Maximum Contaminant Level (MCL) Determination for

Trichloroethylene

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Connecticut Department of Public Health
Environmental and Occupational Health Assessment Program

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Abbreviations

ADAF – age-dependent adjustment factor; ADH – alcohol dehydrogenase; ALDH – aldehyde dehydrogenase; AMET – amount metabolized; ATSDR – Agency for Toxic Substances and Disease Registrry; AUC – area under the curve; BMDL – benchmark dose lower limit; CGS – Connecticut General Statute; CT DPH – Connecticut Dept of Public Health; CTDEEP – Connecticut Dept of Energy and Environmental Proection; CYP – cytochrome P-450; DCA – dichloroacetic acide; DCVG – dichlorovinylglutatione; GST – glutathione transferase; HBV – health-based value; HCC – hepatocellular carcinoma; HED – human equivalent dose; IRIS – Integrated Risk Information System; LED_{10} – lowest effective dose at the 10% effect level; LOAEL – lowest observed adverse effect level; MCL – maximum contaminant level; MCLG – MCL goal; MOA – mechanism of action; MRL – minimum risk level; NAS – National Academy of Science; NAT – n-acetyltransferase; NCI – National Cancer Institute; NHL – non-hodgkin's lymphoma; NJDEP – New Jersey Dept of Environmental Protection; NSRL – no significant risk level; NTP – National Toxicology Program; OEHHA – California Office of Environmental Health Hazard Assessment; OR – odds ratio; PBPK – physiologically based pharmacokinetic; PCE – perchloroethylene; PHG – public health goal; RfC – reference concentration; RfD – reference dose; TCA – trichloroacetic acid; TCE – trichloroethylene; TWA – time-weight averaged; USEPA – United States Environmental Protection Agency;

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Executive Summary

Trichloroethylene (TCE) is a groundwater contaminant found in Connecticut that is associated with a federal Maximum Contaminant Level (MCL) of 5 ug/L. This document describes the scientific basis for creating a state of Connecticut MCL for TCE of 1 ug/L. Recent analyses by USEPA indicate increased evidence for human cancer risk and developmental toxicity that have led to new TCE cancer and non-cancer potency values (USEPA IRIS 2011). The Connecticut Dept of Public Health (CT DPH) has evaluated the risks associated with the current federal MCL in light of these new IRIS potency values. Using standard exposure assumptions the MCL is associated with elevated cancer risk and borderline to elevated non-cancer risk. The cancer risk estimate is further increased by consideration of children's exposure based upon a mutagenic mode of action, and also by considering inhalation exposure. These factors combine to create a cancer risk that is 9 to 21 times greater than de minimis (1 in a million) cancer risk. Non-cancer developmental risk estimates are of elevated concern when considering that the MCL can be associated with a single quarterly monitoring result as high as 20 ug/L and still be acceptable on an annualized basis. TCE developmental risks are relevant to time frames as short as days to weeks of exposure. The findings of elevated cancer and non-cancer risk at the federal MCL led to the derivation of a draft state of Connecticut MCL of 1 ug/L. While risk-based approaches yield drinking water targets below 1 ug/L, detection and other feasibility and policy considerations bring the draft MCL to the proposed value. This value will substantially address both cancer and non cancer risks attributable to TCE in drinking water and has been demonstrated to be both feasible and practical based on the fact that NJ has successfully implemented an MCL of 1 ug/L for many years. When the public health benefit of decreasing TCE in public supplies to 1 ug/L is considered from a cost/benefit perspective, DPH's analysis finds a net benefit.

Background

Trichloroethylene (TCE) is a degreasing solvent that has been extensively used to clean metal parts and machinery and is still used for these purposes today. Prior to 1960 it had also been used in the dry cleaning industry. Uses in consumer products such as adhesives, typewriter correction fluid, spot remover, carpet cleaner, paint stripper and automotive degreasing fluid, have been eliminated in most cases. The historic industrial and commercial uses were associated with spills and discharges that have led to soil and groundwater contamination at locations around Connecticut. Numerous public and private drinking water supplies have been impacted with treatment in place to remove TCE at some of these locations.

The federal Maximum Contaminant Level (MCL) for TCE is 5 ug/L and since TCE is carcinogenic, its MCL-G (goal) established by USEPA is zero. TheMCL was derived in the 1980s and was based upon the practical quantitation level that was obtainable at laboratories across the country at the time. Since that time TCE's carcinogenic concerns have increased with greater evidence for human renal cancer and USEPA has derived an oral cancer potency value on IRIS (2011a, 2011b) of 0.05/mg-kg-d; this value is 5 times above (more potent) than former estimates (USEPA, 2011b). The recent IRIS derivations take into consideration comments from the National Academy of Sciences which provided recommendations for TCE dose response (NAP 2006) and USEPA Science Advisory Board which reviewed USEPA's draft IRIS document (USEPA/SAB 2011).

The need for an updated TCE MCL was acknowledged recently by USEPA based upon its toxicological effects and the ability for modern laboratories to reliably measure TCE in drinking water at concentrations below the MCL (USEPA, 2010). The last update to the USEPA Office of Water website on these compounds stated (Jan 2011): "TCE and PCE are volatile organic compounds used in industrial and/or textile processing. In March, 2010, EPA determined that scientific advances allow for stricter regulations for these carcinogenic compounds and announced that the agency would initiate rulemaking efforts to revise the standards using the strategy's framework." However, that process will take 2 to 5 years to complete, which leaves the possibility that some consumers of public water in Connecticut may be drinking TCE concentrations that are not adequately health protective while USEPA further deliberates the TCE MCL.

The current document describes an evaluation of the current federal MCL and the development of a draft Connecticut MCL for TCE of 1 ug/L. The draft MCL is consistent with the New Jersey state MCL which has been in effect since the 1980s. The draft MCL for Connecticut is a follow-up to the state drinking water Action Level determination for TCE (CT DPH 2011). This document expands upon and updates that determination. The Action Level is used by CT Dept of Energy and Environmental Protection (DEEP) in evaluating groundwater contamination affecting private wells under CGS Section 22a-471, and also provides guidance to local health departments and private citizens who need to understand the results of private well testing. The new MCL will harmonize drinking water targets across private wells and public supplies.

TCE Toxicology

TCE causes a variety of toxic, developmental and carcinogenic effects with the liver and kidney being important target organs for both cancer and non-cancer effects. While TCE's carcinogenic effect is the main risk driver for chronic exposure, developmental toxicity is key to the consideration of short-term risk. There are a range of other non-cancer health effects that have been considered in USEPA's recent reference dose (RfD) development including neurotoxicity, liver damage, kidney damage and immunotoxicity. USEPA's 2011 IRIS posting for TCE included an inhalation unit risk cancer potency based upon rodent and human inhalation studies (4E-06/ug-m3), an oral cancer potency factor extrapolated from the inhalation value (0.05/mg-kg-d), an RfD based upon oral studies in rodents (0.0005 mg/kg/d) and a reference concentration (RfC) that was extrapolated across dose route from the RfD (2 ug/m3). TCE's carcinogenic effect is the main risk driver for chronic exposure as seen by comparing the de minimis (1 in a million) inhalation cancer risk level (0.2 ug/m3) with the inhalation RfC (2 ug/m3, 10 fold higher). Regarding oral exposure, the de minimis cancer risk is achieved with a drinking water concentration of 0.5 ug/L (USEPA, IRIS, 2011a) while the RfD would yield a drinking water target of 3.5 ug/L under standard adult ingestion assumptions (2 L/day ingestion for 70 kg body wt, relative source contribution = 0.2). These simple comparisons suggest that if the drinking water MCL is set at or near de minimis cancer risk that it will also be protective of most non-cancer endpoints as well (Note: see section below for discussion of de minimis risk level in Connecticut). Drinking water targets based upon developmental endpoints (e.g., cardiac defects, immune effects) should not involve long-term averaging of daily dose (as is done for cancer risk) and so the estimate of exposure and perhaps also risk may be

underestimated on a lifetime average dose basis. Thus in a changeable drinking water scenario in which TCE concentrations are variable over time, the developmental endpoint might lead to greater exposure and higher risk than would the carcinogenic effect.

Carcinogenic Effects

TCE has been described by USEPA as "carcinogenic to humans" based on "convincing epidemiologic evidence of a causal association between human exposure and cancer" (USEPA, 2011b). This designation relies upon evidence in humans as well as positive findings in animal studies for several of the same cancer targets seen in humans (liver, kidney, lymphohematopoietic) (Maltoni 1988; NCI 1976; NTP 1990; Fukuda 1983; Wartenberg 2000; Bruning 2003; Charbotel 2006). Animal studies evaluating TCE's ability to induce tumors is summarized in Table 1. TCE has tested positive in rodent oral gavage and inhalation studies with mouse liver and rat kidney being targets in more than one assay and by more than one dose route (Table 1). Other tumor sites that have been reported in animals are the lung and lymphohematopoietic system (leukemia). USEPA's toxicity assessment includes separate calculation of TCE potency for the bioassays and endpoints shown in Table 1.

The human evidence of TCE-induced carcinogenesis is extensive although not entirely consistent. Table 2 summarizes the results of a meta-analysis of the earlier literature as published by Wartenberg in 2000. This table provides evidence for an association of TCE with human renal, liver and leukemia/lymphoma tumors. The table shows that not all studies were positive but that when compiled into the Wartenberg (2000) meta-analysis the overall odds ratio was significant for these endpoints. In USEPA's updated review of the epidemiology data (2011b), the Agency first conducted a systematic review to develop a weight of evidence assessment of the human data and from there chose three endpoints for more detailed meta-analysis: kidney cancer, liver cancer, and non-Hodgkins lymphoma (NHL). Their systematic review of the available epidemiology literature found that 24 studies fulfilled its requirements for inclusion in meta-analysis. These studies included 17 reporting relative risks for NHL yielding an overall relative risk of 1.23 (lower to upper bound 1.07-1.42) (Figure 1). Meta analysis of human kidney cancer yielded a relative risk of 1.27 (1.13-1.43, Figure 2) while the result for liver cancer yielded a relative risk of 1.29 (1.07-1.56, Figure 3). The epidemiological link to NHL has been further documented in a meta-analysis involving 19 workplace studies where TCE was specifically assessed (Karami et al. 2013). The NHL

relative risk was 1.32 (1.14-1.54) while the risk for other lymphatic or hematopoietic cancers was not linked to TCE.

