HEALTH-BASED MAXIMUM CONTAMINANT LEVEL SUPPORT DOCUMENT: 1,4-DIOXANE

New Jersey Drinking Water Quality Institute
Health Effects Subcommittee

Subcommittee Members:
Jessie A. Gleason, M.S.P.H., Chair
Keith R. Cooper, Ph.D.
Judith B. Klotz, M.S., Dr.P.H.
Gloria B. Post, Ph.D., DABT

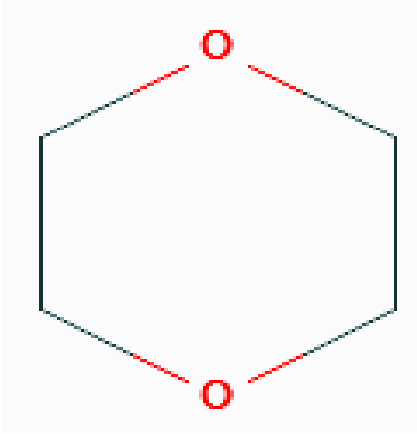
September 30, 2020

Background

- Drinking Water Quality Institute (DWQI)
  - Established by NJ SDWA (1984)
  - Charged with recommending Maximum Contaminant Levels (MCLs)
- Health Effects Subcommittee of DWQI is responsible for developing Health-based MCLs
  - Carcinogens: One in one million risk level from lifetime exposure (10^{-6})
  - Non-carcinogens: Not expected to result in “any adverse physiological effects from ingestion” for a lifetime
- December 2018 - NJDEP Commissioner requested DWQI recommend an MCL for 1,4-dioxane

1,4-Dioxane

- 1,4-Dioxane is a synthetic chemical used as a solvent in products such as adhesives, resins, oils and waxes; and wood pulping



- Historically, 90% was used as a stabilizer for chlorinated solvents, particularly trichloroethane (1,1,1-TCA).
  - As 1,1,1-TCA was phased-out, the production of 1,4-dioxane has declined.

- Also used in the manufacture of pharmaceuticals, certain plastics and rubber, and other products and is an unintended byproduct of surfactants used in personal care products and cosmetics.

Environmental Fate and Transport

- 1,4-Dioxane can be released into the air, water, and soil at locations where it is produced or used as a stabilizer for chlorinated solvents
- It is expected to be degraded in the atmosphere and in general is not a concern in the atmosphere
- In water, 1,4-dioxane is stable
- In soil, highly mobile and can leach in lower soil horizons and groundwater.
- 1,4-Dioxane is detected in surface water almost as frequently as groundwater, but concentrations are generally lower

1,4-Dioxane Occurrence in NJ Public Water Supplies

New Jersey v. National Public Water System (PWS)
1,4-Dioxane Detections in UCMR3 (2013-2015)

	New Jersey PWS		**National PWS (other than NJ)**	
	# Detects	% Detects	# Detects	% Detects
≥ 0.07 µg/L (MRL)	80/174	45.9%	997/4741	21.0%
≥ 0.35 µg/L (Health Reference Concentration*)	30/174	17.2%	315/4741	6.6%

Sources of Human Exposure

- Drinking water is the dominant pathway of exposure
  - Main sources of drinking water contamination:
    - Wastewater discharge (widespread use in consumer products), unintended spills or leaks, historical disposal practices associated with 1,1,1-TCA
    - Inhalation or dermal exposure is not significant compared to ingestion
- 1,4-Dioxane is a byproduct in consumer products (cosmetics and shampoos, household detergents, etc..)
- Present as a food additive and in formulation of pesticides and food packaging

Other Guidance - USEPA

- USEPA – no MCL for 1,4-dioxane
  - Listed on Drinking Water Contaminant Candidate List 3
  - No regulatory determination made on MCL development
- USEPA IRIS cancer slope factor of 0.1 $(mg/kg/day)^{-1}$
- IRIS slope is basis of USEPA (2013) Office of Water Drinking Water Reference Concentration range:
  - 0.35 to 35 ug/L calculated from:
  - risk levels of 1 in 10,000 (10^{-4}) to 1 in 1 million (10^{-6})

Other Guidance - NJDEP

- NJ Ground Water Quality Criteria (GWQC): human health-based ground water concentration
  - 1-in-1 million cancer risk level
  - IRIS is one of the sources of toxicity factors for NJDEP GWQC

Year	Criteria	Basis	Value
2008	Interim Specific GWQC	IRIS (1988)	3 µg/L
2010	Interim Specific GWQC	IRIS (2010)	0.35 µg/L
2018	Ground Water Quality Standard	IRIS (2010/2013)	0.4 µg/L*

*NJDEP GWQS regulations specify rounding to one significant figure.

Other Guidance - States

- Health Effects Subcommittee reviewed basis of available state guidance.
- 13 states with a drinking water or ground water standard or guidance for 1,4-dioxane were identified.
- All 13 states rely on USEPA IRIS (2013) cancer slope factor
- Guidance values range from 0.3 µg/L – 35 µg/L.

