1,4-Dioxane in Drinking Water Legislative Report

The Human Health Risk Assessment evaluating 1,4-dioxane in North Carolina's drinking water, as directed by Session Law 2023-137; 9(a).

North Carolina Department of Environmental Quality

May 1, 2024

1,4-Dioxane Human Health Risk Assessment Report

We thank the following contributors for their exemplary service to North Carolinians through their dedication to the scientific integrity and accuracy of this report.

Contributing Scientists

Frannie Nilsen, PhD – NC Department of Environmental Quality

Elaina Kenyon, PhD – NC Secretaries Science Advisory Board Member, U.S. Environmental Protection Agency

Linda Birnbaum, PhD – Duke University

Betsey Tilson, MD – NC Secretaries Science Advisory Board Member; NC Department of Health and Human Services

Gina Kimble, PhD – NC Secretaries Science Advisory Board Member; Charlotte Water

Jamie DeWitt, PhD – NC Secretaries Science Advisory Board Member; Oregon State University

John Vandenburg, PhD – NC Secretaries Science Advisory Board Member; Duke University

Richard DiGuilio, PhD – NC Secretaries Science Advisory Board Member, Duke University

Tom Augspurger, PhD – NC Secretaries Science Advisory Board Chairperson; U.S. Fish and Wildlife Service

Subject Matter Experts

Bill Lane – NC Department of Environmental Quality

Jared Wilson, MS – NC Department of Environmental Quality

Jenny Graznak – NC Department of Environmental Quality

Robin Barrows – NC Department of Environmental Quality

Peter Ledford – NC Governor's Office

Sushma Masemore, PE – NC Department of Environmental Quality

Tammy Hill – NC Department of Environmental Quality

Virginia Guidry, PhD, MPH – NC Department of Health and Human Services

Zack Moore, MD, MPH – NC Department of Health and Human Services

1,4-Dioxane Human Health Risk Assessment Report

Table of Contents

1,4-Dioxane Human Health Risk Assessment Report

1. Executive Summary

On September 22, 2023, the North Carolina General Assembly directed the Department of Environmental Quality (DEQ) to prepare a human health risk assessment of 1,4-dioxane in drinking water supported by peer-reviewed scientific studies (Session Law 2023-137; House Bill 600, Section 9(a)). The purpose of the assessment is to assess the risk of 1,4-dioxane exposure in drinking water as there are currently no federal drinking water standards for 1,4-dioxane. Protection for North Carolinians from 1,4-dioxane in drinking water would come from water quality standards (WQS) that protect drinking water supplies.

To complete the assessment, DEQ convened a group of experts knowledgeable about 1,4-dioxane exposure and human toxicology. The group of experts included Toxicologists, Human Health Experts, and Exposure Scientists with federal, academic, and private sector affiliations. The content of the analysis, assessment, and report were guided and reviewed by the NC Secretaries' Science Advisory Board (SSAB), the NC Department of Health and Human Services (DHHS), and DEQ leadership. The report uses a diverse set of scientific opinions, including studies produced by the Yale School of Public Health, NC State University (NCSU), the Environmental Protection Agency (EPA), the Centers of Disease Control and Prevention (CDC), private consulting firms, and chemical companies. The feedback on the assessment provided by the SSAB, DHHS, and DEQ was incorporated in this report prior to submission to the Joint Legislative Commission on Governmental Operations.

1,4-Dioxane is a clear liquid primarily used as a solvent to manufacture other industrial and commercial chemicals. It can be released into the air, water, and soil at places where it is produced or used. 1,4-Dioxane easily mixes with water and moves through the soil into the groundwater, where it is stable and degrades very slowly. Long-term exposure to 1,4-dioxane through oral exposure led to cancer development in animal models. The International Agency for Research on Cancer (IARC), the U.S. DHHS, and the EPA have determined that 1,4-dioxane is classified as likely to be carcinogenic to humans, meaning that sufficient weight of evidence exists from animal studies to indicate similar health outcomes in humans.

To understand 1,4-dioxane in drinking water in NC, data collected across NC as part of a national drinking water testing campaign under the Unregulated Contaminant Monitoring (UCMR3) program were analyzed. Based on this UCMR3 data (2013-2015), NC was identified to have the 3rd highest measured concentration of 1,4-dioxane and was ranked 4th highest in the number of impacted drinking water systems in the US. Average 1,4-dioxane concentration of the detections in NC's drinking water (0.92 µg/L) was two times the national UCMR3 average concentration of 0.45 µg/L, with most of the detections occurring in the Cape Fear River Basin. North Carolinians' exposure to 1,4-dioxane is further expanded due to the chemical's presence in surface water, wastewater, and groundwater, which affect the overall quality of drinking water supplies and present additional potential routes of exposure. A review of all available statewide data between 2013-2023 shows that when 1,4-dioxane is detected, the range of environmental occurrence in these waters is between 0.07 – 22,000 µg/L.

A Human Health Risk Assessment (HHRA) is an assessment conducted through a consistent systematic process to estimate the nature and probability of adverse health effects in humans who may be exposed to chemicals in contaminated environmental media, now or in the future. This human health risk assessment of 1,4-dioxane in drinking water was conducted following the approach outlined in EPA's Human Health Risk Assessment to Inform Decision Making Framework. Using this Framework, peer-reviewed studies, EPA's IRIS assessment, CDC's assessment, and Health Canada's assessment were examined. Each assessment took a different approach to deriving a protective toxicity value, but all had the same goal of deriving a health-based toxicity value for oral exposure to prevent cancer. Both EPA IRIS and Health Canada's assessments agree that oral exposure to 1,4-dioxane causes carcinogenic effects in the liver, and more is known about the mode of action (MOA) for carcinogenic effects in liver compared to other organs. Other target organs (e.g., kidney, nasal cavity) develop tumors and the MOA for carcinogenic effects in these tissues are not as well understood. The major difference in the derivation of toxicity values is that the EPA performed the dose-response analysis using data for tumor development in multiple target organs, and the Health Canada dose-response analysis included only liver tumors. The EPA assessment produced a Cancer Slope Factor equivalent to 0.1 mg/kg-day using the most health protective modeling approach that is consistent across multi-media federal regulatory programs. Health Canada produced a health-based criterion equivalent to 0.0054 mg/kg-day which is not specifically labeled to be a cancer-protective value but is described as being protective of the pre-cancerous outcomes.

This report uses the exposure data and health-based values for cancer endpoint dose response information to determine how the risk in NC compares to the national risk. Based on the risk assessment, it is concluded that NC's residents are exposed to 1,4-dioxane concentrations that may be two times the national average in drinking water and as much as 4 times national averages in surface and groundwater. Based on the UCMR3 data, North Carolinians experienced approximately half the protection than the rest of the nation received from 1,4-dioxane in drinking water from 2013-2015 (NC UCMR3 = 38%; US UCMR3 = 78%; Table 4).

A health-based water quality standard can reduce the risk of further exposure. The assessment supports the application of a science-based cancer slope factor equivalent to 0.1 mg/kg-day to derive a WQS that provides adequate lifetime protection of drinking water supplies. Currently, NC residents receive only 21% of the protection that would be offered by a health-based WQS that limits the amount of 1,4-dioxane in drinking water supplies. The conclusions of this legislative report are consistent with the EPA's health-protective approach, the findings of the experts at Yale, NCSU, and the CDC.

2. Background

1,4-Dioxane is a clear liquid solvent primarily used to manufacture other chemicals. It can be released into the air, water, and soil at places where it is produced or used. 1,4-Dioxane easily mixes with water and moves through the soil into the groundwater, where it is stable and degrades very slowly. Long-term exposure to 1,4-dioxane in drinking water led to cancer development in animal models. The International Agency for Research on Cancer (IARC), the U.S. DHHS, and the EPA have determined that 1,4-dioxane is classified as likely to be carcinogenic to humans.

The United States EPA's Integrated Risk Information System (IRIS) program produced an oral exposure toxicity assessment of 1,4-dioxane that was initially published on August 11, 2010, and updated to include a carcinogenicity assessment and an inhalation reference concentration on September 30, 2013. The update provided by the EPA's IRIS program in 2013 added inhalation toxicity to the assessment, but the oral exposure toxicity sections were not updated. Based on the Guidelines for Carcinogen Risk Assessment (EPA, 2005), the IRIS program designated 1,4-dioxane as "likely to be carcinogenic to humans". This classification is based on occurrence of tumors in multiple organs in both male and female rats and mice exposed to 1,4-dioxane in drinking water for two years. 1,4-Dioxane is classified as likely to be carcinogenic to humans through all routes of exposure (EPA IRIS, 2013).

The IRIS program was created in 1985 to provide a database of human health assessments for chemicals found in the environment. The goal of the IRIS Program was to foster consistency in the evaluation of chemical toxicity across the EPA. The IRIS Program has evolved with the state of the science to produce evidence-based assessments and to provide an increasing number of opportunities for public input into the IRIS process. IRIS assessments are not regulations, but the long-term consistency in the assessment criteria provides a critical part of the scientific foundation for decision-making to protect human health under an array of environmental laws (e.g., Clean Water Act; Clean Air Act; Safe Drinking Water Act; Comprehensive Environmental Response, Compensation, and Liability Act).