Table 1. TCE Cancer Bioassay Results – Main Findings in Rats and Mice

Study and Doses	Species/Strain	Tumor Type	Control	Low Dose[a]	High Dose
NCI, 1976 gavage 0,1200, 2400 mg/kg/d	Mice/B6C3F1	HCC (male) HCC (female)	5% 0%	52% 8%	65% 23%
NTP 1990 gavage 0 or 1000 mg/kg/d	Mice/B6C3F1	HCC (male) HCC (female)	29% 13%	NA NA	78% 45%
NTP(1988) gavage 0, 500, 1000 mg/kg/d	Rats / 5 strains – pooled results August rats	Renal (males) Renal (females) Leukemia (female)	0% 1% 2.2%	7% 4% 0%	5% 2% 18%
Maltoni (1988) inhl 0, 113, 338, 675 mg/m^3	Rats / S-D	Renal (male) Renal (fem)	0% 0%	0%, 0% 0%, 0%	3% 1%
Maltoni (1988) inhl 0, 113, 338, 675 mg/m^3	Mice/B6C3F1	Hepatoma (male) Hepatoma (female)	2% 3%	3%, 8% 4%, 5%	16% 11%
Fukuda, 1983 inhal 0, 50, 150 or 450 ppm	Mice/B6C3F1	Lung (female)	2%	6%,16%	15%

[a]In studies with a low and mid dose, both results are shown in this column.
HCC = hepatocellular carcinoma

Table 2. Summary of Epidemiological Associations for TCE and Cancer (Extracted from Wartenberg et al. 2000)

Cancer Endpoint	+ Studies/Total	Influential Studies	Population	Meta Odds Ratio
Kidney	2/5 Tier 1 cohorts	Henschler 1995 OR = 8 (3.4-18.6)	259 German cardboard workers	1.7 (1.1-2.7)
Kidney	1/1 Tier 2 cohorts	Sinks 1992 OR = 3.7 (1.7-8.1)	US paperboard printing workers	NA Only 1 study
Liver	1/3 Tier 1 cohorts	Antilla 1995 OR = 2.3 (1.0-5.3)	3089 Finnish TCE-exposed workers	1.9 (1.0-3.4)
Liver	1/3 Tier 2 cohorts	Dubrow 1987 OR=3.0 (1.1-6.7)	Rhode Island jewelry workers	2.0 (1.3-3.3)
Lympho-hematopoietic	1/3 Tier 1 cohorts	Antilla 1995 OR = 1.5 (1.0-2.3)	3089 Finnish TCE-exposed workers	1.4 (1.0-2.0)
Leukemia	3/6 Community	Cohn 1994 OR = 1.4 (1.1-1.9)	Cancer statistics for 75 NJ towns	Not calculated

Figure 1. USEPA (2011) meta-analysis of NHL Risk from 17 case-control and cohort studies.

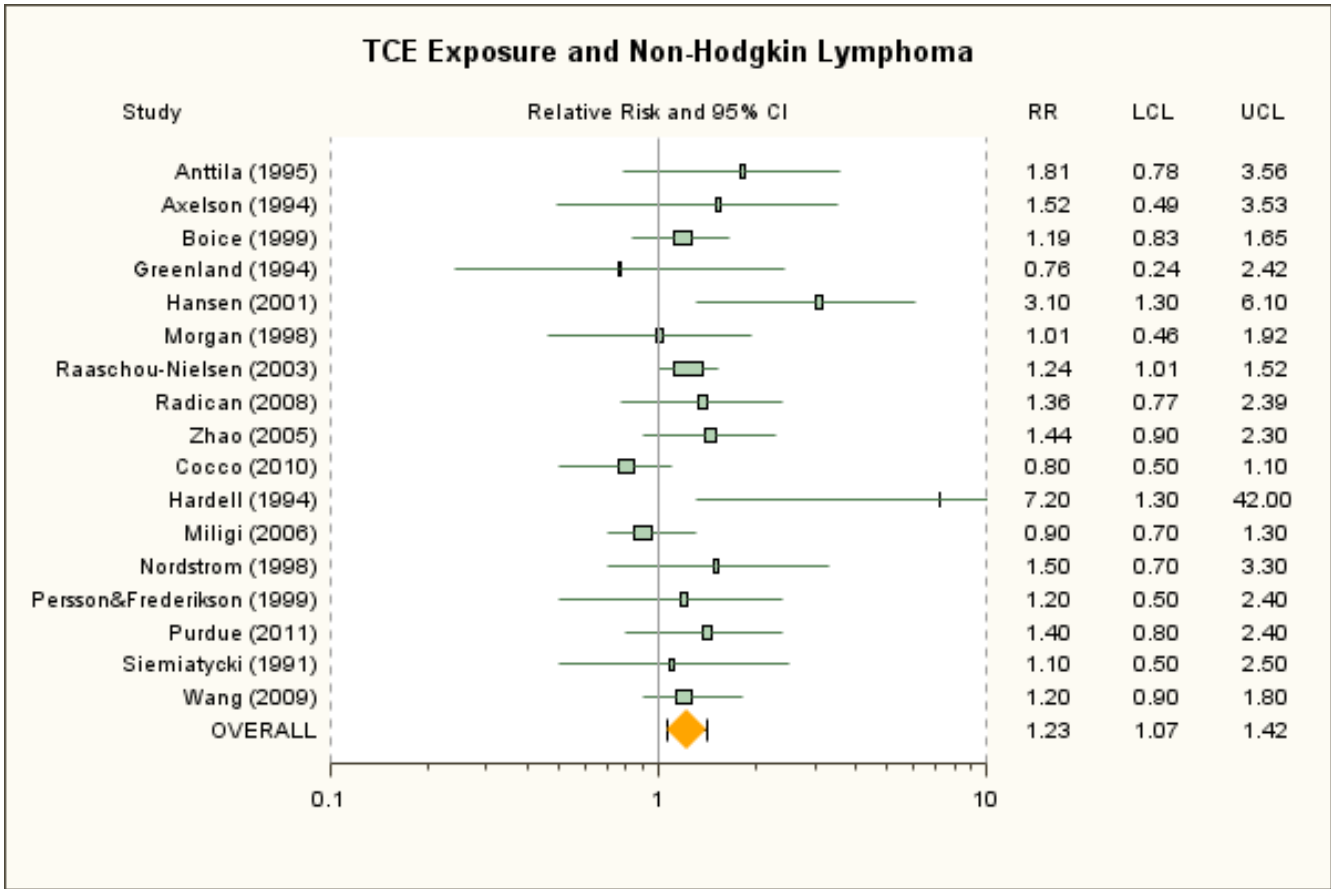


Figure 2. USEPA (2011) meta-analysis of kidney cancer risk from 15 case-control and cohort studies.

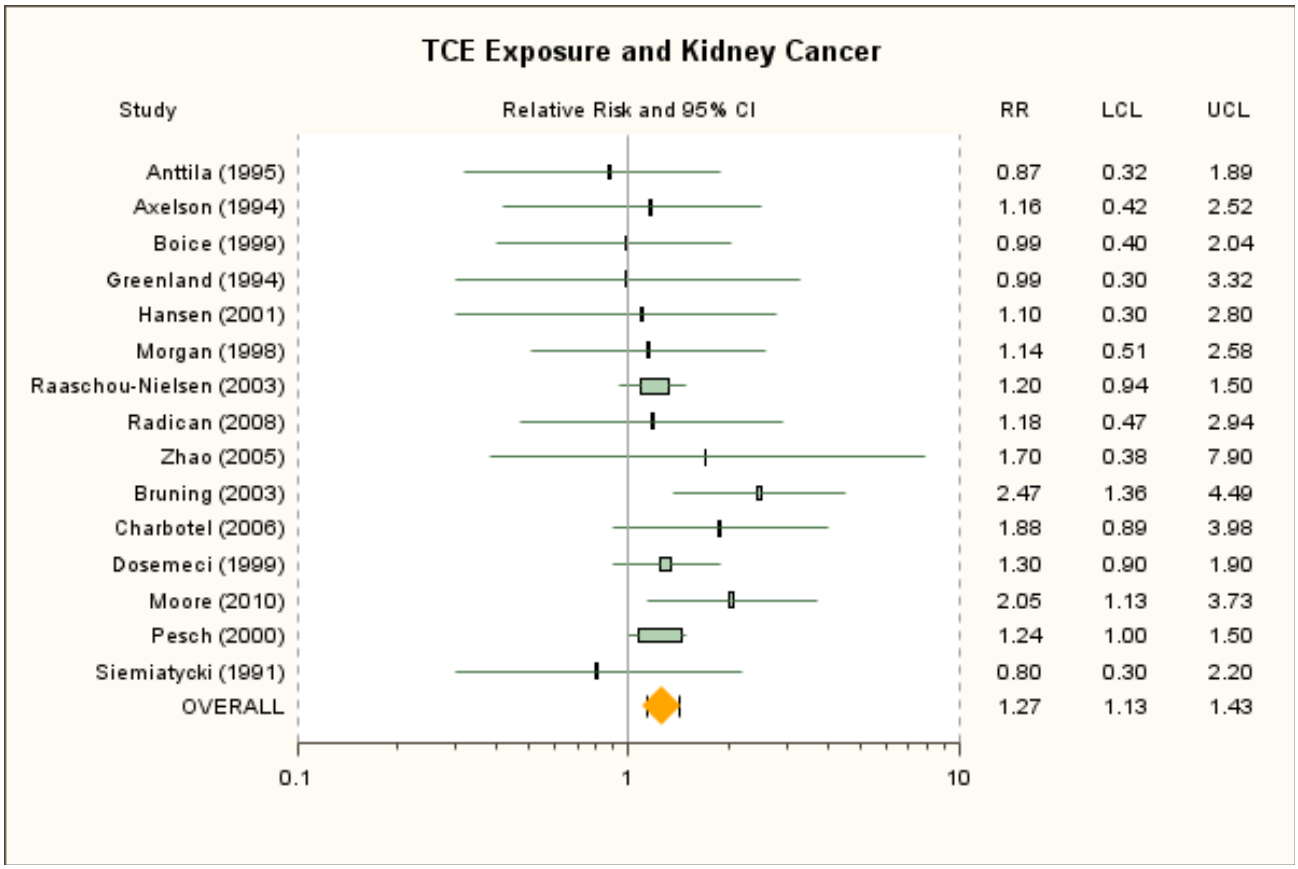
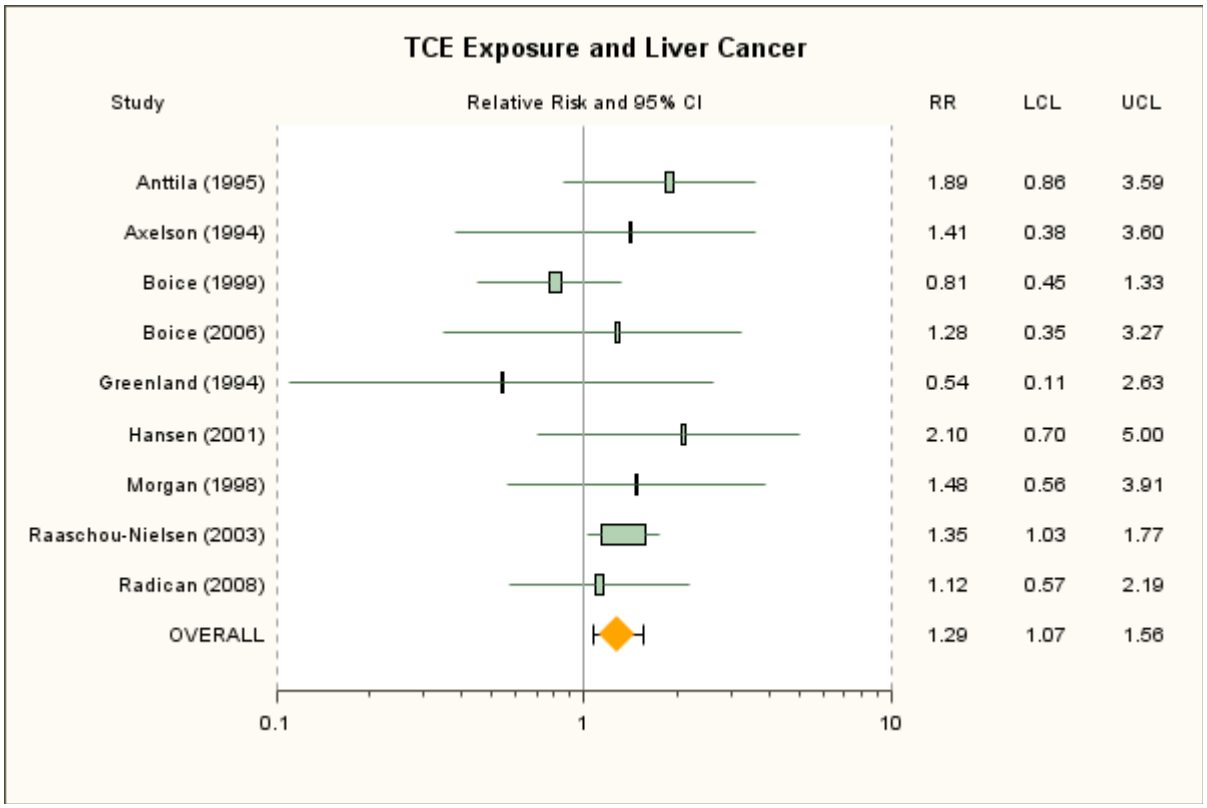


Figure 3. USEPA (2011) meta-analysis of liver cancer risk from 9 case-control and cohort studies.



