

# ***1,2,3-Trichloropropane (1,2,3-TCP): Health Effects & Risk Assessment***

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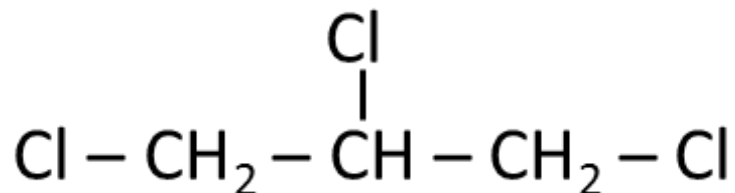
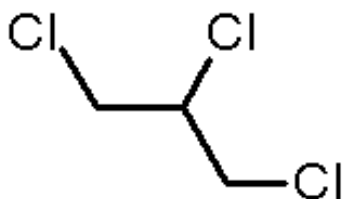
**New Jersey Drinking Water Quality Institute**

**September 30, 2015**

**USGS Water Science Center**

**Lawrenceville, NJ**

# General Information



- Manmade volatile chlorinated hydrocarbon
- Previously found in pesticides as impurity
  - D-D<sup>®</sup> (1,2-dichloropropane & 1,3-dichloropropene)
  - Telone<sup>®</sup> (1,3-dichloropropene)
- Other uses:
  - Solvent, cleaning & degreasing agent, paint remover
  - Intermediate in chemical synthesis
  - Byproduct of production of other chlorinated compounds

# ***Fate & Transport***

- Primary drinking water focus is ground water contamination.
  - Evaporates from surface water
- Does not strongly bind to soil
  - Leaches through soil to groundwater
- Persistent in groundwater
  - Breaks down slowly in the environment

# *Occurrence in New Jersey Drinking Water*

- Detected in public water systems (PWS) with ground water sources and in private wells.
- Data from New Jersey PWS from 1988-present
  - Reporting levels for various monitoring efforts varied widely (0.005 ug/L to 0.5 ug/L).
- Contamination of PWS and private wells has been addressed through treatment removal or alternate water source in many instances.
- Included in Unregulated Contaminant Monitoring Rule 3 (UCMR3) currently underway (2013-2015)
  - Testing of **finished** water, so not detected in PWS where contamination has been addressed.
  - UCMR3 includes all large PWS (>10,000 users), but only very few small (<10,000 users) PWS.

# ***NJ & USEPA Guidance, Standards, and Benchmarks for Drinking Water & Ground Water***

	Year	Health-based Value	Analytical PQL / Reporting Level	Guidance/ Standard
NJDEP Drinking Water Guidance	1999	5 ng/L	25 ng/L	25 ng/L (0.025 µg/L)
NJDEP Ground Water Quality Standard	2005	5 ng/L	30 ng/L	30 ng/L (0.03 µg/L)
DWQI Recommended MCL	2009	1.3 ng/L	30 ng/L	30 ng/L (0.03 µg/L)
USEPA Office of Water UCMR3	2014	0.4 ng/L	30 ng/L	-----

# *Health Effects Overview*

- No relevant human epidemiology studies.
- Animal toxicology
  - Non-cancer effects:
    - Toxicity in liver, kidney, heart, nasal tissue, lung, and other organs.
    - ↓ fertility (females); ↓ number of live offspring per litter.
  - Carcinogenic effects (basis of risk assessment)
    - National Toxicology Program (1993) chronic oral study
    - Caused tumors in multiple organs in male and female mice and rats, including fatal tumors early in life.
- Mode of Action (MOA)
  - Data support mutagenic MOA for carcinogenicity
  - Metabolized to reactive intermediates that form adducts with DNA.

## ***National Toxicology Program (1993) Chronic Study***

- Two year oral (corn oil gavage) study in male and female rats and mice (60 per sex per dose group).
  - Rats: 0, 3, 10, 30 mg/kg/day
  - Mice: 0, 6, 20, 60 mg/kg/day
- Interim sacrifice (8-10 per group) at 15 months.

# ***Results of NTP (1993) Chronic Study***

- Increased tumor incidence at all doses in multiple organs in male & female mice & rats.
  - In general, occurred earlier and at higher incidence as dose increased.
- Tumors in multiple organs at 15 month interim sacrifice in male & female mice & rats.
- Shortened lifespan due to tumors
  - Study was terminated early in high dose mice and mid- and high dose rats.
- NTP conclusion: *Clear evidence for carcinogenicity* in male & female mice & rats.
- DWQI and USEPA risk assessments are based on this study.

