number of sex-species positive/number tested	3/6			
Number of strains positive/number tested	4/11			
Proportion of experiments with statistically significant ($p < 0.05$) results below the high dose (when number of doses > 1)	4/9			
Number of inadequate NCI/NTP experiments	9			

Route	Hamsters	Mice	Rats
Inhalation			
Number of positive tests/Number of tests	0/2	5/8	2/7
Number of strains positive/Number tested	0/1	3/4	1/3
Strongest opinion level	-	+	+
Gavage			
Number of positive tests/Number of tests		4/6	0/5
Number of strains positive/Number tested		1/2	0/3
Strongest opinion level		c	-

Tumor issues			
Route	Hamsters	Mice	Rats
Inhalation			
Target sites with positive opinion	-	4 liver (m)* 3 lung (m)*	2 testis
Highest tumor yield		(17/77), 19/47 liver	(5/81), 24/71
Highest tumor yield index		1.31	1.42
Gavage			
Target sites with positive opinion		4 liver (m)*	-
Highest tumor yield		(8/50), 31/50	
Highest tumor yield index		2.21	
Lethality (sacrifice ratio)		0.34	

Dose issues (mg/kg/day)			
Route	Hamsters	Mice	Rats
Inhalation			
Range of doses	40.5-230	83.2-862	14.1-205
Lowest significant ($p < 0.05$) dose for a positive site		94.9	64.5
Most potent TD_{50} for a positive site		3910	557
Harmonic mean of TD_{50}s from positive experiments		5630	668
MTD/most potent TD_{50}		0.136	0.232
MTD/VSD		94,200	161,000
Number of negative experiments whose potency is consistent with positive experiments	-	0	0
Lowest p-value	$p<0.4^c$	$p<0.002$	$p<0.0005$
Gavage			
Range of doses		2.38-1450[d]	11.9-714
Lowest significant ($p < 0.05$) dose for a positive site		701	
Most postent TD_{50} for a positive site		294	
Harmonic mean of TD_{50}s from positive experiments		514	
MTD/most potent TD_{50}		2.38	
MTD/VSD		1,650,000	
Number of negative experiments whose potency is inconsistent with positive experiments		0	-
Lowest p-value		$p<0.000$	$p<0.4$

Table 1

Acute Toxicity (mg/kg) *Route*	Hamsters	Mice	Rats
Inhalation			
LD_{50}		10880	
LD_{50}/highest MTD		12.6	
LD_{50}/most potent TD_{50}		2.78	
Oral			
LD_{50}		2402	5650
LD_{50}/highest MTD		1.66	7.91
LD_{50}/most potent TD_{50}		8.17	

[a]This table is divided into 5 parts: *Salmonella* mutagenicity, carcinogenic positivity, tumorigenicity issues, dosing issues, and acute toxicity issues. Most of the data presented here have either been reported previously in, or are derivable from, the Carcinogenic Potency Data Base (CPDB) (Gold et al., 1984,1986,1987,1990,1993a).

Mutagenicity Data: *Salmonella* mutagenicity for many of the chemicals in the CPDB are reported in Gold et. al (1993b), with additional data obtained from Zeiger et al. (1987) and the U.S. Environmental Protection Agency Gene-Tox Program (Kier et al., 1986). A chemical is here classified as mutagenic in the *Salmonella* assay if it was evaluated as such by the National Institute of Environmental Health Sciences (NIEHS) or as "positive", with or without activation, by the Gene-Tox Program. If a chemical was evaluated as "weakly mutagenic" by NIEHS, then it is so classified here A chemical evaluated as "questionable" by NIEHS or "nondefinitive" by the Gene-Tox Program is classified here as "equivocal". Negative results by either NIEHS or Gene-Tox are reported as such. In the cases of conflicting opinions between NIEHS and Gene-Tox, the stronger opinion is reported.

Carcinogenicity Data: CPDB cancer data come from two sources: National Cancer Institute/National Toxicology Program (NCI/NTP) testing reports, and the general published literature. Carcinogenic positivity opinions differ between these two sources. Literature opinions are designated: "+" (positive), "-" (negative), and "none" (no opinion stated). Opinions for NCI/NTP are: "c" (clear evidence) "p" (some evidence), "a" (associated evidence), "e" (equivocal evidence), "-" (negative evidence), and "i" (inadequate experiment). The following opinions are considered positive: "+", "c", and "p". For reporting purposes in this table, these opinions are ranked in the following order: "c", "+", "p", "a", "e", "-", "none", and "i". When there is an inadequate test and there is another test with a "-" or "none", the inadequate is also noted. The CPDB reports carcinogenic potency as TD_{50}. TD_{50} is defined as the dose to reduce by half the proportion of tumor-free animals at the end of a standard lifetime (Gold et al., 1984; Sawyer et al., 1984). The CPDB reports TBA (all tumor-bearing-animals) for literature sites. TBA information is only reported in the proposed tables when no other positive sites are available for the species-route, and are noted as such when they are used.

Tumor Issues: Malignancy data are reported based on information published in the CPDB and directly from the original published papers. An "(m)" follows the tissue when there is a malignant tumor type that is positive at that tissue. When at least one dose-response curve for a given positive species-route-tissue is linear, a "*" is listed before the malignancy information. If the only positive opinion(s) for a given species-route-tissue are based on historical evidence, an "h" is listed after the malignancy information. The number of experiments with a positive opinion for a given target organ precedes the name of the target organ. The highest tumor yield for a positive site is reported, preceded by the control incidence in parentheses. The tumor yield index is defined as (1 – tumor yield)/(1 – control yield) for a given site where the yield is the number of animals with tumors at the site divided by the number of animals tested in the group. The sacrifice ratio is the ratio of the TD_{50} calculated for all animals to the TD_{50} for animals that die before sacrifice. If all of the animals die before sacrifice, then the ratio will be one. If nearly all tumors occur at sacrifice, then the TD_{50} for all animals (numerator) will be lower than the TD_{50} calculated for animals dying before sacrifice (denominator), and the ratio will be low. Since lifetable data is usually only available from NCI/NTP, the sacrifice ratio only from this source is calculated. Among carcinogens, the mean sacrifice ratio is 0.49, the median is 0.45, and the standard deviation is 0.31 (n = 169).

