Revised MassDEP Cancer Unit Risk for Tetrachloroethylene

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Executive Summary

An interim unit risk value of 1 x 10^{-5} $(\mu g/m^3)^{-1}$ is recommended for tetrachloroethylene (PCE, also known as perchloroethylene) in air. The unit risk value is based on statistically significant incidence of leukemia in rats, supported by liver tumor data in mice (NTP, 1986; JISA, 1993). Statistically significant increases in the incidence of tumors at several sites have also been observed in certain studies of workers in the dry-cleaning industry (WHO, 2006 and citations there in).

For the calculation of the cancer potency estimates, used as a basis for the unit risk value, the United States Environmental Protection Agency (USEPA, 2005) *Guidelines for Carcinogenic Risk Assessment* were used. Although the mode of action is uncertain for PCE, several lines of evidence suggest that the linear low-dose extrapolation assumption is reasonable. The multistage model (USEPA Benchmark Dose Software, version 1.4.1) was fit to the experimental data in order to estimate the lower 95 percent confidence bound on the dose associated with a 10 percent increased risk of cancer ($BMDL_{10}$), and the slope (potency factor) was calculated using the result ($0.1/BMDL_{10}$).

The dose metric chosen to perform the dose-response assessment was the metabolized dose calculated using Michaelis-Menton steady-state kinetics. Chui and Bois (2006) estimated an upper limit of the fraction metabolized at an environmentally relevant concentration in a human population to be 61%. This calculation was performed using population toxicokinetics, Bayesian statistics and physiological modeling. MassDEP selected this value as a conservative, health protective estimate of the low dose metabolism of PCE in humans.

Proposed Interim Unit Risk Value Derived by MassDEP

Bioassay and exposure route	**Species, Strain Sex, Tumor type**	**Unit Risk Values $(ug/m^3)^{-1}$**	**MassDEP Proposed Interim Unit Risk Value $(ug/m^3)^{-1}$**
NTP, 1986 inhalation	F344 rat male, leukemia	1.7 x 10^{-5}	**1 x 10^{-5}** [a]
JISA, 1993 inhalation	F344 rat male, leukemia	9.3 x 10^{-6}	
NTP, 1986 inhalation	B6C3F1 mice male liver tumors	1.30 x 10^{-5}	1 x 10^{-5}

[a] Mean of the unit risk values based on leukemia in rats incidence observed in the NTP (1986) and JISA (1993) studies. The values were averaged because the tumor bioassays were conducted in the same species. The geometric mean, 1.26 x 10^{-5} $(ug/m^3)^{-1}$, and arithmetic mean 1.32 x 10^{-5} $(ug/m^3)^{-1}$ are both equivalent to 1 x 10^{-5} $(ug/m^3)^{-1}$ when rounded to one significant figure. The male mice liver tumor data yields the same value.

1.0 Introduction

Tetrachloroethylene (PCE, also known as PERC) is a frequent soil and groundwater contaminant. Because it is volatile, indoor air can be contaminated to potentially significant levels in buildings situated over soil or groundwater containing PCE. To reflect new scientific information, the MassDEP Bureau of Waste Site Cleanup (BWSC) recently updated various chemical-specific factors that are used in fate and transport modeling to assess potential exposures and risks from groundwater and soil contaminants. As a result of these updates, the Groundwater 2 (GW-2)[1] standard for PCE decreased from 3000 ppb to 50 ppb leading to more sites of concern for indoor air contamination and the need for further quantitative, site-specific assessments to address PCE inhalation cancer risk. The degree of cancer risk posed by PCE is a matter of considerable national debate and ongoing scientific research. The cancer risk value previously derived and adopted by MassDEP in 1990 has been questioned as being overly health-protective and out-of-date.

To address these issues, BWSC requested the Office of Research and Standards (ORS) to review and update, as necessary, the MassDEP inhalation cancer value for PCE. ORS had planned to revise the MassDEP PCE cancer risk value in light of a pending report by USEPA and scheduled review by the National Academy of Sciences. USEPA has worked for several years to complete an updated toxicity assessment of PCE and was scheduled to release a draft of its report in November 2006 and then again this past summer. In light of the controversy regarding PCE toxicity, a National Academy of Science panel was also selected to review the USEPA report when it is completed.

As the USEPA report and NAS review have been repeatedly delayed, and because BWSC response decisions are needed in the short-term regarding a number of MA contamination sites, ORS has completed a review of recent information and assessments on PCE carcinogenicity by other groups. Based on this review and as an interim step, pending the completion of the USEPA and NAS work, ORS is proposing a revised inhalation unit risk value for PCE. ORS will reevaluate PCE carcinogenicity after the USEPA and NAS work is published.

The purpose of this brief report is to review and update MassDEP's carcinogenic assessment and inhalation unit risk value[2] for PCE in light of more recent assessments by the California Environmental Protection Agency (CAEPA); the Northeast States for Coordinated Air Use Management (NESCAUM); and the World Health organization (WHO). The reassessment addresses new inhalation data from a second series of cancer bioassays by the Japan Industrial Safety Association (JISA, 1993) not available when MassDEP completed its 1990 assessment; new information on the extent of PCE

[1] GW-2 values apply to groundwater that is not protected as drinking water but which may impact buildings. Values are set at levels to prevent significant indoor risk attributable to vapor intrusion.
[2] For more comprehensive review of the overall toxicity of this chemical, readers are referred to documents completed by the groups noted above as well as by the Agency for Toxic Substances and Disease Registry (ATSDR, 1997).

metabolism in humans (e.g. Chui et al. (2007), Chui and Bois (2006), Bois et al. (1996); Covington et al. (2007)); and the adoption by USEPA of a revised interspecies scaling factor for dose extrapolation and new cancer risk assessment guidelines.

2.0 Summary of Carcinogenicity Information

Based on compelling positive data from multiple animal bioassays and equivocal epidemiological data, many groups have classified PCE as a known animal carcinogen and possible to probable human carcinogen. The International Agency for Research on Cancer (IARC) has classified PCE as a category 2A carcinogen (probable human carcinogen, indicating sufficient evidence of carcinogenicity in animals and inadequate evidence in humans) (IARC, 1995b). PCE was previously classified as a possible human carcinogen by the USEPA Integrated Risk Information System (IRIS) program but is currently being reassessed by USEPA. CAEPA (1992, 2001) considers PCE to be an animal carcinogen and a possible human carcinogen.

Brief summaries of the human and animal carcinogenicity information on PCE are presented below.

2.1 Cancer Studies in Humans

The cancer epidemiology data in humans exposed to PCE have been extensively reviewed by ATSDR (1997), IARC (1995a, b), CAEPA (1992), USEPA (1985). Twenty-five epidemiological studies published between 1981 and 2003 were also reviewed by WHO (2006) (see Appendix A for a summary table of the studies including relative risk values). Epidemiological studies have reported possible associations between exposures to PCE and cancer of esophagus, kidney, bladder and urinary tract, cervix, non-Hodgkin's lymphoma, multiple myeloma, liver, pancreas, larynx and lung. The cancer studies showed fairly consistent positive, although typically not statistically significant, associations between exposure to PCE and esophageal and cervical cancer and non-Hodgkin's lymphoma. IARC noted that, "These associations appear unlikely to be due to chance, although confounding cannot be excluded and the total cohort studies combined are relatively small" (IARC (1995b), as cited in WHO (2006)).

None of the epidemiological studies provide data adequate for quantitative risk assessment. As in many epidemiological studies they are confounded by exposure to other chemicals, limited individual exposure data, and other factors that preclude the derivation of quantitative potency estimates.

2.2 Cancer Studies in Animals

The carcinogenicity of PCE has been evaluated in several animal bioassays. The three studies that provide good dose-response data for carcinogenic potency assessment of PCE are summarized briefly below. These include bioassays by the US National Cancer Institute (NCI, 1977), the US National Toxicology Program (NTP, 1986), and the Japan Bioassay Research Centre (JISA, 1993). In these studies, ingestion and inhalation

exposure pathways were assessed using 2 or 3 dose groups (in addition to concurrent controls) in males and females of two strains of mice and one strain of rats. Statistically positive results were observed in each study with the predominant and consistent responses being tumors of the liver in mice and mononuclear cell leukemia (MCL) in rats. Less significant elevations of tumor rates at other sites were also observed in one or more of the bioassays. These studies are briefly discussed in the following paragraphs.

2.2.1 Mouse Oral Study (NCI, 1977)

In the National Cancer Institute study (NCI, 1977), $B6C3F_1$ mice were administered PCE in corn oil by gavage, 5 days/week for 78 weeks with an additional 12 week observation period. Mice were 25 days old at initial treatment. The administered doses of PCE were 536 and 1,072 mg/kg for male mice and 386 and 722 mg/kg for female mice. *A statistically significant increase ($P<0.001$, Fisher Exact test) in hepatocellular carcinoma was observed in both males and females* (See Appendix C, Table C-1). The NCI concluded that under the conditions of this study, PCE was a liver carcinogen to $B6C3F_1$ mice of both sexes. Interpretation of this data is complicated by the fact that epichlorohydrin (ECH), which itself is a direct acting alkylating agent and mutagen that has been demonstrated to be weakly tumorigenic in mice, was apparently used as a stabilizer. However, an analysis by the NCI concluded that ECH at the concentrations likely to have been present was unlikely to have contributed significantly to the observed tumor responses (NCI, 1977).

2.2.2 Rat Oral Study (NCI, 1977)

Male and female Osborne-Mendel rats were treated with 471mg/kg-d or 941mg/kg-d, and 474 mg/kg-d or 949 mg/kg-d PCE, respectively, by gavage in corn oil (78 weeks with an additional 32 week observation period). Early mortality occurred in all groups of rats dosed with PCE. Half of the high-dose males had died by week 44 and half of the high-dose females died by week 66. The survival time of control animals ranged from 88 to 102 weeks. The NCI determined that there was a statistically significant association ($p<0.001$) between increased dosage of PCE and increased mortality. The early mortality observed in rats, and its statistical association with PCE dose, indicate that the maximum tolerated dose was exceeded in this experiment. Because optimum dosages were not used and because significant early mortality occurred, firm conclusions regarding the carcinogenicity of PCE in rats are not possible from this study.

2.2.3 Mouse Inhalation Study (NTP, 1986)

$B6C3F_1$ mice were exposed to 99.9 percent pure PCE by inhalation, 6 hours/day, 5 days/week for 103 weeks at concentrations of 0, 100, or 200 ppm (NTP, 1986). *Hepatocellular adenoma and hepatocellular carcinoma in males and hepatocellular carcinomas in females were observed*. The incidences of hepatocellular carcinoma compared to controls were significantly increased ($P<0.01$, Fisher Exact test) for mid- and high-dose males and females (See Figure 1 and Appendix D, Table D-1). The NTP determined that there was “clear evidence of carcinogenicity” of PCE for both sexes of $B6C3F_1$ mice in this study.

2.2.4 Rat Inhalation Study (NTP, 1986)

F344/N rats were exposed to PCE (99.9% pure) at concentrations of 0, 200, or 400 ppm by inhalation, 6-hours/day, 5-days/week for 103 weeks. Treated male rats had lower survival rates than control animals. Survival rates among female rats showed little variation across dose groups. *A statistically significant increase in mononuclear cell leukemia (a type of large granulocyte leukemia) was observed in mid- and high-dose males and females* compared to concurrent controls (see Figure 2 and Appendix D, Table D-1). The significance of these results has been discounted by some due to the high background rate of MCL in the rat strain under consideration and questions about the relevance of this form of cancer to humans. As discussed in Section 5 of this report, ORS does not agree with these points of view.

In males, increases in renal tubular cell adenomas and adenocarcinomas were also observed. Although these increases were not statistically significant these results may be of toxicological significance in view of the low historical incidence of such tumors in F344/N rats. The NTP determined that, under the conditions of this study, there was "clear evidence of carcinogenicity" of PCE for male F344/N rats, and "some evidence of carcinogenicity" of PCE for female F344/N rats.

2.2.5 Mouse Inhalation Study (JISA, 1993)

Male and females CrJ:BDF1 mice (a different strain than that used in the NCI and NTP bioassays) were exposed to 0, 69, 340, or 1700 mg/m^3 (0, 10, 50, or 250 ppm) PCE (>99% purity) for 6 h/day, 5 days/week, for 104 weeks. *Statistically significant dose-related increases were observed in the incidences of benign and malignant liver tumors in both sexes* (See Figure 1 and Appendix G, Table G-2). In addition, the top-dose males exhibited an increased incidence of benign tumors of the Harderian gland. Adenomas of the spleen and liver, hemangioendothelioma of all organs and adenoma of Harderian gland among males were also marginally elevated, as was hemangioendothelioma of all organs among females.

2.2.6 Rat Inhalation Study (JISA, 1993)

F344 rats of each sex were exposed to PCE (>99% purity) at 0, 340, 1400, or 4100 mg/m^3 (0, 50, 200, 600 ppm) for 6 h/day, 5 days/week, for 104 weeks. *Statistically significant treatment-related increases in mononuclear cell leukemia were observed in both sexes* (See Figure 2 and Appendix G, Table G-2). No other increases in tumor incidences were reported.

3.0 Modes of Action, Metabolism and Basis of Extrapolation to Humans

Estimating the cancer potency of PCE for humans relies on extrapolation of the animal bioassay data taking into account the available information on mode of action, relative metabolism and in the absence of sufficient empirical data, default values and methods. An overview of the available information follows in the sections below.

3.1 Modes of Action

Both genotoxic and non-genotoxic mechanisms of action have been postulated to be involved in PCE's carcinogenicity.

Results of extensive evaluations of PCE's potential genotoxicity, using a variety of in vivo and in vitro test systems, have been reviewed by USEPA (1985), WHO (2006) and CAEPA (1992, 2001). These groups have concluded that there is little, if any evidence, that PCE itself exhibits DNA damaging or mutagenic activity. Instead, the carcinogenicity of PCE is hypothesized to be due to its metabolism via pathways that generate reactive intermediates and metabolites capable of damaging cellular macromolecules including DNA.

A non-genotoxic mechanism, peroxisome proliferation, has also been suggested to account for PCE's liver carcinogenicity. Agents that cause proliferation of peroxisomes have been associated with induction of liver tumors in rodent bioassays. However peroxisome proliferation alone is not sufficient to induce liver tumors (Yang et al., 2007). Trichloroacetic acid (TCA), a major PCE metabolite, can lead to peroxisome proliferation at sufficient exposure levels. However, in its recent PCE assessment, the WHO concluded that PCE peroxisome proliferation does not occur until doses are well above those shown to cause liver tumors in the mouse bioassays (WHO, 2006).

3.2 Metabolism

PCE is well absorbed following oral, inhalation and dermal exposure. PCE metabolism, i.e., activation and detoxification, is complex and there is considerable uncertainty regarding precisely which pathways and reactive moieties are responsible for its carcinogenicity. Several of the enzymes known to be involved exhibit sex- and species-dependent differences in animals (Lash and Parker, 2001).

3.2.1 Metabolic pathways

Two major pathways of PCE metabolism have been identified and reactive intermediates of both pathways can bind covalently to proteins and nucleic acids. The quantitatively most significant pathway involves oxidative metabolism mediated by the hepatic cytochrome P450 system, which may involve multiple P450 enzymes. As illustrated in Figure 3, this pathway leads mainly to the formation of TCA, with minor metabolites reported to include oxalic acid, dichloroacetic acid (DCA), ethylene glycol, trichloroacetyl amide, thioethers, trichloroethanol and its conjugates, N-

trichloroaminoacety-aminoethanol and carbon dioxide (CALEPA, 1992; Lash and Parker, 2001; WHO, 2006). ORS notes that the fates and possible significance of chloride ions/radicals that are cleaved from PCE during oxidative metabolism have not been assessed.

At high exposures, the oxidative pathway becomes saturated and a second pathway, illustrated in Figure 4, involving glutathione conjugation increases in quantitative significance. This pathway, which is suggested to be more important in rats than in humans and mice, leads to the formation of *S*-(1,2,2-trichlorovinyl)-L-glutathione (TCVG), which can be cleaved in the kidneys to yield cytotoxic metabolites. TCVG can be processed by γ-glutamyltransferase and cysteinlyglycine to the *N*-acetyl-S-(trichlorovinyl)-L-cysteine (TCVC) which can then be acetylated to *N*-acetyl-S-(trichlorvinyl)-L-cysteine (N-ac-TCVC) which is excreted in the urine, generally a detoxification pathway. TCVC can also be cleaved in the kidney by cysteine conjugate β-lyase to dichlorothioketene which may react with water to dichloroacetic acid (DCA) or with other cellular macromolecules. The glutathione conjugation pathway results in similar a metabolic profile in both humans and rats, but the yield of one presumed reactive metabolite, DCA[3], is much less in humans than rats (Volkel et al., 1998; Lash and Parker, 2001).