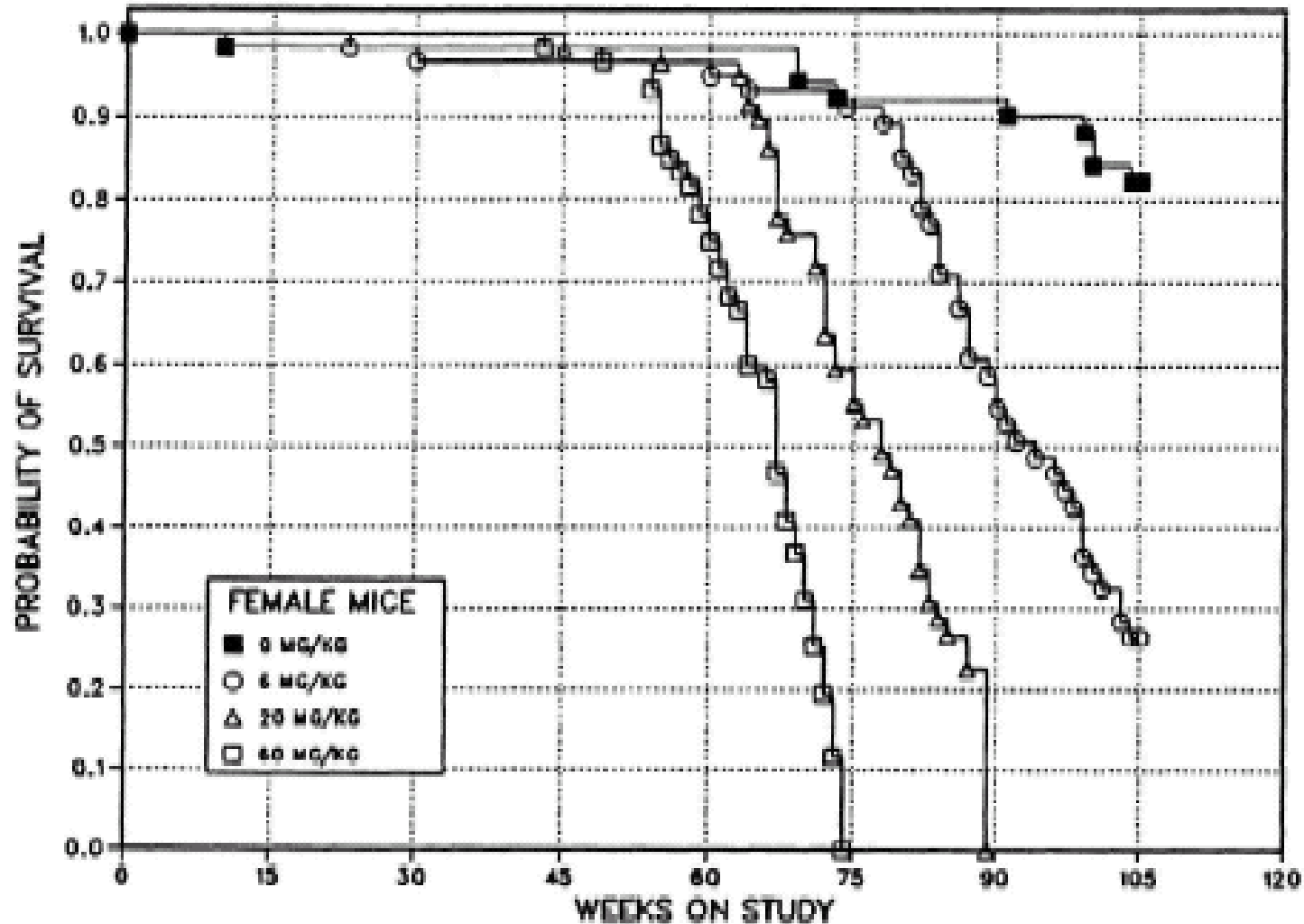


## ***Treatment-related Tumors in NTP (1993) Chronic Oral Study***

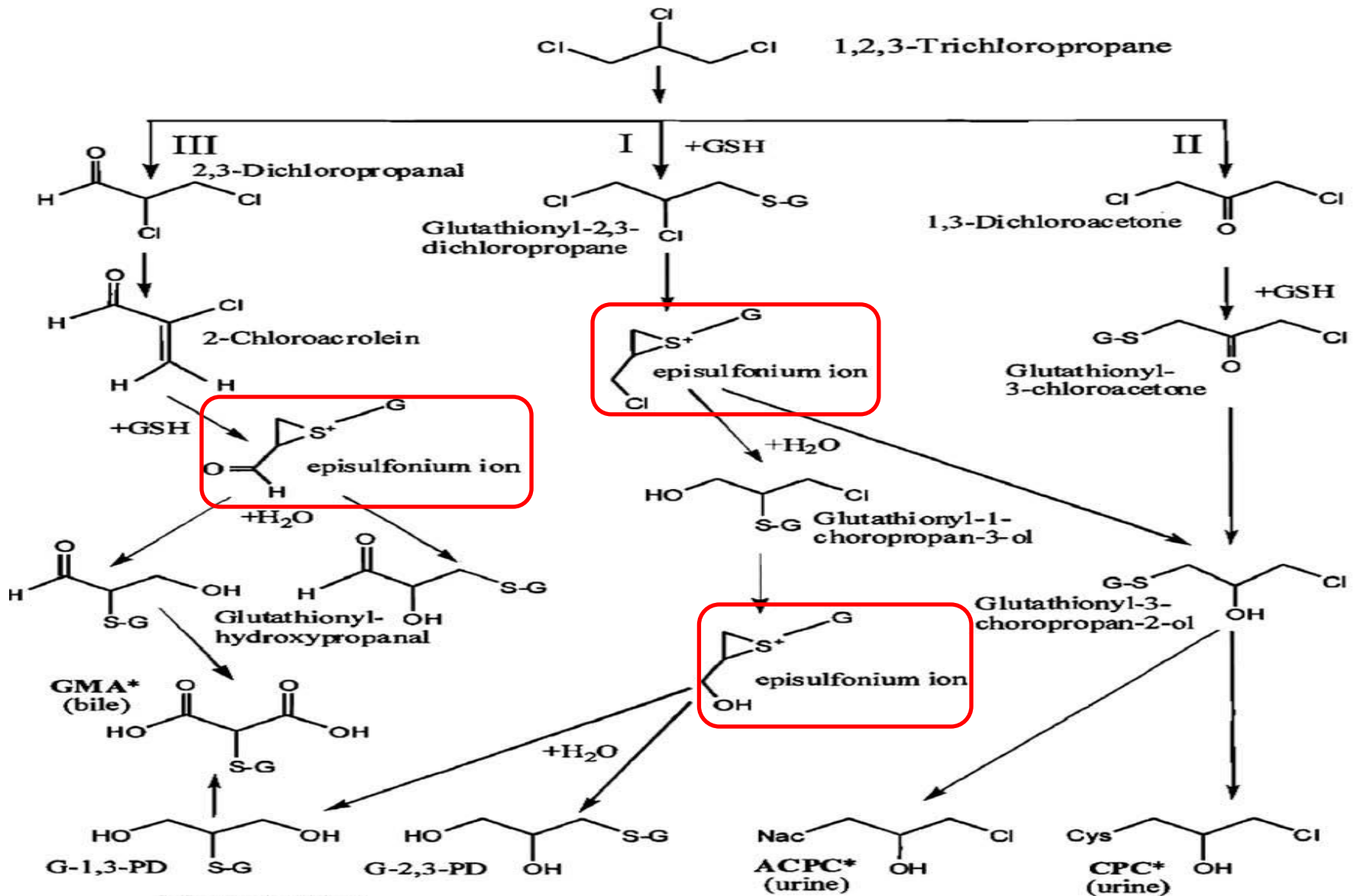
<b><i>Tumor Type</i></b>	<b><i>Rat</i></b>		<b><i>Mouse</i></b>	
	<b><i>Male</i></b>	<b><i>Female</i></b>	<b><i>Male</i></b>	<b><i>Female</i></b>
<b>Oral Cavity</b>	+	+		+
<b>Forestomach</b>	+	+	+	+
<b>Liver</b>			+	+
<b>Pancreas</b>	+			
<b>Kidney</b>	+			
<b>Harderian Gland</b>			+	
<b>Zymbal's Gland</b>	+	+		
<b>Preputial Gland</b>	+	NA		NA
<b>Uterus</b>	NA		NA	+
<b>Clitoral Gland</b>	NA	+	NA	
<b>Mammary Gland</b>	NA	+	NA	

NA – Not relevant or not examined.