After the updated IRIS assessment for 1,4-dioxane was released in 2013, the Third Unregulated Contaminant Monitoring Rule (UCMR3) sampling and monitoring program that included 1,4-dioxane was conducted nationally at drinking water systems (2013 – 2015). The UCMR3 data revealed North Carolina had the third highest measured concentration of 1,4-dioxane nationwide (8.8 µg/L). Four percent of the measurements taken across NC had detectable levels of 1,4-dioxane (limit of detection (LOD) = 0.07 µg/L, Table A-1). Measurements with detections included 24 public water systems, out of 151 sampled, across NC that exceeded the EPA's 1,4-dioxane health-based toxicity value of 0.35 µg/L. NC had one of the highest numbers of drinking water systems impacted nationally (California (73), New York (31), New Jersey (30), North Carolina (24), and Illinois (21); (Adamson *et al.*, 2017)).

Following the UCMR3 data publication, and the various environmental monitoring and regulatory initiatives for 1,4-dioxane that have been ongoing since 2013, DEQ has been directed to prepare a human health risk assessment of 1,4-dioxane in drinking water to better understand the exposure to 1,4-dioxane among North Carolinians and potential health risks from that exposure. This report serves that purpose and is supported by peer-reviewed scientific studies that examine oral exposure data related to drinking water. It should be acknowledged that the actual dose to some human populations may be higher since inhalation of 1,4-dioxane is a viable route of exposure.

3. Methodology

A Human Health Risk Assessment (HHRA) is an assessment conducted by a consistent systematic process to estimate the nature and probability of adverse health effects in humans who may be exposed to chemicals in contaminated environmental media, now or in the future. The HHRA process consists of four-steps: *Exposure Assessment, Hazard Identification, Dose Response Assessment,* and *Risk Characterization* (Figure 1). The Planning and Scoping step that is critical to the success of the HHRA comes before the four-step assessment is conducted. During the planning process, any potential routes of exposure to the chemical and all health outcomes are identified and then organized for evaluation in the four-step process (EPA, 2022). Including all exposure routes, health outcomes, and impacted populations is a routine part of the complete HHRA process and requires years to complete. To better support decision making, the EPA created the Human Health Risk Assessment to Inform Decision Making Framework (EPA 2014). This framework truncates the lengthy HHRA process by ensuring that each of the four-steps are 'fit for purpose' and address the regulatory questions that the assessment is being conducted to answer. This report utilized the EPA's Human Health Risk Assessment to Inform Decision Making Framework following the guidance of the NC Secretaries' Science Advisory Board that the framework is appropriate for the legislative directive DEQ has been given, the objective of the assessment, and is possible to complete within the time frame given.

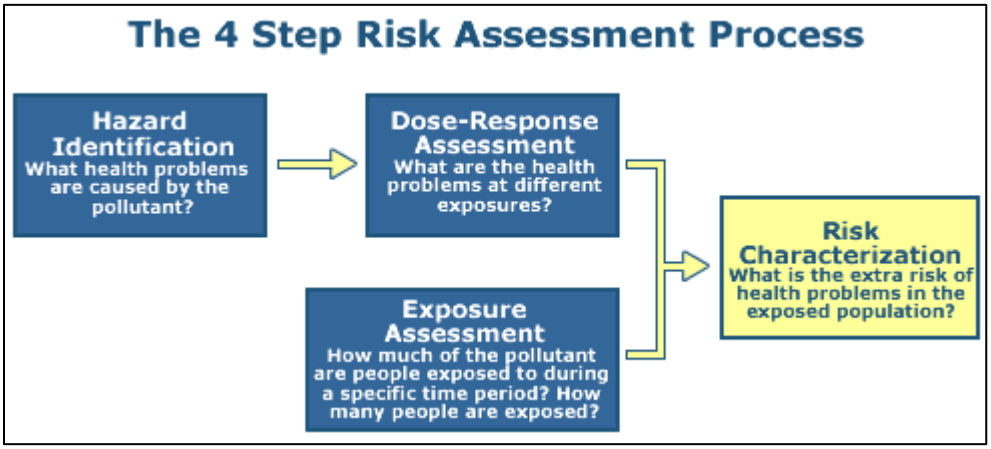

Figure 1: The four-step Human Health Risk Assessment process (EPA, 2022).

DEQ followed the legislative focus on drinking water and the Assessment Framework through its expert group to characterize the risk associated with 1,4-dioxane in drinking water (versus all routes of exposure) in NC in a specific and efficient manner. Due to the time constraint on producing the final report, all formal assessments of 1,4-dioxane produced by a federal agency were included in the *Effects Assessment*; any new peer-reviewed scientific studies published since the last comprehensive report was published were included and reviewed.

The directive of the assessment and report focuses on the cancer outcomes in each of the included publications, since 1,4-dioxane is classified as a likely human carcinogen and the Cancer Slope (Potency) Factor is used in the derivation of a standard according to NC's water quality rules (NCAC 02B.0202 and

02L.0208; (EPA IRIS, 2013)). It should be noted that EPA's use of the term "likely" does not correspond to a quantifiable probability but denotes the weight of the scientific evidence related to cancer outcomes for the chemical (EPA, 2005). There are five classifications for the chemicals assessed for carcinogenicity by the IRIS program, three of the five are assigned to chemicals that have scientific evidence that exposure induces cancer outcomes (Table 1).

Table 1: The Carcinogenic classifications and their weight of evidence descriptors from the EPA Carcinogenic Risk Assessment Guidelines (EPA, 2005).

Classification	Description
"Carcinogenic to Humans"	Indicates strong evidence of human carcinogenicity; covers different combinations of evidence from human and animal studies.
"Likely to Be Carcinogenic to Humans"	Appropriate when the weight of the evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor "Carcinogenic to Humans."
"Suggestive Evidence of Carcinogenic Potential"	Appropriate when the weight of evidence is suggestive of carcinogenicity; a concern for potential carcinogenic effects in humans is raised, but the data are judged not sufficient for a stronger conclusion.
"Inadequate Information to Assess Carcinogenic Potential"	Appropriate when available data are judged inadequate for applying one of the other descriptors.
"Not Likely to Be Carcinogenic to Humans"	This descriptor is appropriate when the available data are considered robust for deciding that there is no basis for human hazard concern.

The remaining sections in this report walk through DEQ's *Exposure Assessment, Effects Assessment*, and *Risk Characterization* that were conducted specifically to respond to the legislative directive.

4. Exposure Assessment

The Exposure Assessment consists of the available 1,4-dioxane data from across NC and the UCMR3 data (2013- 2015) that is publicly available. This section establishes the prevalence of 1,4-dioxane across NC (using wastewater and surface water data) and highlights the difference in prevalence and exposure to 1,4-dioxane in NC (using drinking water data).

The resulting data from the Exposure Assessment were used to inform the Risk Characterization and provided enough detail to determine how many North Carolinians are impacted by 1,4-dioxane in their drinking water and the current concentration of 1,4-dioxane in their drinking water.

The data used in the Exposure Assessment met the required data quality metrics (detailed in Appendix). The analysis plan consists of the approach, method, and metric for conducting and contextualizing the assessment. The steps of the analysis plan are as follows,

- Approach: Describe prevalence and exposure to 1,4-dioxane and estimate the impacted population using all environmental occurrence and drinking water data available to DEQ.
- Method: Compare environmental occurrence data to drinking water data and calculate the percent detections and percent detections above the national average value reported in the UCMR3 data.
- Metric: Compare NC Exposure data to the National UCMR3 data to determine if the exposure experienced by NC is 'average' or 'irregular', based on mean value and standard deviation of the 1,4-dioxane concentrations reported in drinking water from both datasets.

4.1. Exposure Data

The data included in the exposure assessment consists of occurrence data across NC from DEQ's ambient surface water monitoring, wastewater monitoring, and public water supply programs. Drinking water data was also provided from the Fayetteville Public Works Commission (FPWC), the Cape Fear Public Utility Authority (CFPUA), the Pittsboro Water Treatment Plant, and the Piedmont Triad Regional Water Authority (in High Point, NC) for inclusion in this assessment. Each of the datasets provided for the exposure assessment are compared to the suite of data quality metrics provided in the EPA Framework: soundness, applicability and utility, clarity and completeness, uncertainty and variability, and evaluation and review. Descriptions of each data quality metric provided in the EPA Framework are detailed in Table A-2 in the Appendix (EPA, 2014).

All the data sets were determined to be fit for the purpose of this assessment (Table A-2). After the data were evaluated for quality, they were pooled into one large data set and separated into three categories to reflect the overall prevalence of 1,4-dioxane in NC [environmental occurrence], and the two exposure scenarios that have taken place in NC under a Special Order of Consent (SOC) between the Environmental Management Commission (EMC) and the City of Greensboro to reduce 1,4-dioxane in their wastewater effluent [pre-regulatory efforts, and post-regulatory efforts]. The final SOC was issued in December of 2021, and produced additional data related to 1,4-dioxane in the waters of the state. While the SOC was being implemented, DEQ worked with other municipalities to decrease 1,4-dioxane concentrations in other impacted drinking water supplies.