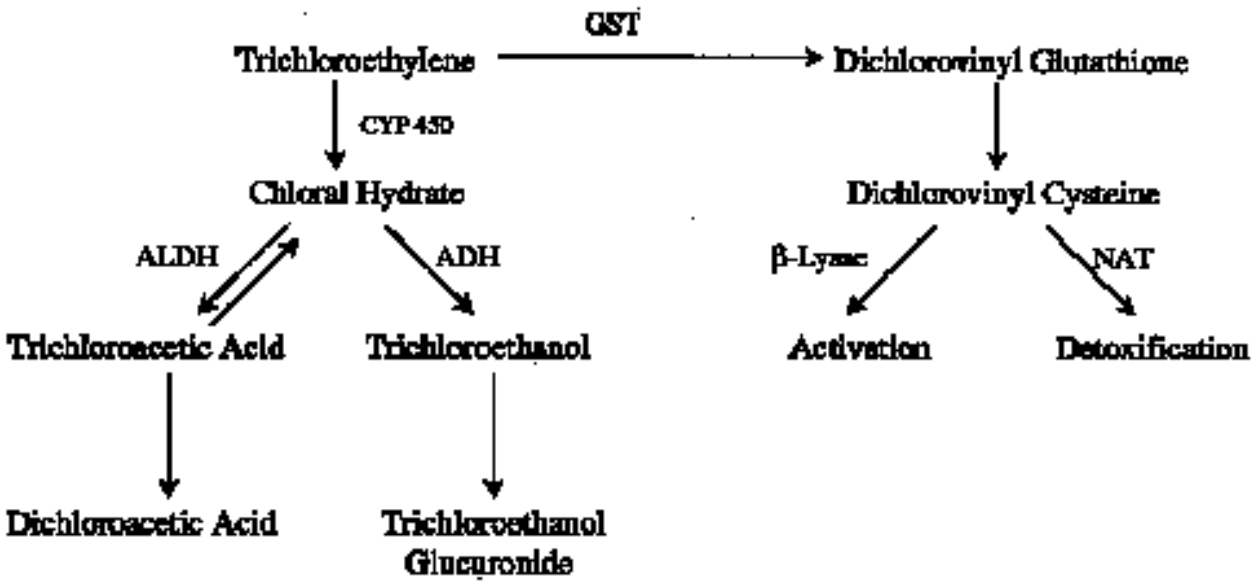
The USEPA (2011b) analysis found that the studies with the highest and most defined exposure to TCE showed the greatest odds ratios and utility for risk assessment. Kidney cancer has perhaps the most compelling combination of human, animal and mechanistic information. The key epidemiology studies include Charbotel et al. (2006), in which 87 renal cancer cases were evaluated relative to 316 controls from a population in the Arce Valley region of France, an area known for its metal working and high solvent exposures. Exposure assessment involved worker history questionnaires along with workplace air measurements and urinary biomonitoring. TCE was associated with a tripling of the odds ratio when exposure was considered as a composite of both cumulative dose and periods of peak exposure. Another population-based case control study was of the Arnsberg region of Germany, also an area of high industrial use of TCE (Bruning et al. 2003). This study involved 134 cases and 401 controls as identified from hospital records in the Arnsberg region. Renal cancer cases were 2.5 times more likely to come from the worker group with the greatest TCE exposure than from the reference group. Zhao et al. (2005) evaluated the mortality records of over 11000 workers in the aerospace industry employed by

Rockwell/Rocketdyne in Ventura CA. TCE exposure was characterized via industrial hygienist ranking of job exposure matrix for TCE and a variety of other toxicants. Overall, the Zhao et al. (2005) dataset was associated with a relative risk of 1.7 in TCE exposed subjects but workers with a high cumulative TCE exposure score had a 4.9 fold elevated risk of renal cancer in comparison to the low exposure worker group, and this risk increased to 7.4 in those with a 20 year lag between exposure and evaluation. This latter result was not statistically significant due to the small number of workers meeting this lag period criterion.

Support for the finding of human renal cancer from workplace TCE comes from follow-up molecular studies of renal cancer cases. For example, mutations in a tumor suppressor gene, the von Hippel-Lindau (VHL) gene, occurred in 100% of the kidney cancers from German TCE workers involved in metal degreasing and other related industries (N=23) (Bruning et al. 1997). Renal cancer from cases unexposed to TCE normally carry VHL mutations in less than half of the cases and these VHL mutations are in exon 2, whereas the mutations associated with TCE were in exons 1, 2 and 3 (Bruning et al. 1997). Similarly, a unique exon 1 VHL mutation was found in a renal cancer from a patient with chronic TCE exposure (Wells et al. 2009). However, not all studies of TCE exposed renal cancer patients have found unique VHL mutations (Charbotel et al. 2007).

While the mechanism of action for TCE carcinogenesis has not been firmly established for any of the cancer endpoints, the kidney evidence is compatible with the concept of TCE formation of genotoxic metabolites from the glutathione conjugate (Moore and Harrington-Brock 2000; Cummings and Lash 2000). As shown in Figure 4, TCE metabolism can take two different pathways, one involving Phase I CYP2E1 oxidation in the liver forming chloral hydrate, trichloracetic acid (TCA) and dichloroacetic acid (DCA) (Pastino et al. 2000). This oxidative pathway is believed to be responsible for TCE-induced liver tumors as both TCA and DCA are liver carcinogens in their own right (Caldwell et al. 2006). In contrast, TCE-induced renal cancer stems from conjugation with glutathione in the liver with transport to the kidney where renal tubule cells further metabolize the conjugate as part of a salvage pathway excretory system. Specifically, amino acids from dichlorovinyl glutathione (DCVG) are cleaved with the resulting DCV-cysteine undergoing beta-lyase activation in the kidney to an unstable and highly reactive chlorothioketene (Cummings and Lash 2000).

Figure 4
TCE Metabolism in Relation to Toxicity
(from Pastino et al. 2000)



Epidemiological support for this mechanism stems from studies which evaluated genetic polymorphisms in glutathione transferases in relation to renal cancer risk in German TCE workers (Bruning et al. 1997) and a cohort of Central European TCE workers (Moore et al. 2010). While the overall cancer risk in these cohorts was elevated, the elevation was most noticeable in those with active GSTT1 and GSTM1 as opposed to the null polymorphism worker groups which had no increase in renal cancer (Bruning et al. 1997; Moore et al. 2010). A followup of a hospital-based renal cancer dataset (Bruning et al. 2003) with small numbers of TCE-related cases did not show a GST polymorphism effect (Wiesenhutter et al. 2007). A study of 100 renal cancer patients in Italy found that the risk was greater in those who had intact as opposed to null GST genes in relation to self-reported exposure to metals, pesticides, and solvents (Buzio et al. 2003). Overall, this line of evidence provides mechanistic support for the induction of human renal cancer by TCE and via a mechanism involving GST-mediated conjugation.

Several recent reviews by USEPA in collaboration with other scientists have summarized the TCE IRIS file and have highlighted the concordance across animal toxicology, epidemiology and mechanistic studies that support the human carcinogenicity of TCE (Rusyn et al. 2013; Chiu et al. 2013).

Cancer Potency Estimates

A cancer slope factor is an estimate of the increase in human cancer risk with increasing dose and thus is an expression of the chemical's potency to produce cancer. Three jurisdictions have issued TCE cancer potency estimates, the state of California Office of Environmental Health Hazard Assessment (OEHHA) (1999, 2009, 2013), the USEPA (2011a) cancer slope and unit risk, and a slope factor adopted by the New Jersey Dept of Environmental Protection (NJDEP, 1987) for establishing a state MCL for TCE. The initial and interim California potency estimates were 5-10 fold below the USEPA 2011a estimate but the most recent determination in California adopts the USEPA IRIS potency. The NJ potency estimate is similar to that derived by USEPA more than twenty years later, although the basis differs. These estimates are described further below.

New Jersey Dept of Environmental Protection

The New Jersey Drinking Water Quality Institute, an advisory body established by the NJ Safe Drinking Water Act to recommend MCLs to NJDEP, developed a document to support a state MCL for TCE of 1 ug/L (NJDEP 1987). The slope factor underlying the MCL calculation (0.03/mg-kg-d) was based upon mouse liver tumors in the National Toxicology Program (NTP) and National Cancer Institute (NCI) bioassays and low dose linear multistage modeling with cross-species extrapolation of potency based upon mouse to human body weight (1/3 power) scaling.

California OEHHA, Public Health Goals, 1999/2009 and No Significant Risk Level

The initial TCE Public Health Goal (PHG) in California (1999) of 0.8 ug/L and the follow-up PHG adjustment in 2009 (1.7 ug/L) relied upon the mouse liver tumor evidence stemming from two studies (gavage study by NCI, 1976; inhalation study by Maltoni et al. 1988), and the lung tumor evidence from one inhalation study (Fukuda et al. 1983) to derive a cancer slope factor of 0.013/mg-kg-d in 1999, followed by a downward potency adjustment in 2009 (0.0059 mg-kg-d). California OEHHA used a pharmacokinetic approach to extrapolate from the mouse internal dose-response to humans based upon two dose metrics, TCA+DCA area under the curve (AUC) or total amount metabolized (AMET) with the

latter ultimately being used to derive the human equivalent lowest effect dose at the 10% effect level (LED_{10}). The LED_{10} is the dose in humans that could be expected to produce a 10% cancer response based upon the dose-response found in animals and after making cross-species pharmacokinetic adjustments. It is used as the point of departure for low dose linear extrapolation. The AMET was estimated in mice for the cancer bioassay doses based upon a modeling risk assessment (Cronin et al. 1995) in which mouse liver Michaelis-Menten metabolism parameters were used to simulate TCE metabolism. Human metabolism was scaled relative to the mouse based upon body weight raised to the ¾ exponent. This creates a 7 fold dosimetric difference in terms of AMET when extrapolating from mice to humans, i.e., it takes 7 fold more intake in humans to reach the equivalent internal dose in mice of metabolized TCE. While the California assessments refer to PBPK modeling approaches in estimating the human LED_{10}, the parameter values used in the human model were not specified. Further, key pharmacokinetic factors such as cross-species differences in enterohepatic recirculation and TCA plasma protein binding were not factored into the analysis of either AMET or TCA+DCA dose metrics.

The California OEHHA (1999, 2009) analyses yielded an array of cancer slope factors based upon liver and lung tumors in mice. This yielded an overall geometric mean slope factor of 0.0055/mg-kg-d, the liver only slope factor was 0.013/mg-kg-d (1999), and the 2009 update yielded a slope factor of 0.0059 for liver.

