April 3, 2024

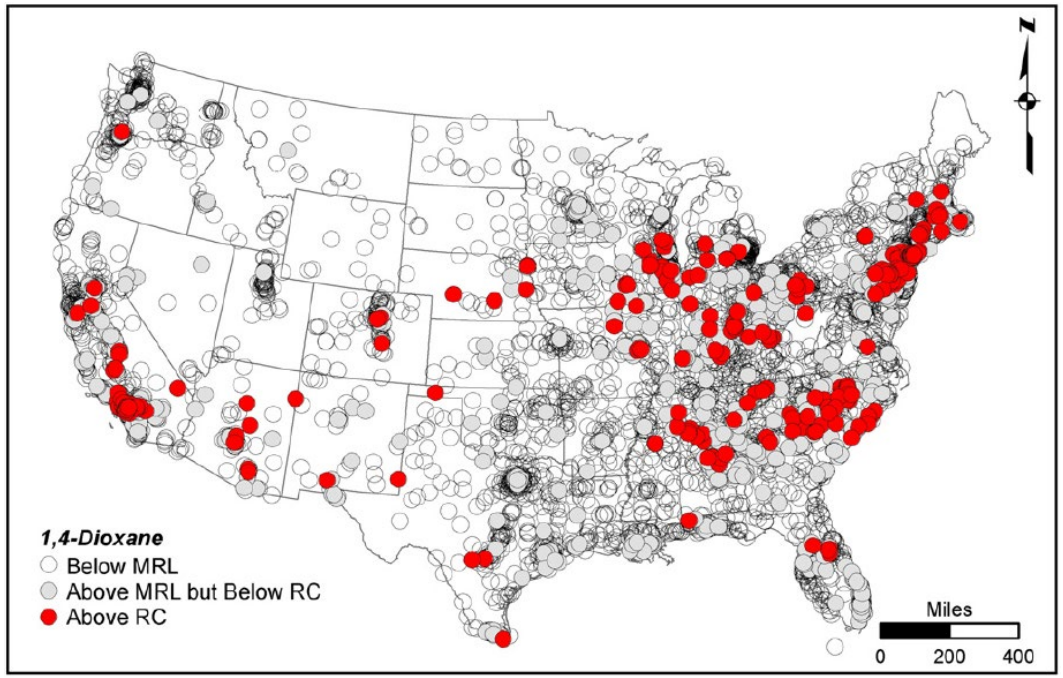
Update on the Human Health Risk Assessment for 1,4-Dioxane in Drinking Water per Session Law 2023-137

NC Secretaries' Science Advisory Board

Frannie Nilsen, PhD

1,4-Dioxane History

- EPA issued the third Unregulated Contaminant Monitoring Rule (UCMR 3) on May 2, 2012.
  - UCMR 3 required monitoring for 30 contaminants (28 chemicals and two viruses) in drinking water between 2013 and 2015.
  - 1,4-Dioxane was included in UCMR3.
  - Results were published in 2017



California (73 systems),
New York (31 systems),
New Jersey (30 systems),
North Carolina (24 systems), and
Illinois (21 systems)
had the most PWSs that
1,4-dioxane exceeded 0.35 µg/L.
(D.T. Adamson et al., 2017)

MRL = Minimal Reporting Level
RC = Reference Concentration; 0.35µg/L
PWS = Public Water Systems

1,4-Dioxane History

- UCMR3 led high ranking states to revaluate the industrial sources of 1,4-dioxane, rules related to water quality standards, and discharge limits in affected permits.

- DEQ began monitoring across the state and many sites began monitoring independently.