For this report, the drinking water exposure data were separated into three categories; environmental occurrence data, before, and after the SOC was implemented (pre-regulatory efforts, and post-regulatory efforts). The datasets that are included in each of the categories are listed below.

- Environmental Occurrence: DEQ surface water (SW), DEQ wastewater (WW), drinking water utility raw/intake water (*i.e.,* surface or ground water) from 2013 through 2023,
- Pre-Regulatory Efforts – Drinking water utility finished water from 2014 through Dec 2021.
- Post-Regulatory Efforts – Drinking water utility finished water from Jan 2022 through present (most recent data retrieved January 2024).

4.2. Exposure Analysis

After the included data were separated into three categories for analysis, the descriptive statistics (mean value, standard deviation (SD), minimum value, maximum value) for each of the three data categories were calculated to characterize the differences in each data category (Table 2). The descriptive statistics for the NC-specific and the national UCMR3 data are included to provide context for the NC exposure data, since UCMR3 sampled drinking water. The percentage of detections of 1,4-dioxane in each category was calculated, and the percentage of detections that were above the UCMR3 national average 1,4-dioxane in drinking water concentration was determined for the exposure categories.

The Environmental Occurrence data was 0.07 – 22,000 µg/L with most of the 36% of statewide detections being from the Cape Fear River Basin (Figure 2, left). The drinking water data values, number of detections, and number of detections above the UCMR national average of 0.45 µg/L all decreased after regulatory efforts were in place. Other areas outside the Cape Fear River Basin saw significant increase in the percentage of samples below the 1,4-dioxane LOD due to actions taken voluntarily. The number of drinking water locations with detections above the UCMR3 average value did increase after the regulatory efforts were in place, likely due to the targeted sampling related to the regulatory effort and not increased environmental occurrences (Table 2, Figure 2, top and bottom right).

Table 2: Descriptive statistics for each of the three categories of data used in the Exposure Assessment.

Data Category	***Total number of measurements***	***Descriptive Statistics^*** *mean ± SD (min-max)* **(µg/L)**	***% Overall Detections (n)****	***Exposure Data Only*** ***% Detections above UCMR3 National mean (n)***
NC Environmental Occurrence (2013-2023)[a]	6,942	172 ± 1,215 (0.07-22,000)	36% (2,521)	
UCMR3 NC Data (2013-2015)[b]	1,324	0.92 ± 1.59 (0.07-8.8)	16% (213)	30% (63)
NC Pre-Regulatory Efforts (2014-2021)[b]	286	2.49 ± 6.33 (0.07-49.8)	73% (209)	65% (135)
NC Post-Regulatory Efforts (2022-2023)[b]	392	1.67 ± 2.43 (0.09-16.1)	35% (138)	70% (97)
UCMR3 National Data (2013-2015)[b]	36,706	0.45 ± 1.02 (0.07-22.93)	9% (3,381)	0.2% (660)

*Detections are defined as measurements that are above the limit of detection (LOD) for the analytical method used, the lowest LOD for all methods used was 0.07µg/L. ^ Descriptive statistics do not include data that was reported as below the LOD.
a- Represents 1,4-dioxane data in NC's surface, waste, and drinking water.
b- Represents 1,4-dioxane data in NC's (rows 2-4) and nationwide (row 5) drinking water.

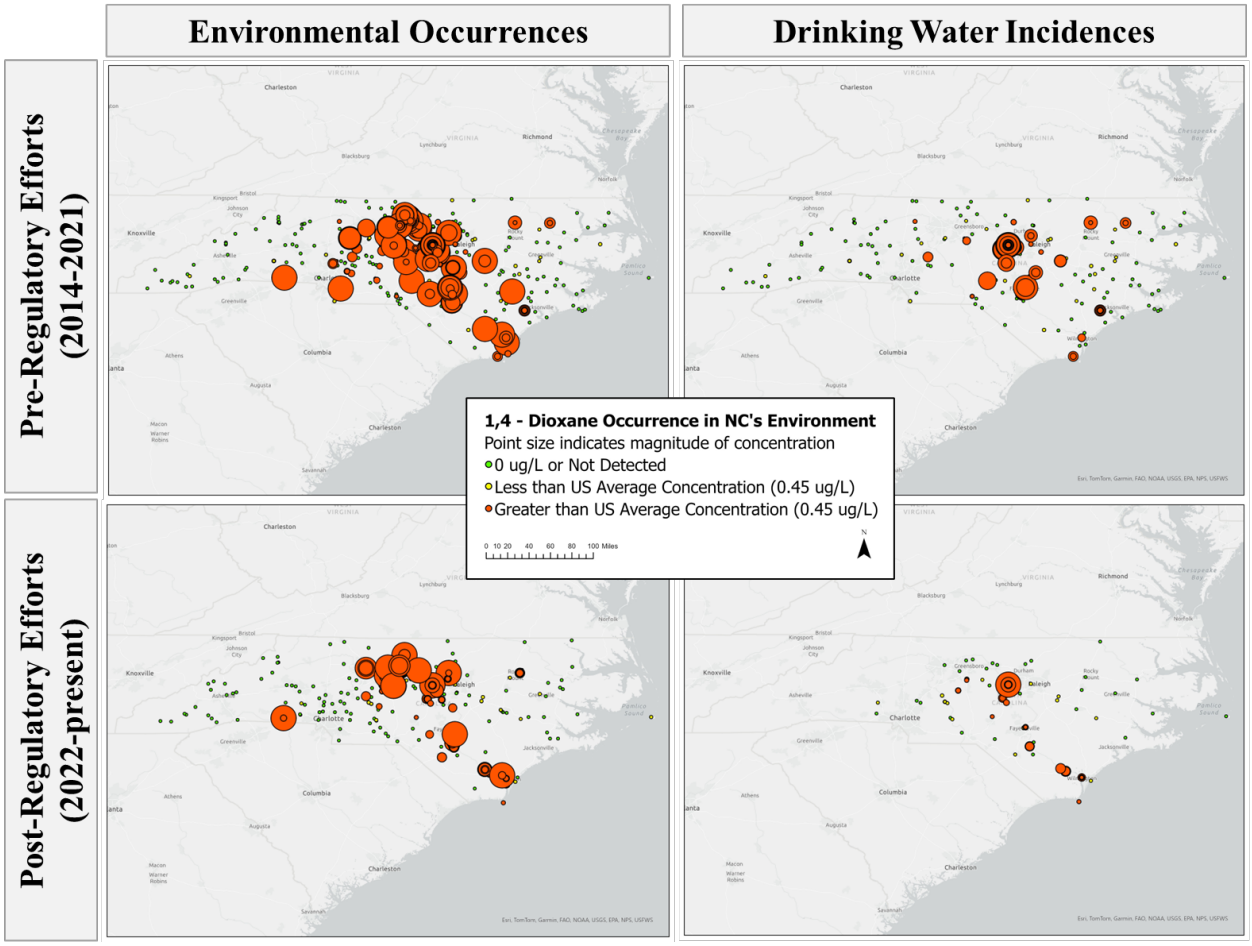

Figure 2: Environmental **occurrence data** of 1,4-dioxane in North Carolina's surface water, wastewater, and drinking water utility raw/intake water (left); **drinking water exposure data** from North Carolina's public water utilities and UCMR3 **before** regulatory efforts were conducted (top right) and **after** the regulatory efforts were conducted (bottom right).

4.3. Exposure Summary

The data examined in this report indicate the following:

1- Most North Carolinians outside of the Cape Fear River Basin are not exposed to 1,4-dioxane at concentrations above the UCMR3 national average value (Figure 2 right, top and bottom).
2- Some of those who are exposed within the Cape Fear River Basin are exposed to the third highest drinking water concentrations in the nation (UCMR3 Data).
3- Regulatory attention focused to reduce concentrations led to decreased 1,4-dioxane environmental and drinking water exposure in the Cape Fear River Basin in NC (Figure 1, top - left and right compared to bottom - left and right).
4- The public outreach efforts regarding 1,4-dioxane exposure in drinking water resulted in many locations in NC decreasing 1,4-dioxane exposure outside of the Cape Fear River Basin due to voluntary and/or other actions.

5. Effects Assessment

The toxicological information provided in the *Effects Assessment* are used to inform the *Risk Characterization* and provides enough detail to determine how the published health-based guidance values for cancer endpoints were calculated and compare the methods/models used in their calculation.

Only peer-reviewed published assessments and/or studies were evaluated against the data quality metrics (described in Appendix). The *Effects Assessment* followed the steps of the analysis plan, which were,

- Approach: Compare existing assessments and evaluate quality of any new data for application of health-based guidance value for cancer endpoint calculations.
- Method: Summarize existing and relevant new literature and compare data used to derive the health-based guidance values for cancer endpoint provided.
- Metric: Compare any new data to EPA guidance for health-based guidance value for cancer endpoint derivation.