The latest TCE determination in California was the setting of the No Significant Risk Level (NSRL) for the Proposition 65 program (California OEHHA 2013) . This TCE document is presented as current California policy and cites very recent documents but as posted (http://www.oehha.ca.gov/prop65/law/pdf_zip/031612ISOR_TCE.pdf) it is not dated. In this document OEHHA adopts the USEPA IRIS cancer potency values for the inhalation and oral dose route (see below) stating that " The U.S. EPA's 2011 extensive review and analysis incorporates the latest available toxicological information on the carcinogenicity of trichloroethylene and derives cancer potencies for the chemical, namely an oral slope factor and an inhalation unit risk. California OEHHA's review of the U.S. EPA assessment found it to be a reliable scientific basis for updating the NSRLs that is consistent with Section 25703 guidance. The trichloroethylene risk assessment underwent internal and external scientific review, as well as a public comment process, before being released as a final document by U.S. EPA." While this California OEHHA document refers to the adoption of USEPA values for the Proposition 65 NSRL determination for TCE, it does not necessarily carry over to the setting of California drinking water

targets. The California MCL and PHG for TCE have not been updated since the new IRIS file became available.

USEPA

The 2011b IRIS TCE assessment considered a wide range of cancer bioassays, epidemiology studies, cancer targets and dosimetry modeling. Renal carcinoma was the endpoint of greatest consistency and potency across studies and so was the major focus of EPA's dose-response analysis. After extrapolating across species to go from intermittent to continuous exposure and based upon toxicokinetic differences between rats and humans, the animal-based oral cancer slope for renal cancer was estimated at 0.25 per mg/kg/d. However, EPA relied primarily upon the human epidemiology database, and particularly the study of Charbotel et al. (2006) in 403 TCE workers in rural France which the highest exposure group had an odds ratio for renal cancer of 2.16. This converted to an inhalation unit risk (cancer potency expressed per unit dose of inhaled agent) of 0.0055/ppm for renal carcinoma alone to which EPA applied a 4 fold adjustment to account for the fact that elevated risks for lymphatic and liver cancer also occur in TCE workers. This combinational approach yielded an inhalation unit risk of 0.022/ppm (4.1E-06 per ug/m3). There are no human cancer data that could be used to develop an oral slope factor. Since the tumor target sites are systemic and not point of contact and since animal studies show concordance of tumor type when switching dose route, USEPA applied a PBPK model to extrapolate from inhalation to oral routes to derive an oral potency factor. This yielded an oral slope factor for renal cancer (adjusted for the combination of liver and lymphatic tumor) of 0.05/mg-kg-d. This oral slope is below the animal-based slope for renal cancer alone (0.25/mg-kg-d) as derived by USEPA (2011b) from the NCI, 1988 oral rat data with dose adjustment based upon amount metabolized via glutathione pathway (USEPA, 2011b, Table 5-37). The human based slope is also near the bottom of the range of possible slope factors listed in USEPA's assessment (0.02-0.4/mg-kg/d). Therefore, the most recent cancer slope from USEPA takes into account a wide range of human and animal data and is not nearly the highest potency that could be chosen from the underlying data. The derivation of an oral cancer potency from inhalation data when oral data are actually available is justifiable by the fact that human data are not available by the oral route, that the target sites are the same by oral and inhalation dosing, that well validated pharmacokinetic models are available to perform this extrapolation, and that the potency estimates based upon rodent oral data are within range of the extrapolated value from human inhalation data.

Selection of a TCE Cancer Potency from Available Values

The USEPA TCE cancer assessment has gone through 3 phases of development and review, beginning with a draft in 2001 (USEPA, 2001) which presented an oral slope range of 0.02 to 0.4 per mg-kg-d. This document was reviewed by the National Academy of Science (NAS) which agreed with the basic analysis and cancer potency derivation but sought greater exploration of uncertainties (NAP 2006). The final USEPA assessment on IRIS (USEPA 2011a) responds to the NAS report with a unified synthesis that identifies a single cancer potency (0.05/mg-kg-d) based upon recent human data and consistent with other human studies and the animal cancer bioassay database, and was reviewed by the USEPA SAB (2011) prior to being finalized. While this value is 8.5 fold greater than the California OEHHA determination in their 2009 PHG document (0.0059/mg/kg/d), the most recent indication from California OEHHA is that they have adopted the IRIS value (California OEHHA, 2013, Prop 65 NSRL determination). The NJDEP cancer slope (0.03/mg-kg-d) is the least robust or up-to-date in that it was derived in the 1980s from a single endpoint (mouse liver tumors), did not consider human data, and did not involve any PBPK modeling.

Based upon these considerations CT DPH relies upon the USEPA oral cancer slope on IRIS of 0.05/mg-kg-d in calculations used to evaluate cancer risk from ingestion of TCE in contaminated drinking water. The inhalation unit risk from IRIS (2011) was also used (4.1E-06/ug-m3 which converts to 0.0144/mg-kg-d in terms of oral equivalents); the California unit risk is two fold lower (2E-06/ug-m3). Given that the IRIS derivation is more recent (2011 vs California OEHHA 2000) and is based primarily upon human studies with support from animal data while the California value is derived from studies in mice only and is more dated (1990), the IRIS inhalation unit risk is used in the remainder of this analysis.

Non-Cancer Endpoints

TCE's array of non-cancer targets is similar to the cancer endpoints (kidney, liver, white blood cells/immune system) and extends beyond to neurotoxicity, male reproductive toxicity and developmental toxicity (cardiac teratogenicity, developmental neurotoxicity) (Chiu et al. 2013). Occupational studies have demonstrated that high level exposures in workers can increase protein leakage into urine suggesting kidney damage (NAP 2006). Animal studies indicate that TCE causes renal toxicity by either the oral or

inhalation route with these effects more prevalent in male rats than in female rats or mice (USEPA 2011b). Dosing of animals with TCE or TCE metabolites found the glutathione conjugate DCVC was most potent in inducing renal toxicity, thus suggesting once again that the GSH conjugation is essential to the renal effects (Lash et al. 2001). The body of evidence supporting TCE-induced liver toxicity in workers or test animals suggest that these are primarily high dose effects and more related to hepatocellular injury (cell swelling, degeneration) than frank necrosis (NAP 2006). Liver weight gains, cytotoxicity, histopathology and leakage of enzymes has been seen in numerous animal studies by gavage, drinking water and inhalation exposure (USEPA 2011b). Upregulation of PPARalpha appears to be a mechanism responsible for some but not necessarily all of the TCE-induced liver effects (Nakajima et al. 2000; Ramdhan et al. 2010). TCE is immunotoxic as indicated by decreased thymus weight in mice exposed by drinking water for 30 weeks (Keil et al. 2009), impaired antibody (PFC) response in mice exposed in utero and postnatally, and the induction of a hypersensitive or autoimmune state as demonstrated in both animals and humans (reviewed in Cooper et al. 2009). These latter effects include increase in anti-DNA antibodies in mice exposed via drinking water (Keil et al. 2009), autoimmune hepatitis and inflammation at other internal organs (Griffin et al. 2000; Cai et al. 2008), epidemiological evidence of workplace hypersensitivity disorder involving the skin and internal organs (Kamajima et al. 2007), increases in inflammatory cytokines in TCE workers (Iavicoli et al. 2005; Bassig et al. 2013), and associations of TCE environmental or workplace exposure with scleroderma and other rheumatoid conditions (USEPA, 2011b).

A key noncancer health outcome associated with TCE both in animal and epidemiology studies is congenital cardiac defects. Epidemiology studies are suggestive but not conclusive as they are ecologic in nature (it is difficult to biomonitor for TCE due to short half life in the body) and thus have a crude estimate of exposure history and co-exposures (Forand et al. 2012; Goldberg et al. 1990). The epidemiological evidence is supported by some but not all of the developmental testing in rats (Johnson et al. 2003; Fisher et al. 2001) while TCE is also a cardiac teratogen in chicks (Rufer et al. 2010). Overall, USEPA has sufficient confidence in this endpoint to use it as part of the RfD-setting basis. USEPA states regarding cardiac defects: “The epidemiological studies, while individually limited, as a whole show relatively consistent elevations, some of which were statistically significant.” CT DPH concurs with this summary statement. The implications of this endpoint are considerable in that the RfD applies to relatively short-term exposures (pregnancy or some fraction thereof) as well as to more chronic exposures.

Dose Response and USEPA RfD

Table 3 summarizes the TCE endpoints, studies, and points of departure used by USEPA to arrive at the RfD and RfC available on IRIS. These endpoints are well documented in animal studies in addition to those highlighted for RfD derivation below with at least some human epidemiology to document relevance across species.

Table 3. USEPA/IRIS RfD and RfC Derivation

Endpoint	NOAEL/POD	Extrapolation Method	Uncertainty Factors	RfD or RfC	Reference
Immunotox – ↓ed thymus wt, ↑ed autoimmne antibodies, B6C3F1 mice exposed via dw x 30 wks as adults	LOAEL = 1.4 mg/L in drinking water which corresponds to HED_{99}=0.048 mg/kg/d	PBPK model using metabolized dose to go from mouse to human, HED_{99} used to account for inter-human TK variability being a low end estimate of the mouse LOAEL	100 fold total 10x LOAEL→NOAEL, 3x mouse → human TD, 3x intra-human TD	RfD = 0.00048 mg/kg/d RfC = 2 ug/m3	Keil et al. 2009
Immunotox - ↓ed antibody response, ↑ed hypersensitivity, B6C3F1 mice exposed via dw in utero, postntl	LOAEL = 0.37 mg/kg/d ingested dose	No extrapolation due to complex modeling needed to simulate mouse perinatal exposure; PBPK model for dose route extrapolation for RfC	1000 fold total 10x LOAEL→NOAEL, 10x mouse → human, 10x intra-human	RfD= 0.00037 mg/kg/d	Peden-Adams et al. 2006
Teratogenicity – cardiac malformation in S-D rats, in utero dw exposure	BMDL for 1% response = 0.0051 mg/kg/d	PBPK model using metabolized dose to go from mouse to human, HED_{99} used to account for inter-human TK variability; PBPK model for dose route extrapolation for RfC	10 fold 3x mouse → human TD, 3x intra-human TD	RfD= 0.00051 mg/kg/d RfC = 2 ug/m3	Johnson et al. 2003

Thus, the IRIS profile presents 3 well documented endpoints (immunotoxicity, teratogenicity, renal toxicity) and 5 studies that converge on an RfD of 0.0005 mg/kg/d. This array of endpoints and RfDs includes two that indicate effects from exposure during the perinatal period – cardiac malformation (Johnson et al. 2003) and immunotoxicity (Peden-Adams et al. 2006). The types of immune system

effects seen in mice include both immunosuppression and increased potential for autoimmune reaction (Keil et al. 2009; Peden-Adams et al. 2006). The Peden-Adams et al. (2006) study evaluated immunotoxicity resulting from TCE exposures that occurred in utero and postnatally, critical periods for immune system development. The Keil et al. (2009) study involved postnatal exposure at a time of greater immune system maturity and thus perhaps less sensitivity. The Johnson et al. (2009) study in rats covered the critical period of in utero cardiac development. TCE effects in these studies suggest that TCE can induce teratogenic and immunotoxic effects from short-term exposure during critical windows of development and that chronic exposure is not needed if sensitive receptors (pregnant women, woman of child-bearing age, young children) are exposed. TCE has also produced developmental neurotoxicity in animal models. USEPA's analysis of candidate RfDs based upon developmental neurotoxiciy indicates approximately 100 fold less sensitivity of this endpoint (USEPA 2011b). USEPA/IRIS also presented two supporting studies not shown in the table because they were not primary to RfD derivation. Both of these endpoints involved renal toxicity, one in female Marshall rats exposed by gavage (NTP 1988; candidate RfD = 0.00034 mg/kg/d) and the other in S-D rats exposed by inhalation (Woolhiser et al. 2006; candidate RfD = 0.0079 mg/kg/d).