State	Number of Detects	% Detects	mean	min	max	sd
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

(D.T. Adamson et al., 2017)

1,4-Dioxane History

DWR 1,4-dioxane Discharge Sampling:

- Greensboro TZ Osborne WWTP
  - October 2019 through current (as part of a settlement agreement between the City of Greensboro, NC Environmental Management Commission, the Haw River Assembly, and Fayetteville Public Works Commission)
- Asheboro WWTP
  - July 2021 through present (ongoing)
- High Point Eastside WWTP
  - June 2022 through present (ongoing)
- Burlington East WWTP
  - November 2019 through April 2020 (when City entered agreement with Haw River Assembly that included routine sampling)
- Reidsville WWTP
  - October 2019 through July 2023

Legislative Report Details

- On September 22, 2023, the North Carolina General Assembly directed DEQ to prepare a human health risk assessment (HHRA) of 1,4-dioxane in drinking water supported by peer-reviewed scientific studies.
  - DEQ must deliver the assessment to the Joint Legislative Commission on Governmental Operations no later than May 1, 2024. (Session Law 2023-137; House Bill 600, Section 9(b).)

- To support the assessment and report,
  - During the Dec 2023 NC SSAB Meeting, DEQ presented the legislative requirement to the Board and requested assistance from some of the experts within.
  - The SSAB discussed the difficulty in meeting the legislative timeline in doing a HHRA and recommended a strategy to meet the requirements in the time given.
  - In Jan 2024, DEQ followed the strategy the Board suggested and convened a group of experts knowledgeable about 1,4-dioxane exposure and toxicity and began the directive activities.

Legislative Report Status Update Contents

Describe the approach to accomplishing the legislative directive

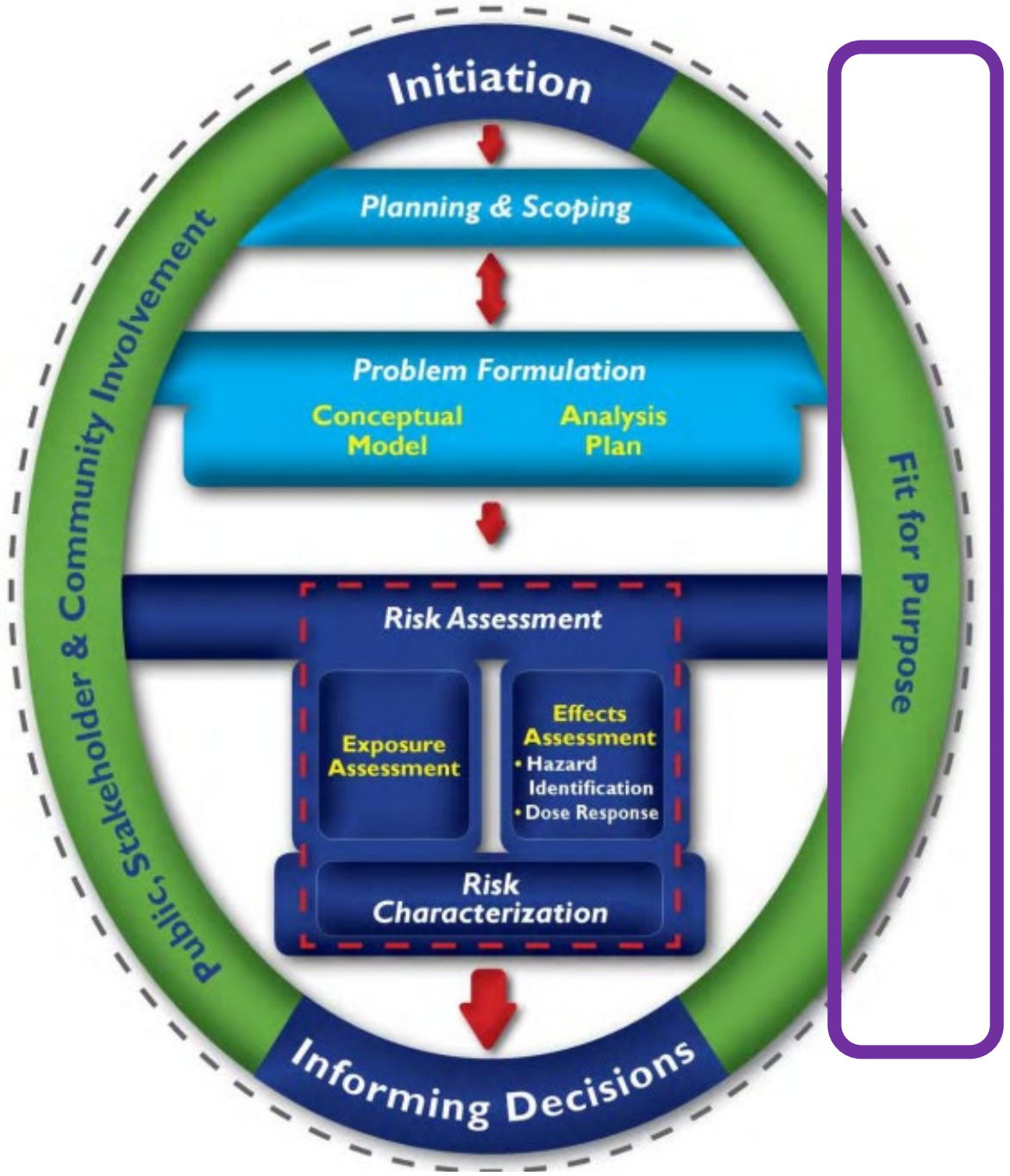
Highlight the included 1,4-dioxane experts, advisory committee, and designated responsibilities