5.1. Effects Data

The publications that were evaluated for use in the effects assessment were the US EPA's Toxicological Review of 1,4-Dioxane (EPA IRIS, 2010), the EPA's Toxicological Review of 1,4-Dioxane (With Inhalation Update) (EPA IRIS, 2013), the EPA's TSCA Risk Evaluation for 1,4-Dioxane (EPA TSCA, 2020), the CDC Agency for Toxic Substances and Disease Registry Toxicological Profile for 1,4-dioxane (ATSDR, 2012), Health Canada's 1,4-dioxane Guidelines for Canadian Drinking Water Quality technical report (Health Canada, 2021), and the European Chemicals Agency Scientific report for evaluation of limit values for 1,4-dioxane at the workplace (ECHA, 2021). Each of these assessments are compared to the suite of data quality metrics provided in the EPA Framework: soundness, applicability and utility, clarity and completeness, uncertainty and variability, and evaluation and review in Table A-4 in the Appendix.

After the assessments were examined for quality, two of the six evaluated were determined not to be appropriate for inclusion in this assessment (Table A-4). The 2021 ECHA report and the EPA's TSCA 2020 Risk Evaluation were excluded from this report because they included occupational/inhalation exposures to 1,4-dioxane that are outside the scope of the legislative directive, which is focused solely on drinking water exposure to 1,4-dioxane. EPA's TSCA 2023 Risk Evaluation Update is still a draft document, is specific to the conditions of use and utilizes existing EPA toxicity values to determine risk for each condition of use, and is not yet allowed to be cited, all of which make it out of scope for inclusion here. The EPA's 2010 Toxicological Review of 1,4-Dioxane from the IRIS program is referenced in the 2013 IRIS Review with the Inhalation Update, and no new oral exposure data is included in the updated assessment (EPA IRIS, 2010, 2013). The 2013 IRIS document is used in this report as it is the most current version of the IRIS assessment, despite the oral exposure information being unchanged from the 2010 document. For this reason, only the 2013 EPA IRIS document, the 2012 ATSDR document, and the 2021 guidance document from Health Canada are included in the following analysis section of the Effects Assessment since they are specific to oral exposure to 1,4-dioxane (Table A-4). The 2020 EPA TSCA document includes a discussion of newer scientific studies that were included in the

2021 Health Canada document and was used to support the comprehensive review of the Health Canada document.

5.2. Effects Analysis

The *Effects Analysis* consists of two parts, the *Hazard Identification* section, and the *Dose-Response Analysis* section. These two components of the Effect Analysis enable the detail and complexity of the quantitative aspects of the included assessments to be evaluated.

5.2.1. Hazard Identification

The *Hazard Identification* section highlights any hazard to human health that may occur from the exposure to 1,4-dioxane in drinking water. This assessment is focused on the cancer-outcomes related to drinking water exposure of 1,4-dioxane. The three toxicity assessments that met scope and quality criteria for inclusion in this assessment are the EPA IRIS assessment, the ATSDR assessment, and the Health Canada assessment. The approaches used to derive oral 1,4-dioxane toxicity values for each of the assessments are compared in Table 3. The assumptions and methods used for deriving the toxicity values are discussed in the *Dose-Response Analysis* below.

All three assessments identify cancer as the primary human health hazard for oral exposure to 1,4-dioxane and classify 1,4-dioxane as likely to be carcinogenic to humans according to the EPA's and the International Agency for Research on Cancer's (IARC) criteria (based on sufficient evidence in experimental animals) (EPA IRIS, 2010; ATSDR, 2012; Health Canada, 2021). The ATSDR assessment also notes that the federal DHHS has stated that 1,4-dioxane is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity in experimental animals (ATSDR, 2012).

There were 8 and 9 years between publication of the 2013 EPA IRIS assessment and the 2012 ATSDR assessment and the publication if the 2021 Health Canada assessment, respectively. Each assessment took a different approach to deriving a protective toxicity value, but all had the same goal of deriving a health-based toxicity value for oral exposure to prevent cancer. The EPA produced a Reference Dose (RfD) and a Cancer Slope Factor (CSF), which are lifetime (70 years) anticipated protective values for the non-cancer, and cancer outcomes, respectively. The ATSDR produced a chronic exposure Minimal Risk Level (MRL), which is anticipated protective for exposure longer than one year. The Health Canada assessment produced a Total Daily Intake (TDI), which is analogous to the RfD used by the EPA, that was based on the carcinogenic and non-carcinogenic effects in the liver (ATSDR, 2012; EPA IRIS, 2013; Health Canada, 2021)

The EPA health-based value for the RfD was based on rat liver and kidney toxicity. The EPA cancer dose-response analysis utilized mouse liver tumors and linear low dose extrapolation based on their MOA analysis (EPA IRIS, 2013). The 2012 ATSDR MRL value was based on liver toxicity in rats (ATSDR, 2012). The 2021 Health Canada TDI is based on pre-cancerous liver lesions in rats (Health Canada, 2021). The main difference between the EPA and ATSDR assessments and the Health Canada assessment is the toxicological MOA that was used to support the derivation of their health-based toxicity values.

These differences are discussed in the *Dose Response Analysis* section below. For a detailed explanation of the modeling approaches used in these assessments refer to the EPA's Benchmark Dose Technical Guidance document (EPA, 2012).

5.2.2. *Dose- Response Analysis*

This *Dose-Response Analysis* is focused on the specific details that supported the cancer-related toxicity values reported in the IRIS and Health Canada assessments discussed in the *Hazard Identification* section.

Although the EPA and Health Canada's assessments result in different values, both cancer assessments use liver effects as the sensitive endpoint and use the Benchmark Dose Modeling Software (BMDS) for data analysis. The interpretation of the data below the observable range (low dose extrapolation method) and choice of data for dose-response modeling is where the assessments differ. There are two major differences in the EPA and Health Canada assessments:

1- Data from different species and target organ effects were used for dose-response analysis.
2- Different low dose extrapolation approaches were selected based on cancer MOA analysis.
    a. Both assessments agree that a non-genotoxic MOA could be operative however, each assessment weighs the supporting data differently to determine which low dose extrapolation approach to use.

Table 3: Comparison of toxicological details of the EPA, ATSDR and Health Canada toxicity assessments.

Assessment Type	**EPA IRIS Assessment**		**Health Canada Non-Cancer Value** (2021)	**ATSDR Non- Cancer Value** (2012)
	EPA Carcinogenicity (2013)	**EPA Non-Cancer Value** (2013)		
Species and Target Organ	Mouse Liver	Rat liver and kidney toxicity	Rat Liver	Rat liver
Endpoint and data used for dose-response modeling	Hepatocellular adenomas and carcinomas, female (Kano *et al.*, 2009)	NOAEL (did not use benchmark dose modeling), male rat (Kociba *et al.*, 1974)	Hepatocellular necrosis, combined male & female data (Kociba *et al.*, 1974)	NOAEL (did not use benchmark dose modeling), male rat (Kociba *et al.*, 1974)
Benchmark Dose Model Used	Log-logistic with linear low dose extrapolation	*Not applicable* (used NOAEL)	Log-Probit	*Not applicable* (used NOAEL)
POD	$BMDL_{50}$ = 32.93 mg/kg-day	NOAEL = 9.6 mg/kg-day	$BMDL_5$ = 5.4 mg/kg-day	NOAEL = 9.6 mg/kg-day
POD_{HED}	$BMDL_{50HED}$ = 4.95 mg/kg-day	*Not calculated*	*Not calculated*	*Not calculated*
Total UF applied	*Not applicable*	300 (UF_A=10, UF_H=10, UF_D=3)	1000 (UF_A=10, UF_H=10, UF_D=10)	100 (UF_A=10, UF_H=10)
Risk probability	1 in a million (10^{-6})	*Not applicable*	*Not applicable*	*Not applicable*
Low Dose Extrapolation method	Linear, no threshold	Assumes threshold, uses UFs[1]	Threshold (non-linear), uses UFs	Assumes threshold, uses UFs[1]
Health-based criterion	CSF = 0.1 $(mg/kg\text{-}day)^{-1}$	RfD = 0.03 mg/kg-day	TDI = 0.0054 mg/kg-day	MRL = 0.1 mg/kg-day
Criterion description	Cancer protective factor for humans.	Lifetime (70 years) exposure can be experienced with no non-cancer effects occurring in humans.		

UF= uncertainty factor; UF_A = animal to human extrapolation; UF_H =human interindividual variation; UF_D = incompleteness or limitations in chemical data base; POD = Point of departure; POD_{HED}= POD human equivalent dose; NOAEL/LOAEL= no or low observed adverse effect level; BMDL= lower (specified) confidence limit of specified benchmark response (%) level; BMD = benchmark dose.

Species and Target Organ Selection

A main difference in the toxicity values produced by all three assessments, is that only the EPA's CSF value was derived using mouse toxicity data, the other three non-cancer protective values were derived based on rat toxicity data (Table 3). The Health Canada TDI is not specifically labeled to be a cancer-protective value, but is described in the report as being protective of the pre-cancerous outcomes, and is therefore assumed protective of the cancer outcomes as well (Health Canada, 2021).