Dose Issues: The p-value for the lowest significant dose is based on the (1-tail) Fisher exact test between the control tumor incidences and the tumor incidences at that dose. The following method for calculating the most potent TD_{50} is used: For each positive species-route, if there is a positive site with $p<0.01$ then the lowest TD_{50} is reported from these. If there is no positive site with $p<0.01$ then the lowest TD_{50} is reported. For calculation of MTD/TD_{50} and MTD/VSD ("virtually safe dose", see Gaylor et al., 1989), the TD_{50} used is the most potent one for the species-route. The MTD used is the highest dose tested for the experiment from which the TD_{50} is taken. MTD/TD_{50} is a measure of tumor yield, having a mean value of 2.4. The ratio MTD/VSD is defined as 6.93 x 105 x MTD/TD_{50}. To calculate harmonic mean TD_{50} values: if there is a positive site with $p<0.01$, then the lowest TD_{50} is selected from each positive experiment; if there is no positive site with $p<0.01$, then the lowest TD_{50} is selected. For each species-route, a harmonic mean of these TD_{50} values is reported. To determine consistency of potency between negative and positive experiments for a given chemical-species-route when there are both negative and positive experiments, the highest non-infinite upper confidence limit for positive TD_{50}s is selected. If the lowest lower confidence limit of a TD_{50} for a negative experiment is greater than this upper confidence limit, then this is considered inconsistent. If there are no positive sites with a non-infinite TD_{50}, then inconsistency was not determined. The p-value for the most significant result indicates the signficance associated with testing whether the slope for the dose-response curve is different from zero (2-tail). When the highest dose tested, the most potent TD_{50}, or lowest p-value is from an experiment where there were survival problems, this is noted and the next value without survival problems is also reported if there is one. When all the positive experiments for a given species-route have survival problems, this is noted for the harmonic mean of TD_{50}s.

Acute Toxicity Data: Acute toxicity data has been taken from Dialog version the Registry of Toxic Effects of Chemical Substances (RTECS) and from 11th edition of The Merck Index when no RTECS value was available. RTECS reports at most one acute toxicity value per species and route, either an LD_{50} or LD_{Lo}. RTECS reports the most potent published value. The RTECS route, "oral" is in most cases gavage, so oral LD_{50} is preferentially matched with gavage TD_{50}. When there is no gavage TD_{50}, oral LD_{50} is matched with either diet or water.

[b] Only TBA (all tumor bearing animals) was reported in this group.

[c] Only TBA (all tumor bearing animals) was reported in this group.

[d] Survival problems occurred at this dose level. The next highest dose level (without survival problems) was 724 mg/kg/day in the same experiment.

Table 2
Summary of Cancer Bioassays for TCE, TCE Metabolites and Water-Chlorination By-products, Based on the Carcinogenic Potency Database[a]

CHEMICAL CPDP Paper #	Spe- cies	Sex	Str- ain	Rou- te	Tis- sue	Tum- or	TD_{50}	LCL	P- value	Opin- ion
TRICHLOROETHYLENE[b]										
1010	h	f	syg	inh	tba	mal	9220	821	0.739	-
1010	h	m	syg	inh	tba	ben	5640	999	0.343	-
1010	m	f	nmh	inh	---	mly	846	339	0.027	n
1011	m	f	hic	gav	for	tum	41.3	6.73	0.236	-
1626	m	f	icm	inh	lun	adc	3380	1460	0.017	+
BT305	m	f	swi	inh	liv	hpt	121000	19800	0.185	n
BT306m	m	f	b6c	inh	lun	tum	6320	3330	0.001	+
(BT306m	m	f	b6c	inh	liv	hpt	13600	5280	0.05	+)
c04546	m	f	b6c	gav	liv	hpc	1930	1060	0.003	c
c04547	m	f	b6c	gav	liv	hpa hpc	411	215	<0.0005	c
(c04547	m	f	b6c	gav	liv	hpc	673	314	<0.0005	c)
(c04547	m	f	b6c	gav	lun	a/a	2780	877	0.008	t)
(c04547	m	f	b6c	gav	mul	mlp	4880	1480	0.031	n)
1011	m	m	hic	gav	for	tum	16.9	4.16	0.092	-
1010	m	m	nmh	inh	tba	mal	∞	1120	1	-
2071	m	m	b6c	wat	liv	hpc	502	6.06	0.9	n
BT305	m	m	swi	inh	liv	hpt	3910	1980	0.002	+
BT306m	m	m	b6c	inh	liv	hpt	5030	2220	0.005	+
BT306n	m	m	b6c	inh	liv	hpt	4530	1340	0.244	+
c04546	m	m	b6c	gav	liv	hpc	421	277	<0.0005	c
c04547	m	m	b6c	gav	liv	hpc	294	163	<0.0005	c
1010	r	f	wsh	inh	tba	ben	2120	448	0.351	-
1626	r	f	cdr	inh	mgl	fba	982	320	0.133	n
BT301	r	f	sda	gav	tba	mix	∞	98.1	1	n
BT304m	r	f	sda	inh	kid	uac	43200	7030	0.176	n
BT304n	r	f	sda	inh	liv	nnd	9680	2380	0.06	n
c04546	r	f	osm	gav	nci	neg	5620	302	0.883	-
c04547	r	f	f34	gav	liv	hpa hpc nnd	9980	2460	0.172	m
1010	r	m	wsh	inh	tba	mal	351	141	0.025	-
BT301	r	m	sda	gav	---	leu	428	162	0.075	n
BT304m	r	m	sda	inh	tes	ldc	557	336	<0.0005	+
(BT304m	r	m	sda	inh	kid	uac	9490	2870	0.021	n)
BT304n	r	m	sda	inh	mgl	tum	120	56.2	<0.0005	n