Describe the approach to each of the sections using the 1,4-dioxane data included in the draft report.

Describe the approach to finishing the report by the May 1, 2024, deadline.

Overall Approach

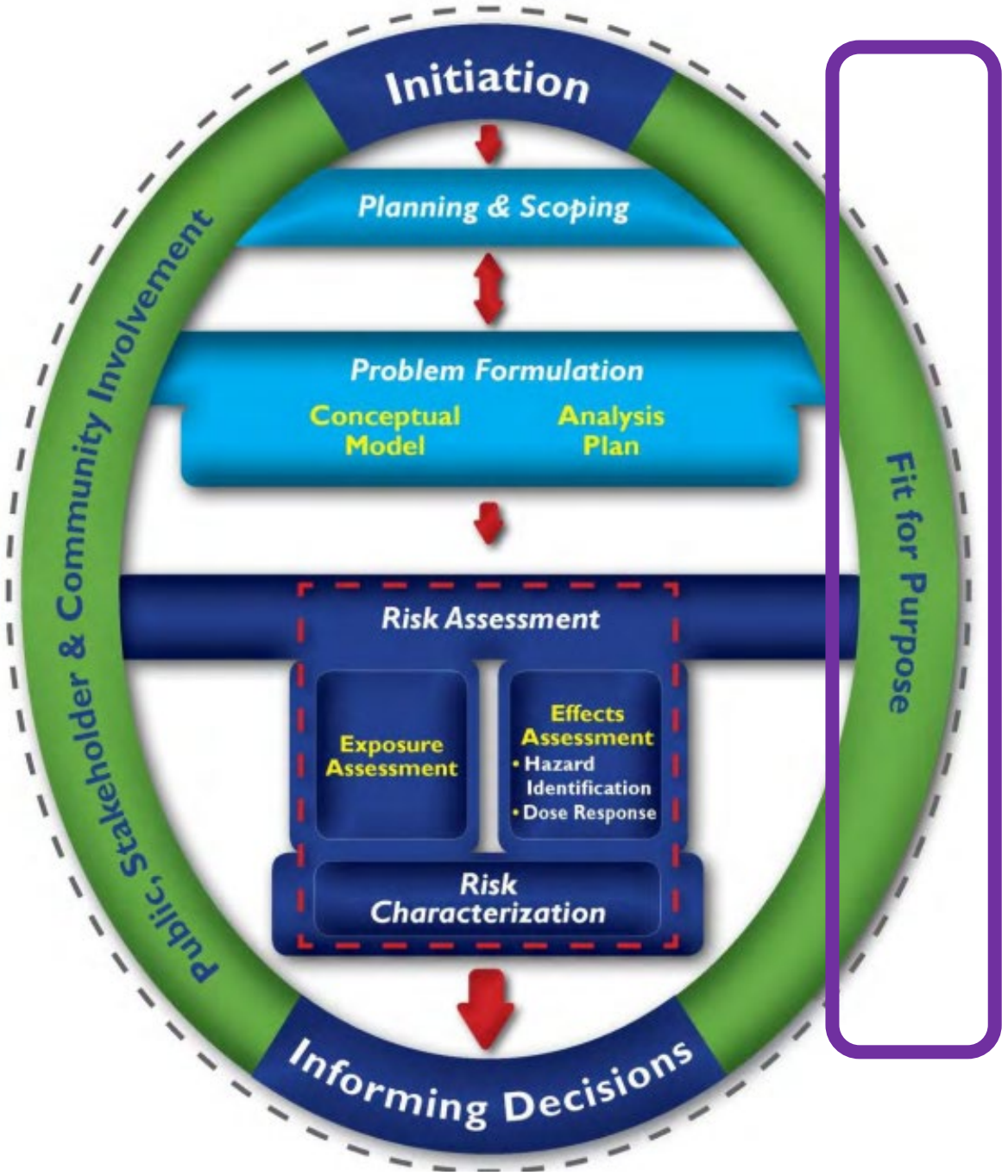
EPA's HHRA for Decision Making Framework