Humans and laboratory animals excrete most of the PCE absorbed at high exposure/dose levels unchanged in expired air, with minor amounts excreted as urinary and fecal metabolites. Due to possible saturation of metabolic pathways at high exposure levels, the fraction of absorbed PCE metabolized at lower doses could be considerably greater.[4]

The studies of PCE metabolism in humans have consistently considered TCA to be the quantitatively dominant metabolite. However, a major purpose of the studies has been to ascertain if PCE exposure in the work place can be quantified by measurements of trichloro-compounds in urine. Thus the studies do not reflect an attempt to measure all possible metabolites of PCE (CAEPA, 1991). Also, at the lower concentrations that receptors are exposed to in the environment vs. the workplace, other metabolites and pathways may be more important.

3.2.2 Human Metabolism at Low Exposure Concentrations

The fraction of PCE intake that is metabolized by humans at low exposure concentrations, i.e., environmental, not occupational levels, is matter of great debate and uncertainty. The extent of human metabolism of PCE has been estimated from several studies with occupational or controlled exposure to PCE, (summarized in Table 1) and estimates range from 1% to 37% (Ikeda et al, 1977; Bolanowska and Golaka, 1972). As shown in Table 1, studies at higher exposure concentrations tend to report a lower fraction metabolized than the studies at lower exposure concentrations. Empirical results

[3] DCA is a product of both P450 oxidative metabolism and glutathione metabolism. However, most of the DCA found in the urine is thought to originate from the glutathione pathway (Volkel et al., 1998).
[4] In addition to potential high to low dose differences in total metabolism, the relative proportion and total mass of specific metabolites generated could also vary across exposure levels.

Table 1. Studies Evaluating Metabolism of Tetrachloroethylene in Humans

Study	Subjects	Routs of Exposure	Exposure Conc.	Exposure Duration	Exposure Setting	Metric for estimating Metabolism and (% metabolized)	Time of Measurement of Metabolism	Measurement Provided
Bolanowska and Golaka 1972	3 males, 2 females	Inhalation	66 ppm	6 hrs with 2 x 30 min breaks	Chamber	PCE in exhaled air (37% total metabolized = total PCE absorbed - PCE recovered); urinary TCA reported as "several %"	For 40 hrs after exposure	PCE in exhaled air; urinary TCA
Ikeda et al., 1977	34 male workers in 7 different workshops	Inhalation and dermal	0-400 ppm	8 hrs/d, 5 d/wk	Occupational	Urinary TCA, TCE; total trichloro-compounds (TTC) ≈ **1%** of exposure conc.; TTC = 2x urinary TCA	Urine samples collected at 1 P.M. during the 2nd half of work week; urine for the half-life collected up to 60 hours after end of work week (5-8 hr days)	Urinary TCA, TCE (tetrachloroethanol); ambient air; metabolic saturation below 100 ppm; T½ = 144 hrs,
Fernandez, 1978	23 males, 1 female	Inhalation	100, 150, or 200 ppm	1, 2, 4, 6, or 8 hrs	Exposure chamber	Urinary TCA as **1.85 %** of absorbed dose.	Most subjects for 4 hrs, after exposure, for 4 subjects 8 days after exposure	PCE in alveolar air; urinary TCA and TCE for 2 subjects 72 hrs after exposure
Ohtuski et al., 1983	Workers- 20 males, and 19 females in dry cleaning removing glue from silk cloth	Inhalation and dermal	Time weighted average from carbon felt dosimeters range from 1-800ppm	8 hr shift	Occupational	Urinary TTC as **2%** of absorbed dose; 38% of absorbed PCE is exhaled, 60% remained in body to be eliminated later.	At end of 8 hr shift and before beginning of shift (16 hr from end of shift on previous day for a subset.	Urinary excretion of TTC; PCE in exhaled air in subset; TWA of PCE in ambient air. Metabolic saturation at > 100 ppm
Monster et al., 1979	6 males	Inhalation	72 or 144 ppm at rest; 142 ppm with workload	4 hrs for at rest exposure, 2 x 30 min with workload	Gas mask	**~1%** of uptake excreted in urine as TCA, 80-100% exhaled unchanged as PCE (no apparent saturation of metabolism at the concentrations tested)	Up to 70 hrs	Minute volume, PCE in exhaled air; PCE and TCA in blood; TCA in urine
Volkel et al., 1998	3 males and 3 females humans, and 3 male and 3 female rats	Inhalation	10, 20, 40 ppm	6 hrs	Dynamic exposure chamber	**~1%** of uptake excreted in urine as TCA (authors report no metabolic saturation at 40 ppm).	Up to 78 hrs after start of exposure (72 hrs after exposure ended)	Urinary excretion of TCA, N-ac-TCVC, DCA; T ½, humans and rats urinary TCA, DCA, BW and TCA in blood
Chiu et al., 2007	7 males	Inhalation	1 ppm	6 hrs	Open exposure chamber	Alveolar retention, urine for 6 days post exposure; fraction of intake exhaled; metabolic clearance, estimated blood/air partition coefficient, **18.5%** metabolized (total metabolites)	Alveolar air and urine for 6 days following exposure, venous blood for 5 days following exposure	PCE in alveolar air; PCE and TCA in venous blood and urine

from recently analyzed toxicokinetic data from six individuals exposed to 1 ppm PCE for 6 hours provide new estimates of the fraction of PCE intake that is metabolized (Chui et al., 2007).

The fraction of PCE metabolized across the six individuals with 4 individuals exposed on two separate occasions (i.e., 10 exposure occasions total) ranged from minus 4% to 34%; the average fraction metabolized was 18.5%. The fraction metabolized for each individual (and occasion) evaluated by Chui et al. (2007) are presented in Appendix B, Table B-1.

Uncertainty about the PCE exposure level associated with saturation of oxidative metabolism contributes to the range of values estimated for the fraction metabolized in humans. Data from several studies on the urinary excretion of PCE metabolites in humans suggest that full saturation may not occur until exposures exceed 10 – 100 ppm in some individuals (Ohtsuki et al., 1983[5]; Volkel et al., 1998[6]; Ikeda et al., 1977). These data are supported by the recent 1 ppm data from Chui et al. (2007), that do not indicate saturation of total metabolism. If this is correct, the fraction of PCE metabolized at low exposure concentrations would be expected to be similar to that observed in human high dose experiments. However, each of these studies was conducted in few healthy occupationally exposed individuals or healthy adult volunteers and contains considerable uncertainty with respect to overall metabolism. Thus, the estimates from these studies underestimate the population variability in oxidative metabolism which may arise from genetic polymorphisms in the enzymes that metabolize PCE, age at exposure, exposure to other chemicals that may influence metabolic capacity, etc., ultimately overestimating the concentration at which saturation may occur in the general population. Published analyses report estimates for human population low-dose (i.e., 1 ppb) metabolism of PCE that range from less than 1% to 61% (Bois et al, 1996; Chui and Bois, 2006).

Mass balance data (e.g., total absorbed dose compared to unmetabolized PCE and metabolites), which would allow for total metabolism to be more accurately estimated, are limited. Many studies have relied on TCA excreted in urine as the relevant measure of PCE metabolism. This neglects other metabolites, losses through feces, and perhaps most significantly, losses attributable to binding to macromolecules. Differences in analytical methods and sensitivity, as well as potential dose dependent metabolism of TCA, further complicate interpretation of the data on the fraction of PCE metabolized in humans.

Other studies have evaluated the mass balance issue by estimating metabolism as the difference between total absorbed PCE and total recovered metabolites and/or exhaled (un-metabolized) PCE. However, the accuracy of this later approach has been questioned due to the potential for unmeasured losses of un-metabolized PCE, e.g., due to

[5] This study related measured TTC in the urine to PCE air concentrations measured using personal carbon felt dosimeters to derive TWA 8 hour exposures. Excretion was largely linear to >100 ppm. Interpretation is somewhat uncertain as exposures were estimated on the basis of air concentrations only and no blood concentration data was collected, and differences in activity rates were not accounted for. Additionally urinary metabolite values were not normalized to creatinine.

[6] The Volkel et al. (1998) data shows different excretion rates for TCA at PCE exposures of 10 ppm vs. 20, 40 ppm, suggesting saturation of metabolism to TCA had not occurred at 10 ppm.

uncertainties/inaccuracies in estimating minute volume, which would lead to inappropriately high estimates of total metabolism.

Physiologically based pharmacokinetic (PBPK) models have been constructed to estimate the extent of human metabolism of PCE. Most of these models have focused on the metabolites of the oxidative pathway, primarily TCA, assuming it is the active moiety. This assumption excludes consideration of the potential activity of other active metabolites of PCE and may underestimate risk. PBPK models estimating the fraction metabolized to TCA, yield central estimates of the fraction of PCE metabolized to this product that are typically less than 3% (USEPA, 1985; Clewell et al, 2005; Covington, et al. 2007).

Because the mode of action and active moieties of PCE have not been well characterized, the available toxicokinetic data for humans is incomplete and potentially underestimates production of active metabolites.

To estimate the fraction of PCE metabolized by humans at low exposure concentrations while taking into consideration the variability found across humans, partial saturation of metabolism at high concentrations and uncertainty in the active metabolite(s), Bois et al. (1996) used population pharmacokinetics, Bayesian statistics and physiological modeling and human exposure data from Monster et al. (1979) that evaluated total metabolites of PCE, including TCA. The model accounted for population variability and uncertainty in human metabolism using Bayesian statistics and data informed prior distributions of physiologic parameters (blood flows, tissue volumes), blood:air partition coefficients, tissue:blood partition coefficients, and Km and Vmax in the liver. The model also included estimates of variance of the experimental measurements.

The upper 95^{th} confidence interval value for low exposure PCE metabolism (0.001 ppm) modeled by Bois et al. (1996) was 58% (the median value was $36^{\%}$, the 95^{th} confidence interval was 15% to 58%). To be health protective in their assessment of cancer risk, CAEPA (2001) selected the upper 95^{th} confidence interval value of 58% from this analysis as a conservative estimate of human PCE metabolism at low air concentration exposures. Chui and Bois (2006) updated this analysis and concluded that the range of values was broader, with a 95^{th} confidence interval value equal to 61%. The modeled population toxicokinetics 95% confidence interval extrapolated from the Monster et al. (1979) data to an exposure concentration of 50 ppm was 0.45 – 26% (Chui and Bois, 2006). A very preliminary analysis of the data from the recent 1 ppm exposure study using the population toxicokinetic model estimated the 95% confidence interval to be 0.6% to 30% at 1 ppm (Chui, personal communication, 2007).

Further complicating the situation is the potential for variability in the kinetics of PCE metabolism and excretion attributable to co-exposures to other agents that may differentially inhibit or induce specific metabolic pathways. Recent data demonstrated significant inter-occasion differences in the excretion of PCE (and trichloroethylene) (Figure S 12 in Chiu et al., 2007). In one individual the urinary excretion of TCA six days following two different exposures to PCE at 1 ppm exceeded 20 *ug* on one occasion

while almost no urinary TCA excretion was observed in the second[7]. Also, considerable variation in genes coding for CYP2E1 and glutathione-S-transferase, which are known to metabolize PCE, have been associated with differential metabolism of substrates that are specific to these enzymes (Hauqui et al., 2004; Burim et al., 2004).

ENVIRON and CIIT (Covington et al., 2007) recently criticized CAEPA's selection of 58% as the fraction of PCE metabolized in humans. Based on their own Monte Carlo uncertainty analysis, and using a revised PBPK model, they derived an upper 95th percentile estimate of 2.1% for the fraction of PCE metabolized to TCA by humans following inhalation exposures. Because of the relatively small number of subjects included in the analysis; the exclusion of other data sets; modifications to the PBPK model (i.e. inclusion of a kidney metabolism pathway) that have not been supported with empirical data; and a focus on metabolism to TCA rather than total metabolism, ORS has concluded that this evaluation is likely to underestimate the range of possible human PCE metabolism[8]. The 2.1% 95th percentile estimate is also inconsistent with recent metabolic data from Chui et al. (2007) who estimated that the *average* total metabolism following exposures of 6 adult men to 1 ppm PCE was about 18.5%.

Although much uncertainty regarding low dose metabolism remains, the new Chiu et al. (2007) study indicates metabolism in humans at lower dose levels (i.e., 1 ppm) is at least 18.5% of the absorbed dose, the reported mean of a small group of individuals (healthy adult men). The range in the broader population is likely to be much greater. Thus, to be health protective MassDEP has opted to use 61% (the 95% upper confidence interval estimated by Chui and Bois, 2006) to calculate human metabolized dose at low exposure concentrations. This value is the most recent published estimate of the possible range of low-dose PCE metabolism in adults.

3.3 Dose Metric for Cross-Species Extrapolation

Most estimates of cancer potency for use in risk assessment rely on animal bioassay data necessitating extrapolation across species and from high animal bioassay exposure levels to lower environmental exposure concentrations. The appropriate dose metric for the extrapolation for any chemical is dependent upon the mode of action of the chemical. Although the mode of action for PCE tumorogenicity in animals and humans is not well known, there is consensus that the active moiety is not PCE, but one of its metabolites. Thus, two of the approaches considered for extrapolating the PCE bioassay data include explicit estimates of metabolism, 1) physiologically-based pharmacokinetic (PBPK) models, and 2) metabolized dose using simple steady-state kinetics. An alternative approach that does not explicitly estimate metabolism, duration adjusted continuous equivalent administered concentrations was also used to estimate inhalation cancer risk.

Many PBPK models have been developed with the intent of reducing the uncertainties inherent in cross-species and high dose to low dose extrapolations. At this time these

[7] Although, the extremely low values from the one occasion raise questions as to possible experimental error, the results cannot be completely discounted.
[8] These issues are discussed further in Appendix VI.

models for PCE are limited by uncertainties: 1) regarding mechanism of action; 2) about the carcinogenic activities and potencies of the various metabolite(s) potentially responsible for PCE's ultimate carcinogenic activity; 3) over the relative quantitative significance of various metabolic pathways across species and between high and low dose exposures; and, 4) in the variability in metabolism between individuals and life stages. Even when looking at simplified dose metrics such as total metabolism or production of TCA, these models yield a wide range in outputs (Chui and Bois, 2006; Hattis, et al. 1990, 1993; CAEPA, 1992). The models are also still being refined to better account for new experimental data or proposed metabolic pathways[9].

The metabolized dose approach is an approach that utilizes empirical information on animal and human metabolism while relying on broader assumptions than a full PBPK model. This cross-species extrapolation approach was used to derive potency values for PCE carcinogenicity in the assessments by MassDEP (1990), NESCAUM (1986), and CAEPA (1992; 2001). This approach estimates PCE's cancer potency in animals based on total metabolite production derived using Michaelis-Menton kinetic parameters derived from animal experiments, extrapolates these results to humans using default $BW^{3/4}$ scaling, and then adjusted the cancer potency by the fraction of PCE metabolized in the human population at environmental exposure concentrations (CAEPA, 2001). The details of this approach are in the section below. The advantages of this approach are that it:

1) makes no assumptions regarding the active metabolite while acknowledging the likely involvement of metabolism in activating PCE;
2) includes some accounting for dose-dependent nonlinearities in total metabolized dose through use of simple steady-state Michaelis-Menton kinetics;
3) accounts for potential cross-species differences in absorption, metabolism, excretion and sensitivity using standard BW scaling, which assumes that on the average, absorption, metabolism excretion and sensitivity scales between species as a function of BW to a power.

However, the metabolized dose approach is sensitive to assumptions about the fraction of PCE that is metabolized by humans.

Alternatively, duration adjusted continuous equivalent administered concentrations based on the USEPA (1994) human equivalent concentration (HEC) methodology can be used for cross-species extrapolation. The advantage of this approach is that it is very simple, assumes that humans will metabolize PCE similarly to the bioassay animals and that the concentration response in the observed (high) range of exposure concentrations will be the same as that which occurs at environmental (low) exposure concentrations. Thus, this approach makes no assumptions regarding which kinetic model is best, which metabolite pathway is responsible for PCE carcinogenicity or which physiological and metabolic parameters are appropriate and requires no explicit assumption regarding the fraction of

[9] For example in recent papers Clewell et al. (2005) and Covington, et al. (2007) updated the PBPK model of Gearhardt et al. (1993) to include possible metabolism in the kidney, a new metabolic component that improved the model's fit to certain experimental data. Validation of this putative pathway and the associated metabolic parameters assumed in the model revision has, to our knowledge, not been reported.