# *Dose-related Early Mortality in Female Mice in Chronic Study of 1,2,3-TCP*



# Metabolism of 1,2,3-TCP to Reactive Intermediates

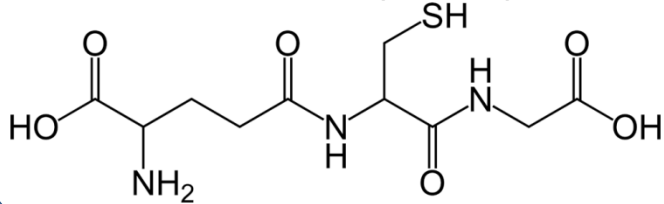


# Formation of DNA Adduct from 1,2,3-TCP

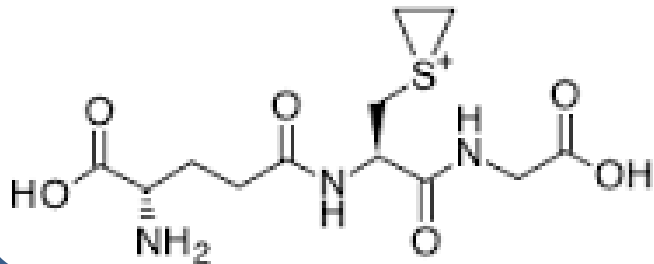
1,2,3-TCP Metabolites

+

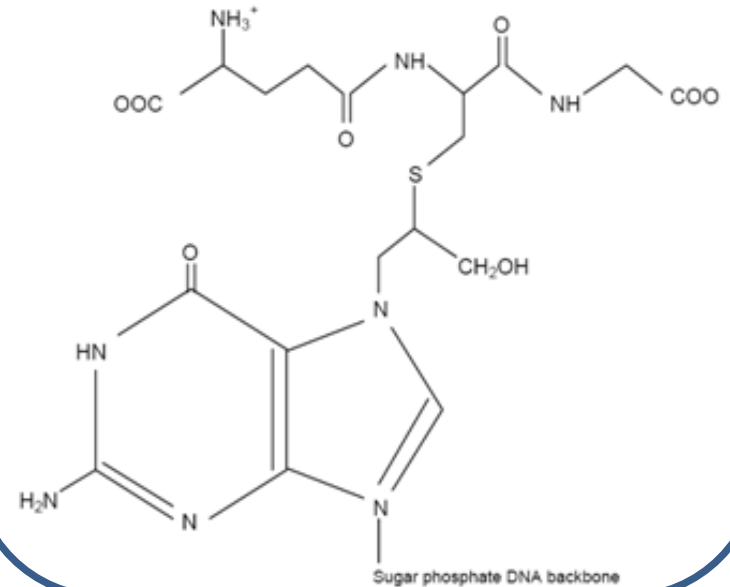
Glutathione (GSH)



Reactive Episulfonium Ions



DNA Adduct



# ***DWQI Health-based MCL (March 2009)***

- Based on forestomach tumors in female mice in NTP (1993) study.
  - Most sensitive tumor endpoint.
  - Considered relevant to humans (IARC; USEPA IRIS) although humans do not have this organ.
- Time-to-tumor model
  - Used instead of standard low-dose extrapolation model when high tumor incidence even at low dose and many animals with early mortality.
  - **Cancer potency factor is 26 (mg/kg/day)<sup>-1</sup>**
  - Most potent carcinogen evaluated by DWQI.
- **Health-based MCL is 0.0013 µg/L (1.3 ng/L).**
  - One in one million ( $10^{-6}$ ) lifetime cancer risk
  - Standard exposure assumptions (2 L/day drinking water consumption; 70 kg adult body weight).

## ***More Recent Information Relevant to Health-based MCL Development***

- Health Effects Subcommittee will evaluate relevant information that became available after March 2009 to determine whether Health-based MCL will be updated.
  - USEPA IRIS cancer assessment (September 2009)
  - USEPA Office of Water UCMR3 Health Reference Level (2014)
  - Literature search
  - Request for submission of new information

# ***USEPA IRIS Cancer Assessment (September 2009)***

- Likely to be carcinogenic to humans
- Data support mutagenic mode of action (MOA) for cancer
- Cancer potency factor is  $30 \text{ (mg/kg/day)}^{-1}$ 
  - Slightly more stringent than DWQI potency factor,  $26 \text{ (mg/kg/day)}^{-1}$
  - Based on time-to-tumor modeling of female mouse data (NTP, 1993), as is DWQI potency factor.
  - Based on combined incidence of all tumor types.
  - One of the most stringent cancer potency factors in IRIS database.
- Recommends application of **Age Dependent Adjustment Factors (ADAFs)** in 1,2,3-TCP risk assessment.
  - Account for greater susceptibility to mutagenic carcinogens from early life exposure.