(BT304n	r	m	sda	inh	tes	ldc	835	375	0.017	+)
c04546	r	m	osm	gav	nci	neg	16000	305	0.956	-
ACETALDEHYDE										
1766	h	f	syg	inh	lar	mix	728	219	0.039	+
(1766	h	m	syg	inh	lar	mix	461	158	0.013	+)
1766	h	m	syg	inh	res	mix	461	158	0.013	+
(1766	h	m	syg	inh	lar	cic	641	193	0.034	+)
1757	r	f	wis	inh	nse	adc	370	263	<0.0005	+
(1757	r	f	wis	inh	nse	sqc	1030	624	<0.0005	+)
(1757	r	f	wis	inh	nse	cic	3000	1360	0.006	+)
1863	r	f	wsr	inh	nac	mix	148	85.3	<0.0005	+
(1863	r	f	wsr	inh	nac	adc	201	110	<0.0005	+)
(1863	r	f	wsr	inh	nac	sqc	574	234	0.009	+)
1757	r	m	wis	inh	nse	adc	185	137	<0.0005	+
(1757	r	m	wis	inh	nse	sqc	627	380	<0.0005	+)
1863	r	m	wsr	inh	nac	mix	88.5	54.4	<0.0005	+
(1863	r	m	wsr	inh	nac	sqc	200	105	<0.0005	+)
(1863	r	m	wsr	inh	nac	adc	190	102	0.001	+)
BROMODICHLOROMETHANE										
c55243	m	f	b6c	gav	liv	hpa				
(c55243	m	f	b6c	gav	liv	hpc	144	69.9	0.001	c)
c55243	m	m	b6c	gav	mul	mlp	74.2	28.1	0.007	n
(c55243	m	m	b6c	gav	kid	tla				
						uac	137	61.8	0.014	c)
(c55243	m	m	b6c	gav	kid	uac	336	116	0.026	c)
c55243	r	f	f34	gav	kid	tla				
						uac	143	79.8	<0.0005	c
(c55243	r	f	f34	gav	col	acn				
						apn	200	103	<0.0005	c)
(c55243	r	f	f34	gav	kid	uac	272	128	0.001	c)
(c55243	r	f	f34	gav	col	apn	364	157	0.003	c)
(c55243	r	f	f34	gav	col	acn	411	168	0.006	c)
1681	r	f	wis	wat	liv	nnd	544	307	0.001	+
1681	r	m	wis	wat	pit	tum	911	382	0.053	n
						hpc	28.9	18.6	<0.0005	c
c55243	r	m	f34	gav	col	acn				
					col	apn				
					rec	acn				
					rec	apn	30.7	22	<0.0005	c
(c55243	r	m	f34	gav	col	acn				
					rec	acn	35.6	24.9	<0.0005	c)
(c55243	r	m	f34	gav	col	apn				
					rec	apn	55.6	36.8	<0.0005	c)
(c55243	r	m	f34	gav	kid	tla				

						uac	152	81.6	<0.0005	c)
(c55243	r	m	f34	gav	kid	uac	213	103	<0.0005	c)
(c55243	r	m	f34	gav	tnv	men	350	143	0.041	n)
(c55243	r	m	f34	gav	lun	a/a	447	169	0.041	n)
CHLORAL HYDRATE										
2072m	m	m	b6c	wat	liv	hpc	74.1	17.6	0.07	n
2072n	m	m	b6c	wat	liv	mix	106	53.2	<0.0005	+
CHLOROACETALDEHYDE										
2072m	m	m	b6c	wat	liv	hpc	17.4	2.8	0.2	n
2072n	m	m	b6c	wat	liv	hpc	119	65.6	<0.0005	+
CHLORODIBROMOMETHANE										
c55254	m	f	b6c	gav	liv	hpa				
						hpc	139	64.4	0.021	s
c55254	m	m	b6c	gav	liv	hpc	33.5	12.5	0.005	e
c55254	r	f	f34	gav	liv	hpa				
						hpc				
						nnd	591	204	0.098	m
c55254	r	m	f34	gav	liv	hpa				
						hpc				
						nnd	150	46.3	0.172	m
CHLOROFORM										
1003	d	f	beg	diet	tba	mix	10	2.22	0.226	-
1003	d	m	beg	diet	tba	mix	13.3	5.39	0.007	-
1671	m	f	b6c	wat	liv	hpc	20200	2690	0.493	-
710m	m	f	ici	gav	lun	tum	316	81.3	0.235	-
c02686	m	f	b6c	gav	liv	hpc	48	35.2	<0.0005	c
710m	m	m	c5l	gav	lun	mix	728	134	0.471	-
710m	m	m	cba	gav	tba	mix	∞	64.7	1	-
710m	m	m	cfl	gav	kid	mix	153	66.6	<0.0005	+
710m	m	m	ici	gav	kid	mix	139	62.8	<0.0005	+
710n	m	m	ici	gav	kid	mix	278	91.2	0.071	+
710o	m	m	ici	gav	kid	mix	95.5	47.1	<0.0005	+
c02686	m	m	b6c	gav	liv	hpc	56.2	38.7	<0.0005	c
1681	r	f	wis	wat	liv	nnd	883	429	0.004	+
711	r	f	sda	gav	tba	mal	276	86	0.125	-
c02686	r	f	osm	gav	thy	cca				
						ccr				
						fca				
						fcc	126	65.8	0.003	n
1671	r	m	osm	wat	kid	mix	519	265	<0.0005	+
(1671	r	m	osm	wat	—	nfm	2200	676	0.034	n)
1681	r	m	wis	wat	kid	adc	5300	862	0.278	+