PCE metabolized at low exposure concentrations. However, this approach also does not explicitly account for the broad consensus that PCE metabolism is likely to be necessary for its carcinogenic activity to be expressed; allows for no accounting of non-linearities in metabolism from low to high doses; and does not fully consider interspecies differences in absorption of the administered dose, metabolic activation and detoxification, or pharmacodynamics.

Because of the uncertainties in the PBPK models available for cross-species extrapolation, we have focused on the approaches used by CAEPA (2001) and WHO (2006) to derive potential PCE cancer potency factors,

- the first is based on estimates of total metabolized dose in animals using simple steady-state Michaelis-Menton kinetics; cross-species extrapolation using $BW^{3/4}$ scaling (CAEPA, 2001) and estimation the fraction of PCE metabolized in humans; and
- the other based on duration adjusted applied concentrations (WHO, 2006).

As each approach entails advantages and disadvantages, MassDEP evaluated the predicted potencies and associated unit risks for PCE using both. However, ultimately, the interim inhalation unit risk for PCE was derived using the metabolized dose method used by CAEPA (1992; 2001)[10].

3.4 Methods Applied for Cross-Species Extrapolation

3.4.1 Metabolized Dose Method

Using the method of CAEPA (1992; 2001), the metabolized doses (*M*) for PCE for the inhalation studies were derived using Michaelis-Menton equation (Equation 1):

$$M = \frac{D \times V_{max} (w_1/w_2)^{1/3}}{D + K_m (w_2/w_1)^{1/3}} \qquad \textit{(Equation 1)}$$

Where: *M* and *Vmax* are in mg/kg-d and *D* and *Km* are in ppm assuming 6 hours of exposure.

To estimate the amount of PCE metabolized by mice in the NTP (1986) and the JISA (1993) inhalation studies, Equation 1 was fit to a mouse V_{max} = 170 mg/kg-d, determined from the PCE oral data of Buben and O'Flaherty (1985), and a mouse Km of 126 ppm, estimated from the rat inhalation data of Pegg et al. (1979). The oral study by Buben and O'Flaherty (1985) was used to calculate metabolic parameters for mice since the inhalation data obtained by Schumann et al. (1980) were insufficient to calculate the required parameters because only one inhalation exposure level was tested. However the Schumann et al. (1980) inhalation data were used for validation. The amount of PCE

[10] The MassDEP/DPH Advisory Committee on Health Effects addressed this issue. At the meeting (MassDEP, 2007b) three members recommended the use of metabolized dose, while two recommended the use of the duration adjusted HEC. The remaining members did not express an opinion.

metabolized was estimated using V_{max} = 170 mg/kg-d, K_m = 126 ppm, w_1 = 0.0245 kg (the mean body weight of the mice in the Schumann et al. (1980) study), and w_2 = 0.037 kg for the male mice, and 0.032 kg for the female mice in the NTP bioassay, and w_2 = 0.037 kg for the male mice, and 0.034 kg for the female mice in the JISA bioassay.

To estimate the amount of PCE metabolized by rats in the NTP (1986) and the JISA (1993) inhalation studies, Equation 1 was fit to the data obtained from the inhalation metabolism study of Pegg et al. (1979) conducted in male Sprague-Dawely rats exposed to radiolabeled PCE at concentrations ranging from 10 ppm to 600 ppm. The amount of PCE metabolized was estimated using: V_{max} = 52.982 mg/kg-d, K_m = 273.32 ppm, w_1 = 0.25 kg (the mean body weight of the rats in the Pegg et al. (1979) study), and w_2 = 0.44 kg for the male rats, and 0.32 kg for the female rats for both the NTP (1986) and JISA (1993) bioassays.

Once estimated using Equation 1, the metabolized dose was adjusted for duration because animals were exposed for 5 days per week. The mouse or rat TWA metabolized doses calculated using Equation 1 are then converted to human equivalent TWA doses by using $BW^{3/4}$ scaling. Cross-species scaling of carcinogen doses by the ¾ power of body weight is adopted as proposed by the USEPA (1992) instead of the previous use of 2/3 power of body weight (MassDEP, 1990; CAEPA, 1992).

3.4.2 Duration Adjusted Applied Concentration Method

The duration adjusted applied concentration method uses the method described by USEPA (1994) for category 3 gases with extra-respiratory effects. Each exposure concentration (ppm) was duration adjusted by 5 days/7 days, and 6 hours/24 hours to estimate a continuous exposure concentration. The human equivalent concentration (HEC) was equivalent to the duration adjusted concentrations because the ratio of the blood:air partition coefficient was set to the default value of 1. Scaling across species using applied concentration for inhalation exposures is based on the assumption that inhalation rates are proportional to the basal metabolic rate that scales allometrically based on body weight to the ¾ power (USEPA, 1992). Thus, use of applied concentration for inhalation exposures is equivalent to $BW^{3/4}$ scaling for ingestion exposures.

4.0 Summary of Past PCE Carcinogenic Risk Assessments by MassDEP (1990); CAEPA (1992; 2001) and WHO (2006)

4.1 MassDEP (1990)

Since the toxicity evaluations of PCE by various groups indicated that the levels at which PCE might cause systemic toxicity were higher than the levels that cause cancer, MassDEP in the late 1980's decided to derive an inhalation cancer risk value for PCE. The Department evaluated both the NCI (1977) gavage study in mice (Appendix C, Table C-1 to C-3) and the NTP (1986) inhalation study in mice and rats (Appendix DC, Table D-1 to D-3) to calculate a unit risk and ambient air level that is protective of public

health. Using the tumor data from these studies and other available data on PCE toxicity and toxicokinetics, as well as the risk assessment methodologies applicable at the time, MassDEP derived a human health protective inhalation cancer unit risk value for PCE of 5.5×10^{-5} $(\mu g/m^3)^{-1}$.

This value was in the range of those recommended in a regional assessment by NESCAUM (1986). In its' assessment, NESCAUM used the 1986 NTP inhalation study data for liver tumors in male and female mice and calculated an estimate of the 95th lower confidence level of the average daily dose associated with lifetime excess cancer risk of 1×10^{-6}. This estimate was extrapolated to humans using a conversion factor based on dose per unit surface area. Assuming various metabolic rates in humans and mice, unit risk values ranging from 1×10^{-5} $(\mu g/m^3)^{-1}$ to 1×10^{-4} $(\mu g/m^3)^{-1}$ were calculated[11], spanning the value derived by MassDEP.

The MassDEP inhalation unit risk value did, however, differ significantly from that initially derived by USEPA in 1985, and subsequently withdrawn, which equaled 4.8×10^{-7} $(\mu g/m^3)^{-1}$ (USEPA, 1985; 1986). The MassDEP and USEPA unit risk values differed so significantly in large part because of alternative assumptions regarding the fraction of PCE metabolized by humans at environmentally relevant exposure concentrations. MassDEP used an upper-bound value of 70% while USEPA assumed a value of less than 1%. MassDEP scientists concluded that the USEPA value was not appropriate as it was based on limited data derived from high concentration human exposures. Because of saturable metabolic pathways, MassDEP concluded that the fraction of PCE metabolized at low doses would likely be much greater than that derived by USEPA. CAEPA reached a similar conclusion in their subsequent 1992 analysis, where they assumed a human metabolism value of 18.5%, and in their most recent inhalation risk evaluation (2001) where they selected a value of 58% (see Section 4.3).

4.1.1 Unit Risk Derivation in MassDEP 1990 Assessment

Both the NCI gavage and NTP inhalation studies were reviewed and deemed to provide adequate dose-response data for analysis. Similar to USEPA (1985), MassDEP concluded that the tumorigenicity of PCE was likely to be attributable to metabolic activation. Thus, for dose-response assessment, MassDEP calculated the average daily-metabolized dose as a function the administered dose. Total metabolized dose was estimated as opposed to metabolism to TCA alone. Details of the assessment can be found in MassDEP, 1990.

The corresponding cancer potency values and unit risks are summarized in Table 2 below. Similar to USEPA (1985) MassDEP ultimately selected the gavage study to

[11] At the request of the NESCAUM Air Toxic Committee H. Strauss and Associates (1992), independent consulting toxicologists, reviewed the toxicity related literature on PCE published after the NESCAUM (1986) document. They concluded that there were no compelling scientific reasons to modify the potency factor range in the 1986 report, noting that the data supporting a threshold mechanism of action was not strong and that the fraction of PCE metabolized by humans remained uncertain and could range up to 60%.

derive its inhalation unit risk value for PCE[12]. This choice was due to concerns regarding the adequacy of the data and modeling for estimating metabolism of PCE following inhalation exposures. Although the slope factors and corresponding unit risks derived from the various data sets did not differ dramatically (Table 2), MassDEP concluded in 1990 that the calculation of the metabolized dose based on the gavage study was more reliable than that based on the inhalation study and thus based its unit risk value on this data. The calculation of the human equivalent metabolized doses, based on a simple steady-state pharmacokinetic approach, with appropriate adjustments and assumptions, are presented in detail in Appendix C, Table C-2. The derivation of unit risk values using the NTP inhalation data are summarized in Appendix D.

MassDEP ultimately selected a unit risk of 5.5×10^{-5} $(\mu g/m^3)^{-1}$ based on female combined liver carcinoma and adenoma data from the NCI (1977) gavage bioassay. This value represents the 95% UCL using the multistage model and a human equivalent metabolized dose. MassDEP selected 70% as the value for the fraction of PCE in air metabolized by humans at environmental levels of exposure. This was determined to be a theoretical upper limit based on the fraction of inhaled air per breath reaching the alveolar site of absorption, the PCE blood:air partition coefficient and assumed complete metabolism at low doses. As low dose empirical data were not available and there were good theoretical reasons to believe that high dose metabolic saturation was likely to occur, MassDEP concluded that it was appropriate to rely on an upper-bound value[13].

The details of the calculation of metabolized doses are presented in Appendix D, Table D-2 and corresponding unit risk values are summarized in Appendix D, Table D-4.

[12] The USEPA based its 1985 inhalation unit risk value on the NCI (1977) oral study as well. Metabolites of PCE were assumed to be the ultimate carcinogens, and simple steady-state kinetics was used to determine metabolites as a function of administered dose.

[13] Subsequent assessments of human exposure data and population pharmacokinetic model results yielded an upper 95th confidence interval value of 58% (Bois et al, 1996) as used by CAEPA in their 2001 assessment (see following pages) and, more recently, 61% (Chui and Bois, 2006).

Table 2. Comparison of Potency Factors and Unit Risk Values Calculated by MassDEP Based on the NCI (1977) and NTP (1986) Studies (MassDEP, 1990)

Study, Route Tumor Type	**Species Sex**	**Cancer Potency 95% UCL $(mg/kg\text{-}d)^{-1}$**	**Unit Risk[a] $(\mu g/m^3)^{-1}$**
NCI (1977) oral Hepatocellular carcinomas	$B6C3F_1$ mice Male	3.38×10^{-1}	6.76×10^{-5}
	Female	2.76×10^{-1}	**5.52×10^{-5}** [b]
NTP (1986) inhalation Hepatocellular adenoma and carcinoma	$B6C3F_1$ mice Male	1.43×10^{-1}	2.86×10^{-5}
	Female	5.15×10^{-2}	1.03×10^{-5}
NTP (1986) inhalation Mononuclear Cell Leukemia	F344 rats Male	3.00×10^{-1}	6.00×10^{-5}
	Female	1.66×10^{-1}	3.32×10^{-5}

[a] Estimated excess lifetime cancer risk.
[b] Unit risk value selected by MassDEP

4.2 CAEPA (1992)

CAEPA relied on the NTP mouse/rat inhalation study to derive cancer potency and unit risk values for PCE (Appendix E, Table E-1). CAEPA also evaluated the oral data from the NCI (1977) gavage bioassay, but only used this information for comparative purposes.

In their assessment of the NTP inhalation animal bioassay data, CAEPA assumed that metabolites are responsible for the tumorigenicity of PCE. CAEPA calculated the metabolized dose in the exposed animals using a simple steady state pharmacokinetic approach and pharmacokinetic parameters estimated from studies on the oral route of exposure. Cancer slope factors based on metabolized dose were derived using the estimated animal metabolized doses and then extrapolated to humans using surface area scaling ($BW^{2/3}$). Human inhalation unit risk as a function of applied dose (i.e. exposure concentration) was then derived assuming 18.5% metabolism on PCE at low exposure concentrations.

Table 3. Comparison of Cancer Potency Factors and Unit Risks Calculated by CAEPA Based on the NCI (1977) and NTP (1986) Studies (CAEPA, 1992)

Study **Route** **Tumor Type**	**Species** **Sex**	**Potency as a Function of Animal Metabolized Dose[a] $(mg/kg\text{-}d)^{-1}$**	**Potency as a Function of Human Equivalent Metabolized Dose[b] $(mg/kg\text{-}d)^{-1}$**	**Potency as a Function of Human Applied Dose[c] $(mg/kg\text{-}d)^{-1}$**	**Unit Risk[d] $(\mu g/m^3)^{-1}$**
NCI (1971) Oral Hepatocellular carcinomas	B6C3F1 mice Male Female	3.2×10^{-2} 2.2×10^{-2}	4.2×10^{-2} 3.1×10^{-1}	8.1×10^{-2} 5.8×10^{-2}	9.3×10^{-6} 6.6×10^{-6}
NTP (1986) Inhalation **Hepatocellular adenoma/ carcinoma**	B6C3F1 mice Male **Hattis et al. (1987) PB-PK equivalent (Male)** Female	2.4×10^{-2} 9.8×10^{-3}	3.0×10^{-1} **2.8×10^{-1}** 1.3×10^{-1}	5.6×10^{-2} **5.2×10^{-2}** 2.4×10^{-2}	6.3×10^{-6} **5.9×10^{-6} [e]** 2.8×10^{-6}
NTP (1986) Inhalation Mononuclear Cell Leukemia	F344 rats Male Female	6.4×10^{-2} 4.0×10^{-2}	3.5×10^{-1} 2.4×10^{-1}	6.5×10^{-2} 4.4×10^{-2}	7.4×10^{-6} 5.1×10^{-6}

[a] Animal daily metabolized dose calculated as described in Appendix E, Table E-2.
[b] Human equivalent metabolized dose metric assumes that the animal daily metabolized dose extrapolates to humans based on $BW^{2/3}$ or surface area scaling.
[c] The potency factors as functions of human applied doses are derived from Tables 5-5 and 5-6 of CAEPA (1992) adjusted to assume 18.5% human metabolism. The values presented in Tables 5-5 and 5-6 by CAEPA (1992) assumed 25% metabolism of PCE at environmentally relevant exposure levels, however CAEPA based their unit risk value on the assumption of 18.5% percent human metabolism.
[d] Unit risk calculated as: potency as a function of (human applied dose per mg/kg-d) ÷ 1000 (μg/mg) x 20 m^3 (assuming a 70 kg person inhaling 20 m^3 air) x 0.4 (alveolar ventilation rate correction) ÷ 70 kg (Appendix E, Table E-3).
[e] Unit risk selected by CAEPA (1992).

The details of the metabolized dose calculations are presented in Appendix E, Table E-2 and the methods used to derive the slope factors and unit risks using the metabolized dose estimates and the tumor incidence data in mice and rats are summarized in Appendix E, Table E-3.

CAEPA calculated a total of 144 potency values based on metabolized dose and applied dose in their analysis, using both the oral and inhalation data and various pharmacokinetic models. A summary of the potency and unit risk values derived by CAEPA based on the oral and inhalation studies are presented in Table 3. CAEPA ultimately selected the results based on an assessment by Hattis et al. (1987) model (highlighted in bold in Table 3).

4.3 CAEPA (2001)

CAEPA (2001) in its derivation of a Public Health Goal for PCE in drinking water evaluated both the NCI (1977) oral and the NTP (1986) inhalation studies. Data from the oral bioassays were used to assess carcinogenic risks associated with consumption of drinking water. The inhalation data was used to assess risks attributable to the volatilization of PCE from drinking water.