Table 3 also shows that the RfC on IRIS of 2 ug/m3 stems from oral studies used in RfD derivation, but with an across-dose route extrapolation involving PBPK modeling. This extrapolation is feasible because the toxicity targets are not point of entry but internal (immune system, developing fetus, kidney). The extrapolation is well supported by the underlying PBPK model and so this does not introduce a large degree of uncertainty. Ironically the TCE oral cancer slope factor is based upon a dose route extrapolation in the opposite direction (inhalation to oral) from epidemiology studies in which workers were exposed primarily by inhalation. For the RfC, USEPA evaluated inhalation studies but they were more limited for the critical non-cancer endpoints (immunotoxicity, developmental toxicity, renal toxicity) than what was available for the oral route. The lowest inhalation-based candidate RfC derived by USEPA was 0.001 ppm (renal effect, Woolhiser et al. 2006), which converts to 5.7 ug/m3 and is not very different from the RfC derived by USEPA of 2 ug/m3 based upon dose-route extrapolation.

ATSDR Minimum Risk Level (MRL)

In January 2013 ATSDR provided an addendum to their earlier (1997) Toxicological Profile for TCE. In the addendum, ATSDR adopted the USEPA (2011a) RfD (0.0005 mg/kg/d) and RfC (2 ug/m3) as their chronic duration oral and inhalation MRLs. The addendum also rescinded the acute and intermediate MLRs that were developed in 1997 because were deemed to be no longer health protective on the basis that the chronic health endpoints are also relevant for shorter periods (e.g., < 15 days, the ATSDR definition of acute, and less than 1 year, the ATSDR definition of intermediate duration) and the new chronic MRL is much lower than the previous acute or intermediate MRLs.

Risk Characterization

TCE in potable water poses risks for both cancer and non-cancer endpoints and this stems from both water ingestion and non-ingestion (inhalation/dermal) exposure pathways. This characterization focuses upon the risk associated with the current MCL of 5 ug/L to evaluate the public health need for MCL adjustment. Given the findings of this risk characterization, subsequent sections derive an updated draft MCL.

Cancer Risk Standard Calculation

The default approach for utilizing the TCE oral slope factor in conjunction with the standard drinking water scenario to derive an MCL for TCE is shown below. The default approach has no time pro-rating factor because it is assumed that exposure will last for a full lifespan (default assumption 70 yrs).

*Risk Level = Cancer potency factor * Water concentration * (Water ingestion rate/Body wt)*

Where: Cancer potency factor = 0.05/mg-kg-d (USEPA, IRIS file)

Water concentration = 0.005 mg/L (USEPA MCL)

Water ingestion rate = 2 liters/day (Adult drinking water default)

Body weight = 70 kg (Adult body weight default)

Risk Level = 0.05/mg-kg-d*0.005 mg/L*2 L/day * 1/70 kg = = **7E-06**.

Further, TCE exposure will include inhalation exposure that is not included in this calculation and children may be at increased risk. The potential for these factors to alter the estimate of TCE risk at the current MCL is considered below.

Accounting for Inhalation Exposure

TCE is highly volatile with a vapor pressure of 74 mm Hg and a Henry's Law coefficient of 0.011 atm-m3/mol. This will lead to its volatilization during bathing and showering and general household tap water use, especially those uses involving elevated water temperature (dishwashing, cooking, bathing/showering). The tap water volatilization pathway has been most extensively characterized with chloroform and to some degree with TCE, other solvents, and also radon. The highest inhalation exposure is in the bathroom while bathing or showering as the bathroom is a small microenvironment which receives a high volume of water in a short period of time. However, the greatest cumulative exposure over the course of the day is from the remainder of the house rather than the bathroom because of the small amount of time spent in the bathroom.

Table 4 shows calculations for two exposure scenarios for non-ingestion exposure of TCE stemming from its presence in tap water: inhalation exposure to the general household air from TCE volatilized from household uses of tap water which include uses in the bathroom, kitchen and laundry room. Further, a separate calculation is made for inhalation exposure during a 15 minute shower because of the higher rate of exposure during this activity. Additionally, dermal exposure becomes a substantial contributor when showering and so this pathway is included for the showering calculations.

Data for bathroom shower stall concentrations of TCE are based upon measurements of chlorinated solvent concentrations in bathrooms from simulated showers, with most of the data derived with chloroform (Kerger, et al., 2000; Jo, et al., 1990a; Giardano and Andelman, 1996). These studies involved a wide range of water temperatures, water flow rates, water concentrations and bathroom ventilation rates. They yielded a range of air concentration (ug/m3) to water concentration (ug/L) ratios from a low of 3.5 in Kerger et al., to 27.5 for Giardino and Andelman. For the current calculations, the estimate from the Jo, et al. (1990) studies was used directly without adjustment: 6.3 as a mid-range estimate from the available literature. TCE is less volatile than chloroform (160 mm Hg for chloroform, 74 mm Hg for TCE) but has a 3 fold higher Henry's Law coefficient because of water solubility

differences. In side by side shower experiments, Giardano and Andelman (1996) showed a 60% volatilization efficiency for chloroform and an 80% volatilization efficiency for TCE. In a study of TCE volatilization from shower water Mckone and Knezovich (1991) demonstrated a transfer efficiency of 61% from water into air. These volatilization data indicate that the use of the air/water ratio found empirically for chloroform, for which several shower stall studies are available, is a reasonable surrogate for TCE.

The shower stall air concentration at the TCE MCL is calculated as:
Air concentration = TCE water concentration (ug/L) * Air/water ratio (L/m3)
= 5 ug/L * 6.3 L/m3 = 31.5 ug/m3 or 0.0315 mg/m3

This air concentration is used in Table 4 to estimate total daily exposure.

The bathing/showering scenario can also involve substantial dermal uptake as high body temperature creates extensive skin perfusion with blood and thus more rapid chemical uptake across the skin. This has been estimated in experiments by Jo et al., 1990b in which volunteers showered normally or with a skin covering to prevent dermal exposure. Jo et al. (1990b) found that the dermal uptake of chloroform during a shower to be 48% of the total uptake. A PBPK modeling approach for estimating TCE uptake from inhalation and dermal during a shower indicated substantial dermal uptake, with the fraction being 36% of the total (Haddad et al. 2006). The field results from Jo et al. (1990b) were used because they represent actual measurements rather than model estimates; thus 48% dermal has been factored into Table 4 bathing and showering exposure by first estimating the inhalation only exposure and then dividing this value by 0.52 to obtain the total (inhalation+dermal) showering uptake of TCE. The dermal only is then the total minus inhalation as follows:

Total showering TCE exposure = Inhalation + Dermal
Where:
Inhalation uptake (mg/kg/d)

*= shower air concentration (ug/m3) * ventilation rate (m3/hr) * exposure time (hr)/body wt (kg)*

Where:

Shower stall air concentration = 0.0315 mg/m3 (see above)

Ventilation rate (adult resting) = 0.83 m3/hr

Exposure time = 0.25 hr (15 min shower)

Body weight = 70 kg

Thus, Inhalation Uptake = 0.0315 ug/m3*0.83m3/hr*0.25 hr/70 kg = 9.3E-05 mg/kg/d

Dermal uptake = (inhalation uptake/0.52) – inhalation uptake = 8.6E-05 mg/kg/d

These values for dermal and inhalation uptake of TCE while showering are included in Table 4.

Data for whole house TCE air concentrations comes from calculations provided in Maxwell, et al., 1991 in which they estimate air concentrations of volatile compounds emanating from contaminated tap water based upon default assumptions about water use rate per day and household air exchange rate. These calculations assumed 100% volatilization which they conclude is reasonable for highly volatile compounds (like TCE).

Household Indoor Air Conc (mg/m3) =
*Water Use * Water Concentration/air exchange * mixing factor*

Where according to Maxwell, et al. (1991):

Water use rate = 30 L/hr

Air exchange rate = 338 m3/hr

Mixing factor (unitless) = 0.15 to 0.5 (use 0.33), and

Water concentration = 0.005 mg/L (USEPA MCL)

This equation yields a household air concentration of 1.35 ug/m3 as shown in Table 4.

Table 4. Estimated TCE Inhalation Dose From the Combined Exposures of Showering and Household Water Uses for a Tap Water Concentration of 5 ug/L

Source of Exposure	Air Concentration ug/m3	Exposure Factors	Dose mg-kg-d
Showering –inhalation	31.5	0.83 m3/hr inhalation rate for 15 min	9.3 E-05
Showering – dermal		Dermal 48% of total uptake[1]	8.6 E-05
Household water uses - inhalation	1.35	0.83 m3/hr for 16 hr	2.6 E-04
Household TWA air conc	1.25[2]		
Total Inhalation + Dermal Exposure			4.4 E-04

[1]See above text for derivation of dermal uptake fraction of total.
[2]This value represents a time weight-averaged household air concentration considering 15 minutes in the shower stall at 31.5 ug/m3, 16 hrs at 1.35 ug/m3 and then 8 hrs away from home.

The inhalation contribution to total daily TCE exposure from tap water is calculated as follows (0.005 mg/L tap water concentration used to run calculations):

Total daily dose = Oral ingestion + Inhalation/Dermal uptake

Where:

Oral ingestion only: 0.005 mg/L * 2 L/day * 1/70 kg = 1.43 E-04 mg-kg-d

Inhalation/Dermal: 4.4 E-04 mg-kg-d (see table above)

Total = 5.83 E-04 mg-kg-d

Thus,

Inhalation/dermal is estimated to be 3 times greater than oral ingestion.

Total (oral plus inhalation/dermal) is estimated to be 4 fold greater than oral alone.

This inhalation contribution is similar to that assumed by California OEHHA in their PHG calculations. California OEHHA assumes 7.1 L/day of water ingestion equivalents (total dose from water converted into coming ingestion units) when considering the amount of exposure from ingestion plus inhalation. The CT DPH estimate is an intake of 8 L/day water equivalents.

This has the effect of increasing the TCE dose associated with the current MCL 4 fold to 5.8E-04 mg/kg/d. When calculating the cancer risk associated with this dose, the risk from the oral+dermal component is calculated with the oral slope factor from IRIS while the inhalation component is calculated based upon unit risk from IRIS to yield a composite cancer risk of 1.66E-05 as follows:

Total cancer risk = (oral+dermal exposure dose) (CSF) + (inhalation dose) (Unit Risk)
Oral+dermal dose = 1.43E-04 + 8.6E-05 = 2.3E-04 mg/kg/d
Oral+Dermal cancer risk = 2.3E-04mg/kg/d*0.05/mg/kg/d = 1.15E-05
Inhalation dose = 9.3E-05 (showering) +2.6E-04 (household water use) = 3.53E-04 mg/kg/d
Inhalation cancer risk = 3.53E-04 mg/kg/d * 0.01435[1]/mg-kg-d = 5.1E-06
Combined Oral+Dermal+Inhalation Cancer risk = 1.15E-05+5.1E-06 = 1.66E-05

[1]The inhalation unit risk is expressed here in units of mg-kg-d for ease of calculation.