711	r	m	sda	gav	tba	mix	∞	115	1	-
c02686	r	m	osm	gav	kid	tla				
						uac	119	65.5	0	c
DICHLOROACETIC ACID										
2071	m	m	b6c	wat	liv	mix	49.3	24.9	<0.0005	+
2072	m	m	b6c	wat	liv	mix	48.1	26.2	<0.0005	+
2073m	m	m	b6c	wat	liv	hpc	85.1	36.2	<0.0005	+
(2073m	m	m	b6c	wat	liv	mix	0	0	0	+)
(2073n	m	m	b6c	wat	liv	hpc	61.9	32.5	<0.0005	+)
2073n	m	m	b6c	wat	liv	mix	48.1	26.2	<0.0005	+
FORMALDEHYDE										
(BT7001	r	f	sda	wat	---	lls	996	386	0.027	+)
BT7001	r	f	sda	wat	---	leu	815	316	0.039	+
BT7001	r	m	sda	wat	---	lls	424	213	<0.0005	+
(BT7001	r	m	sda	wat	---	leu	480	213	0.009	+)
(BT7001	r	m	sda	wat	git	mix	1410	517	0.011	+)
TRIBROMOMETHANE										
c55130	m	f	b6c	gav	liv	hes				
					spl	hes	1110	311	0.033	=
c55130	m	m	b6c	gav	sub	fbs				
						sar	81.9	28	0.01	n
c55130	r	f	f34	gav	lgi	adc				
						pla	469	219	0.001	c
(c55130	r	f	f34	gav	lgi	pla	632	270	0.003	z)
(c55130	r	m	f34	gav	lgi	adc				
						pla	1050	298	0.017	s)
c55130	r	m	f34	gav	thy	fcc	656	237	0.025	n
TRICHLOROACETIC ACID										
2071	m	m	b6c	wat	liv	hpc	513	220	0.001	+
2,4,6-TRICHLOROPHENOL										
292	m	f	b6a	inh	liv	hpt	220	35.8	0.234	n
292	m	f	b6c	inh	tba	mix	27	11.5	0.001	n
c02904	m	f	b6c	diet	liv	hpa				
						hpc	1410	874	<0.0005	c
292	m	m	b6a	inh	tba	mix	1050	24.7	0.939	n
(292	m	m	b6c	inh	tba	mix	17.9	8.25	<0.0005	n)
292	m	m	b6c	inh	liv	hpt	68	20.5	0.044	n
c02904	m	m	b6c	diet	liv	hpa				
						hpc	856	457	0.009	c
c02904	r	f	f34	diet	nci	neg	∞	301	1	-

c02904	r	m	f34	diet	---	mle	405	222	0.007	c
(c02904	r	m	f34	diet	---	leu				
						lym	445	227	0.018	c)

[a]Source: Gold et al. (1984,1986,1987,1990,1993a), and analyses done using similar methods applied to data from three studies (Herren-Freund, et al., 1987; DeAngelo et al., 1991; Daniel et al., 1992) not yet included in the Carcinogenic Potency Database (CPDB). Abbreviations used are: TD_{50} = estimated dose that halves the probability of remaining tumorless (not listed when P-value > 0.05), LCL = lower 2-tail 99% confidence limit on TD_{50}, P-value = probability that bioassay data indicate a nonpositive dose-response, NCI = National Cancer Institute, NTP = National Toxicology Program. Also used are:

Species: d = dog, h = hamster, m = mouse, r = rat; Sex: f = female, m = male.

Strain: aci = ACI, aug = August, b6a = B6AKF1, b6c = B6C3F1, beg = beagle, c5l = C57BL, cba = CBA, cdr = Charles River CD, cf1 = CF-1, cfl = CFLP, f34 = Fischer 344, hic = Ha/ICR, ici = ICI, icm = ICR, Inn = Innes, mar = Marshall, nmh = Han: NMRI, osm = Osborne-Mendel, sda = Sprague-Dawley, swi = Swiss, syg = Syrian Golden, wis = Wistar, wsh = Han: WIST, wsr = Wistar-random.

Route: gav = gavage, inh = inhalation, wat = water.

Tissues: --- = all target sites, adr = adrenal gland, col = colon, for = forestomach, git = gastrointestinal tract, kid = kidney, lar = larynx, lgi = large intestine, liv = liver, lun = lung, mgl = mammary gland, mul = multiple organs, nac = nasal mucosa, nci = NCI/NTP TBA (negative only), nse = nose, per = peritoneum, pit = pituitary gland, rec = rectum, res = respiratory system, spl = spleen, sub = subcutaneous tissue, tba = all tumor bearing animals, tes = testis, thy = thyroid gland, tnv = tunica vaginalis. For each study/species/sex/strain/route (SSSSR) for which significant (defined here as those with a P-value > 0.05) and nonnegative (i.e., opinion ≠ "-"; see below) results are reported in the CPDB, the most sensitive tissue/tumor response (i.e., that with the lowest TD_{50} value) is indicated by a nonparenthesized data row. For cases in which the CPDB contains multiple, significant (i.e., $P \leq 0.05$) SSSSR-specific tissues/tumors that are potentially malignant, all corresponding data are included in this table; in this case, all but that row containing the lowest TD_{50} value are parenthesized. For each study/species/sex/strain/route (SSSSR) for which only negative ("-", see below) or nonsignificant (defined here as those with a P-value > 0.05) results are reported in the CPDB, only the most significant tissue/tumor response (i.e., that with the lowest TD_{50} value) is included in this table.

Tumors: a/a = alveolar/bronchiolar adenoma, acn = adenocarcinoma (not otherwise specified [NOS]), adc = adenocarcinoma, apn = adenomatous polyp (NOS), ben = benign tumor, cca = c-cell adenoma, ccr = c-cell carcinoma, cic = carcinoma in situ, coa = cortical adenoma, fba = fibroadenoma, fbs = fibrosarcoma, fca = follicular-cell adenoma, fcc = follicular-cell carcinoma, hes = hemangiosarcoma, hpa = hepatocellular adenoma, hpc = hepatocellular carcinoma, hpt = hepatoma, ict = interstitial-cell tumor, itm = interstitial-cell tumor (malignant), ldc = Leydig-cell tumor, leu = leukemia, lls = lymphoblastic leukemia-lymphosarcoma, lym = lymphoma, mal = malignant tumor, men = mesothelioma (NOS), mix = more than one tumor type (tumor types specified in published paper), mle = monocytic

leukemia, mlp = malignant lymphoma (lymphocytic type), mly = malignant lymphoma, msm = mesothelioma (malignant), neg = NCI/NTP TBA (negative only), nfm = neurofibroma, nnd = neoplastic nodule, pla = polypoid adenoma, sar = sarcoma, spm = sarcoma (NOS, unclear primary or metastatic), sqc = squamous-cell carcinoma, srn = sarcoma (NOS), tla = tubular-cell adenoma, tum = tumor or more than one tumor type (tumor types not specified in published paper), uac = tubular-cell adenocarcinoma.