The methodology used by CAEPA (2001) to calculate metabolized doses in animals was similar to that used by CAEPA (1992). In the 2001 CAEPA assessment a time-to-tumor analysis was used for all data sets. The dose rates and the individual tumor and mortality data were fit to the multistage-in-dose, Weibull-in-time model. The slope factors based on this approach are presented in Appendix F, Table F-1 along with those derived by CAEPA in 1992. Summaries of the slope factors and unit risk values for inhalation exposure are presented in Table 4 below.

Table 4. Cancer Potency Factors and Unit Risks Calculated by CAEPA Based on the NTP (1986) Studies (CAEPA, 2001)

Species Sex	Study	Tumor Type	Potency as a Function of Human Equivalent Metabolized Dose [a] $(mg/kg\text{-}d)^{-1}$	Potency as a Function of Human Applied Dose [b] $(mg/kg\text{-}d)^{-1}$	Unit Risk $(\mu g/m)^{-1}$
$B6C3F_1$ mice Male	NTP 1986	Hepatocellular Adenoma or Carcinoma	0.19	0.11	1.3×10^{-5}
$B6C3F_1$ mice Female	NTP 1986	Hepatocellular Adenoma or Carcinoma	0.071	0.04	4.6×10^{-6}
F344 rat Male	NTP 1986	Mononuclear Cell Leukemia	0.25	0.15	1.7×10^{-5}
F344 rat Female	NTP 1986	Mononuclear Cell Leukemia	0.17	0.01	1.3×10^{-6}
All species	NTP 1986	All Tumor types Geometric mean of 4 potency factors	0.15 [c]	0.087	9.9×10^{-6}

[a] From Table 12 (CAEPA, 2001).
[b] The slope factors as functions of human applied doses are calculated by MassDEP for this evaluation by assuming 58% percent human metabolism of PCE at environmentally relevant exposure levels. CAEPA (2001) did not present unit risk values, but used the potency values derived for inhalation exposure to account for PCE contribution to total cancer risk from inhalation of volatiles in drinking water.
[c] CAEPA (2001) used the geometric mean of the potency factors based on mouse liver tumor and rat mononuclear cell leukemia stating that the four potency values do not differ greatly.

In addition to using a time-to-tumor model to calculate cancer potency, the CAEPA (2001) analysis applied the revised US EPA (1992) cross species scaling factor $mg/kg^{3/4}/day$ (vs. $mg/kg^{2/3}/day$ scaling used in the CAEPA (1992) assessment). CAEPA

also revised the estimated fraction of PCE metabolized by humans from 18.5% to 58% at environmentally relevant exposure levels based on the work of Bois et al. (1996).

The final CAEPA (2001) cancer slope factor was based on the geometric mean of the four potency factors associated with male and female mouse liver tumors and rat mononuclear cell leukemias and corresponds to a unit risk value (9.9×10^{-6} $(\mu g/m^3)^{-1}$)[14]. This is about 2 times higher than the CAEPA (1992) unit risk (5.9×10^{-6} $(\mu g/m^3)^{-1}$). The difference is attributable to the increased human metabolic rate value used, offset by the reduced cross-species scaling factor.

4.4 World Health Organization (2006)

WHO used the inhalation study in mice conducted by the Japan Bioassay Research Center (JISA, 1993). The data on male hepatocellular adenoma and carcinoma was used for the determination of a unit risk value. The applied concentrations were adjusted for duration since exposures were for 5 days per week and 6 hours per day. These duration adjusted exposure concentrations were used with the tumor incidence data for dose-response assessment. The 95% lower bound on the point of departure for the datasets was calculated using the multistage model in BMDS version 1.3.2 (USEPA, 2000). The unit risk selected by WHO was 5.2×10^{-6} $(\mu g/m^3)^{-1}$ (Appendix G, Table G-3). This unit risk can be compared to unit risks derived by MassDEP and CAEPA summarized by approach and dataset in Table 5.

[14] This is the unit risk that would result from the CAEPA 2001 slope factor analysis and was derived by ORS.

Table 5. Summary of Potency Factors and Unit Risk Values Derived by Various Groups Based on Cancer Bioassays

Agency	Bioassay and exposure route	Species Strain Sex	Dosimetric	Cross species extrapo-lation	Human % metabolism	Unit Risk $(ug/m^3)^{-1}$
Earlier Derivations						
MassDEP 1990	NCI, 1977 oral	B6C3F1 mice HC male female	Metabolized	$mg/kg^{2/3}$	70%	6.8×10^{-5} **5.5×10^{-5}** [a]
NESCAUM 1986; Strauss, 1992	NTP, 1986 inhalation study	B6C3F1 mice, male and female liver tumors	Metabolized	$mg/kg^{2/3}$	Using a range of assumed metabolism in humans and mice	1×10^{-5} to 1×10^{-4}
CAEPA, 1992	NTP, 1986 inhalation	B6C3F1 mice male liver tumors	Metabolized	$mg/kg^{2/3}$	18.5%	5.9×10^{-6} [b]
More Recent Derivations						
CAEPA, 2001	NTP, 1986 inhalation	B6C3F1 mice male liver tumors	Metabolized	$mg/kg^{3/4}$	58%[d]	1.3×10^{-5}
MassDEP, 2007	NTP, 1986 inhalation	B6C3F1 mice male liver tumors	Applied concentration (HEC)	NA	NA	6.8×10^{-6}
CAEPA, 2001	NTP, 1986 inhalation	F344 rat male leukemia	Metabolized	$mg/kg^{3/4}$	58%[d]	1.7×10^{-5}
MassDEP, 2007	NTP, 1986 inhalation	F344 rat male, leukemia	Applied concentration (HEC)	NA	NA	2.2×10^{-6}
MassDEP, 2007	JISA, 1993 inhalation study	Crj-JBDF1mice male, liver tumors	Metabolized	$mg/kg^{3/4}$	61%	6.9×10^{-6}
WHO, 2006	JISA, 1993 inhalation	Crj-JBDF1mice Male, liver tumors	Applied concentration (HEC)	NA	NA	5.2×10^{-6} [c]
MassDEP, 2007	JISA, 1993 inhalation	F344 rat male, leukemia	Metabolized	$mg/kg^{3/4}$	61%	9.3×10^{-6}
WHO, 2006	JISA, 1993 inhalation	F344 rat male, leukemia	Applied concentration (HEC)	NA	NA	1.2×10^{-6}

[a] Current MassDEP number; [b] Current CAEPA number; [c] Current WHO number; [d] MassDEP used a value of 61% based on a more recent analysis of Chiu and Bois (2006), which was not available at the time of the CAEPA assessment. Due to rounding use of this value results in the same unit risk.

HC = hepatocellular carcinoma; liver tumors = combined hepatocellular carcinoma or adenoma; leukemia= mononuclear cell leukemia (MCL)

5.0 Basis of Revised MassDEP Unit Risk Value

5.1 Hazard Identification and Carcinogenic Classification

Although the overall data is not conclusive and is insufficient to derive potency estimates, epidemiological studies have in several cases reported data suggestive of an association between PCE exposures and elevated rates of cancer in humans.

Results from animal bioassays are conclusive. PCE has been demonstrated to be carcinogenic in three separate animal studies (NCI, 1977; NTP, 1986; JISA, 1993). Statistically significant increases in the incidence of liver tumors and leukemias were observed in these studies. Positive response occurred in two species (mouse and rat) and three strains of animals and in both males and females.

Based on these results MassDEP agrees with the assessments reviewed previously, which concluded that it was appropriate to treat PCE as a known animal carcinogen and a possible/probable human carcinogen. MassDEP has also concluded that the animal data is sufficient to derive a cancer potency factor for PCE.

5.2 Mechanism of Action

Based on the WHO (2006) assessment, MassDEP does not believe that the available data is sufficient to conclude that PCE's liver tumorigenicity is due to peroxisome proliferation, a potential threshold mechanism of action. In addition, to our knowledge, no association between MCL and peroxisome proliferation has been documented.

Although PCE itself has not been found to be mutagenic or genotoxic in *in vitro* and *in vivo* assays, established metabolic pathways for PCE are known to generate potentially genotoxic reactive intermediates. Thus, although the precise pathways and metabolites responsible for PCE's carcinogenicity remain uncertain, MassDEP agrees with previous assessments that it is appropriate to assess PCE cancer potency using methods that incorporate a non-threshold mechanism of action and low-dose linearity in the dose response.

5.3 Choice of Critical Studies and Endpoints to Derive Unit Risk Value

5.3.1 Exposure Route

In its 1990 assessment MassDEP used data from the NCI (1977) oral mouse bioassay to derive an inhalation toxicity number despite the availability of an inhalation study for reasons discussed previously. Because the use of route specific data is generally thought to reduce the uncertainty introduced by route-to-route extrapolation of response data, we have decided to now rely on the data from the inhalation bioassays in our derivation of a revised interim unit risk value for PCE. This decision is supported by the fact that two

inhalation studies have now been conducted (NTP, 1986; JISA, 1993) in which similar tumor responses were observed.

5.3.2 Study Choice

Data from both inhalation studies were deemed to be adequate for dose response analysis. Resulting potency factors and unit risks have been derived for both.

5.3.3 Response Endpoints

MassDEP believes that it is appropriate to consider both the hepatocellular adenoma and carcinoma ("liver tumor") data in both strains of mice and the data on mononuclear cell leukemia (MCL; also known as large granular lymphocytic leukemia) observed in F344 rats. The MCL data has been questioned in the past because of: (1) the high background rate of MCL in F344 rat; and (2) concerns about the relevance of this tumor type to humans (Ishmael and Dugard, 2006). With respect to the first issue, both the JISA (1993) and the NTP (1986) inhalation studies exhibited statistically and biologically significant increases in the incidence of MCL in exposed animals when compared to concurrent controls. It is therefore very likely that this response is attributable to PCE exposure and not simply due to random variations in the background tumor rate. With respect to the second issue, similarities between the leukemia observed in the F344 rats and two uncommon forms of human large granular lymphocytic leukemias have been observed, invalidating claims that the rat MCL results are not relevant to humans (Thomas et al. 2007). Moreover, the NTP Board of Scientific Counselors considered the incidence of rat leukemia to be a valid finding, because of the shorter time to the onset of the disease and the greater severity in the treated animals compared with control animals (WHO, 2006).

In carcinogen risk assessment, to address the various uncertainties in a health protective manner, MassDEP typically relies on the most sensitive endpoint, species, sex and study to derive cancer potency values and unit risks. This approach is used unless there are compelling mechanistic or data quality issues to support another approach.

CAEPA (2001) used the geometric mean of four potency factors associated with male and female mouse liver tumors and rat mononuclear cell leukemias.

MassDEP chose to use the mean of the inhalation unit risks based on tumor response data for mononuclear cell leukemia (MCL) observed in F344 rats from both the NTP (1986) and JISA (1993) studies. Combining the estimates from these two studies is considered appropriate because they were conducted in the same strain of rats, using the same exposure conditions, resulting in similar dose-response curves. The unit risk estimate based on male mouse liver tumors from the NTP (1986) study is essentially the same as the unit risk based on mean of the unit risks based on rat MCL, supporting MassDEP's final value.

5.4 Estimating the Fraction of PCE Metabolized by Humans at Low Exposure Concentrations

Although much uncertainty regarding low dose metabolism remains, the new Chiu et al. (2007) study indicates metabolism in a small sample of adult humans at 1 ppm, still a high dose in comparison to the ppb exposure level of concern in environmental settings, ranged up to 34% with an average of 18.5% (as shown in Table B-1, Appendix B). As discussed previously, Chui and Bois (2006) estimated the 95% upper confidence value for PCE metabolism at ppb exposure levels to be 61% based on population toxicokinetics. In light of the considerable uncertainties involved in estimating PCE metabolism in people and because metabolism in some individuals may substantially exceed average metabolism, MassDEP has concluded that a precautionary approach is warranted to be protective of public health. Thus, MassDEP has opted to use the Chui and Bois (2006) 61% estimate to calculate human metabolized dose at low environmental exposure concentrations.

5.5 Choice of Dose Metrics to Derive Unit Risk Value

Metabolized dose was selected as the dose metric for derivation of the interim unit risk for PCE. As described previously, the assessments of PCE carcinogenicity by MassDEP (1990), NESCAUM (1986), and CAEPA (1992; 2001) derived potency values based on metabolized dose. CAEPA (2001) estimated PCE's cancer potency in animals based on total metabolite production derived using Michaelis-Menton kinetics, extrapolated these results to humans using default $BW^{3/4}$ scaling, and then adjusted the cancer potency by the fraction of PCE metabolized in the human population at environmental exposure concentrations. While metabolized dose was selected as the dose metric for the interim unit risk for PCE, the unit risks derived using the applied concentration dose metric are close to those derived using metabolized dose.

6.0 Conclusions

- The MassDEP recommended interim unit risk value for PCE is **1×10^{-5}** $(ug/m^3)^{-1}$ (Table 6) based on bioassay data from the NTP (1986) and JISA (1993) inhalation studies.

- MassDEP calculated various unit risk values using two approaches: the metabolized dose approach (consistent with the approach used by CAEPA, 2001) and the applied concentration approach (consistent with WHO, 2006.). The calculated unit risk values using the two approaches ranged from 1.2×10^{-6} to 1.7×10^{-5} $(ug/m^3)^{-1}$ (Table 5).

- Based on Advisory Committee input, metabolized dose was selected as the final dose metric. However, the use of applied dose yields an essentially equivalent unit risk, 7×10^{-6} $(ug/m^3)^{-1}$.

- Both leukemia in rats and liver tumors in mice were considered as response endpoints to be used in the unit risk calculation for PCE. The unit risk values based on rat leukemia data and mouse liver data are comparable as seen in Table 6). MassDEP proposes an interim unit risk value of $1 \times 10^{-5}(\mu g/m^3)^{-1}$ for PCE based on rat ***leukemia*** data supported by the male mouse liver tumor data.

- Although there is considerable uncertainty in the estimates of animal and human metabolism of PCE, the mode of action of PCE and its metabolites, MassDEP believes that the proposed interim unit risk value is a reasonable, health protective estimate of human potency given the information available at this time.

Table 6. Proposed Interim Unit Risk Value Derived by MassDEP

Bioassay and exposure route	**Species, Strain Sex, Tumor type**	**Unit Risk Values $(ug/m^3)^{-1}$**	**MassDEP Proposed Interim Unit Risk Value $(ug/m^3)^{-1}$**
NTP, 1986 inhalation	F344 rat male, leukemia	1.7×10^{-5}	**1×10^{-5}** [a]
JISA, 1993 inhalation	F344 rat male, leukemia	9.3×10^{-6}	
NTP, 1986 inhalation	B6C3F1 mice male liver tumors	1.30×10^{-5}	1×10^{-5}

[a] Mean of the unit risk values based on leukemia in rats incidence observed in the NTP (1986) and JISA (1993) studies. The values were averaged because the tumor bioassays were conducted in the same species. The geometric mean, 1.26×10^{-5} $(ug/m^3)^{-1}$, and arithmetic mean 1.32×10^{-5} $(ug/m^3)^{-1}$ are both equivalent to 1×10^{-5} $(ug/m^3)^{-1}$ when rounded to one significant figure. The male mice liver tumor data yields the same value.