A mitigating factor is that when developing a more inclusive and realistic risk assessment, the exposure window for residence at one location can be considered the 90th percentile of residing in one location , 30 years, rather than the default of 70 years. Given that multiple regions of Connecticut are affected by TCE in groundwater, it is possible that when someone moves they still may encounter TCE in water. Therefore, it is appropriate to be aware of both the 30 year and 70 year assumption and display a range of drinking water cancer risks associated with the MCL based upon this range: **7.1E-06 to-1.66E-05**. Thus, the additional cancer risk from inhalation/dermal exposure relative to the standard calculation presented above for oral ingestion only (7E-06) is up to a 2.37 fold increase.

Accounting for Children's Cancer Risk

The increased vulnerability of children to carcinogens has been most clearly demonstrated with mutagenic carcinogens (Ginsberg, 2003; Barton et al. 2005). While the mechanism of action (MOA) for TCE-induced carcinogenesis is somewhat uncertain, a strong case can be made for a mutagenic MOA for human kidney cancer while a mutagenic MOA for the liver and hematopoietic tumors is plausible. This mutagenic MOA theoretically can lead to a 10 fold greater potency in the first 2 years of life and a 3 fold greater potency between ages 3 and 15 years of age, applied as age-dependent adjustment factors (ADAFs) (USEPA, 2005). When factoring in the greater potency for these age windows by the greater

water ingestion rate and then pro-rating over the 70 year lifespan one gets a 2.35 fold increased risk factor due to adding in these early life stages:

Calculation of Increased Cancer Risk Considering Mutagenic Mode of Action

Total risk across lifespan = (0-2 yr pro-rated risk) + (3-<16 yr pro-rated risk) + 16-70 yr pro-rated risk)

Where:

Children's additional risk for first 2 yrs of life =

(2 yrs) (10x potency) * (3.1 fold greater water ingestion[**])/70 yrs = 0.9 fold increased risk

Children's additional risk for 3-<16 yrs of life =

(13 yrs) (3x potency) * (1.19 fold greater water ingestion[**])/70 yrs = 0.664 fold

Total added children's risk = 1.56 fold

Added to adult risk (16-70 yrs) = 55 yrs (1x potency) (1x water ingestion rate)/70 yrs = 0.79

Total risk across life stages = 0.79 (adult) + 1.56 (early life) = 2.35

[**]Children's water ingestion factors are derived from USEPA (2011c), Exposure Factors Handbook, Table 3-19, 90th % values. During the first two years of life, infants and young children can be assumed to ingest 89 ml/kg/day (Exposure Factors Handbook, Table 3-19, 90th % value) while the comparison value for adults is 28.6 ml/kg/d (90th % value of 2 L/day divided by 70 kg). This leads to a 3.11 fold greater water ingestion rate during the most vulnerable life stage for mutagenic carcinogens. Averaging over the 3-15 yr old age range from data in the Exposure Factors Handbook indicates a 90th percentile water ingestion rate of 34 ml/kg/d which is 1.19 fold greater than adult.

This analysis suggests that for the TCE carcinogenicity endpoint most associated with a mutagenic MOA (renal cancer), the overall risk is 2.35 fold greater than that calculated based strictly upon adult (70 yr) exposure.

However, the USEPA IRIS cancer potency factor for TCE is comprised of 3 different endpoints (liver and lymphatic tumors in addition to renal) which led USEPA to increase the oral potency 4 fold relative to the slope based upon renal tumors alone. It is unknown whether the liver and lymphatic tumors are based upon a mutagenic MOA and so applying the children's vulnerability factor to the overall IRIS slope factor would be uncertain. The USEPA IRIS file recommends applying ADAFs for mutagenic MOA to the renal cancer endpoint but not the other cancer endpoints (USEPA IRIS 2011). The current analysis thus focuses the early life cancer risk increase on renal cancer but includes the other endpoints in Table 5 (below) to show the range of uncertainty inherent in the decision to apply ADAFs to just one of the three cancer endpoints. This leads to a TCE oral slope range of 0.059 to 0.109/mg-kg-d, an increase in the

USEPA/IRIS slope of 27-235% when children's vulnerability is taken into account. Similarly, the inhalation unit risk on IRIS is comprised of 25% renal cancer risk with non-Hodgkin's lymphoma and liver cancer risk contributing the rest. Thus both the oral and inhalation slope factors go up by a similar amount in consideration of children's vulnerability to the mutagenic MOA of TCE. Since the mutagenic MOA is best defined for TCE-induced kidney cancer, the lower cancer potency estimates (0.059/mg-kg-d –oral and 0.018/mg-kg-d - inhalation) is carried through the calculations, with acknowledgement that the potency may be nearly 2 fold higher if the mutagenic MOA is relevant to all cancer endpoints.

Table 5. TCE Oral Slope Factors from USEPA/IRIS with Additional Children's Vulnerability Factor

	Kidney	**Non-Hodgkin's Lymphoma**	**Liver**	**Combined**
IRIS oral slope (risk/mg-kg-d)	9.33E-03	2.16E-02	1.55E-02	4.64E-02
IRIS slope with child factor (kidney only)	2.19E-02	2.16E-02[1]	1.55E-02[1]	5.9E-02[1]
% increase				27%
IRIS slope with child factor (all endpoints)	2.19E-02	5.08E-02	3.64E-02	1.09E-01
% increase				235%

[1]Child factor not added to NHL or liver tumor slopes.

Application of the potencies modified for children (5.9E-02/mg-kg-d oral, 0.018/mg-kg-d inhalation) with the inhalation risk contribution brings the cancer risk at the current MCL to a range of 0.9-to2.1E-05 (slope range derived in previous section increased by 27%).

Cancer Risk De Minimis Target

The Connecticut Department of Public Health uses a 1 in a million lifetime cancer risk as the de minimis target in developing public health recommendations for drinking water and other environmental media. This target is widely used in the risk assessment/regulatory community (Adler, 2007). For example, Section 112 of the Clean Air Act instructs USEPA to use a 1 in a million risk target when considering the residual risk of industrial emissions for the maximally exposed individual. Cleanup targets in USEPA's

CERCLA program define the starting point for considering waste site cleanup as 1 in a million cancer risk. FDA's target for regulating food additives exempt from the Delaney Clause is that the incremental lifetime cancer risk to the 90th percentile food consumer is no greater than 1 in a million. The Nuclear Regulatory Commission uses a preventive target that translates to approximately 1 in a million cancer risk to nearby residents when considering the licensure of nuclear reactors (NRC, 1986; Adler 2007). In Connecticut, the CT DPH dioxin ambient air standard was based upon 1 in a million cancer risk (Rao and Brown, 1990) and the CT DEEP remediation standard regulation (RSR) cleanup targets are also based upon this target. While CT DPH and these other regulatory agencies target 1 in a million risk for each carcinogen in each regulated medium, this goal can be affected by technical and economic feasibility, natural or anthropogenic background and other considerations such that the site-specific risk target may vary upwards from 1 in a million to 1 in ten thousand (10^{-6} to 10^{-4} cancer risk) (e.g., USEPA, CERCLA). However, by maintaining the target chemical risk at the 1 in a million level, CT DPH endeavors to ensure that the particular source does not make a substantial contribution to background cancer risk from the sum of environmental chemicals. This background risk has been calculated to be in the 10^{-4} to 10^{-3} range (e.g., Woodruff et al. 2000). The de minimis risk target also ensures that when combined with exposures from other media, that the cumulative risk for that particular chemical will remain within the 10^{-6} to 10^{-4} risk range.

Non-Cancer Risk

The non-cancer risk associated with the current MCL is judged based upon the USEPA IRIS RfD (0.0005 mg/kg/d or 0.5 ug/kg/d). The exposure dose associated with chronic daily consumption of tap water at the MCL using default exposure parameters is:

*Ingestion Exposure at MCL = water concentration * water ingestion rate/body wt*

= 5 ug/L*2 L/day* 1/70 kg = 0.143 ug/kg/d

This dose is 29% of the RfD while the goal for drinking water contaminants is 20% of the RfD when considering other sources of TCE exposure and the relative source contribution (RSC) concept. In other words, the oral exposure dose at the current MCL is 43% above the target of 0.1 ug/kg/d (RfD/5 to

account for RSC). The RSC factor is especially important for volatile chemicals in potable water because the majority of the daily dose is not from direct ingestion but from inhalation + dermal exposure.

Another consideration is that one of the developmental endpoints associated with the RfD, immunotoxicity in mice, stems from a perinatal study involving in utero and postnatal exposures during a critical period of immunological development in mice (Peden-Adams et al. 2006). Effects were found at 3 and 8 weeks postnatal. From the study design it is impossible to determine whether immunotoxicity occurred as a result of in utero exposure, postnatal exposure or a combination of the two. However, this study raises the possibility that the postnatal period is a critical window of vulnerability and that the RfD should be evaluated based upon postnatal exposures rather than the default drinking water assumption of 2 liters/day for a 70 kg body weight. Given that young children drink considerably more fluid per body weight than adults, this would cause the RfD to be surpassed beyond the 43% exceedance calculated above. This uncertainty regarding perinatal non-cancer risk underscores the concern that the current MCL is not necessarily protective against non-cancer risk.

Given that pregnancy is a critical time of exposure to TCE, risks associated with the MCL should take into account the possibility that pregnant woman may drink more fluid per body weight than the default assumption of 2 liters/day for 70 kg body weight. This consumption rate will vary over the course of pregnancy and since the vulnerable period of TCE exposure for cardiac defects or immune effects is not known, there is some uncertainty applying a specific water consumption rate for pregnancy. The USEPA Exposure Factors Handbook (2011 edition) indicates that water ingestion rates for pregnant women are generally similar to that for other adult groups (both mean and 95^{th} percentile values, Tables 3-1, 3-3 of USEPA 2011) so this does not appear to involve a large exposure adjustment. The state of Minnesota uses a pregnancy water ingestion rate that is 1.5 fold higher than the default adult ingestion rate based upon using the 95^{th} percentile water intake rate while the default of 2 liters/day is approximately the 90^{th} percentile. Use of a higher water ingestion rate would increase exposure and risk estimates associated with the current MCL. The current assessment relies upon the default water ingestion rate (2L/70 kg) as it is a well accepted upper bound value that broadly applies across adult groups including pregnant woman.

Non-cancer risk can also be considered relative to the TCE RfC (2 ug/m3). Table 4 above provides an estimate of the peak TCE exposure around the home, that occurring in the shower stall when taking a

shower (31.5 ug/m3). Table 4 also shows the 24 hour time weight-averaged (TWA) air concentration, 1.25 ug/m3. This analysis shows that the current MCL is associated with an average indoor air concentration that is 60% of the RfC (2 ug/m3) and a concentration during bathing and showering that would surpass the RfC by 16 fold. However, the bathing and showering exposure is brief (assumed here to be 15 minutes) while the RfC is set upon developmental endpoints (cardiac malformations, perinatal immunotoxicity) that involve more continuous, albeit still short-term exposure (likely on the order of days to weeks). To put the showering peak concentration into context, this is the dose equivalent of being at the RfC 4 hrs/day on a chronic basis (16 fold exceedance of RfC for 0.25 hr). Given the uncertainty associated with the time frame against which to apply the RfC and RfD to prevent developmental effects during pregnancy, a dose equivalent that represents 4 hrs/day at the RfC presents a considerable uncertainty. Additional exposures that may add to the peak and TWA indoor air exposures are the time spent in the bathroom before and after the shower, baths which are typically a longer event, dermal uptake, and longer time (more than 16 hrs per day) at home.