Opinion: c = Clear evidence (positive, NCI/NTP), s = Some evidence (positive, NTP), + = Positive (literature), - = Negative, n = No opinion [literature only], v = a Berkeley mix of all "c" (clear-evidence) sites within an NCI/NTP experiment, e = an equivocal opinion from NTP. The following "opinions" are for single sites or Berkeley mixes: "=" = dose-related trend (significant), n = Fisher exact is significant ($p<.1$) [NCI/NTP only], t = Fisher exact is significant ($p<.05$), z = Fisher exact and dose-related trend are significant, m = Berkeley mandatory site (liver or thyroid).

[b] Studies reported by NTP as "inadequate" are excluded from this table.

Table 3
Summary of Estimated TCE Carcinogenic Potency, Taking into Account TCE Metabolism[a]

Study, species strain	Sex, weight (dosed animals)	Daily experimental applied dose or concn., D	LTWA metabol. dose[a], M (mg/kg-day)	Tumor		95% UCL potency[d] of metabolized dose q_1^* (M) (mg$M$/kg-day)$^{-1}$	
				Type[b]	Incidence[c]	BW[e]	SA[f]
NCI 1976 mice B6C3F1	M, 34 g	0 mg/kg	0		1/20		
		1169 mg/kg	369.6	HCC	26/48	0.0025	0.032
		2339 mg/kg	739.4		31/40		
					TT-IT	0.0033	0.042
					TT-LT	0.00034	0.0044
		0 mg/kg	0		0/18		
	F, 29g	869 mg/kg	274.7	HCC	4/42	0.00073	0.0098
		1739 mg/kg	549.8		11/37		
NCI 1976 mice B6C3F1 (analyzed by Fisher and Allen, 1993)	M, 31 g	0 mg/kg	0		1/20		
		1169 mg/kg	176.5[g]	HCC	26/50	0.0050	0.066
		2339 mg/kg	211.4[g]		31/48		
	F, 25 g	0 mg/kg	0		0/20		
		869 mg/kg	158.7[g]	HCC	4/50	0.00090	0.013
		1739 mg/kg	196.2[g]		11/47		
NTP 1990, mice, B6C3F1	M, 37g	0 mg/kg	0		8/48		
		1000 mg/kg	563	HCC	30/50	0.0019	0.023
					TT-IT	0.0029	0.036
					TT-LT	0.0013	0.016
		0 mg/kg	0	HCC or	11/48		
		1000 mg/kg	563	HCA	38/50	0.0029	0.036
					TT-IT	0.0048	0.059
					TT-LT	0.0018	0.022
	F, 33g	0 mg/kg	0		2/41		
		1000 mg/kg	563	HCC	13/41	0.00096	0.012
					TT-IT	0.0011	0.014
					TT-LT	0.00077	0.0099
		0 mg/kg	0	HCC or	4/41		
		1000 mg/kg	563	HCA	19/41	0.0014	0.018
					TT-IT	0.0019	0.024
					TT-LT	0.0011	0.014
NTP1990[h], rats F344/N	M, 340 g	0 mg/kg	0		0/33		
		500 mg/kg	198	RTC	0/20	0.00074	0.0043
		1000 mg/kg	282		3/16		
		0 mg/kg	0		0/45		
		500 mg/kg	198	RTC or	2/39	0.00065	0.0038
		1000 mg/kg	282	RTA	3/26		
					TT-IT	0.00034	0.0020
					TT-LT	0.00068	0.0040

Study, species strain	Sex, weight	Daily dose or concn., D	LTWA metabol. dose[a], M	Tumor Type[b]	Tumor Incidence[c]	95% UCL potency[d] q_1^* (M) BW[e]	q_1^* (M) SA[f]
Henschler *et al.* 1980, mice HanNMRI	F, 30 g (?)	0ppmv-6hr	0		9/29		
		100ppmv-6hr	33.2	ML	17/30	0.0074	0.098
		500ppmv-6hr	166		18/28		
Fukuda *et al.* 1983, mice ICR	F, 30 g (?)	0ppmv-7hr	0		1/49		
		50ppmv-7hr	25.8		3/50		
		150ppmv-7hr	77.4	LA	8/50	0.0014	0.019
		450ppmv-7hr	232		7/46		
Maltoni *et al.* 1986, mice Swiss	M, 41 g	0ppmv-7hr	0		4/90		
		100ppmv-7hr	35.3		2/90		
		300ppmv-7hr	106	MH	8/90	0.00082	0.0098
		600ppmv-7hr	212		13/90		
Maltoni *et al.* 1986, mice B6C3F1	M, 31 g	0ppmv-7hr	0[g]		1/85		
		100ppmv-7hr	108.4[g]		1/86		
		300ppmv-7hr	301.3[g]	MH	3/88	4.3×10^{-5}	0.00056
		600ppmv-7hr	355.9[g]		6/88		
(analyzed by Fisher and Allen, 1993)	F, 25 g	0ppmv-7hr	0[g]		2/90		
		100ppmv-7hr	111.5[g]		3/90		
		300ppmv-7hr	249.7[g]	MH	4/89	6.4×10^{-5}	0.00090
		600ppmv-7hr	285.7[g]		9/87		

[a]Sources: Bogen (1988), except where indicated by note *g* (see below). Lifetime, time-weighted-average metabolized dose, M, in mg/kg-day. See Bogen *et al.* (1988) (and note *g*) for details on derivation as a function of D.