Figure 1. Tetrachloroethylene Carcinogenicity: Hepatocellular Carcinomas and Adenomas Combined in Mice

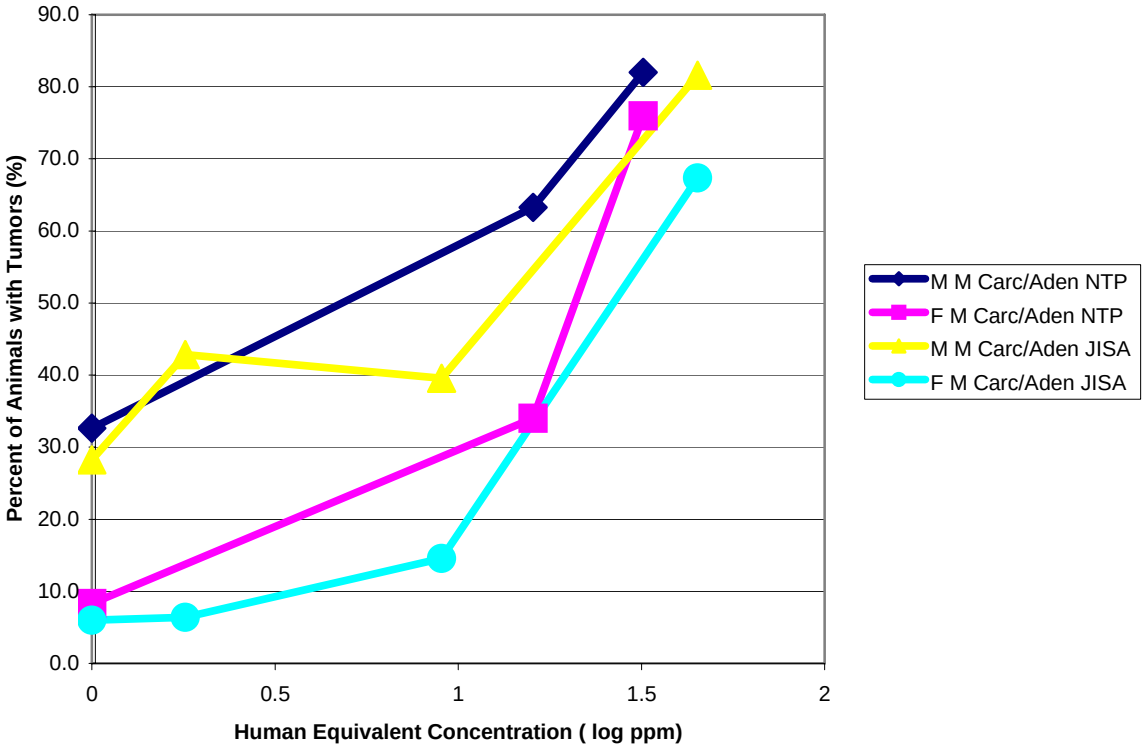


Figure 2. Tetrachloroethylene Carcinogenicity: Mononuclear Cell Leukemia in Rats

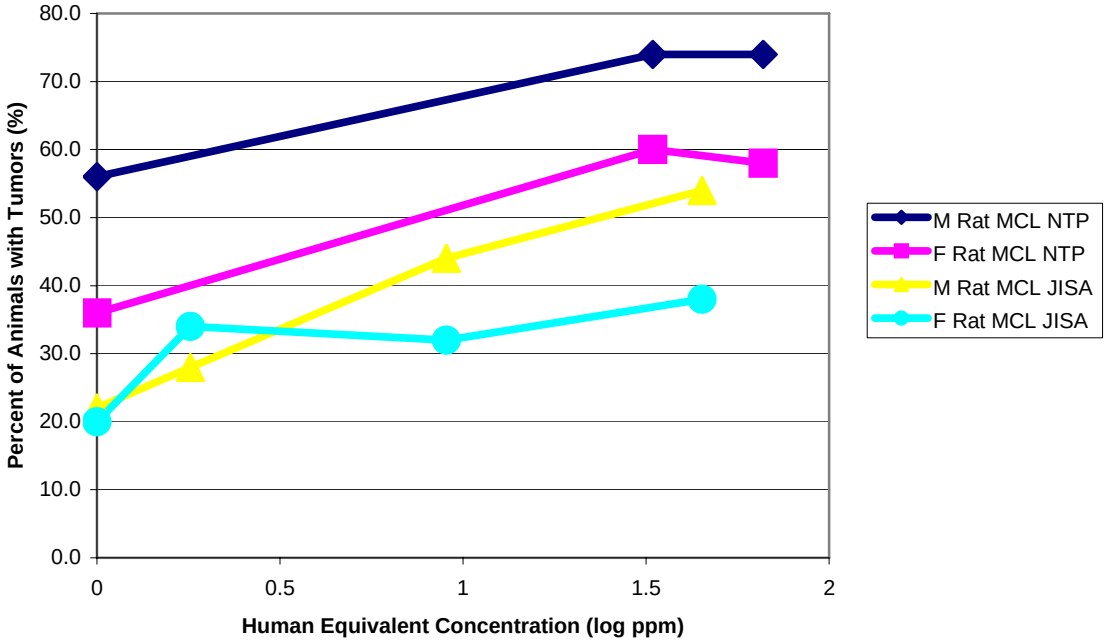


Figure 3. Oxidative biotransformation pathway of tetrachloroethylene (de Raat, 2003, as cited in WHO, 2006)

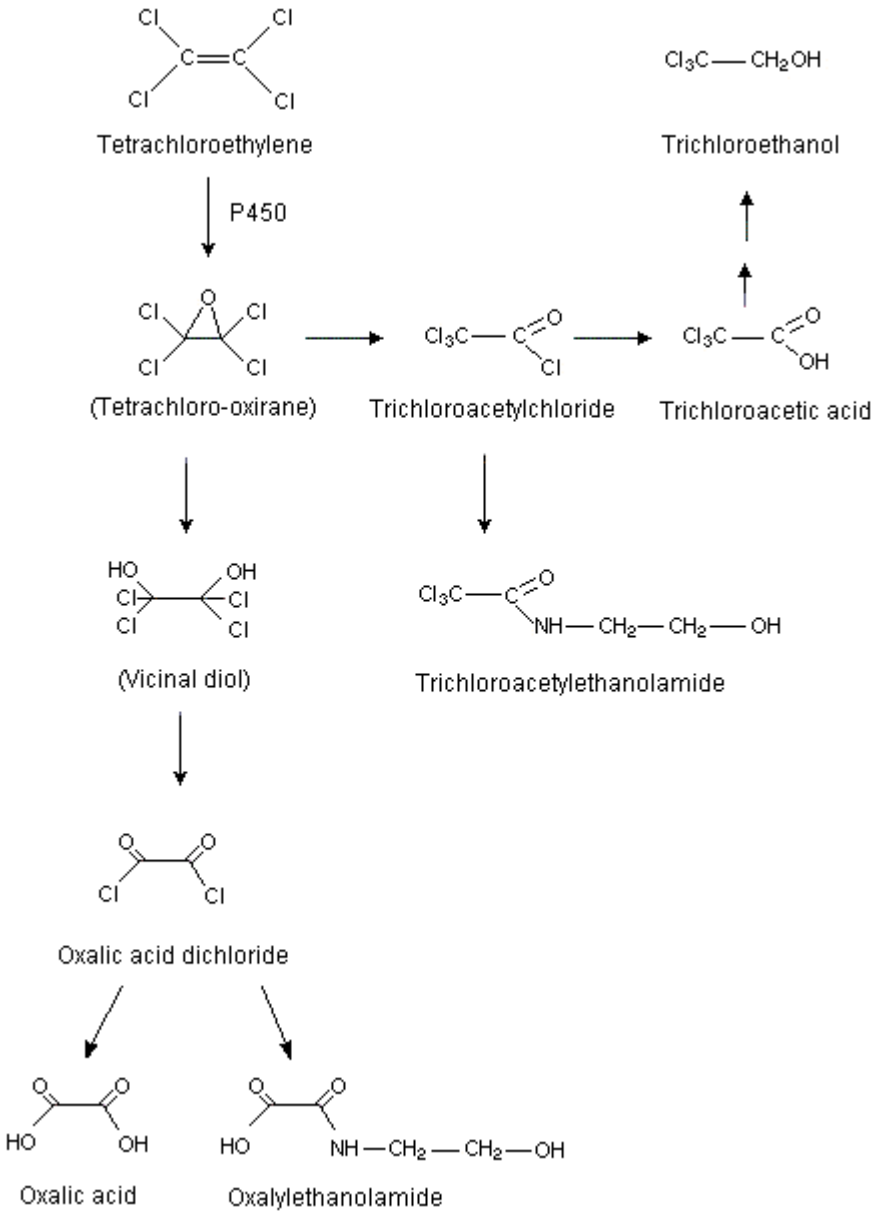
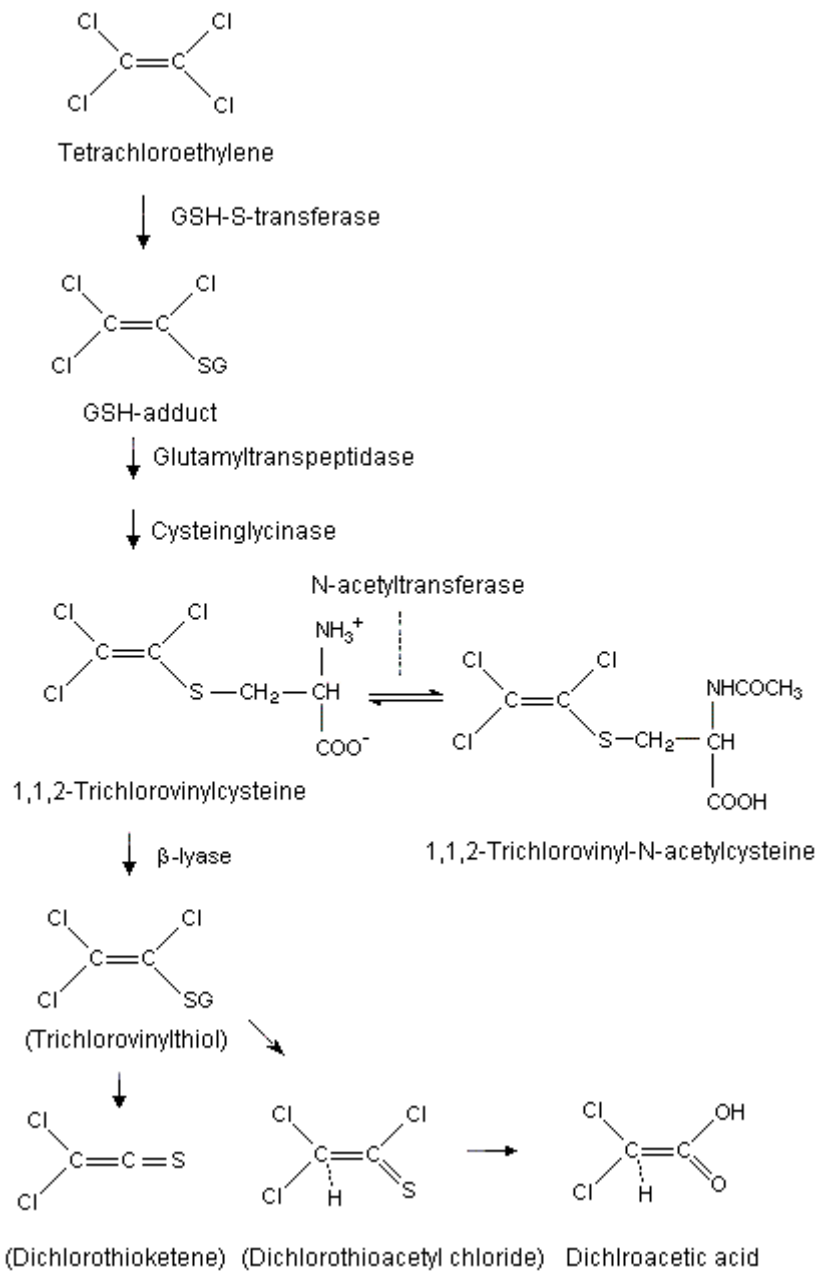


Figure 4. Conjugative biotransformation pathway of tetrachloroethylene (de Raat, 2003, as cited in WHO, 2006).



Note that 1,2,2-trichlorovinylcysteine and 1,2,2-trichlorovinyl-*N*-acetylcysteine were named as 1,1,2- compounds in this source document.

7.0 References

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Appendix A

Summary of Epidemiology Studies of Tetrachloroethylene Exposure from WHO (2006)

Table A-1. Summary of human carcinogenicity studies.

Subjects	Organs/cancer type	Indication of risk	Reference
1708 dry cleaning workers in the USA Exposed to tetrachloroethene (PCE) for at least 1 year before 1960 and followed up to 1996 625 exposed only to PCE [PCE-only] 1083 exposed to PCE and other solvents [PCE-plus]		**SMR [CI]; no. of cases [notes]**	Ruder et al. (2001)
	All cancer [cohort]	1.25 [1.11–1.41]	
	All cancer [PCE-only]	1.08 [0.85–1.36]	
	All cancer [PCE-plus]	1.35 [1.16–1.55]	
	Tongue [cohort]	5.00 [1.62–11.68]; 5	
	Oesophagus [cohort]	2.47 [1.35–4.14]; 14 [similar risks for PCE-only and PCE-plus groups]	
	Intestine except rectum [cohort]	1.48 [1.01–2.09]; 32	
	Trachea, bronchus, and lung [cohort]	1.36 [1.05–1.73]; 65	
	Bladder and other urinary tract [cohort]	2.22 [1.06–4.08]; 10	
	Cervix [cohort]	1.95 [1.00–3.40]; 12 [similar risks for PCE-only and PCE-plus groups]	
	Kidney [cohort]	1.41 [0.46–3.30]; 5	
5369 dry cleaning workers in the USA At least 1 year of employment between 1948 and end of 1993		**SMR [CI]; no. of cases; notes**	Blair et al. (2003)
	All cancer	1.2 [1.1–1.3]	
	Oesophagus	2.2 [1.5–3.3]; 26 2.1; "little or no exposure" 2.2; "medium/high exposure"	
	Lung	1.4 [1.1–1.6]; 125	
	Cervix	1.6 [1.0–2.3]; 27	

	Larynx, bladder, and Hodgkin's disease	Increases, not statistically significant. For larynx, SMR 2.7 [1.0–5.8] for "medium/high exposure"	
671 white female laundry and dry cleaning workers in the USA Died in the period 1963–1977		**PMR [CI]**	Katz & Jowett (1981)
	Kidney	2.5 [1.0–5.2]	
	Bladder	1.9 [0.62–4.5]	
	Skin	2.6 [0.73–6.8]	
	Cervix	1.4 [0.68–2.6]	
	Rectum	1.3 [0.45–2.7]	
	Lymphosarcoma	1.8 [0.65–3.8]	
440 laundry and dry cleaning workers in the USA Died in the period 1975–1981		**SMOR [CI]; no. of deaths**	Duh & Asal (1984)
	All cancer	0.9 [0.7–1.2]	
	Lung	1.7 [1.2–2.5]; 37	
	Kidney	3.8 [1.9–7.6]; 7	
	Cervix	1.3 [0.3–5.3]; 2	
	Bladder and liver	Deficits, not statistically significant	
	Oesophagus	No data given	
14 457 aircraft maintenance workers in the USA Died in the period 1952–1982 Employed at least for 1 year and exposed to over 20 different solvents		**SMR [CI]; no. of deaths**	Spirtas et al. (1991)
	Multiple myeloma (in women)	1.7 [0.2–6.2]; 2	
	Non-Hodgkin's lymphoma	3.2 [0.87–8.1]; 4	
	No information on other cancers		

10 600 Danish laundry and dry cleaning workers, aged 20–64 years; 10-year follow-up of Danish 1970 census information 510 cancer cases		**SIR [CI]; no of cases; notes**	Lynge & Thygesen (1990)
	All cancer	1.0	
	Pancreas	1.7 [1.1–2.6]; 22	
	Liver (women) [no increase in men]	3.4 [1.4–7.0]; 7	
	Kidney, bladder, and cervix	Small deficits, not statistically significant	
	Non-Hodgkin's lymphoma	No increase (men showed a slight increase, O/E: 5/1.8; and women showed a slight deficit, O/E: 3/6)	
	Oesophagus	No data given	
10 600 Danish laundry and dry cleaning workers A nested case–control study of 17 cases of liver cancer (14 women, 3 men) and 16 of renal cancer (9 women, 7 men) that developed between 1970 and 1987	Liver	None of the 17 cases worked in the dry cleaning industry	Lynge et al. (1995)
	Kidney	13/16 worked in laundries, 3 as dry cleaners; RR for dry cleaning workers 0.7, CI 0.2–2.6	
849 Finnish workers (557 women) exposed to tetrachloroethene followed from 1967 to 1992 during which time there were 31 cancer cases		**SIR [CI]; no. of cases**	Anttila et al. (1995)
	All cancer	0.9 [0.61–1.3]	
	Cervix	3.2 [0.39–11.6]; 2	
	Non-Hodgkin's lymphoma	3.8 [0.77–11.0]; 3	
	Pancreas	3.1 [0.63–9.0]; 3	
8163 deaths among former laundry and dry		**PMR [CI]; no. of deaths**	Walker et al. (1997)
	Oesophagus (black men)	2.15 [1.11–3.76]; 12	

cleaning workers in the USA	Oesophagus (black women)	1.84 [0.84–3.49]; 9	
	Oesophagus (white women)	1.89 [0.51–4.83]; 4	
	Oesophagus (white men)	0.75 [0.16–2.19]; 3	
	Larynx (white men)	3.18 [1.17–6.93]; 6	
	Cervix (black women)	1.18 [0.59–2.12]; 11	
	Cervix (white women)	1.05 [0.46–2.08]; 8	
	Pancreas (black men)	1.18 [0.32–3.02]; 4	
	Pancreas (white men)	1.28 [0.58–2.43]; 9	
	Kidney	Deficits (not significant) in white men, black men, and white women, slight excess (PMR 1.32) in black women	
Aircraft manufacturing workers A subcohort of 2631 employees "who had potential for routine exposure" to tetrachloroethene Employed for at least 1 year, on or after January 1960 to the end of 1996 No information was available on the levels of exposure		**SMR [CI]; no. of deaths; notes**	Boice et al. (1999)
	All cancer	1.07 [0.90–1.26]	
	Oesophagus	1.47 [0.54–3.21]; 6	
	Stomach	1.42 [0.57–2.93]; 7	
	Biliary passages and liver	2.05 [0.83–4.23]; 7	
	Pancreas	1.50 [0.72–2.76]; 10	
	Lung	1.08 [0.79–1.44]; 46	
	Non-Hodgkin’s lymphoma	1.70 [0.73–3.34]; 8	
	Cervix	0 deaths	
	Kidney	0.69 [0.08–2.47]; 2	
	Bladder	0.70 [0.09–2.53]; 2	
Swedish dry cleaning,		**RR [CI]; no. of cases**	Travier et al.