A major difference in the derivation of the toxicity values related to cancer outcomes in each of the assessments is that the EPA performed the dose-response analysis using data for tumor development in multiple target organs, and the Health Canada dose-response analysis included only liver tumors. The target organs used in the dose-response analysis are directly related to the type of extrapolation model used to derive the toxicity value relevant to humans. The extrapolation model is based on the toxicological MOA that occurs in the target organs that results in carcinogenic outcomes. The MOA details are discussed below. The resulting toxicity value from each assessment is also dependent upon the Uncertainty Factors (UFs) identified in each assessment, which vary based on the species, target organ, and other details of the data examined within the assessment (Table 3).

Mode of Action (MOA) Information

The MOA details specific to the target organ selected are critical in determining the appropriate low dose extrapolation model used to derive health-based values, because it can inform the shape of the dose-response curve at lower doses than those observed experimentally (EPA, 2005). There are two types of extrapolation approaches, the linear extrapolation approach and the non-linear extrapolation approach, and there are guidelines for when each should be used and when they should be used together. Linear extrapolation is also the appropriate approach when the MOA information is unclear because it is the most-health protective extrapolation approach (EPA, 2005).

Most of the available 1,4-dioxane MOA information is related to liver outcomes and not the tumors associated with the kidney, nasal cavity, mammary tissues, and peritoneal cavity (EPA IRIS, 2013). Both the EPA IRIS and the Health Canada assessments identify liver as the critical effect, but the EPA IRIS assessment reaches that conclusion by the systematic review and dose-response analysis for all possible target organs whereas the Health Canada assessment identifies it solely based on the availability of toxicity information (EPA IRIS, 2013; Health Canada, 2021).

Since the EPA examined many target organs for derivation of the toxicity values, and systematically reviewed scientific literature for all carcinogenic outcomes, the selection of the Linear Low-Dose extrapolation approach is appropriate due to the lack of MOA information for all the carcinogenic endpoints examined (EPA, 2005; EPA IRIS, 2013). Health Canada examined only liver endpoints and determined that liver tumors develop after a metabolic threshold is reached, then selected the Non-Linear extrapolation approach based solely on liver toxicity and excluded all other organs that are relevant to cancer and non-cancer outcomes. The EPA reviewed the critical studies that supported Health Canada's extrapolation approach, and reported that "*Based on evidence that cytotoxicity is not a necessary key event, the lack of consistent dose-response concordance between key events in the MOA and*

carcinogenicity, data gaps in support of key events, and the plausibility of alternative MOAs that would also be consistent with experimental observations, EPA determined that existing evidence is not sufficient to support the MOA for liver tumors proposed by Dourson et al. (2014, 2017)*."* (EPA TSCA, 2020).

The concept of metabolic saturation or metabolic threshold, where toxic effects only occur after a certain concentration of 1,4-dioxane has accumulated in tissues, is widely debated in the toxicology literature. There are only a few empirical studies that investigate the MOA details for 1,4-dioxane carcinogenicity that have been published since the IRIS assessment was completed in 2013. These studies investigated the MOA of liver carcinogenicity, and while the underlying mechanisms have begun to be elucidated, the complete pathway for liver-based carcinogenicity remains unclear. Four studies published between 2021 and 2022 identify two very different MOAs for liver tumor development which highlights the complexity of cancer biology and the difficulty in establishing a specific MOA for any single cancer outcome (Chappell, Heintz and Haws, 2021; Lafranconi *et al.*, 2021, Charkoftaki *et al.*, 2021; Chen *et al.*, 2022).

Risk Assessment Approaches

There are two different risk assessment approaches that can be used, and the selection of approach is based on the MOA information. Two recent literature reviews were conducted to support the different risk assessment approaches. The Lafranconi *et al.* (2023) review highlights the scientific studies that support the metabolic saturation and threshold approach. The Ginsberg, Chen and Vasiliou (2022) review highlights scientific studies that do not support the threshold approach and demonstrate that the low dose extrapolation approach is appropriate as well as including consideration of other issues such as possible impact of additional background exposures on liver effects. The short time between the publication of these two reviews demonstrates that the scientific community has not reached consensus on this topic, and there is uncertainty concerning the optimal risk assessment approach.

The EPA IRIS and Health Canada assessments examined here supported two different risk assessment approaches based on the selection of target organ and MOA information available. The EPA identified female mouse liver carcinoma as their critical effect for the target organ, since the CSF is based upon the dose-response data for the most sensitive species and gender (EPA IRIS, 2013). Since the MOA for 1,4-dioxane mediated carcinogenic action for peritoneal, mammary, nasal, and kidney tumors is not well understood and, in most cases, unknown, a linear low-dose extrapolation approach was used to estimate human carcinogenic risk associated with 1,4-dioxane exposure (EPA, 2005). Health Canada examined only liver outcomes for the derivation of the TDI value and determined that carcinogenic outcomes only occur at high doses that elicit metabolic saturation, so a threshold-based non-linear approach was taken, and a non-cancer health-based value was calculated for the protection of human health effects from 1,4-dioxane exposure (Health Canada, 2021).

The IRIS assessment agrees with the toxicity of 1,4-dioxane at high concentrations and provides that *"the CSF for 1,4-dioxane should not be used with exposures exceeding the point of departure ($BMDL_{50HED}$ = 4.95 mg/kg-day), because above this level the fitted dose-response model better characterizes what is known about the carcinogenicity of 1,4-dioxane".* The IRIS assessment also states that, "*It is suggested that liver toxicity is related to the accumulation of the parent compound following metabolic saturation at high doses; however, no in vivo or in vitro assays have examined the toxicity of metabolites resulting from*

1,4-dioxane to support this hypothesis." (EPA IRIS, 2013). This supports the linear-low dose extrapolation risk assessment approach, as the MOA for the concept of metabolic saturation is still not well understood since no work has been done to elucidate the toxicity of 1,4-dioxane compared to 1,4-dioxane's metabolites.

EPA identified areas of uncertainty where the threshold approach is not supported by the criteria that EPA requires for divergence from the linear low-dose extrapolation approach. This uncertainty included the lack of understanding of which compound (1,4-dioxane vs. metabolites) is causing the high-dose response related to metabolic saturation. Without scientific studies that remove this uncertainty and clarify which compound is active during metabolic saturation events, there is not enough evidence and certainty related to the MOA to move from the more protective modeling approach to the less protective approach. This was not mentioned in the Health Canada assessment, and it was provided as rationale in the EPA's assessment to support their risk assessment approach. In the 2020 TSCA document (page 173), the EPA reviewed the two studies that supported Health Canada's conclusions and determined that there are data gaps in the MOA pathway as well as the plausibility that additional MOAs are operative (EPA TSCA, 2020). This rationale supports the linear low-dose extrapolation approach that the EPA consistently assigns for chemicals with unknown MOAs to protect humans from unknown toxic mechanisms and effects.

5.3. Effects Summary

The *Effects Analysis* sections highlighted,

1. The EPA and Health Canada assessments agree that oral exposure to 1,4-dioxane causes carcinogenic effects in the liver, and that the carcinogenic liver effects MOA are the most well-understood.
2. The EPA IRIS assessment provides the most consistent value across regulated chemicals, and with federal and other state regulatory programs.
    a. There have been a few peer-reviewed scientific publications since both assessments were produced, but there are not enough additional data to support non-linear low-dose extrapolation approach for all target organs.
3. The CSF provided by the EPA IRIS assessment of 0.1 $(mg/kg\text{-}day)^{-1}$ was derived using the most health protective modeling approach and will provide science-based protection to North Carolinians from exposure to 1,4-dioxane in their drinking water.

It is important to note the strengths and limitations of studies included in this assessment. The strengths of the studies lie in the evidence of multiple tumors in multiple species and sexes in well-conducted laboratory studies, and multiple high-quality assessments by EPA and other organizations. A limitation of the included studies is related to the gaps in knowledge related to MOA of 1,4-dioxane carcinogenicity. This limitation is common in toxicology and the EPA has a consistent approach to conduct risk assessment when there are knowledge gaps in the MOA information (EPA IRIS, 2013).

6. Risk Characterization

The *Risk Characterization* is the final, integrative step of risk assessment. This step integrates the *Exposure Assessment* and *Effects Assessment* into quantitative and qualitative estimates of risk for the evaluated population (EPA, 2014).

The Risk Characterization analysis plan is outlined below. There are no data quality metrics for this section since the data that is being used in this section has already passed the data quality metrics in the preceding sections.

- Approach: Compare exposure data with drinking water values based on the health-based guidance value for protection from cancer.
- Method: Risk will be determined based on the extent to which mean drinking water concentration, and the 95% confidence interval that people are exposed to is above a WQS derived using NC rule 02B.0208 based on the CSF of 0.1 $(mg/kg\text{-}day)^{-1}$, and the Margin of Exposure (MOE) calculation to determine relative protectiveness of the derived WQS compared to other values examined.
- Metric: The percent of exposure data that is above the derived WQS value will be related to the risk and magnitude of protection using the MOE calculation, the results will be compared to the UCMR3 data to determine how the risk in NC compares to the national risk.