[b]HCC, hepatocellular carcinoma; HCA, hepatocellular adenoma; RTC, renal tubular-cell adenocarcinoma; RTA, renal tubular-cell adenoma; ML, malignant lymphoma; LA, lung adenocarcinoma; MH, malignant hepatoma.

[c]Tumor-incidence denominator excludes animals dying before the occurrence of the first corresponding tumor type observed in the NCI (1976) and NTP (1990) studies. TT-IT, time-to-tumor data using an "incidental-tumor" model; TT-LT, time-to-tumor data using a "lethal-tumor" model (see note *d*).

[d]"Potency" here means the low-dose dose-response slope expressed by an upper-bound linear multi-stage coefficient such that at very low doses, risk = (potency × dose), according to a multistage (or, with time-to-tumor data as input, a time-dependent multistage) risk-prediction model (Crump and Watson, 1979; U.S. EPA, 1980; Anderson *et al.*, 1983; Howe and Crump, 1983; Crump and Howe, 1984). 95% UCL, one-tailed 95% upper confidence limit.

[e]BW, body weight interspecies dose-extrapolation method; equivalent doses assumed to be in mg/kg, so $M_{human} = M_{animal}$.

[f]SA, surface area interspecies dose-extrapolation method; equivalent doses assumed to be in mg/kg$^{2/3}$, so $M_{human} = M_{animal}$ [(animal weight)/70kg]$^{1/3}$.

[g]Source: Fisher and Allen (1993). Note: unadjusted tumor-incidence data were used to calculate virtual safe (10^{-6}-risk) doses in this study; the latter doses were used here to calculate the corresponding potencies listed for the BW method.

[h]This rat study was designated as "inadequate" by NTP (1990).

Table 4
Physical-chemical data for TCE and Water-Chlorination By-Products, and Corresponding Estimated Normalized Multiroute Household Exposures[a]

Chemical	*MW*	Log_{10} K_{ow}	Log_{10} *H*	E_o (L)	E_r (L)	E_d (L)	ΣE_i (L)
Acetaldehyde	44.05	0.450	-0.393	1.36	2.0	0.247	3.61
Bromodichloromethane	163.83	2.10	-1.03	1.36	2.0	0.158	3.52
Chloral hydrate (CH)	165.42	-1.07	-2.29	1.36	1.7	0.00212	3.06
Chlorodibromomethane	208.29	2.24	-1.42	1.36	1.9	0.0706	3.33
Chloroform	119.4	1.97	-0.706	1.36	2.	0.364	3.72
Dichloroacetic acid (DCA)	128.95	1.74	-3.99	1.36	0.2	0.298	1.86
Formaldehyde	30.03	0.350	-4.89	1.36	0.029	0.444	1.83
Tribromomethane	252.75	2.37	-1.63	1.36	1.9	0.0302	3.29
Trichloroacetic acid (TCA)	163.39	3.73	-4.28	1.36	0.11	2.20	3.67
Trichloroethylene (TCE)	131.4	2.42	-0.352	1.36	2.	0.495	3.86
2,4,6-Trichlorophenol	197.45	3.69	-5.60	1.36	0.0056	0.920	2.29

[a] *MW* = molecular weight (g/mol); K_{ow} = octanol:water partition coefficient (unitless); *H* = dimensionless Henry's law constant (or inverse "Ostwald coefficient"); E_i = ingestive-equivalent exposure to, contact with, or uptake of a chemical in household water, equal to the total amount of that chemical ingested (i = o); respired (i = r), or dermally absorbed (i = d) that is present in one liter (L) of that water; ΣE_i = the sum of ingestive-equivalent intakes E_i, for i = o,r,d.

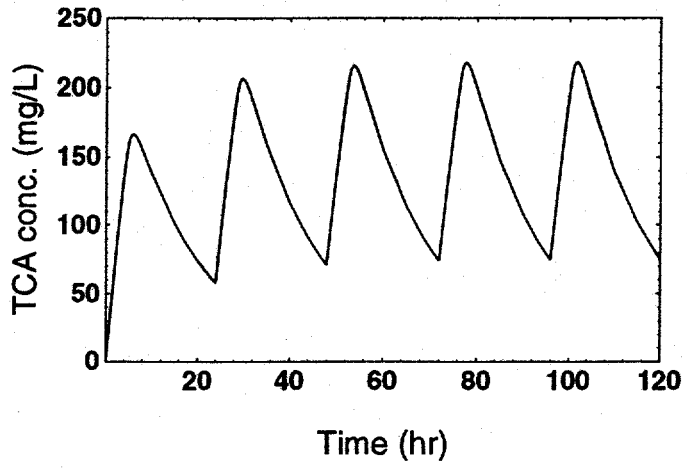

Figure 1. Blood concentration of trichloroacetic acid (TCA) in female B6C3F1 mice administered 1739 mg/kg of trichloroethylene (TCE) by gavage in corn oil, once per day for five days, as predicted by the physiologically based pharmacokinetic (PBPK) model of Fisher et al., (1991) and Allen and Fisher (1993). This was the high dose used in the NCI (1976) bioassay involving this exposure route and mouse strain. The first and last predicted peak concentrations are 166 and 218 mg/L (the latter value being ~31% higher than the former), reached at times of 5.96 and 102 hr, respectively. By 72 hr after a final TCE dose (e.g., the 5th of 5 daily exposures per wk), TCA concentration is predicted to decrease virtually to zero, so no week-to-week accumulation of TCA concentration is expected.