laundry, and ironing workers Occupation census 1960 and 1970 compared with cancer registry incidence data between 1971 and end of 1989	Hodgkin's disease (men/women combined)	2.69 [1.01–7.19]; 4	(2002)
	Leukaemia (women)	2.53 [1.44–4.46]; 12	
	Laryngeal cancer (men)	2.42 [0.91–6.45]; 4	
	Oesophagus	0.34 [0.05–2.39]; 1	
86 868 electronics factory workers in China, Province of Taiwan Factory operated between 1968 and 1992 Between 1985 and 1997, there were 316 cancer deaths Average exposure duration was only 1.6 years Wells nearby contaminated with tetrachloroethene and trichloroethylene		**SMR [CI]; no. of deaths; notes**	Chang et al. (2003)
	All cancer (females)	1.00	
	All cancer (males)	0.65	
	Kidney (women)	1.18 [0.24–3.44]; 3	
	Kidney (men)	0 deaths	
	Oesophagus	0 deaths	
Laundry, dry cleaning, and garment service workers in the USA Employment for ≥6 months		**OR [CI]**	Stemhagen et al. (1983)
	Liver (men)	2.5 [1.0–6.1]	
Dry cleaning workers in the USA		**OR [CI]**	Suarez et al. (1989)

Dry cleaning services	Liver (men)	0.98 [0.44–2.2]	
Dry cleaning operators	Liver (men)	0.55 [0.17–1.8]	
Case–control study in the USA, 80 liver cancer cases and 146 controls	Liver	No cases (and 4 controls) had worked in laundry and cleaning occupations for ≥6 months	Austin et al. (1987)
Swedish study, occupation in 1960 linked to cancer incidence data during 1960–1979 There were 7405 kidney cancer cases		**SIR, notes**	McLaughlin et al. (1987)
	Kidney (men)	0.99 for working in dry cleaning and laundry establishment (18 cases)	
	Kidney (women)	0.86 for working in dry cleaning and laundry establishment (25 cases)	
Population-based German case–control study of 277 cases and 286 controls	Renal cell cancer	OR 2.52 [1.23–5.16] for exposure to "chlorinated solvents"	Schlehofer et al. (1995)
Population-based German case–control study of 935 cases and 4298 matched controls Exposure to tetrachloroethene assigned as medium, high, or substantial (substantial > high)	**Renal cell cancer, men**	**OR [CI]; no. of cases**	Pesch et al. (2000)
	Medium exposure	1.4 [1.1–1.7]; 154	
	High exposure	1.1 [0.9–1.4]; 119	
	Substantial exposure	1.4 [1.0–2.0]; 50	
	Renal cell cancer, women		
	Medium exposure	0.7 [0.4–1.3]; 12	
	High exposure	1.1 [0.7–1.9]; 19	
	Substantial exposure	0.7 [0.3–2.2]; 4	
Population-based case–control study in the USA	Kidney (women)	OR 2.8 [0.8–9.8] for dry cleaning as the predominant lifetime occupation (8 exposed cases, 1 exposed control)	Asal et al. (1988)

	Kidney (men)	OR 0.7 [0.2–2.3] for dry cleaning as the predominant lifetime occupation (3 exposed cases, 6 exposed controls)	
Canadian population-based multisite, case–control study (controls were people with cancer at other body sites)	Kidney	OR 2.0 [0.8–5.1] for employment in dry cleaning or laundry industry, for any duration, at least 5 years before disease onset	Siemiatycki (1991); IARC (1995)
	Oesophagus	None of the 99 oesophageal cancer cases had been a launderer or dry cleaner	
Australian population-based case–control study of renal cell cancer (489 cases), renal pelvic cancer (147 cases), and 523 controls		**OR [CI] (for any employment in dry cleaning)**	McCredie & Stewart (1993); IARC (1995)
	Renal cell cancer (men)	2.7 [1.1–6.7]	
	Renal cell cancer (women)	2.5 [0.97–6.4]	
	Renal pelvic cancer (men)	6.1 [2.0–19]	
	Renal pelvic cancer (women)	4.7 [1.3–17]	
Danish population-based case–control study of 365 renal cell carcinoma cases and 396 controls		**OR [CI] for any employment in dry cleaning; no. of cases**	Mellemgaard et al. (1994)
	Kidney (males)	2.3 [0.2–27]; 2	
	Kidney (females)	2.9 [0.3–33]; 2	
Population-based multisite, case–control study in the USA of 491	Larynx	OR 2.7 [0.6–10.9]; 5 cases (risk increased with years employed in dry cleaning industry)	Vaughan et al. (1997)

cases of cancer of the oral cavity and pharynx, 235 cases of laryngeal cancer, 404 cases of cancer of the oesophagus and gastric cardia, and 724 controls	Oesophagus	OR 3.6 [0.5–27.0]; 2 cases, both employed in dry cleaning industry for a very short time	
Study of 672 women with breast cancer (diagnosed 1987–1993) and 66 controls from the same 8 towns in the USA as the cases Women were exposed to tetrachloroethene when it leached from the vinyl lining of water distribution pipes during the late 1960s through the early 1980s Relative delivered tetrachloroethene doses were estimated	Breast	OR 1.5–1.9 for the 75th percentile of delivered dose (0–15 years of latency) OR 1.3–2.8 for >90th percentile of delivered dose (0–15 years of latency)	Aschengrau et al. (1998, 2003)
Population-based multisite case–control study in the USA of colorectal cancer (326 cases), lung cancer (256 cases), brain cancer (37	Lung	**OR [CI] for exposure level above the 90th percentile**	Paulu et al. (1999)
	0 years of latency 5 years of latency 7 years of latency 9 years of latency	3.7 [1.0–11.7] 3.3 [0.6–13.4] 6.2 [1.1–31.6] 19.3 [2.5–141.7]	

cases), and pancreatic cancer (37 cases) Exposure to tetrachloroethene occurred when it leached from the vinyl lining of water distribution pipes during the late 1960s through the early 1980s	Colon–rectum 11 years of latency 13 years of latency	 1.7 [0.8–3.8] 2.0 [0.6–5.8]	

Appendix B

Individual Subject and Occasion Data from Chui et al. (2007)

Table B-1. Individual Subject and Occasion Data for Subjects Exposed to 1 ppm Tetrachloroethylene for 6 hours from Chui et al. (2007)

	A - 1	B - 1	B - 2	C - 1	C - 2	D - 1	E - 1	E - 2	F – 1	F - 2
Covariates										
BW (kg)	70.5	75.6	75.6	75.2	75.2	70.5	72	72	69.5	69.5
% Fat	0.11	0.204	0.204	0.204	0.204	0.129	0.105	0.105	0.18	0.18
Fat (kg)	7.755	15.4224	15.4224	15.3408	15.3408	9.0945	7.56	7.56	12.51	12.51
Minute Volume (L/min)	7.4	7.6	7.6	7.4	7.4	7.1	7.2	7.2	7.8	7.8
Fraction metabolized (total)[a]	**19.6%**	**18.9%**	**33.0%**	**19.8%**	**24.7%**	**-1.7%**	**7.9%**	**34.3%**	**-3.7%**	**29.3%**

[a] Total fraction metabolized was calculated by Chui (2007) as one minus the total exhaled (umol) divided by the total intake (umol).

Appendix C

MassDEP (1990)
Derivation of Unit Risk for PCE from the
NCI (1977) Oral Gavage Study

Table C-1: Dose-Response Data Cancer Bioassays of PCE from the NCI Gavage Study (MassDEP, 1990)

Study, Route, species	Sex Weight (kg)	Administered Dose (mg/kg-d) [a]	Tumor Type	Tumor Incidence [b]
NCI, 1977, Gavage, Mice (B6C3F1)	Male 0.030	0 (mg/kg-d) 536 1072	Hepatocellular Carcinoma	2/20 32/49 27/48
	Female 0.025	0 386 772	Hepatocellular Carcinoma	0/20 19/48 19/45

[a] Administered dose of PCE in corn oil in mg/kg-d, dosed by gavage 5 days per week over 78 weeks of dosing.
[b] Tumor incidence denominator excludes animals dying before the occurrence of the first corresponding tumor type observed in the study.

Table C-2: Dose Calculation for Dose-Response Assessment of PCE Using the NCI Gavage Study (MassDEP, 1990)

Study species (1)	Administered Dose (D) (mg/kg-d) (2)	TCA Metabolites in Urine (M_u) [a] (mg TCA/kg-d) (3)	Metabolized PCE [b] (mg/kg-d) (4)	LAD based on PCE Urinary Metabolites[c] (mg/kg-d) (5)	LAD based on Total Metabolites[d] (mg/kg-d) (6)	Surface Area Adjusted LAD[e] (mg/kg-d) (7)
NCI, 1977 Male mice (B6C3F1)	0 536 1072	0 60.95 84.18	0 61.84 85.42	0 36.27 50.10	0 45.34 62.63	0 3.46 4.77
Female mice	0 386 772	0 50.19 73.32	0 50.93 74.40	0 29.87 43.63	0 37.34 54.54	0 2.65 3.87

[a] Column 2 is the administered dose, D, used to calculate the dose metabolized (M_u) to urinary trichloroacetic acid (TCA) that is presented in Column 3. M_u is calculated using the Michaelis-Menton equation ($M_u = D \times Vmax_u / D + Km$). $Vmax_u$, the apparent maximum rate of urinary metabolite production, and Km, the apparent Michaelis constant, are from pharmacokinetic data of Buben and O'Flaherty (1985). Buben and O'Flaherty treated Swiss-Cox mice with PCE doses ranging from 20 to 2000 mg/kg 5 days/week for six weeks. Metabolism was estimated by measuring the daily excretion of TCA in the urine. The $Vmax_u$ is estimated from this study was 136 mg/kg-d and the Km was 660 mg/kg-d.
[b] Column 4 is the metabolized dose expressed as mg of PCE by multiplying the metabolized dose by the ratio of the molecular weight (MW) of PCE to the MW TCA (165.8/163.4).
[c] In column 5 is the lifetime average dose (LAD) which is calculated as PCE adjusted metabolized dose (M_u) x 5/7 x 78/95. The final term derives from the fact that animals were dosed for 78 weeks and were killed at 95 weeks of age.
[d] Column 6 represents total metabolized dose. The LAD, which is the urinary metabolite is converted to total metabolite based on the assumption that urinary metabolites are 80% of the total metabolite (LAD/0.8 = LAD adjusted urinary total metabolite).
[e] Column 7 presents the human equivalent dose based on body weight scaling of the LAD based on total urinary metabolites $(BW_{animal}/70)^{1/3}$.

Table C-3. Tumor Incidences and Potencies Determined from the NCI Gavage Study (MassDEP, 1990)

			Potency (q^*)		
Species and Sex B6C3F1 mice	Human Equivalent Dose	Tumor Incidence Hepatocellular Carcinoma	q^* $(mg/kg/d)^{-1}$	q^* LLE adjusted[a] $(mg/kg/d)^{-1}$	Unit Risk[b] $(\mu g/m^3)^{-1}$
Male	0 3.46 4.77	2/20 32/49 27/48	2.578×10^{-1}	3.38×10^{-1}	6.76×10^{-5}
Female	0 2.65 3.87	0/20 19/48 19/45	2.106×10^{-1}	2.76×10^{-1}	5.52×10^{-5}

[a] Potency values were adjusted for less than lifetime exposure (LLE) by multiplying q^* by $(104/95)^3 = 1.31$. This is based on 104-week nominal lifetime for mice and the fact that the mice were killed at 95 weeks of age.

[b] MassDEP unit risk values based on the assumption that the human metabolized dose is equal to 70% of inhaled dose at low PCE exposure levels

- The 70% metabolism assumption is based on the consideration that it is more likely that the proportion of the inhaled dose which is metabolized varies with dose and that at low enough doses nearly all of the absorbed dose is metabolized. Anderson et al. (1981) have presented a theoretical curve showing that under low exposure conditions the proportion of the inhaled doses of inhaled gases that is metabolized approaches a maximum of 67% at blood: air coefficients greater than 10. The human blood: air coefficients for PCE that are reported by various investigators range from 10 – 20 (ATSDR, 1997).
- Based on the above metabolism assumption and also assuming a 70 kg person inhaling 20 m^3 of air, the metabolized dose from exposure to 1 $\mu g/m^3$ PCE is equal to 1 $\mu g/m^3$ x 20 m^3 x 1/70 kg x 1/1000 mg/μg x 0.7 = 2×10^{-4} mg/kg/-d, i.e., 1 $\mu g/m^3$ exposure concentration in air is equivalent to 2×10^{-4} mg/kg-d metabolized dose of PCE.
- The unit risk for inhalation exposure to 1 $\mu g/m^3$ PCE is then q^* $(mg/kg\text{-}d)^{-1}$ x 2×10^{-4} mg/kg-d per $\mu g/m^3$.

Appendix D

MassDEP (1990)
Derivation of Unit Risk for PCE from the
NTP (1986) Inhalation Study

Table D-1. Dose-Response Data from the NTP (1986) Inhalation Study (MassDEP, 1990)

Study species	Sex Weight (kg)	Exposure concentration (ppm)	Tumor Type			
			Hepatocelluar carcinoma (HC)		Hepatocellular adenoma and carcinoma (HAC)	
			A[a]	B	A	B
NTP, 1986 Mice (B6C3F1)	Male 0.037	0 100 200	7/49 25/49 26/50	7/49 29/49 29/50	17/49 31/49 41/50	18/49 36/49 45/50
	Female 0.025	0 100 200	1/48 13/50 36/50	1/48 18/50 46/50	4/48 17/50 36/50	5/48 23/50 46/50
			Mononuclear Cell Leukemia			
			A	B		
F344 rats	Male 0.44	0 200 400	28/50 37/50 37/50	32/50 40/50 45/50		
	Female 0.32	0 200 400	18/50 30/50 29/50	27/50 36/50 33/50		

[a] A: Observed incidence, B: Tumor incidence rates adjusted for early mortality.

Table D-2. Dose Calculation for B6C3F$_1$ Mice for Dose-Response Assessment of PCE Using the NTP (1986) Inhalation Study (MassDEP, 1990)

					Human Equivalent LAD (mg/kg/d) (5)	
Species and Sex	**Exposure Concentration [a] (ppm) (1)**	**Body burden [b] (mg/kg) (2)**	**Metabolized dose [c] (mg/kg-d) (3)**	**LAD [d] (mg/kg-d) (4)**	**Male [e]**	**Female [e]**
B6C3F$_1$ mice	0	0	0	0	0	0
	100	165	145	104	8.45	8.05
	200	330	290	207	16.8	15.5

[a] Applied exposure in the experiment.

[b] The body burden calculation is based on the data of Schumann et al. (1980). In this study the body burden in mice at the end of exposure to 10 ppm for 6 hours is 16.5 mg/kg-d. When normalized to exposure concentration (16.5/10) the body burden of 1.65 mg/kg/ppm is calculated, which means for each ppm of PCE exposure the body burden is 1.65 mg/kg-d. Assuming linearity between exposure concentration and body burden each of the exposure concentrations in Column 1 are multiplied by 1.65 mg/kg/day/ppm to give the values in Column 2.

[c] From the Schumann et al. study 88% of the body burden is metabolized. Multiplying each of the body burden values in Column 2 by 88% results in metabolized dose listed in Column 3.