6.1. Risk Characterization Data Analysis

6.1.1. Statistical Comparison

To determine the risk of 1,4-dioxane exposure in drinking water, the data presented in the *Exposure Assessment* was compared to the derived WQS that is based on the toxicity values discussed in the *Effects Assessment*.

Here, *Exposure Assessment* datasets mean values, and the upper and lower 95% confidence intervals (UCI_{95}, LCI_{95}) were compared to the derived WQS of 0.35 µg/L (Figure 3)[1]. The mean value in the NC Pre-Regulatory Efforts dataset was 2.49 µg/L (LCI_{95} = 1.63; UCI_{95} = 3.35), and the mean value in the NC Post-Regulatory Efforts dataset was 1.67 µg/L (LCI_{95} = 1.26; UCI_{95} = 2.07) (Table 1, A-3). Both datasets mean values are greater than the mean values for the UCMR3 NC dataset (mean = 0.92 µg/L; LCI_{95} = 0.42; UCI_{95} = 0.49), and nationwide dataset (mean = 0.45 µg/L; LCI_{95} = 0.71; UCI_{95} = 1.13). All four datasets mean values are greater than the derived WQS of 0.35µg/L (Table 2, Figure 3). The LCI_{95} of all four datasets are also above the derived WQS.

These values indicate that while the drinking water in NC is a source of 1,4-dioxane exposure at higher concentrations than the national values, the entire country is exposed to 1,4-dioxane in concentrations above the value that is predicted to cause one case of cancer in a million people (0.35 µg/L; Table 2, Table A-1). Since all the datasets in this assessment contain mean values that are above the derived WQS, an

[1] derived WQS formula as per 15A NCAC 02B.0208
= [(Risk Level x Adult Weight) / (CSF x (Daily Water Intake + (Fish Consumption x Bio Accumulation Factor))] * 1000
= [$(10^{-6}$ x 70kg) / $(0.1(mg/kg\text{-}day)^{-1}$ x (2L/day + (0.022g/person/day x 0.5L/kg))] * 1000 = 0.35 µg/L

MOE calculation was conducted to provide greater detail about each of the exposure scenarios of the included datasets. The MOE is used to characterize the risk of an exposure by comparing exposure data to the toxicity values so the risk of a specific exposure scenario can be further understood.

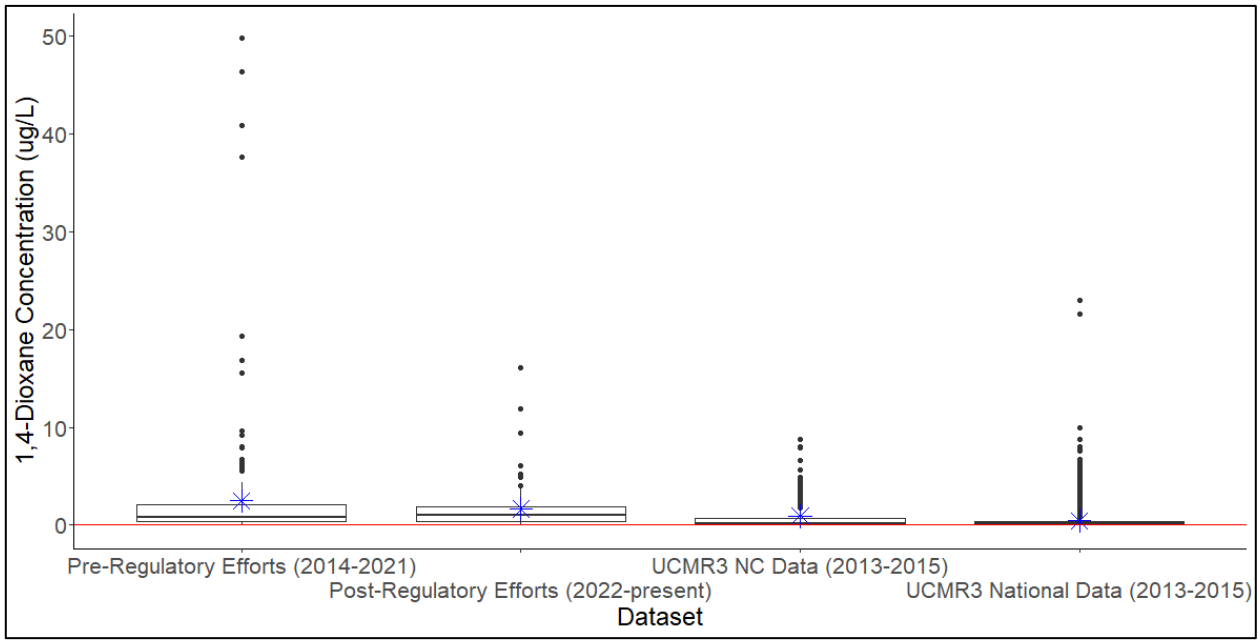

Figure 3: Boxplots of the drinking water exposure data examined in this report. The black center line represents the median of the dataset. The top and bottom of the boxplot are the 1st and 3rd inter quartile range, the dots displayed are the outliers of each dataset. The mean value is represented by a blue asterisk. The EPA's health-based value of 0.35 µg/L is indicated with a red line.

6.1.2. Margin of Exposure (MOE) Analysis

The MOE is the ratio between a reference point in the dose–response data from experimental studies and the estimated human exposure. The MOE approach is preferred over other risk assessment approaches because it is based on the available animal dose–response data, without extrapolation, and on human exposures; and because it does not give a numerical risk estimate that may be regarded as quantification of the actual risk (Barlow *et al.*, 2006). For carcinogenic compounds, the MOE equation uses the Benchmark Dose Level (BMDL) that the toxicity value is based and compares it to the estimated human exposure value. An MOE value of 10,000 and above, based on a BMDL from an animal study, indicates a low concern from a public health point of view and that might be considered a low priority for risk management actions. The rationale for this value includes a 100-fold difference between the BMDL and human exposure to account for species differences and human variability, and an additional 100-fold difference includes the uncertainties related to human variability in cell cycle control due to the shape of the dose–response curve below the BMD and the dose level below which the cancer incidence is not increased are unknown (Barlow *et al.*, 2006).

The equation is:

MOE = BMDL (mg/kg-day)/Estimated Human Exposure(mg/kg-day)

Here, the (32.93 mg/kg-day) is applied in this calculation to contextualize and compare the estimated human exposure scenarios identified in the datasets examined, since the datasets have mean values above the derived WQS value of 0.35 µg/L. Overall, when the MOE calculation is applied to the mean drinking water values (in mg/L), the MOE value increases as the drinking water values decrease, which is mathematically expected as lower drinking water values are more protective.

When all the *Exposure Assessment* dataset mean values were evaluated with the MOE equation, all the mean values yielded MOE values above 10,000 which is considered low risk to the human population (Table 4). Since all the mean values used in the *MOE Analysis* were considered protective, the MOE from each dataset was compared to the MOE from the derived WQS, to determine how protective each drinking water mean value is compared to the derived WQS that is based on the IRIS toxicity value (CSF = 0.1 (mg/kg-day)$^{-1}$). The comparison was conducted by dividing each dataset MOE by the derived WQS MOE to get a percent protectiveness for ease of comparison.

Table 4: The drinking water values examined in this report presented with paired toxicological values for Margin of Exposure (MOE) calculations.

Exposure Assessment Drinking Water Dataset	**Drinking Water (DW) Mean Value**		**Estimated Daily Exposure (mg/kg-day)**	**MOE ≥ 10,000 = Protective**	**MOE % Protectiveness**
	(µg/L)	**(mg/L)**	*= (DW mg/L * 2 L/day) / 70 kg*	*= BMDL / Estimated Daily Exposure*	*= MOE / 0.35 MOE*
NC UCMR3	0.92	0.00092	0.00003	1,252,771	38%
Pre-Regulatory Efforts	2.49	0.00249	0.00007	462,871	14%
Post-Regulatory Efforts	1.67	0.00167	0.00005	690,149	21%
Derived WQS*	0.35	0.00035	0.00001	3,293,000	100%
National (US) UCMR3	0.45	0.00045	0.00001	2,561,222	78%

*value is the derived WQS using the CSF of 0.1 (mg/kg-day)$^{-1}$, not a mean measured value.

6.2. Risk Characterization Summary

The data examined in this assessment and characterized in this section show the relative risk of both real-world and estimated daily exposures to 1,4-dioxane in drinking water in NC. The NC UCMR3, Pre-, and Post-Regulatory Efforts data highlight the exposures experienced by North Carolinians from 2013 – present. The national UCMR3 data demonstrates that while NC's average exposure is greater than much of the rest of the nation, 1,4-dioxane in drinking water is a national issue that was identified through EPA's UCMR program.