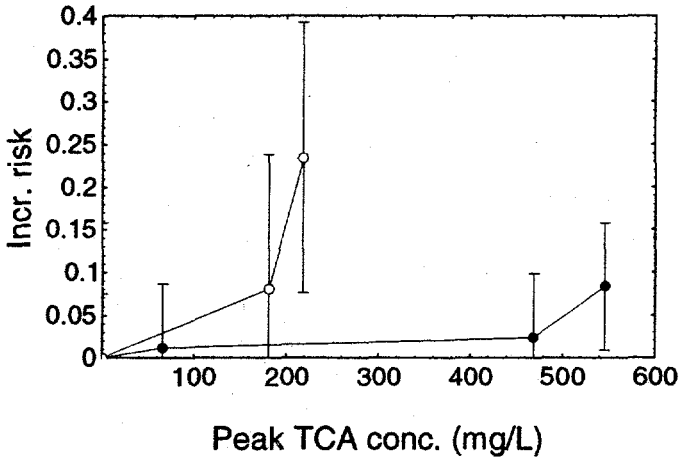

Figure 2. Liver cancer rate is plotted as a function of predicted weekly peak blood concentrations of trichloroacetic acid (TCA) in the NCI (1976) female B6C3F1 mice administered 0, 869 and 1739 mg/kg-day of trichloroethylene (TCE) by gavage in corn oil 5 day/wk (open points), or the Maltoni et al. (1986) female B6C3F1 mice administered 0, 100, 300 and 600 ppm TCE by inhalation 7 hr/day for 5 day/wk (solid points), as predicted by a physiologically based pharmacokinetic (PBPK) model (Fisher et al., 1991; Allen and Fisher, 1993). Error bars reflect binomial sampling error for estimated increased risk.

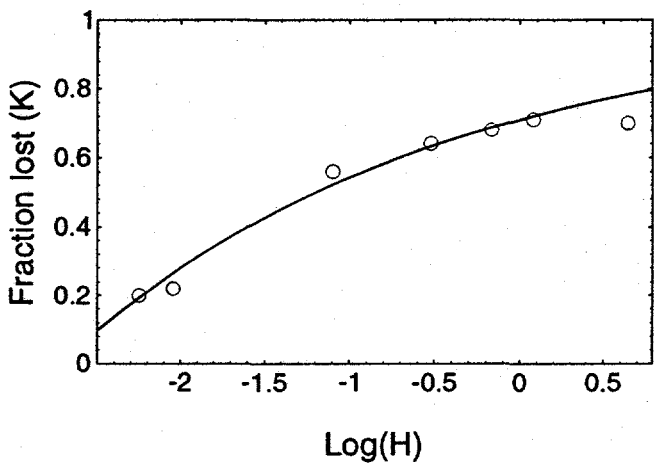

Figure 3. Model predicting the average fraction (K) of an organic chemical contaminant lost from shower water during showering, as a function of the dimensionless Henry's law constant (H, the inverse Ostwald coefficient). Values of H and experimentally determined (or estimated*) values of K are plotted for seven compounds (appearing from left to right): 1,2-dibromo-3-chloropropane*, 1,2,3-trichloropropane, chloroform, trichloro-ethylene, tetrachloroethylene, carbon tetrachloride, and radon. The curve shown is the function $K = 1 - 0.2905H^{-0.197}$, which was fit to data corresponding to the six organic compounds ($R^2 = 0.99$, $p = 10^{-4}$).