[d] Metabolized dose is adjusted for exposure duration by multiplying metabolized dose in Column 3 by 5/7 (exposure was for 5 days per week) to give the lifetime average dose (LAD) in Column 4.

[e] LAD is converted to human equivalent dose based by the cross species scaling factor $(bw_{animal}/70\ kg)^{1/3}$ with the body weight (bw) in the numerator equal to the average terminal body weight of the animal group in kilograms. The human equivalent doses in Column 5 are used with the corresponding tumor incidence rates to derive a slope factors presented in Table D-4.

Table D-3. Dose Calculation for F344 Rats for Dose-Response Assessment of PCE Using the NTP (1986) Inhalation Study (MassDEP, 1990)

						Human Equivalent LAD [e] (mg/kg/d) (6)	
Species and Sex	**Exposure Concentration (ppm) (1)**	**Body Burden [a] (mg/kg) (2)**	**Percent of Body Burden Metabolized [b] (3)**	**Metabolized Dose [c] (mg/kg-d) (4)**	**LAD [d] (mg/kg-d) (5)**	**Male**	**Female**
F344 rats	0	0	0	0	0	0	0
	200	110.8	25.6	28.4	20.3	3.80	3.36
	400	221.6	18.8	41.7	29.8	5.58	4.95

[a] The body burden is calculated based on the data of Pegg et al. (1979). In rats exposed to 10 or 600 ppm PCE for 6 hours excreted PCE and its metabolites in the expired air, urine and feces at levels of 5.92 and 310 mg/kg-d respectively. When normalized to exposure concentrations, the body burden at 10 or 600 ppm were 0.592 (5.92/10) mg/kg/ppm or 0.517 (310/600) mg/kg/ppm. The mean of the two values is 0.554 mg/kg/ppm. This expression simply means that for every ppm of PCE exposure the body burden is 0.554 mg/kg/day. The exposure concentrations in the NTP study are multiplied by this value to derive the body burden at each exposure level in column 2.

[b] The data from Pegg et al. (1979) indicate that the proportion of the body burden that is metabolized in rats is 32% and 12% at 10 and 600 ppm, respectively. Linear extrapolation estimates that at 200 ppm exposure concentration 25.6%, and at 400 ppm 18.8 % of the body burden is metabolized (note that less is metabolized at higher concentration than at lower exposure concentration, suggesting metabolic saturation).

[c] The metabolized dose in Column 4 is estimated by multiplying the body burden values in Column 2 by the corresponding values in Column 3.

[d] The metabolized dose is adjusted for continuous exposure by multiplying the metabolized dose by 5/7 (treatment was 5 days per week) to give the LAD in Column 5.

[e] LAD is converted to human equivalent dose in Column 6 using a cross species scaling factor $(bw_{animal}/70\ kg)^{1/3}$ with the body weight (bw) equal to the average terminal body weight of the animal group. The human equivalent doses are used with the corresponding tumor incidence rates to derive a slope factors presented in Table D-4.

Table D-4. Carcinogenic Potency from Dose-response Assessment of PCE Using the NTP (1986) Inhalation Study (MassDEP, 1990)

Species	Tumor type	Potency [a] q_1^* (mg/kg-d)$^{-1}$	Unit Risk [b] ($\mu g/m^3$)$^{-1}$
Male Mouse	Hepatocellular carcinoma Hepatocellular adenoma and carcinoma combined	7.31×10^{-2} 1.43×10^{-1}	1.46×10^{-5} 2.86×10^{-5}
Female Mouse	Hepatocellular carcinoma Hepatocellular adenoma and carcinoma combined	3.16×10^{-2} 5.15×10^{-2}	6.32×10^{-6} 1.03×10^{-5}
Male Rat	Mononuclear Cell Leukemia	3.00×10^{-1}	6.00×10^{-5}
Female Rat	Mononuclear Cell Leukemia	1.66×10^{-1}	3.32×10^{-5}

[a] The human equivalent doses from Tables C-2 and C-3, for mice and rats respectively, are used with corresponding tumor incidence rates (Table C-1) to derive the slope factors above.

[b] Based on the above metabolism assumption and also assuming a 70 kg person inhaling 20 m^3 of air, the metabolized dose from exposure to 1 $\mu g/m^3$ PCE is equal to 1 $\mu g/m^3$ x 20 m^3 x 1/70 kg x 1/1000 mg/μg x 0.7 = 2×10^{-4} mg/kg-day, i.e., 1 $\mu g/m^3$ exposure concentration in air is equivalent to 2×10^{-4} mg/kg-d metabolized dose of PCE. The unit risk for inhalation exposure to 1 $\mu g/m^3$ PCE is then q_1^*(mg/kg-d)$^{-1}$x 2×10^{-4} mg/kg-d / $\mu g/m^3$

- B6C3F1 mice produced tumors when treated with PCE orally or by inhalation, indicating that in this strain of mice the target organ for PCE carcinogenicity is the liver. The potency factors derived using either the oral or the inhalation study in mice are not very different. The unit risk derived from the oral study in male and female mice ranged from 5.52×10^{-5} to 6.76×10^{-5} ($\mu g/m^3$)$^{-1}$ while the potency factors derived from the inhalation study in male and female mice ranged from 6.32×10^{-6} to 2.86×10^{-5} ($\mu g/m^3$)$^{-1}$, MassDEP selected the potency factor of 2.76×10^{-1} (mg/kg-d)$^{-1}$ based on the oral gavage study in female mice and calculated a unit risk value of 5.52×10^{-5}($\mu g/m^3$)$^{-1}$ for PCE. The choice for this oral data is said to be due to more accurate metabolic parameters available to determine metabolized doses in the exposed mice and rats in the oral study than in the inhalation study.

Appendix E

CAEPA (1992)
Derivation of Unit Risk Values for PCE Using the NTP (1986) Inhalation Study

Table E-1. Dose-Response Data from the NTP (1986) Inhalation Study (CAEPA, 1992)

Study species	Sex Weight (kg)	Exposure concentration (ppm) [a]	Tumor Type [b]	
			Hepatocelluar carcinoma (HC)	**Hepatocellular adenoma and carcinoma (HAC) [c]**
NTP, 1986 B6C3F$_1$ Mice	Male 0.037	0 100 200	7/49 25/47 26/50	16/49 31/47 40/50
	Female 0.025	0 100 200	1/44 13/42 36/47	4/44 17/42 38/47
			Mononuclear Cell Leukemia [b]	
NTP, 1986 F344 rats	Male 0.44	0 200 400	28/50 37/48 37/50	
	Female 0.32	0 200 400	18/49 30/50 29/50	

[a] Applied exposure concentration in ppm, 5d/wk, 6h/d over 2-years.
[b] Data from CAEPA, 1992, Table 5-1.
[c] Tumor incidence denominator excludes animals dying before the occurrence of the first corresponding tumor type observed in each study.

Table E-2. CAEPA (1992) Carcinogenicity Risk Assessment Using the NTP (1986) Inhalation Study

	Applied Concentration (C) (ppm)	TWA Applied dose (TWA_d) [a] (mg/kg-d)	Daily Metabolized dose (M) [b] (mg/kg-d)	
			CAEPA Michaelis-Menton kinetics	**Hattis et al. (1987) Equiv. PB-PK**
B6C3F1 Mice Male 0.037kg	0 100 200	0 146.6 [c] 293.2 [c]	0 43.3 [d] 61.4 [d]	0 44.5 [e] 74.6 [e]
B6C3F1 Mice Female 0.032 kg	0 100 200	0 153.9 [c] 307.8 [c]	0 46.7 [d] 65.8 [d]	
F344 Rat Male 0.44 kg	0 200 400	0 143 [f] 286 [f]	0 11.8 [g] 17.2 [g]	0 14.1 [e] 22.2 [e]
F344 Rat Female 0.32 kg	0 200 400	0 159 [f] 318.1 [f]	0 14.0 [g] 20.0 [g]	

[a] Source Table 5.1 CAEPA (1992).

[b] Source Table 5.2 CAEPA (1992).

[c] Total respired dose averaged over time in mice: TWA_d = C ppm x 6.78 mg/m^3/ppm x 6 h/24 h x 5 d/wk/7d/wk x 0.0345 m^3/day x (body weight of assay animal (kg)/0.025 kg)$^{2/3}$ ÷ Body weight of assay animal. Note that inhalation rate is adjusted to represent the test animal.

[d] Metabolized dose *M* calculated using Michaelis-Menton equation where:

$$M = \frac{D \times V_{max} \, (w_1/w_2)^{1/3}}{D + K_m \, (w_2/w_1)^{1/3}}$$

Where D = inhaled concentration in ppm, M = total metabolites formed, V_{max} = maximum rate of metabolism and K_m = apparent Michaelis constant (all in mg/kg-d). The parameter w_1 is the body weight of the animals used in the calibration experiment and w_2 is that of the animals to be simulated (e.g. those in the bioassay). Where: V_{max} = 170 mg/kg-d, determined from the PCE oral administered data of Buben and O'Flaherty (1985) and Km was calculated to be 126 ppm. Km was estimated from the rat inhalation data of Pegg et al. (1979). Body weights used, w_1 = 0.0245 kg [the mean body weight of the mice in the Schumann et al. (1980)study], and w_2 = 0.037 kg for the male mice, and 0.032 kg for the female mice, in the NTP bioassay. The metabolized dose was adjusted for duration as exposure was only for 5 days per week.

[e] Hattis et al. (1987) equivalent PB-PK method.

[f] Total respired dose averaged over time in rats: TWA_d = C ppm x 6.78 mg/m^3/ppm x 6 h/24 h x 5 d/wk/7d/wk x 0.105 m^3/day x (body weight of assay animal (kg)/0.113 kg)$^{2/3}$ ÷ Body weight of assay animal. Note that inhalation rate is adjusted to represent the test animal.

[g] Data on total metabolites formed in Sprague-Dawley rats exposed by inhalation, obtained by Pegg et al. (1979), were used to derive metabolic parameters. Values used were V_{max} = 52.982 mg/kg-d, K_m = 273.32 ppm, w_1 = 0.25 kg [the mean body weight of the rats in the Pegg et al. (1979) study], and w_2 = 0.44 kg for the male rats, and 0.32 kg for the female rats, in the (NTP, 1986) bioassay.

Table E-3. Tumorigenic Potency of PCE: Summary of Values Based on Different Approaches to Dose Calculation (CAEPA, 1992) Using data from NTP, 1986

Species, sex, weight	TWA Administered dose[a]	Michaleis-Menton Metabolized dose mg/kg-d[b]	Tumor[c] Type	Tumor[c] Incidence	Potency as a function of TWA administered dose[d] q_1^* $(mg/kg/d)^{-1}$	Potency as a Function of Animal Metabolized Dose[e] (q_1^*) $(mg/kg/d)^{-1}$	Potency as a Function of Human Equivalent Metabolized Dose [f] (q_1^*) $(mg/kg/d)^{-1}$	Potency as a Function of Human Applied Dose [g] (q_1^*) $(mg/kg/d)^{-1}$	Unit Risk [h] $(\mu g/m^3)^{-1}$
B6C3F1 Male mice	0	0	Hepatocellular	16/49	0.0059	0.024	0.30	0.056	6.3×10^{-6}
	146.6	43.3	Adenoma and Carcinoma	31/47					
0.037 kg	293.2	61.4		40/50		0.022	0.28	0.052	**5.9×10^{-6} [i]**
B6C3F1 female mice	0	0	Hepatocellular	4/44					
	154.9	46.7	Adenoma and Carcinoma	17/42	0.0039	0.0098	0.13	0.024	2.8×10^{-6}
0.032 kg	307.8	65.8		38/47					
F344 Rat male	0	0	Mononuclear cell leukemia	28/50	0.004	0.064	0.35	0.065	7.4×10^{-6}
	143	11.8		37/48					
0.44 kg	286	17.2		37/50					
F344 Rat female	0	0		18/49	0.0026	0.040	0.24	0.044	5.1×10^{-6}
	154.9	14.0		30/50					
0.32 kg	307.8	20.0		29/50					

[a] and [b] see Table E-2

[c] Tumor incidence denominator excludes animals dying before the occurrence of the first corresponding tumor type observed in each study (source Table E-1)

[d] Slope factor (q_1^*) as a potential risk estimate is calculated using the a linearized multistage model and is the 95% upper confidence bound of the cancer potency. Here q_1^* is determined using the administered dose in the dose response analysis. This column is included to show that potency factors estimated using the administered doses are lower than those calculated using metabolized doses. No further analyses are performed on them. (Source CAEPA, 1992, Table 5-3)

[e] Potency calculated as function of animal metabolized dose. (Source CAEPA, 1992, Table 5-6)

[f] Slope factor is based on animal metabolized dose, and is adjusted by surface area interspecies dose extrapolation method: $(\text{human weight}/\text{animal weight})^{1/3}$. (Source CAEPA, 1992, Table 5-6).

[g] The slope factor is adjusted as a function of human applied dose using 18.5% (CA assumption) human metabolism at low environmental exposure levels. Presented in Table 5-6 (CAEPA, 1992) as LLNL assuming 25% metabolism. This value was adjusted to 18.5% metabolism by MassDEP (2007). Note: CAEPA initially used 25% as the values for low dose human metabolism in their 1992 draft report. In their final 1992 document 18.5% is noted as the final value, but calculations in some tables continue to rely on the 25% value.

[h] The potencies were converted to unit risk as follows: q_1^* (surface area)/mg/kg-d ÷ 1000 (μg/mg) x 20 m^3 (assuming a 70 kg person inhaling 20 m^3 air) x 0.4 (alveolar ventilation rate correction) ÷ 70 kg

[i] The slope factor derived based on Hattis et al. (1987) equivalent PB-PK method was selected by CAEPA (1992) as the final slope factor to calculate a unit risk value for PCE.

Appendix F

CAEPA: 1992 and 2001
Comparison of Methods Used for
Derivation of Unit Risk for PCE Using the
NTP (1986) Inhalation Study

Table F-1. Comparative Summary of the CAEPA (1992 and 2001) Slope Factors and Unit Risks[a]

Study	Species, Sex	Tumor site and Type	Potency as a Function of Human Equivalent Metabolized Dose [b] $(mg/kg/d)^{-1}$		Potency as a Function of Human Applied Dose $(mg/kg\text{-}d)^{-1}$		Unit Risk $(\mu g/m^3)^{-1}$	
			Cross species scaling factor $BW^{2/3}$ (1992)	Cross species scaling factor $BW^{3/4}$ (2001)	18.5% metabolism (1992)	58% metabolism (2001)[a]	1992	2001
NTP, 1986 Inhalation	Mouse, Male	Hepatocellular adenoma and carcinoma	0.28		0.052		**5.9×10^{-6}**	
Geometric mean of the four values below [c]						0.087		**9.9×10^{-6}**
NTP, 1986 Inhalation	Mouse, Male Female	Hepatocellular adenoma and carcinoma		0.19 0.071		0.11 0.04		1.26×10^{-5} 4.57×10^{-6}
NTP, 1986 Inhalation	Rat, Male Female	MCL		0.25 0.17		0.15 0.099		1.71×10^{-5} 1.13×10^{-5}

[a] The slope factors as functions of human applied doses were calculated by MassDEP for this evaluation by assuming 58% percent human metabolism of PCE at environmentally relevant exposure levels. CAEPA (2001) did not present unit risk values, but used the potency values derived for inhalation exposure to account for PCE contribution to total cancer risk from inhalation of volatiles in drinking water.

[b] Potency values from Table 5-6 (CAEPA, 1992, Hattis) and Table 12 of CAEPA (2001).

[c] CAEPA averaged the slope factors derived from the male and female mouse hepatocellular adenoma and carcinoma data and rat mononuclear cellular leukemia data in the NTP inhalation study stating that the differences between the slope factors were small. MassDEP typically relies on the most sensitive species and endpoint to calculate slope factors.