EPA's HHRA for Decision Making Framework

Approach: Follow EPA's Human Health Risk Assessment to Inform Decision Making Framework to evaluate the Cancer Risk of 1,4-Dioxane in Drinking Water in North Carolina.

Goal: Final report to legislature regarding carcinogenic risk of 1,4-Dioxane in NC drinking water on May 1, 2024.



Risk Assessment Components

Exposure Assessment

- **How and to what range of concentrations/doses are populations/life stages of interest exposed?**
- **How do risk management options affect existing/resulting conditions of exposure?**

Effects Assessment

- **Hazard ID: What adverse endpoints are associated with agents or stressors of concern? Are there data to identify susceptible populations or support a MOA for the agent or stressor?**
- **Dose-Response Assessment: What is the relationship between exposure/dose and the likelihood of each endpoint at the exposure range of interest? How does MOA and other relevant information affect choices of low-dose extrapolation?**

Risk Characterization

- **What is the nature and magnitude of risk for existing conditions and for options?**
- **What are the sources and magnitude of uncertainty and variability in all steps of the risk assessment?**

1,4-Dioxane Work Group

Exposure Assessment Team Members

Person	Role	Responsibilities	Qualifications
Jared Wilson, MS (DEQ)	Team Lead	Data compilation and mapping	Geographic Information Systems Specialist, Data Analysis and Curation Resource.
Jenny Graznak (DEQ)	Occurrence Expert	Data provision and evaluation	1,4-Dioxane Consent Order Implementation, Monitoring, and Permitting Resource.
Tammy Hill (DEQ)	Exposure data specialist	Data provision and evaluation	1,4-Dioxane Monitoring and Data Curation Resource.