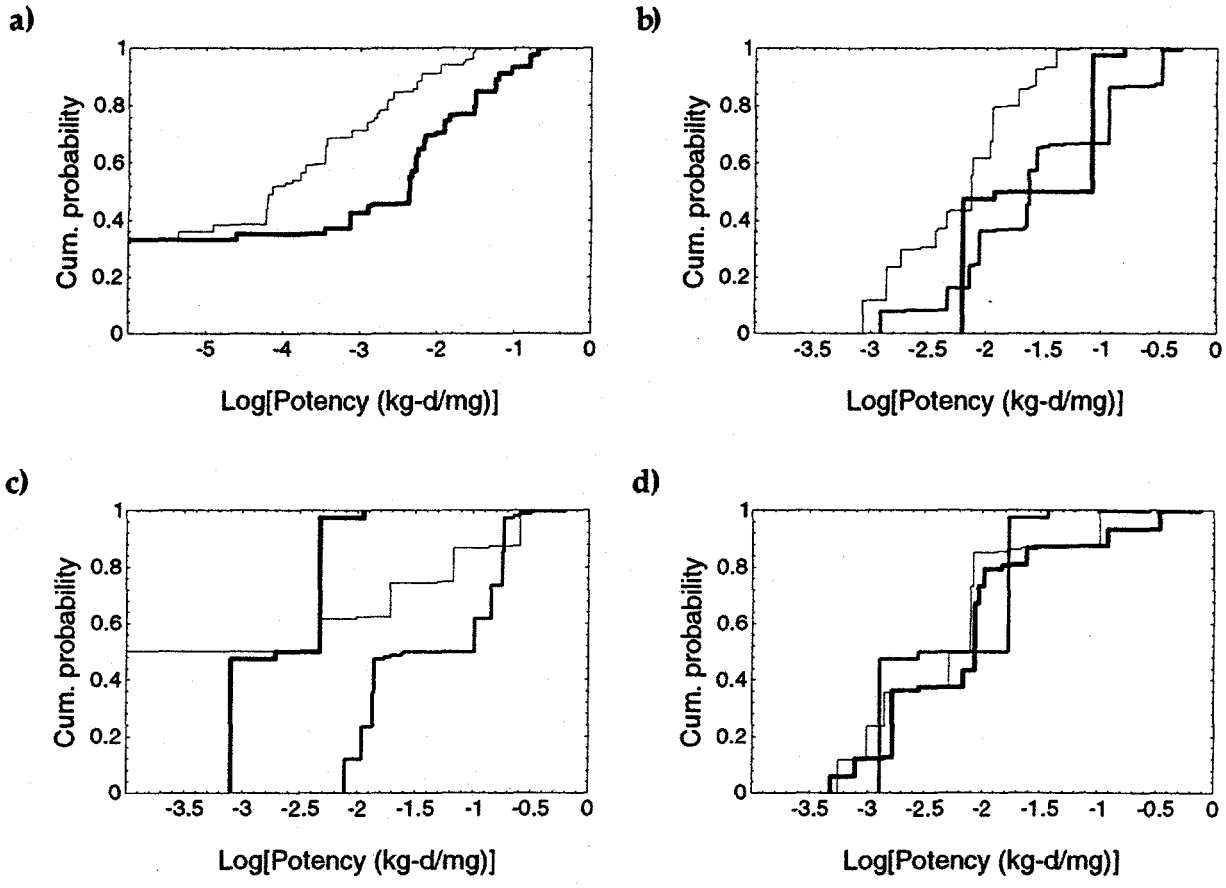

Figure 4. Cumulative probability distributions (cdfs) characterizing uncertainty in log10 values of carcinogenic potency of lifetime time-weighted average human exposures to (from thinnest to thickest curves, respectively): **(a)** trichloroethylene, chloroform; **(b)** acetaldehyde, bromodichloromethane, chloral hydrate; **(c)** chlorodibromomethane, dichloroacetic acid, formaldehyde; **(d)** tribromomethane, trichloroacetic acid, 2,4,6-trichlorophenol. Cdfs were calculated from TD_{50} and related data concerning animal bioassay results reported in the Carcinogenic Potency Database (CPDB). The cdfs reflect uncertainty in estimated potency for nonnegative studies arising from: statistical potency-estimation error conditional on the CPDB one-hit time-to-tumor dose-response extrapolation model; interspecies potency extrapolation using body-weight- and body-surface-area-based methods, which were averaged assuming equal likelihood (AAEL); maximum site-specific potencies estimated from multiple studies involving the same species/strain/sex (AAEL); multiple averaged species/strain/sex-specific potencies pertaining to the same species (AAEL); and averaged species-specific potencies pertaining to multiple species (AAEL). Additionally, the cdfs reflect uncertainty arising from the presence of negative study results (defined as any data set for which $p > 0.05$ or CPDB-designated "-", conditional on estimated potency being significantly less than the lowest significant potency among all non-"-" studies pertaining to the same species). Such negative studies were taken to reflect potency values of zero, AAEL with those from nonnegative studies.

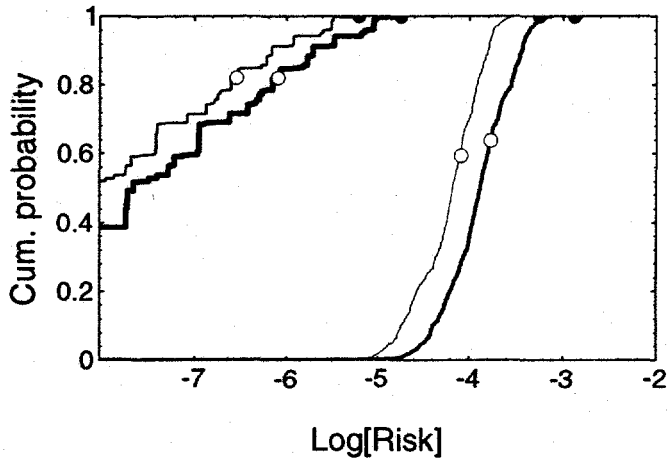

Figure 5. Cumulative probability distributions characterizing uncertainty in the $\log_{10}$ value of potential human cancer risk associated with exposure to TCE in domestic water at 5.0 ppb (2 leftmost curves), vs. that associated with combined exposure to 10 carcinogenic chlorination byproducts (CBP) in water scaled to EPA's newly proposed Maximum Contaminant Level (MCL) for total trihalomethanes (TTHM), equal to a TTHM concentration of 80 ppb (2 rightmost curves). The latter scaling was based on the ratio of average of four quarterly median concentrations for each CBP to that of TTHM reported by Krasner et al. (1989) for water sampled from 35 water treatment utilities during 1988-1989. The thinner of each pair of nearby curves denotes estimated ingestion risk, assuming a mean U.S. fluid intake (1.4 L/d), while the thicker denotes estimated total risk from all household exposure pathways (ingestion + inhalation + dermal). Open points = expected risk (average with respect to all considered sources of uncertainty in potency); solid points = maximum risk (aggregated-upper-bound/worst case with respect to all considered sources of uncertainty in potency).

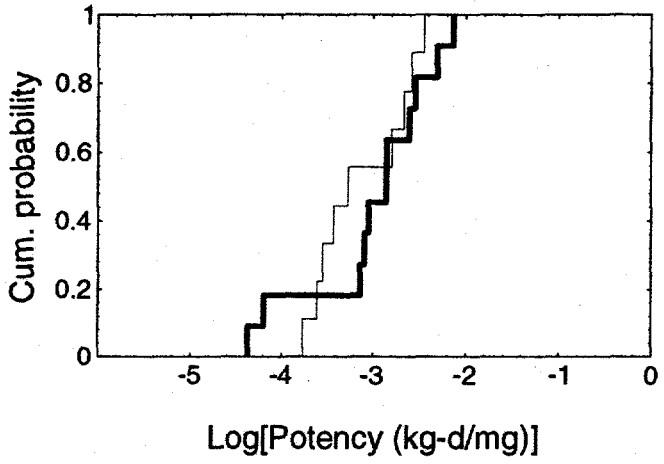

Figure 6. Cumulative probability mass functions characterizing variability in upper one-tail 95% confidence limits on the $\log_{10}$ value of TCE's carcinogenic potency in mice, as calculated from data on 9 nonnegative mouse studies listed in the Carcinogenic Potency Data Base (CPDB) (thin curve), and from the 11 potency estimates that took into account TCE pharmacokinetics for mouse studies listed in Table 3 (thick curve). CPDB-derived potency estimates are expressed as increased risk per lifetime time-weighted-average (LTWA) daily amount (in mg/kg body weight) of applied TCE dose, while those taking into account pharmacokinetics are expressed as increased risk per estimated LTWA daily amount (in mg/kg body weight) of TCE metabolized. Both mice and humans are expected to metabolize virtually all (or a major portion) of any very low applied TCE dose arising from ingestive (or respiratory or dermal) exposure (Bogen, 1988). The two curves thus reflect comparable potency measures, yet do not reflect a significant difference in estimated potencies (2-tail T-test, $p > 0.35$), even if the two smallest pharmacokinetic-based values are not considered (2-tail T-test, $p > 0.16$).