Appendix G

MassDEP (2007)
Derivation of Unit Risk for PCE Using the
Japan Industrial Safety Association (JISA, 1993) Inhalation Study

Table G-1. MassDEP Metabolized Dose Estimates Using the JISA (1993) Inhalation Study and Metabolized Dose Methodology (CAEPA, 1992, 2001)

Species, Sex	Applied Concentration ppm (C)	Daily Metabolized dose (M) (mg/kg-d)	
		Animal Metabolized Dose [a]	**Human Equivalent Metabolized Dose $(bw_a/bw_h)^{1/4}$ [b]**
Male Mice 0.043kg	0 10 50 250	0 6.20 25.14 62.53	0 0.97 3.91 9.76
Female Mice 0.034 kg	0 10 50 250	0 7.23 28.59 69.73	0 1.07 4.24 10.09
Male Rat 0.44 kg	0 50 200 600	0 4.12 11.82 20.22	0 1.16 3.33 5.69
Female Rat 0.32 kg	0 50 200 600	0 5.00 14.00 23.29	0 1.3 3.64 6.06

[a] Metabolized dose M calculated using Michaelis-Menton equation where:

$$M = \frac{D \times K_m \ (w_1/w_2)^{1/3}}{D + K_m \ (w_2/w_1)^{1/3}}$$

Where D = inhaled concentration in ppm, M = total metabolites formed (mg/kg-day), V_{max} = maximum rate of metabolism (mg/kg-day) and K_m = apparent Michaelis constant (ppm). The parameter w_1 is the body weight of the animals used in the calibration experiment and w_2 is that of the animals to be simulated (i.e., those in the bioassay).
For mice, values used were V_{max} = 170 mg/kg-d, K_m = 126 ppm, w_1 = 0.0245 kg [the mean body weight of the mice in the Schumann et al. study], and w_2 = 0.043 kg for the male mice, and 0.034 kg for the female mice, in the JISA (1993) bioassay.
For rats, values used were V_{max} = 52.982 mg/kg-d, K_m = 273.32 ppm, w_1 = 0.25 kg [the mean body weight of the rats in the Pegg et al. (1979) study], and w_2 = 0.44 kg for the male rats, and 0.32 kg for the female rats, in the JISA (1993) bioassay. Body weights from the JISA (1993) study were estimated from terminal growth curves and were judged to be equivalent to the terminal body weights in the NTP (1986) bioassay.
[b] Human equivalent metabolized is derived using a cross species scaling factor $(bw_{animal}/70 \text{ kg})^{1/4}$ with the body weight equal to the average terminal body weight of the animal group.

Table G-2. MassDEP Carcinogenicity Risk Assessment Based on the JISA (1993) Inhalation Study Using Metabolized Dose Methodology (CAEPA, 1992, 2001)

	Human Equivalent Metabolized Dose [a] (mg/kg-d)	Tumor Incidence [b]	Potency as a function of human equivalent metabolized dose [c] $(mg/kg\text{-}d)^{-1}$	Potency as a function of human applied dose (61% metabolism) [d] $(mg/kg\text{-}d)^{-1}$	Unit Risk [e] (ug/m^3)
Crj-BDF1Mice – Hepatocellular Adenoma or Carcinoma					
Male 0.043kg	0 0.97 3.91 9.76	13/46 21/49 19/48 40/49	0.099	0.060	6.9×10^{-6}
Female 0.034 kg	0 1.07 4.24 10.09	3/50 3/47 7/48 33/49	0.042	0.025	2.9×10^{-6}
F344 Rats - Mononuclear Cell Leukemia					
Male 0.44 kg	0 1.16 3.33 5.69	11/50 14/50 22/50 27/50	0.1336	0.081	9.3×10^{-6}
Female 0.32 kg	0 1.3 3.64 6.06	10/50 17/50 16/50 19/50	0.069	0.042	4.8×10^{-6}

[a] See Table G-1.
[b] Tumor incidence adjusted for early mortality.
[c] Slope factor calculated using the US EPA benchmark dose software, version 1.4.1 multistage model (USEPA, 2007) and is the 95% upper confidence bound of the cancer potency. Here slope factor is determined using human equivalent metabolized dose in the dose response analysis.
[d] The slope factor derived from human equivalent metabolized dose is adjusted as a function of human applied dose using 61% human metabolism at low environmental exposure levels.
[e] The potencies were converted to unit risk as follows: slope factor (mg/kg-d) ÷ 1000 (µg/mg) x 20 m^3 (assuming a 70 kg person inhaling 20 m^3 air) x 0.4 (alveolar ventilation rate correction) ÷ 70 kg.

Table G-3. MassDEP Carcinogenicity Risk Assessment Based on the JISA (1993) and NTP Inhalation Studies Using Duration Adjusted Applied Concentration and Rat Mononuclear Cell Leukemia (MCL) Data

	Exposure Concentration (ppm)	HEC (ppm) [a]	Incidence of MCL [b]	Potency as a function of HEC [c] $(ppm)^{-1}$	Unit risk $(\mu g/m^3)^{-1}$ [d]
JISA (1993) F344/Dcrj Rats					
Male	0 50 200 600	0 9 36 108	11/50 14/50 22/50 27/50	0.0077	1.1×10^{-6}
Female	0 50 200 600	0 9 36 108	10/50 17/50 16/50 19/50	0.0038	5.5×10^{-7}
NTP (1986) F344 Rats					
Male	0 200 400	0 36 72	28/50 37/48 37/50	0.015	2.2×10^{-6}
Female	0 200 400	0 36 72	18/50 30/50 29/50	0.011	1.6×10^{-6}

[a] Human equivalent concentration for a category 3 gas assuming blood air partition coefficient is 1 is equivalent to the applied exposure concentration in ppm, x 5d/7d, 6h/24h over 2-years.
[b] Early mortality adjusted tumor incidence.
[c] Slope factor as a potential risk estimate is calculated using the US EPA benchmark dose software, version 1.4.1 multistage model (USEPA, 2007) and is the 95% upper confidence bound of the cancer potency.
[d] The potencies were converted to unit risk as follows: slope factor ÷ (6.78 mg/m^3 x 1000 μg/mg).

Table G-4. MassDEP Carcinogenicity Risk Assessment Based on the JISA (1993) and NTP (1986) Inhalation Studies Using Applied Concentration and Mouse Hepatocellular Adenoma or Carcinoma Data (WHO, 2006)

Mice	Exposure Concentration (ppm)	HEC (ppm) [a]	Incidence of Hepatocellular adenoma or carcinoma [b]	Potency as a function of HEC [c] $(ppm)^{-1}$	Unit risk [d] $(\mu g/m^3)^{-1}$
JISA (1993) Crj-BDF1 mice (WHO, 2006)					
Male	0 10 50 250	0 1.8 9 45	13/46 21/49 19/48 40/49	0.035	5.1×10^{-6}
Female	0 10 50 250	0 1.8 9 45	3/50 3/47 7/48 33/49	0.023	3.3×10^{-6}
NTP (1986) B6C3F1 mice (MassDEP, 2007)					
Male	0 100 200	0 18 36	16/49 31/47 40/50	0.047	6.8×10^{-6}
Female	0 100 200	0 18 36	4/44 17/42 38/47	0.034	5.0×10^{-6}

[a] Applied exposure concentration in ppm, x 5d/7d, 6h/24h over 2-years
[b] Early mortality adjusted tumor incidence as reported by WHO (2006).
[c] Slope factor as a potential risk estimate is calculated using the USEPA benchmark dose software, version 1.4.1 multistage model (USEPA, 2007) and is the 95% upper confidence bound of the cancer potency
[d] The potencies were converted to unit risk as follows: slope factor ÷(6.78 mg/m^3/ppm x 1000 μg/mg).

Table G-5. Summary of Slope Factors and Unit Risks Calculated from the NTP (1986) and JISA (1993) Studies Using Either Metabolized Dose or Applied Concentration

Study, Agency	Potency as a function of human equivalent metabolized dose $(bw_h/bw_a)^{1/4}$ $(mg/kg/d)^{-1}$	Potency as a function of human applied dose assuming 58% metabolism at low doses $(mg/kg/d)^{-1}$	Unit Risk (UR) $(\mu g/m^3)^{-1}$
NTP (1986) CAEPA, 2001 male mouse liver tumor	0.19	0.11 (58% metabolism) 0.12 (61% metabolism)	1.3×10^{-5} [a] 1.3×10^{-5}
NTP (1986)- CAEPA, 2001 Geometric mean of male and female mouse liver tumor and rat leukemia potencies	0.15	0.087 (58% metabolism) 0.091 (61% metabolism)	9.9×10^{-6} [a] 1.0×10^{-5}
NTP (1986) CAEPA, 1992 male mouse liver tumor	0.28 $(bw_{human}/bw_{animal})^{1/3}$	0.050 (18.5% metabolism)	5.9×10^{-6} [b]
JISA (1993) male mouse liver tumor	0.099	0.057 (58% metabolism) 0.06 (61% metabolism)	6.5×10^{-6} 6.9×10^{-6}
NTP (1986) MassDEP, 2007 male mouse liver tumor	Slope = 0.047/ppm (applied concentration - HEC)	NA	6.8×10^{-6}
JISA (1993) WHO, 2006 male mouse liver tumor	Slope = 0.035/ppm (applied concentration -HEC)	NA	5.1×10^{-6} [c]

[a] Although CAEPA used updated value in their Public Health Goal (PHG) derivation, they have not formally derived a unit risk value. The unit risk of 1.3×10^{-5} per ug/m^3 is based on the male mouse liver data, while the unit risk of 9.9×10^{-6} per ug/m^3 is based on the average of the slope factors as recommended by CAEPA (2001).
[b] Current CAEPA number.
[c] WHO (2006) number
NA = not applied.

Table G-6. Summary of Potency Factors and Unit Risk Values Derived by Various Groups Based on Cancer Bioassays in Rats and Mice

Agency	Bioassay and exposure route,	Species Strain, sex	Tumor type	Dosimetric	Cross species extrapolation	Human Potency	Human % metabolized	Unit Risk ($\mu g/m^3$) $^{-1}$
MassDEP, 1990	NCI, 1977 oral	$B6C3F_1$ mice/F344 rat male	Liver tumor	Metabolized	$mg/kg^{2/3}$	0.21	70%	**5.52×10^{-5} [a]**
NESCAUM 1986; Strauss, 1992	NTP, 1986 inhalation study	Mice, rats	Liver tumor	Metabolized	$mg/kg^{2/3}$	range	(1) Assuming 100% metabolism in mice and humans, (2) 100% in mice and 70% in humans, (3) 20% in mice and 70% in humans	1×10^{-5} to $1\ 10^{-4}$
CAEPA, 1992	NTP, 1986 inhalation	$B6C3F_1$ mice, male	Liver tumor	Metabolized	$mg/kg^{2/3}$	0.28	18.5%	5.9×10^{-6} [b]
CAEPA 2001	NTP, 1986 inhalation	B6C3F1 mice, male	Liver tumor	Metabolized	$mg/kg^{3/4}$	0.19 [c]	61%	1.3×10^{-5}
MassDEP, 2007	NTP, 1986 inhalation	B6C3F1 mice, male	Liver tumor	Applied concentration (HEC)	NA	0.047/ppm	NA	6.8×10^{-6}
CAEPA 2001	NTP, 1986 inhalation	F344 rat, male	MCL	Metabolized	$mg/kg^{3/4}$	0.25 [c]	61%	**1.7×10^{-5} [d]**
MassDEP, 2007	NTP, 1986 inhalation	F344 rat, male	MCL	Applied concentration (HEC)	NA	0.015	NA	2.2×10^{-6}
MassDEP, 2007	JISA, 1993 inhalation study	Crj-JBDF male mice	Liver tumor	Metabolized	$mg/kg^{3/4}$	0.099	61%	6.9×10^{-6}
WHO, 2007	JISA, 1993 inhalation study	Crj JBDF1mice, male	Liver tumor	Applied concentration (HEC)	NA	0.035/ppm	NA	**5.2×10^{-6} [e]**
MassDEP, 2007	JISA, 1993 inhalation study	F344 rat, male	MCL	Metabolized	$mg/kg^{3/4}$	0.134	61%	**9.3×10^{-6} [d]**
WHO, 2006	JISA, 1993 inhalation study	F344 rat, male	MCL	Applied concentration (HEC)	NA	0.007/ppm	NA	1.1×10^{-6}

[a] Current MassDEP unit risk. [b] Current CAEPA unit risk (CAEPA, 1992). [c] MassDEP calculated the unit risk using 61% for the estimated human metabolized fraction and the potency derived by CAEPA (2001) that used mouse liver tumor data and a time to tumor dose-response model that yields slightly different cancer slope factors from the multistage cancer model in BMDS. CAEPA (2001) used the geometric mean (0.15/mg/kg-d) of the potencies from rat and mouse bioassays for inhalation unit risk derivation.
[d] MassDEP recommends using the average of these two unit risks, yielding a unit risk of $1 \times 10^{-5}/\mu g/m^3$. [e] WHO (2006) unit risk. NA = Not applied.

Appendix H

Brief Critique of Covington et al., 2007 Paper

In their analysis Covington et al. (2007) used data on PCE metabolism to TCA (rather than total metabolism) from a total of 14 adult subjects from three different inhalation exposure studies. These included data from Volkel et al. (1998), in which 6 adult subjects were exposed to PCE at 10, 20 or 40 ppm for 6 hours. Blood and urine TCA were measured post exposure. Group data was used in the analysis as no individual data were available, limiting assessment of inter-individual variability. Secondly, data on urinary TCA excretion from 2 subjects exposed to 150 ppm of TCE for 8 hours, as reported by Fernandez et al. (1976), was also included in the analysis. Data from the remaining 22 subjects in the Fernandez et al. study were excluded as "the majority of the data were (only) for post exposure alveolar concentrations of PCE, which ….can be problematic for estimating kinetic parameters". However, alveolar concentrations of PCE provide a useful estimate of the total fraction of PCE metabolized and could have provided additional empirical data to evaluate modeling results.

Lastly, some of the data from 6 subjects exposed to 72 or 144 ppm PCE for 4 hours was included from Monster et al. (1979). Again individual data was not used. In this case the authors included only the urinary TCA concentration data reported by Monster et al. but excluded the data on concentrations of TCA in the subject's blood. The rationale for this is stated as, "a preliminary evaluation performed with a one compartment PK model for TCE determined that it was not possible to reproduce the urinary excretion of TCA reported in the study using the reported blood concentrations of TCA from the same study together with the published PK parameters for TCA." However, the "published PK parameters" for TCA cited were derived from studies using trichloroethylene (TRI). Chui et al. (2007) note the many metabolites of TRI and the fact that TCA from TRI metabolism appears to be predominantly derived from back conversion of TCOH, complicate conclusions regarding the consistency or inconsistency of TCA kinetics across TRI and PCE studies. The lack of model fit therefore may be due to limitations of the model and/or the parameters used rather than the empirical data.

To improve the model output fit to the observed data included in the analysis, Covington et al. (2007) also modified the PK model of Gearhart et al. (1993), to include assumed metabolism and direct excretion of PCE metabolite by the kidney. The kidney metabolic activity was assumed to be 10% of that estimated for the liver. Inclusion of a kidney metabolism parameter was not supported by empirical data. Other than improved model fit, the only evidence in support of including a kidney metabolism term was, as stated by the authors, that "while agreement of the modified model with the data on TCA excretion does not in itself demonstrate that the kidney contributes to the metabolic clearance of PCE, such a possibility is supported by data indicating that several CYP isoforms (P450 enzymes) contribute to the metabolism of anesthetics in the human kidney". While kidney metabolism may in fact be occurring, it is also possible that the discrepancy between model outputs and the limited empirical data used in the assessment is due to limitations in the model.

Because of these issues, ORS believes that the assessment by Covington et al. (2007) is likely to underestimate the range of uncertainty in modeled human PCE metabolism. This

conclusion is supported by a recent paper assessing metabolism following human PCE exposures at lower concentrations than previously tested (Chui et al. 2007). In this study 6 adult male subjects from 22 to 52 years of age were exposed to 1 ppm PCE for 6 hours. The *average* recovery of PCE by exhalation was calculated to be about 82%, indicating average total metabolism of about 18%. The authors note that uncertainty and variability were substantial in this assessment so an upper bound estimate would be substantially higher.

ORS has therefore decided not to rely on the cited 95th percentile value of 2.1% for human metabolism of inhaled PCE from the Covington et al. paper. Instead, ORS has determined that the upper 95th percentile value of 61% derived by Chiu and Bois, 2006 is an appropriate health protective estimate for human population metabolism of PCE at low exposure concentrations. This paper updated the 1996 analyses of the Monster et al. 1979, data, which was the basis of CAEPA's decision to use a 58% metabolism value for humans. The more recent Chui and Bois analysis used an "improved Markov Chain Monte Carlo (MCMC) sampler, longer MCMC chains and additional convergence checks". The updated upper 95th percentile estimate for fractional human metabolism at low exposure concentrations derived from this analysis was 61%, with a median of 26% and a lower bound of 2%.

Appendix I

Benchmark Dose Analysis Modeling Summaries
(see document: Appendix I- BMDS output.xls)