1,4-Dioxane Work Group

Effects Assessment Team Members

Person	Role	Responsibilities	Qualifications
Frannie Nilsen, PhD (DEQ)	Team Lead; Work Group Lead	Project Lead/Manager; compare existing CSF source information for evaluation	Environmental toxicologist
Elaina Kenyon, PhD (EPA)	Experimental Toxicology Data Expert	Evaluate models used to derive CSFs between difference information sources	Research toxicologist in the EPA's Center for Computational Toxicology and Exposure

Risk Characterization Team Members

Person	Role	Responsibilities	Qualifications
Frannie Nilsen, PhD (DEQ)	Team Lead; Work Group Lead	Project Lead/Manager; Synthesize exposure and effects data to understand risk	Environmental toxicologist

1,4-Dioxane Work Group

Complete Assessment Review Panel Members

Person	Role	Responsibilities	Qualifications
Linda Birnbaum, Ph.D., D.A.B.T.	Human Health Expert	Evaluate data provided to inform risk	Human exposure and toxicokinetic expert
NC SSAB	Reviewer	Toxicology Expert Board	Toxicologists; Health Effects Experts
External Reviewer 1			
External Reviewer 2			

Does the Board have any recommendations?

Advisory Committee Members

Person	Qualifications
Zack Moore, MD MPH	State Epidemiologist, NCDHHS
Betsey Tilson, MD MPH	State Health Director, NC DHHS
Sushma Masemore, PE	Assistant Secretary for the Environment, NC DEQ
Virginia Guidry, PhD MPH	Section Chief of the Occupational and Environmental Epidemiology Branch, NCDHHS
Kennedy Holt, MSPH	Toxicologist for the Occupational and Environmental Epidemiology Branch, NCDHHS

Risk Assessment Components

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Planning & Scoping

- **The content of each of the Risk Assessment Components was planned and scoped to fit the specific directive given by the General Assembly.**
- **The Exposure Assessment, Effects Assessment, and Risk Characterization sections included detailed planning steps.**
    1. **Problem formulation –** distill the problem so it is specific to the regulatory question being asked
    2. **Analysis Plan –** details the approach to the problem, the method of analysis, and the metric used to determine the result that will serve the regulatory question
    3. **Data Quality Metrics –** evaluate the available data, and determine what data is appropriate to include

Analysis Plan	Exposure	Effects	Risk
Approach	Describe occurrence and impacted population	Compare existing literature sources and evaluate CSF models	Compare occurrence data with CSF dose response information
Method	Analysis and summary of DEQ monitoring data	Use existing assessments and new studies to summarize literature and compare data used to derive each CSF	Risk will be determined based on the avg concentration that people are exposed to falling above the derived CSF for cancer outcome for each source
Metric	Compare to UCMR3 data	Compare to EPA guidance for CSF derivation	The % of occurrence data that is above the CSF will be related to Risk

Exposure Assessment – Analysis Plan

Exposure Assessment Analysis Plan	
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 % detections, % detections above the proposed WQS, and the number of residents exposed above the proposed WQS.
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.

Exposure Assessment – Data Quality

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:

- 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.

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	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Effects Assessment – Analysis Plan

Effects Assessment Analysis Plan	
Approach	Compare existing assessments and evaluate quality of any new data for application of CSF models.
Method	Summarize existing and relevant new literature and compare data used to derive the CSFs provided.
Metric	Compare any new data to EPA guidance for CSF derivation.

Effects Assessment – Data Quality

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:

- 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.

Data Quality Metric	EPA IRIS 2010	EPA IRIS 2013	EPA TSCA 2023	EHCA 2021	Health Canada 2021
Soundness	✓	✓	✓	✓	✓
Applicability and 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 and 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	✓

Effects Assessment – Data Analysis

1. Hazard Identification: Comparison of existing 1,4-D data source information.
2. Dose-Response Analysis: An evaluation of current Cancer Slope Factor derivation and differences between sources