  Variations are due to differences in:
  - Cancer risk level (10^{-4} to 10^{-6})
  - Exposure assumptions

Toxicokinetics

- Health Effects Subcommittee review of information from USEPA IRIS (2013).
- Limited data suggest dermal absorption of 1,4-dioxane is low
- Tissue distribution: No data in humans.

  Rat studies: levels in blood higher than other tissues
- Excretion: 1,4-Dioxane and its metabolites are primarily excreted in urine in humans exposed via inhalation
  - Rapid excretion - The human half-life approx. 1 hour after exposure to 50 ppm in air for 6 hours
  - No excretion data following oral exposure

Health Effects Subcommittee Review

- Health Effects Subcommittee review focused primarily on:
  - Carcinogenicity studies
  - Related mode of action information
  - Rationale: All USEPA and state guidelines, including NJDEP GWQS (2018), are based on the USEPA IRIS (2013) cancer slope factor,

- Review used USEPA IRIS (2013) evaluation as its starting point and included information submitted to DWQI in response to public input and literature search of more recent information

Human Health Studies

- Primarily focused on reviews by USEPA (2013), EU (2002) and others:
- Limited number of human health studies
- All of the studies are based on inhalation (no drinking water studies)
- Low quality of human study reporting, data obtained from secondary sources, study details missing, small cohort sizes (low study power).
- Potential for increased risk of cancer could not be adequately evaluated from epidemiologic data

Toxicological Studies - Carcinogenicity

- 1,4-Dioxane caused tumors in multiple organs in studies in rats, mice and guinea pigs
- Subcommittee report includes a Table summarizing carcinogenicity studies of 1,4-dioxane in laboratory animals including sites at which tumor incidence was increased
- Health Effects Subcommittee agrees with USEPA IRIS (2013) conclusions that 1,4-dioxane should be described as “likely to be carcinogenic to humans” based on the USEPA (2005) Guidelines for Carcinogen Risk Assessment.

Carcinogenic Mode of Action

- Health Effects Subcommittee reviewed studies cited by USEPA IRIS (2013) and more recent studies
- Further, reviewed NJDEP (2015 and 2018) responses to comments on the draft NJDEP (2010) Interim Specific GWQS and proposed NJDEP (2018) GWQS.
- Several comments suggest a threshold mode of action (i.e. a Reference Dose)
- Health Effects Subcommittee conducted a detailed review of the relevant publications and ***concluded that the mode of action by which 1,4-dioxane causes tumors is not established.***
  - This is consistent with the conclusions of USEPA IRIS (2013) and NJDEP (2015, 2018).

USEPA (2005) Guidelines

- Guidelines for Carcinogen Risk Assessment (2005)
  - When tumors occur through a mutagenic mode of action or the mode of action for carcinogenicity is not established then:
    - Risk assessment for carcinogens is based on low-dose linear extrapolation (i.e. non-threshold approach using a cancer slope factor)
- Health Effects Subcommittee concluded that the mode of action for 1,4-dioxane carcinogenicity has not been established.
- Therefore, the cancer risk assessment for 1,4-dioxane was based on low-dose linear extrapolation (i.e. a cancer slope factor).

Health-based MCL for Carcinogenic Effects

- USEPA IRIS (2013) Cancer Slope Factor of 0.1 $(mg/kg/day)^{-1}$
- Cancer slope factor based on incidence of liver tumors in female mice (Kano et al., 2009)
  - Most sensitive of the tumor types in several chronic studies of male and female mice and rats
- One-in-one million (10^{-6}) cancer risk level specified in the NJ Safe Drinking Water Act
- Current default USEPA exposure assumptions: 80 kg adult body weight and 2.4 L/day adult daily water consumption (0.03 L/kg/day)
  - Small change from previous default assumptions of 70 kg and 2 L/day (0.029 L/kg/day)

Calculation of Health-based MCL for Carcinogenic Effects

Daily dose resulting in 1-in-1 million (10^{-6}) lifetime cancer risk:

10^{-6} / 0.1 (mg/kg/day)$^{-1}$ = 1 x 10^{-5} mg/kg/day = **0.01 µg/kg/day**

Where: 0.1 (mg/kg/day)$^{-1}$ = cancer slope factor

Health-based Maximum Contaminant Level for 1,4-dioxane based on daily dose:

$$\frac{0.01\ \mu g/kg/day \times 80\ kg}{2.4\ L/day} = \mathbf{0.33\ \mu g/L}$$

Where: 80 kg = body weight; 2.4 L/day = daily water consumption

Health-based MCL Recommendation

- Health-based MCL for carcinogenic effects is 0.33 µg/L.
- For comparison, Health-based MCL for non-carcinogenic effects is 200 µg/L.
  - Based on USEPA (2013) Reference Dose of 0.03 mg/kg/day (liver and kidney toxicity in rats), and default exposure assumptions (80 kg body wt., 2 L/day water ingestion, 20% Relative Source Contribution)

- **Therefore, the recommended Health-based MCL is 0.33 µg/L**.