Implementation of the MCL including the time frame for testing and determination of violations, is a factor in evaluating the current MCL relative to health benchmarks. That's because the time frame for the TCE health effect may require chronic exposure (cancer effects) or may only require short-term exposure (perinatal risks such as cardiac malformations and immunosuppression). Yet the manner in which public water supplies are regulated assumes that long-term exposure is most important – the running annual average of quarterly samples is compared back to the MCL, not the maximum detect in any quarter. Water systems with a TCE detect must monitor for TCE quarterly. It is possible for a high detect in a single quarter to not trigger an MCL violation when averaged with the other quarterly results. The maximum detect in a single quarter that would not exceed the current MCL on an annualized basis is 20 ug/L (20 in one quarter, non-detect in the other 3 quarters : 20/4= 5 ug/L). However, a single quarter (3 months) of exposure may be sufficient to cause a substantial developmental risk. The daily dose associated with a TCE concentration of 20 ug/L is 0.572 ug/kg/d from water alone. That exceeds the RfD (0.5 ug/kg/d or 0.0005 mg/kg/d) and is 4.6 fold above the RfD when considering the contribution from non-ingestion (inhalation/dermal) exposures associated with TCE in potable water (see Table 7). Thus within the MCL regulatory framework, the current MCL is associated with exposures that can be well in excess of the developmental RfD on a short duration time frame that coincides with the window of vulnerability for such outcomes. Consideration of such short-term scenarios here is not unprecedented as USEPA and other regulatory bodies have established short-term guidelines to prevent exceedance of the

RfD and RfC that address time frames much shorter than 3 months although these guidelines have not addressed contaminated drinking water (USEPA removal actions in Regions 3, 9, 10; Mass DEP draft acute guidance, 2013).

Risk Characterization Summary

The current MCL of 5 ug/L is associated with a lifetime cancer risk that is 7 fold above de minimis 1 per million cancer risk. This risk is further elevated when considering the inhalation exposure that is inevitable when TCE is present in potable water (estimate of 7.1 to 16.6 fold above de minimis). Exposure during early life stages may increase this risk further assuming a mutagenic MOA for TCE-induced renal tumors. This increases the cancer risk estimate to 9 to 21 fold above de minimis. These risks would be greater if TCE's mutagenic MOA are applicable to all the cancer endpoints that comprise the potency factor on IRIS. Non-cancer risk is also exceeded when considering the RfD (43% exceedance of the RfD when allowing for relative source contribution) and is within range of the RfC (60% of it, without counting dermal exposure and assuming 16 hours/day at home). There is also the uncertainty regarding acute peak TCE exposures in the bathing/showering scenario that are well in excess of the RfC. The potential for postnatal vulnerability to TCE immune effect raises the concern that scenarios involving bottle feeding with tap water could drive up short term exposure and developmental immunotoxicity risk. Further, at the current MCL the RfD can be exceeded 5.7 fold in a sampling quarter without triggering an MCL violation because of annual averaging.

Thus, for both cancer (renal, liver, lymphoma) and non-cancer (cardiac birth defects, immune function) endpoints, the current MCL is associated with risks that are above population risk targets commonly used in public health and which may be higher than predicted by the current calculations when considering the above uncertainties. The following sections derive a draft MCL that comes closer to meeting public health risk targets while also considering feasibility.

MCL Derivation

MCL derivation parallels the risk characterization above in which the current MCL was evaluated. First the standard approach for deriving drinking water standards is used and then further consideration is given to factors which can alter the risk calculation (e.g., inhalation exposure, children's vulnerability, less than lifetime exposure, short-term non-cancer risk). The resulting risk-based MCL is then considered in light of feasibility of the draft MCL in terms of detection limits and treatability. As described below, this process leads to risk-based targets below 1 ug/L but the draft MCL was set at 1 ug/L based upon the demonstration of its feasibility and practicality by virtue of its longstanding use as the state MCL in New Jersey.

Standard Approach for Cancer-Based MCL

The standard calculation used by the USEPA, Office of Drinking Water in assessing cancer risk is to assume 70 year ingestion of the water at the adult body weight of 70kg and adult ingestion rate of 2 liters/day. For a 1 in a million de minimis risk target this yields an MCL of 0.69 ug/L as follows:

*Risk-based target = cancer risk target * 1/cancer slope * unit conversion (mg to ug) * body wt/water ing*
Which equates to:

1E-06 target risk * 1 mg-kg-d/0.05 risk * 1000 ug/kg/d/mg-kg-d * 70 kg/2 L-d = 0.69 ug/L

Additional Considerations for Cancer Risk-based Approach

The standard derivation described above assumes 70 year residence in one location as an adult. This may be over-conservative with respect to residence time but underconservative with respect to other sources of TCE exposure (inhalation) and with respect to children's vulnerability. The following derivation takes these factors into account:

Cancer risk-based MCL, 70 years exposure = 0.69 ug/L/(1.27*2.37) = 0.23 ug/L
Cancer risk-based MCL, 30 years exposure = (0.69 ug/L*70)/(1.27*2.37*30) = 0.53 ug/L

Where: 0.69 ug/L is the standard approach risk-based target

1.27 is the children's vulnerability factor as derived above

2.37 is the inhalation/dermal additional cancer risk factor derived above via separate consideration of oral, dermal and inhalation pathways

70/30 is the lifetime vs. less than lifetime adjustment factor for time living in one residence

Given that the default 70 year residence in one location may be an overestimate for most people and that the 90th percentile for residence at one location is 30 years, one can consider the 30 year risk as most relevant to the MCL. However, some individuals may live at one location longer than 30 years or when they move they may again encounter TCE contaminated groundwater. Therefore, it is appropriate to consider a range of concentrations for the MCL, 0.23 to 0.53 ug/L, to be protective against cancer risk. Note that if the TCE mutagenic mechanism applies to all cancer endpoints, these risk-based MCLs would be lower still.

Non-Cancer Endpoints

The RfD derived by USEPA (2011a) and subsequently endorsed by ATSDR (2013) can be used in the traditional equation to derive a drinking water target as follows:

*Non-cancer water target = (RfD*body wt/water ing rate) * RSC*

Where:

RfD = 0. 0005 mg/kg/d = 0.5 ug/kg/d

Adult body wt = 70kg

Adult water ingestion rate = 2L/d

RSC (relative source contribution) = 0.2 (standard default for volatile organic chemicals)

Thus, the non-cancer water target = 0.5 ug/kg/d *(70kg/2L) *0.2 = 3.5 ug/L

This derivation assumes a 70 kg person ingests 2 liters/day for a chronic period with a relative source contribution (RSC) adjustment factor of 0.2 to allow for the possibility that a substantial fraction of the daily TCE exposure may come from sources other than ingestion of this contaminated source. Inhalation is separately considered in the cancer-based derivation because there is no RSC in that case. For non-cancer it is reasonable to assume that the RSC covers the non-ingestion routes of TCE exposure from household water use, as well as non-household sources of TCE (e.g., outdoor air).

It is also reasonable to evaluate the possible household air concentrations against the TCE RfC (2 ug/m3). As described above when evaluating the current MCL, potable water concentrations of 5 ug/L and below will be associated with a whole house TCE TWA exposure that is less than the RfC. As indicated in Table 6, lower TCE water targets under consideration yield peak air concentrations within range or below the RfC.

Table 6. Comparison of Different Drinking Water Targets to the TCE RfC

Drinking Water Target	TCE Water Conc (ug/L)	Household TWA Air Conc (ug/m3)	Peak Air Conc[1] (ug/m3)	Ratio to RfC[2]
USEPA MCL	5	1.25	31.5	0.6 - 16
Candidate MCL	1	0.25	6.3	0.13 – 3.2
Cancer risk-based targets	0.23 to 0.53[3]	0.06-0.13	1.45-3.34	0.03 – 1.7

[1]Peak air concentration in shower stall during bath or shower. See Table 4 for derivation of air concentrations associated with USEPA MCL. Other air concentrations are linearly related to the input water concentration (2nd column).
[2]Range represents TWA concentration or peak concentration ratio to RfC.
[3]As derived on Page 34, 30-70 year exposure assumption.

Finally, the candidate MCLs can be evaluated relative to the maximum quarterly result possible that could still meet the MCL on an averaged annual basis. Developmental effects such as cardiac malformation and perinatal immunotoxicity may occur from relatively brief exposure during pregnancy; while the length of TCE exposure during gestation needed to produce these risks is unknown, one must assume it is on the order of days to weeks (less than a trimester of pregnancy). Given this short-term nature of the RfD it is important that it is met by the maximum quarterly result that could be associated with the MCL. The following table summarizes this comparison.

Table 7. Comparison of Different Drinking Water Targets to the RfD Considering Peak Quarterly Dose Possible

Drinking Water Target	TCE Water Conc (ug/L)	Peak Water Conc[1] (ug/L)	Peak Ingestion Dose (ug/kg/d)[2]	Peak Total Dose (ug/kg/d)[3]	Ratio to RfD
USEPA MCL	5	20	0.57	2.28	4.6
Candidate MCL	1	4	0.114	0.46	0.9

Cancer risk-based targets	0.23 to 0.53[4]	0.92-2.12	0.027-0.061	0.108-0.244	0.22 – 0.49

[1]Peak quarterly water concentration that could still meet annual average MCL.
[2]Dose at 2 liters ingestion per day for 70 kg body weight.
[3]Dose including ingestion, inhalation and dermal exposure.
[4]As derived on Page 25, 30-70 year exposure assumption.

This table shows, as described in a previous section, that the current MCL can be associated with exposures above the RfD on a time frame of concern for fetal development (3 months or 1 trimester of pregnancy). It takes a 5 fold lowering of the MCL, down to 1 ug/L to ensure that a groundwater TCE peak in a given quarter will not exceed the RfD. As a cross-check of the cancer-based target, it will also be protective of this short-term developmental risk as the cancer-based approach leads to a value below 1 ug/L (Table 7).

Risk-Based MCL Summary

The risk-based target range for 1 in a million cancer risk (0.23 to 0.53 ug/L) is approximately an order of magnitude below the non-cancer-based target (3.5 ug/L) indicating that cancer risk is the driving force in deriving the draft MCL. The cancer-based MCL range is also well below the target needed on an annualized basis that will ensure that no single quarter will exceed the developmental RfD. As shown in Table 6 above, the cancer-based MCL also yields indoor air concentrations that are within range of the RfC even under the acute exposure possible during bathing and showering. In other words, an MCL based upon de minimis cancer risk will also be protective against non-cancer outcomes when acute, subacute, or chronic exposure is considered. As shown in Tables 6 and 7, a candidate MCL of 1 ug/L is also protective relative to the RfD and RfC, while cancer risk calculations place it in the 10^{-6} to 10^{-5} risk range. As described below, feasibility and prior precedent elsewhere (New Jersey) has led to the policy decision to set the draft TCE MCL at 1 ug/L.

Feasibility

The feasibility of the proposed TCE drinking water target hinges upon whether it can be reliably quantitated using existing accredited analytical methodologies, and whether treatment technologies are available that can reduce raw water concentrations below the MCL.

Treatment

Trichloroethylene is efficiently removed from raw water with standard granular activated carbon systems and aeration systems. Essentially the same filtration device and capacity would be used to address TCE contamination of 5 ug/L as needed to address 1 ug/L or below. The costs of granular activated carbon (GAC) filtration and aeration vary depending upon the amount of water being filtered and in the case of GAC filtration, the frequency of changeouts needed to maintain effective filtration without breakthrough. The cost of these options for a system not currently treating for VOC contamination but having to do so because of lowering the TCE MCL are detailed in a separate CT DPH impact analysis ( ) but used in summary fashion below.