The *MOE Analysis* provides insight into the difference in exposure that NC experiences relative to the rest of the nation, since NC was identified as one of the states with some of the highest 1,4-dioxane concentrations in drinking water by the UCMR3 sampling effort (Table A-1)(Adamson *et al.*, 2017).

Based on the UCMR3 data, North Carolinians experienced approximately half the protection from 1,4-dioxane exposure than the rest of the nation received from 1,4-dioxane in drinking water from 2013-2015 (NC UCMR3 = 38%; US UCMR3= 78%; Table 4). While the UCMR3 national mean 1,4-dioxane value in drinking water above the detection level (0.45 µg/L) is above the derived WQS (0.35 µg/L), it offered a greater amount of protection for other states than NC received during that time. Compared to the national

UCMR3 data, NC currently (2022 – present) receives only ~1/4 of the protection from 1,4-dioxane exposure the rest of the nation receives (NC Post-regulatory efforts = 21%; US UCMR3 = 78%, Table 4), and half of the protection that was provided when the UCMR3 samples were taken (2013-2015; NC UCMR3 = 38%, NC Post-regulatory efforts = 21%).

Further, the assessment supports the application of a science-based cancer slope factor equivalent to 0.1 mg/kg-day to determine a health-based WQS that provides adequate lifetime protection of drinking water. Currently, NC receives only 21% of the protection that would be offered by the derived WQS.

7. References

Adamson, D.T. *et al.* (2017) '1, 4-Dioxane drinking water occurrence data from the third unregulated contaminant monitoring rule', *Science of the Total Environment*, 596, pp. 236–245.

ATSDR, C. (2012) 'Toxicological Profile for 1,4-dioxane'. Available at: https://www.atsdr.cdc.gov/ToxProfiles/tp187.pdf (Accessed: 22 April 2024).

Barlow, S. *et al.* (2006) 'Risk assessment of substances that are both genotoxic and carcinogenic: Report of an International Conference organized by EFSA and WHO with support of ILSI Europe', *Food and chemical toxicology*, 44(10), pp. 1636–1650.

Chappell, G.A., Heintz, M.M. and Haws, L.C. (2021) 'Transcriptomic analyses of livers from mice exposed to 1, 4-dioxane for up to 90 days to assess potential mode (s) of action underlying liver tumor development', *Current Research in Toxicology*, 2, pp. 30–41.

Charkoftaki, G. *et al.* (2021) 'Identification of dose-dependent DNA damage and repair responses from subchronic exposure to 1, 4-dioxane in mice using a systems analysis approach', *Toxicological Sciences*, 183(2), pp. 338–351.

Chen, Y. *et al.* (2022) 'Oxidative stress and genotoxicity in 1, 4-dioxane liver toxicity as evidenced in a mouse model of glutathione deficiency', *Science of The Total Environment*, 806, p. 150703.

Dourson, M. *et al.* (2014) 'Mode of action analysis for liver tumors from oral 1, 4-dioxane exposures and evidence-based dose response assessment', *Regulatory Toxicology and Pharmacology*, 68(3), pp. 387–401.

Dourson, M.L. *et al.* (2017) 'Update: Mode of action (MOA) for liver tumors induced by oral exposure to 1, 4-dioxane', *Regulatory Toxicology and Pharmacology*, 88, pp. 45–55.

ECHA (2021) *ECHA Scientific report for evaluation of limit values for 1,4-dioxane at the workplace Prepared by the European Chemicals Agency*. Available at: https://echa.europa.eu/documents/10162/ffebd37d-e38c-0b15-7376-229481dd9619 (Accessed: 10 April 2024).

EPA (2005) 'Guidelines for Carcinogen Risk Assessment'. Available at: https://archive.epa.gov/raf/web/pdf/cancer_guidelines_final_3-25-6.pdf (Accessed: 3 January 2024).

EPA (2012) 'Benchmark Dose Technical Guidance'. Available at: https://www.epa.gov/sites/default/files/2015-01/documents/benchmark_dose_guidance.pdf (Accessed: 22 December 2023).

EPA (2014) *Framework for Human Health Risk Assessment to Inform Decision Making*. EPA/100/R-14/001. Available at: www.epa.gov/raf.

EPA (2022) 'Conducting a Human Health Risk Assessment'. Available at: https://www.epa.gov/risk/conducting-human-health-risk-assessment (Accessed: 23 April 2024).

EPA IRIS (2010) *Toxicological Review of 1,4-Dioxane (CAS No. 123-91-1) In Support of Summary Information on the Integrated Risk Information System (IRIS)*. EPA/635/R-09/005-F. Available at: https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=326 (Accessed: 10 April 2024).

EPA IRIS (2013) *Toxicological Review of 1,4-Dioxane (with Inhalation Update) (CAS No. 123-91-1) In Support of Summary Information on the Integrated Risk Information System (IRIS)*. EPA/635/R-11/003F. Available at: https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=326 (Accessed: 10 April 2024).

EPA TSCA (2020) *Final Risk Evaluation for 1,4-Dioxane. CASRN: 123-91-1*. Available at: https://19january2021snapshot.epa.gov/sites/static/files/2020-12/documents/1._risk_evaluation_for_14-dioxane_casrn_123-91-1.pdf (Accessed: 10 April 2024).

Ginsberg, G., Chen, Y. and Vasiliou, V. (2022) 'Mechanistic considerations in 1, 4-dioxane cancer risk assessment', *Current opinion in environmental science & health*, 30, p. 100407.

Health Canada (2021) *Guidelines for Canadian Drinking Water Quality Guideline Technical Document 1,4-Dioxane*. Available at: https://www.canada.ca/en/health-canada/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-guideline-1-4-dioxane.html (Accessed: 10 April 2024).

Kano, H. *et al.* (2009) 'Carcinogenicity studies of 1, 4-dioxane administered in drinking-water to rats and mice for 2 years', *Food and chemical toxicology*, 47(11), pp. 2776–2784.

Kociba, R.J. *et al.* (1974) '1, 4-Dioxane. I. Results of a 2-year ingestion study in rats', *Toxicology and Applied Pharmacology*, 30(2), pp. 275–286.

Lafranconi, M. *et al.* (2021) 'A 90-day drinking water study in mice to characterize early events in the cancer mode of action of 1, 4-dioxane', *Regulatory Toxicology and Pharmacology*, 119, p. 104819.

Lafranconi, M. *et al.* (2023) 'An integrated assessment of the 1, 4-dioxane cancer mode of action and threshold response in rodents', *Regulatory Toxicology and Pharmacology*, p. 105428.

8. Appendix

8.1. Acronym List

BMD – Benchmark Dose
BMDL – Benchmark Dose Level
BMDS – Benchmark Dose Modeling Software
CFPUA – Cape Fear Public Utility Authority
CSF – Cancer Slope Factor
DEQ – Department of Environmental Quality
DW – Drinking Water
ECHA – European Chemical
EMC – Environmental Management Commission
EPA – Environmental Protection Agency
FPWC – Fayetteville Public Works Commission
HED – Human Equivalency Dose
IARC – International Agency for Research on Cancer
IRIS – Integrated Risk Information System
LCI_{95} – Lower 95% Confidence Interval
MAC – Maximum Allowable Concentration
MOA – Mode of Action
MOE – Margin of Exposure
NOAEL – No Observable Adverse Effect Level
NC – North Carolina
POD – Point of Departure
RfD – Reference Dose
RSC – Relative Source Contribution
SOC – Special Order of Consent
SW – Surface Water
SD – Standard Deviation
TDI – Total Daily Intake
TSCA – Toxic Substance Control Act
UCI_{95} – Upper 95% Confidence Interval
UCMR3 -3rd Unregulated Contaminant Monitoring Rule
UF_A – Uncertainty Factor based on animal to human extrapolation.
UF_H – Uncertainty factors based on human interindividual variation.
UF_D– Uncertainty Factor based on incompleteness or limitations in chemical data base.
WQS – Water Quality Standard
WW – Wastewater

8.2. Supplementary Tables and Figures

Table A-1: The summary statistics for the UCMR3 state-level 1,4-dioxane measurements that were above the limit of detection (LOD, 0.07 µg/L) for the method used in the monitoring program.