# ***Age Dependent Adjustment Factors (ADAFs)***

- USEPA (2005) guidance for risk assessment of carcinogens with a mutagenic mode of action
  - USEPA had not yet used this approach when DWQI Health-based MCL was developed (March 2009).
  - USEPA has now used this approach for risk assessment of 1,2,3-TCP and other contaminants.
- ↑ cancer potency factor to account for greater susceptibility to mutagenic carcinogens during early life
  - ↑ 10-fold for exposures during first 2 years of life (birth until 2nd birthday)
  - ↑ 3-fold for exposures during next 14 years of life (2nd birthday to 16th birthday).
- Potency factor adjustments are combined with age-specific exposure values (e.g. drinking water consumption values).



***USEPA Office of Water***  
***Health Reference Level for 1,2,3-TCP***

- Benchmark for evaluation of UCMR3 data.
- **0.4 ng/L (0.0004 µg/L)** at one-in-one million ( $10^{-6}$ ) cancer risk level.
- Based on
  - USEPA IRIS cancer potency factor,
  - Age Dependent Adjustment Factors
  - Age-specific drinking water consumption values (USEPA Exposure Factors Handbook, 2011).

# ***Comparison of Basis of New Jersey and USEPA Health-based Water Values for 1,2,3-TCP***

	Year	Health-based Value <sup>a</sup>	Cancer Potency Factor
NJDEP Drinking Water Guidance	1999	5 ng/L	<ul style="list-style-type: none"> <li>• 7 (mg/kg/day)<sup>-1</sup></li> <li>• Rats, multiple sites (NTP, 1993).</li> </ul>
NJDEP Ground Water Quality Criterion	2005	5 ng/L	
DWQI Health-based MCL MCL <sup>b</sup>	2009	1.3 ng/L	<ul style="list-style-type: none"> <li>• Linearized multistage model</li> <li>• USEPA HEAST (1995)</li> </ul>
USEPA Office of Water UCMR3 Health Reference Level	2014	0.4 ng/L	<ul style="list-style-type: none"> <li>• 26 (mg/kg/day)<sup>-1</sup></li> <li>• Female mice, forestomach (NTP, 1993).</li> <li>• Time-to-tumor model</li> <li>• DWQI (March 2009)</li> </ul>
			<ul style="list-style-type: none"> <li>• 30 (mg/kg/day)<sup>-1</sup></li> <li>• Female mice, combined tumors (NTP, 1993).</li> <li>• Time-to-tumor model with Age Dependent Adjustment Factors.</li> <li>• USEPA IRIS (September 2009).</li> </ul>

<sup>a</sup> All health-based values are based on one-in-one million lifetime cancer risk.

# ***Literature Search for Recent Relevant Information***

- No new scientific studies identified.
- Two publications on risk assessment of 1,2,3-TCP:
  - Tardiff and Carson (2010). Derivation of a reference dose and drinking water equivalent level for 1,2,3-trichloropropane. *Food Chem. Toxicol.* 48: 1488-510.
  - Meek et al. (2014). Mode of action human relevance (species concordance) framework: Evolution of the Bradford Hill considerations and comparative analysis of weight of evidence. *J. Appl. Toxicol.* 34: 595-606.

# *Summary*

- 1,2,3-TCP is a potent mutagenic carcinogen.
  - It caused tumors at multiple sites beginning early in life in both sexes of two species of rodents.
- The basis and numerical value of the cancer potency factors developed by DWQI (March 2009) and USEPA IRIS (September 2009) are in close agreement.
- Current USEPA guidance recommends Age Dependent Adjustment Factors in chronic drinking water risk assessment of 1,2,3-TCP.
  - ADAFs would reduce the Health-based MCL by about 2.5-fold.
- The MCL recommendation for 1,2,3-TCP will likely be determined by the analytical Practical Quantitation Level (PQL) rather than the Health-based MCL.