Analytical Detection

Routine scans of drinking water for volatile organic chemicals using EPA Method 524.2 (purge & trap/ GC/MS) can reliably measure a range of analytes to a practical quantitation limit (PQL) of 0.5 ug/L. This includes TCE. If the Reference Level/MCL were set below this concentration, an additional analysis to specifically target TCE at a suitable quantitation limit would be required. This would involve specific ion monitoring (SIM) at a cost comparable to the general scan, each being $125-150. In situations where TCE was known to be the major drinking water contaminant, it might be possible to forego the first scan and just go to the more sensitive SIM. However, there would be many routine testing situations in which both rounds of testing would be needed. Thus, a TCE MCL below 0.5 ug/L may increase the costs of water supply testing by $125-150 per test round. While laboratories are accredited for EPA Method 524.2, there is no accreditation for the SIM technique.

Drinking Water Targets in Other States

Other states with that have developed their own TCE targets in drinking water are California (PHG of 1.7 ug/L – July 2009), New Jersey (MCL of 1 ug/L formally adopted in 1989), Florida (MCL of 3 ug/L from mid-1980s), and Minnesota (Health-Based Value - HBV of 0.4 ug/L, 2013). The California PHG is risk-based but non-enforceable and is used to provide guidance relative to the state MCL for TCE (5 ug/L) which is set based upon factors in addition to public health risk. The NJ MCL is a risk-based determination which is derived from a calculation of de minimis (1 in a million) cancer risk from a drinking water concentration of 1.2 ug/L and a PQL determination of 1 ug/L (NJDEP 1989). This determination is more stringent than the federal MCL because the federal MCL was set based upon a PQL of 5 ug/L. The NJ MCL was promulgated into New Jersey regulations and has been fully enforceable for public water supplies since 1989. The Florida MCL was set in the mid-1980s based upon the guidance level that was in effect at that time from USEPA (3 ug/L). When USEPA developed the slightly higher MCL of 5 ug/L, Florida kept their MCL at the more stringent level. They find this level to be feasible and enforceable (Personal communication, Gregory Parker, Florida DEP, Drinking Water Program, July 23, 2009). The Minnesota Department of Health (May 2013) derived a non-regulatory drinking water Health-Based Value for TCE of 0.4 to 2 ug/L to protect against a range of TCE health effects including developmental immunotoxicity (0.4 ug/L) and cancer (2 ug/L) (available at http://www.health.state.mn.us/divs/eh/risk/guidance/gw/tcetechguide.pdf).

Policy Decision to Set the Draft MCL at 1 ug/L

While the current USEPA MCL for TCE is 5 ug/L, USEPA's MCL-goal (MCLG) is zero because TCE is a carcinogen. Decreasing the MCL towards the MCLG is a general public health goal where this is feasible and practical. Movement in this direction is a priority in the case of TCE due to the increasing evidence of human cancer and developmental risk which is reflected in the recent increases in TCE potency on USEPA's IRIS website. The current USEPA MCL was set based upon analytical detection feasibility in the 1980s and the Agency has acknowledged that lower detection limits are achievable (USEPA, 2010). CT DPH's assessment finds that drinking water targets below the MCL and closer to the MCLG are feasible and warranted based upon estimates of human cancer risk and non-cancer developmental risk. The choice of TCE cancer slope factor and related calculations yield a de minimis

(1E-06 risk) TCE drinking water concentration of 0.23 to 0.53 ug/L. While an MCL in this range might be desirable for the protection of public health, other factors modify the manner in which the risk-based determination is applied. In particular, analytical methodology is routine and cost efficient when targeting 0.5 ug/L rather than lower values. Further, we are not aware of any drinking water targets below 1 ug/L. 1 ug/L has been in use and enforceable as the state MCL for over two decades in New Jersey, demonstrating the feasibility of this target. This target yields a cancer risk estimate that is above de minimus but still between 1E-05 and 1E-06. This target is protective against the sub-acute and chronic TCE risks associated with developmental and kidney toxicity outcomes. Therefore, the underlying toxicology, technical feasibility and prior precedent considerations support a policy decision to set the Connecticut TCE drinking water MCL at **1 ug/L.**

Benefits Assessment

Decreasing the TCE MCL from 5 to 1 ug/L will involve economic costs and health benefits. The economic costs are addressed in a separate impact analysis with the results used here to help put the benefits into context. The main benefits are in the areas of cancer risk prevention and prevention of a variety of non-cancer effects including autoimmunity and developmental (birth) disorders.

The starting point for estimating the cancer risk benefit is the risk estimate for the combination of kidney, liver and NHL cancers derived above for the current MCL: 9 - 21E-06. Taking the midpoint of this range yields 15 extra cancer cases per million exposed individuals, assuming 30 to 70 year exposure with this exposure encompassing early life stages. Lowering the MCL to 1 ug/L decreases this range to 2 to 4 (midpoint of range = 3) extra cancer cases. This is a lowering of 12 cases per million exposed individuals. Public water systems can be treated with aeration methods to lower the TCE content to 1 ug/L. Regarding the costs to lower TCE in drinking water to 1 ug/L, CT DPH's impact analysis found that there are 11 public supplies which would be required to mitigate TCE that currently don't do so because they have levels between 5 and 1 ug/L. The CT DPH analysis of the cost for installation and maintenance of aeration and accompanying monitoring, averaged across the different sized water supplies that would be affected, is $2.0/person/year or $2,000,000 for a million people (CT DPH 2014). The cost for treatment with GAC would likely be higher so the cost/benefit assessment is based upon the likelihood that aeration would be selected by the water supply.

This aeration cost is associated with the benefit of 12 fewer cancer cases (theoretically some combination of renal, liver and NHL) converting to an annual cost of $167,000 per cancer case prevented. According to US government statistics, the medical diagnostic, treatment and hospitalization costs per cancer case are approximately $50,000 in the first year, $5,000-10,000/year in subsequent years and approximately $100,000 for the final year of life. These medical costs are variable based upon the type of cancer and other factors as shown at http://costprojections.cancer.gov/annual.costs.html. Aside from the medical costs, cancer-related death leads to cumulative lost earnings and family disruption. USEPA has determined that an avoided cancer death from tightening controls on carcinogen exposure is associated with a $6.1 million dollar benefit; this is based upon wage-risk studies conducted in a regulatory analysis of the arsenic MCL (USEPA 2001b). These avoided medical costs and economic losses due to premature illness and death are thus well in excess of 6 million dollars per case prevented and thus exceed the modest cost of water treatment associated with lowering the MCL from 5 to 1 ug/L.

Regarding non-cancer health benefit, the MCL reduction would lower the reference dose (RfD) exceedance possible in any monitoring quarter from 4.6 fold to < 1 fold (Table 7). This has the greatest bearing on the risk of TCE-induced developmental risk because of the short window of exposure necessary for this effect to occur. Lowering of the MCL to 1 ug/L would lower the TCE daily dose estimate from 2.28 ug/kg/d to 0.46 ug/kg/d (Table 7). Ideally one would have a dose response function describing TCE developmental toxicity at doses in the range of the existing and proposed MCL to interpret the benefit of reducing this daily dose. While this is not available, it is informative that a neighborhood in Endicott NY having relatively low indoor air exposures to TCE had a statistically significant 2.15 fold increase in cardiac birth defects at a median indoor air concentration of 16 ug/m3 (range 0.18 to 140 ug/m3)(Forand et al. 2012). This exposure was from inhalation only as the contaminated groundwater created a vapor intrusion exposure but was not used for drinking water. The corresponding median exposure dose in this neighborhood assuming 16 hours/day at home at a breathing rate of 20 m^3/24 hours for a 70 kg body weight is 3.1 ug/kg/d. This is similar to the 2.28 ug/kg/d TCE daily exposure dose possible for a peak monitoring quarter at the current MCL. This suggests that the current MCL is associated with a tangible risk of congenital heart defects. We note that the epidemiology is not extensive regarding this endpoint and the Endicott study was ecological in design and was limited with respect to control for cigarette smoking. However there were 15 cardiac defect cases in the study area which provides relatively robust data and confidence that this is not a statistical anomaly associated with a rare outcome. Further, this epidemiology evidence is consistent with TCE-induced cardiac

teratogenicity in rats and chicks and emerging mechanistic evidence for TCE effects on in utero heart development (Chiu et al. 2013). The initial concern for TCE and cardiac malformation came from 246 cases in an Arizona community exposed to TCE in drinking water ranging from 6 to 239 ug/L (Goldberg et al. 1990). The National Academy of Science's review of TCE (NAP 2006) found that the epidemiology studies relating TCE with cardiac defects are of limited value individually, but as a whole show relatively consistent elevations for cardiac malformations with similar relative effect sizes of 2 to 3‑fold. The Forand et al. (2012) study is further evidence of this association and is particularly useful because it provides an indication of TCE exposure in a community at elevated incidence for this outcome.

The Endicott study did not provide any dose response information as the neighborhood affected by TCE was treated was a single uniform exposure group. However, it is useful to provide the general magnitude of adverse developmental effect possible from TCE in this dose range. The cardiac defect odds ratio in the TCE-affected neighborhood was 2.15 (Forand et al. 2012). Given that the background rate of congenital cardiac defects in the US population is approximately 1% (CDC Congenital Heart Defect Webpage), an odds ratio of 2.15 is an increase of 1.15 cases per 100 people exposed or 11500 cases per million people. That is the increase associated with the median exposure (3.1 ug/kg/d) in Endicott NY. The peak quarterly dose associated with the current MCL is 74% of the median dose in Endicott NY and so can be assumed to yield 74% of the risk which would be 8510 cases per million exposed. If we assume a linear relationship between dose and effect over the dose range of interest, then the number of congential cardiac defect cases would decrease from 8510 to 1702, a decrease of 6808 cases per million water consumers. At an average treatment and maintenance cost for treating TCE in drinking water of $2.00/person (CT DPH 2014), this corresponds to $2,000,000/million people. This treatment cost will theoretically prevent 6808 cases of congenital heart defects for a cost per case prevented of $294. The CDC estimates that the medical cost associated with an infant with any type of congenital heart defect averages $100,000 with this cost rising if the defect is severe (CDC, Congenital Heart Defect Webpage: http://www.cdc.gov/ncbddd/heartdefects/data.html). This cost estimate is just for health care costs and so underestimates the total cost associated with congenital heart defects (e.g., physical limitations, premature death). Another source of benefit underestimation is that the aeration system is likely to reduce the TCE content of the finish water to below 1 ug/L as aeration is quite effective at removing chlorinated solvents and will continue working below the regulatory target. However, since the aeration system would be specified and tested to confirm MCL compliance, we have estimated the benefit associated with a

lowering from 5 to 1 ug/L but realize that this is the minimum reduction of TCE concentration that would be achieved.

While there a number of uncertainties in this benefit analysis (actual dose response for TCE-induced cardiac defects; whether the median exposure in Endicott best represents the dose responsible for the increased odds ratio; actual costs associated with the disease; degree of lowering of TCE concentration beyond 1 ug/L), it provides a reasonable screening level basis for evaluating the beneficial impact of lowering the TCE MCL on cancer risk and congenital cardiac defects. A more conservative estimate of non-cancer benefit can be generated by assuming that all of the congenital defects in the Endicott TCE cohort occurred at the upper end of measured concentrations in that neighborhood (140 ug/m3). This yields a benefit of 770 cases prevented per million exposed when lowering the drinking water exposure from 5 to 1 ug/L for a cost per case of $2597. Even on this basis it would appear that there would be a positive cost/benefit result - more benefit ($100,000) than cost ($2597) per case prevented. In addition it is noted that the actual costs and benefits associated with lowering the TCE MCL to 1 ug/L depend on how many water systems will need to install treatment now and in the future and how many people these water systems serve.

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