State	Number of Detects	% Detects	Mean (µg/L)	Minimum (µg/L)	Maximum (µg/L)	Standard Deviation (µg/L)
IL	185	14%	0.58	0.07	22.93	2.33
NY	318	20%	0.59	0.07	10.00	1.07
NC	49	4%	1.69	0.07	8.80	2.31
CA	863	13%	0.68	0.07	7.80	1.17
AZ	88	8%	0.37	0.07	6.70	0.85
PA	271	20%	0.24	0.07	6.20	0.53
NJ	293	20%	0.42	0.07	5.60	0.78
AL	190	18%	0.31	0.07	4.20	0.52
NH	5	4%	2.00	0.10	3.64	1.62
CT	23	7%	0.41	0.08	3.60	0.72
SC	157	34%	0.25	0.07	3.60	0.37
CO	90	16%	0.45	0.07	3.20	0.72
NM	7	2%	0.52	0.08	2.60	0.93
WI	44	7%	0.39	0.07	2.59	0.56
TN	78	12%	0.31	0.07	2.48	0.39
DE	18	14%	0.39	0.08	2.20	0.55
OH	49	7%	0.28	0.07	2.10	0.33
NE	23	11%	0.41	0.07	1.31	0.36
TX	72	2%	0.15	0.07	1.15	0.16
WV	16	12%	0.42	0.09	1.10	0.30
IN	101	23%	0.23	0.07	1.10	0.18
UT	7	1%	0.32	0.09	1.07	0.35
KY	34	5%	0.25	0.07	0.89	0.18
IA	28	11%	0.27	0.07	0.73	0.19
RI	14	13%	0.21	0.07	0.72	0.21
GU	3	1%	0.30	0.09	0.71	0.36
FL	126	9%	0.15	0.07	0.71	0.11
HI	6	2%	0.23	0.07	0.63	0.22
GA	77	10%	0.16	0.07	0.61	0.12
NN	1	4%	0.59	0.59	0.59	*NA*
OK	10	2%	0.21	0.09	0.55	0.15
VA	23	5%	0.13	0.07	0.51	0.09
PR	7	1%	0.19	0.08	0.42	0.11
MI	10	1%	0.20	0.07	0.40	0.12
LA	28	5%	0.14	0.08	0.40	0.07
WA	13	1%	0.16	0.07	0.36	0.11
NV	5	2%	0.14	0.09	0.30	0.09
MS	4	1%	0.20	0.16	0.22	0.03
AR	5	2%	0.16	0.12	0.19	0.03
KS	7	3%	0.13	0.08	0.18	0.03
MN	9	2%	0.11	0.07	0.18	0.04
OR	5	1%	0.11	0.08	0.17	0.04
MO	6	1%	0.12	0.08	0.15	0.03
ID	4	1%	0.09	0.07	0.13	0.03
VT	1	2%	0.11	0.11	0.11	*NA*
MA	6	0%	0.09	0.07	0.10	0.01
MT	2	2%	0.08	0.07	0.08	0.00

8.2.1. Data Quality Metrics

The EPA Framework data quality metrics were used to determine if the included data/assessments are appropriate for inclusion in the assessment (EPA Guidance 2014).

The metrics are as follows:

- Soundness – Scientific methods are consistent with application.
- Applicability and Utility – Dataset is relevant for this use.
- Clarity and Completeness – Assumptions, quality assurance information, data sources, and analyses used to generate information are documented.
- Uncertainty and Variability – Both described in dataset and methods used for analysis.
- Evaluation and Review – Data independently verified/ peer- reviewed.

Table A-2: Data quality metrics for each of the unique datasets included in the *Exposure Assessment.*

Data Quality Metric	DEQ SW	DEQ WW	DEQ PWS	FPWC Data	CFPUA Data	Pittsboro Data	High Point Data	Cary Data	Sanford Data	UCMR3 Data
Soundness	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Applicability and Utility	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Clarity and Completeness	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Uncertainty and Variability	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Evaluation and Review	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔

Table A-3: Descriptive statistics for the datasets presented in the *Exposure Assessment* section and analyzed in the *Risk Characterization* section.

Data Category	Detections (n)	Mean (µg/L)	Min (µg/L)	Max (µg/L)	Standard Deviation (µg/L)	Standard Error (µg/L)	Lower 95% CI (µg/L)	Upper 95% CI (µg/L)	Non-detections (n)
NC Environmental Occurrence	2521	171.99	0.07	22000.00	1215.35	47.44	124.55	219.43	4421
NC Post-Regulatory Efforts (2022-present)	138	1.67	0.09	16.10	2.43	0.41	1.26	2.07	254
NC Pre-Regulatory Efforts (2014-2021)	209	2.49	0.07	49.80	6.33	0.86	1.64	3.35	77
UCMR3 National Data (2013-2015)	3381	0.45	0.07	22.93	1.02	0.03	0.42	0.49	33325
UCMR3 NC Data (2013-2015)	213	0.92	0.07	8.80	1.59	0.21	0.71	1.13	1111

Table A-4: Data quality metrics for each of the assessments evaluated in the 1,4-dioxane *Effects Assessment.*

Data Quality Metric	EPA IRIS 2010	EPA IRIS 2013	ATSDR 2012	EPA TSCA 2020	EHCA 2021	Health Canada 2021
Soundness	✔	✔	✔	✔	✔	✔
Applicability & Utility	✔	*The inhalation update of 2013 is not applicable to the regulatory scenario*	✔	*Not applicable to the regulatory scenario; includes occupational exposures, focused on dermal and inhalation routes of exposure.*		✔
Clarity & Completeness	✔	✔	✔	✔	✔	✔
Uncertainty/Variability	✔	✔	✔	✔	✔	✔
Evaluation and Review	✔	*No new oral exposure data was added to this assessment*	✔	*The derived ECEL is for inhalation exposures. No ingestion limits derived in this assessment; risk criteria = 10^{-4}*	*The conclusions are related to occupational exposures*	✔

Table A-5: Extended version of toxicity value comparison table in the *Effects Assessment* section.

Assessment Type	EPA IRIS Assessment		Health Canada Non-Cancer Value (2021)	ATSDR Non- Cancer Value (2012)
	EPA Carcinogenicity (2013)	**EPA Non-Cancer Value** (2013)		
Species and Target Organ	Mouse Liver	Rat liver and kidney toxicity	Rat Liver	Rat liver
Endpoint and data used for dose-response modeling	Hepatocellular adenomas and carcinomas, female (Kano *et al.*, 2009)	NOAEL (did not use benchmark dose modeling), male rat (Kociba *et al.*, 1974)	Hepatocellular necrosis, combined male & female data (Kociba *et al.*, 1974)	NOAEL (did not use benchmark dose modeling), male rat (Kociba *et al.*, 1974)
Benchmark Dose Model Used	Log-logistic with linear low dose extrapolation	*Not applicable* (used NOAEL)	Log-Probit	*Not applicable* (used NOAEL)
POD	$BMDL_{50}$ = 32.93 mg/kg-day	NOAEL = 9.6 mg/kg-day	$BMDL_5$ = 5.4 mg/kg-day	NOAEL = 9.6 mg/kg-day
POD_{HED}	$BMDL_{50HED}$ = 4.95 mg/kg-day	*Not calculated*	*Not calculated*	*Not calculated*
Total UF applied	*Not applicable*	300 (UF_A=10, UF_H=10, UF_D=3)	1000 (UF_A=10, UF_H=10, UF_D=10)	100 (UF_A=10, UF_H=10)
Risk probability	1 in a million (10^{-6})	*Not applicable*	*Not applicable*	*Not applicable*
Low Dose Extrapolation method	Linear, no threshold	Assumes threshold, uses UFs[1]	Threshold (non-linear), uses UFs	Assumes threshold, uses UFs[1]
Health-based criterion	CSF = 0.1 $(mg/kg\text{-}day)^{-1}$	RfD = 0.03 mg/kg-day	TDI = 0.0054 mg/kg-day	MRL = 0.1 mg/kg-day
Criterion description	Cancer protective factor for humans.	Lifetime exposure can be experienced with no non-cancer effects occurring in humans.		
Rationale	Data supporting MOA other than mutagenic inconclusive; female mouse data most sensitive endpoint for carcinogenicity in a rodent model	NOAEL from most sensitive species used. BMD analysis not feasible as incidence of hepatic necrosis not reported in Kociba et al., 1974)	MOA analysis supports a non-genotoxic MOA involving cytotoxicity followed by regenerative hyperplasia. Histopathology data from Kociba et al. (1974) available and evaluated in (Dourson *et al.*, 2014, 2017)	The lack of quantitative information regarding incidences of non-neoplastic lesions reported in Kociba et al., 1974 precludes the use of BMD methodology for MRL derivation
Database limitations noted	More data needed on role of metabolites; evidence for cell proliferation, but uncertainty on whether mitogenesis or cytotoxicity is responsible for increased cell turnover	Lack of multigeneration reproductive toxicity study	"Poor characterization of reproductive and developmental toxicity, as well as inadequate characterization of effects in a second species (mice)"	No database limitations discussed.

1 The U.S. EPA RfD is defined as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime." This method assumes a threshold exposure and uses uncertainty factors to account for data gaps due to animal to human extrapolation (UFA), human interindividual variation (UFH), incompleteness or limitations in chemical data base (UFD), and others as needed. The RfD method is used for non-cancer endpoints.

2 Point of departure (POD) can be either a no or low observed adverse effect level (NOAEL or LOAEL) from an animal (or human) study or a specified benchmark response (%) level (BMD) or lower (specified) confidence limit (BMDL). If animal data are used, the POD is often converted to a human equivalent dose (PODHED) using a dosimetric adjustment based on PBPK modeling or allometric scaling (default if other more robust data unavailable).

3 Calculation for IRIS assumes 70 kg human drinking 2 liters per day. Calculation for Health Canada assumes 70 kg human drinking 1.5 Liters per day with 0.2 (20%) exposure from drinking water.