Assessment Type	U.S. EPA RfD[1] (2010)	Health Canada HBV[2] (2021)	U.S. EPA Carcinogenicity[3] (2013)
Species and Target Organ	Rat liver and kidney toxicity	Rat Liver	Mouse Liver
Endpoint and data used for dose-response modeling	NOAEL (did not use benchmark dose modeling), male rat (Kociba et al., 1974)	Hepatocellular necrosis, combined male & female data (Kociba et al., 1974)	Hepatocellular adenomas and carcinomas, female (Kano et al., 2009)
Benchmark Dose Model Used	Not applicable (used NOAEL)	Log-Probit	Log-logistic with linear low dose extrapolation
POD[4]	NOAEL rat = 9.6 mg/kg-day	BMDL5 = 5.4 mg/kg-day	BMDL50 = 32.93 mg/kg-day
POD_{HED}	Not calculated	Not calculated	$BMDL50_{HED}$ = 4.95 mg/kg-day
Total UF applied	300 (UF_A=10, UF_H=10, UF_D=3)	1000 (UF_A=10, UF_H=10, UF_D=10)	Not applicable
Risk probability	Not applicable	Not applicable	1 in a million (10^{-6})
Oral Cancer Slope Factor	Not applicable	Not applicable	0.1 $(mg/kg\text{-}day)^{-1}$
Low Dose Extrapolation method	Assumes threshold, uses UFs[1]	Threshold (non-linear), uses UFs	Linear, no threshold
Health-based criterion	RfD = 0.03 mg/kg-day	TDI = 0.0054 mg/kg-day	CSF = 0.011 mg/kg-day
Drinking Water Limit[5]	Not applicable (non-cancer)	50 μg/L	0.35 μg/L (10^{-6} risk level)
Rationale	NOAEL from most sensitive species tested. 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. (2014) available and evaluated in Dourson et al. (2014, 2017)	Data supporting MOA other than mutagenic inconclusive; female mouse data most sensitive indicator carcinogenicity in a rodent model
Database limitations noted	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)"	More data needed on role of metabolites; evidence for cell proliferation, but uncertainty on whether mitogenesis or cytotoxicity is responsible for increased cell turnover

Risk Characterization– Analysis Plan

Risk Characterization Analysis Plan	
Approach	Compare exposure data with CSF dose response information
Method	Risk will be determined based on the mean concentration, and the 90% confidence interval of the mean concentration that people are exposed to falling above the derived WQS based on the appropriate CSF values; Margin of Exposure calculation will be used to determine if different exposure scenarios will have health impacts.
Metric	The % of exposure data that is above the WQS values will be related to Risk based on each CSF source and will be compared to the UCMR3 data to determine how the Risk in NC is related to the national risk. The Margin of Exposure results will inform potential health impact risk.

Risk Characterization Approach

Risk Characterization - *Risk characterization is the final, integrative step of risk assessment. This step integrates exposure assessment and effects assessment into quantitative and qualitative estimates of risk for the evaluated population.*

Method:

- Use a Margin of Exposure calculation to contextualize the Exposure data with the toxicology information provided in the Effects Assessment.
- Compare descriptive statistics of exposure data related to toxicologically derived drinking water values.

Risk Information	2010 IRIS Assessment		Health Canada	
Drinking Water Value (ug/L)	EPA: 0.35		Canada: 50.0	
CSF	0.011 mg/kg/day		0.0054 mg/kg/day	
Exposure Factors	70kg; 2.0 L/day	80kg; 2.4 L/day	70kg; 1.5L/day (Canada) 70kg; 2.0L/day (NC)	80kg; 2.4 L/day
NC Water Quality Standard based on CSF (ug/L)	0.32	0.3	0.65	0.62

Questions to answer:

1. What is the nature and magnitude of risk of existing conditions based on the source information?
2. How does this compare to national data (UCMR3)?
3. Are exposure levels in NC applicable to acute effects from short term exposures?

1,4-Dioxane Report Timeline

Completed?	Due Date	Task
✓	Jan 8, 2024	Convene Work Group; formally request participation, define specifically what the expectations are of participation; send reference documents for review ahead of first meeting.
✓	Jan 18, 2024	Initiation of team, first team meeting; discuss scope and problem formulation, conceptual model, and analysis plan with Work Group; meet with Exposure and Effects Teams separately to assign tasks and begin work.
✓	Jan 24, 2024	Draft Outline and detailed planning sections (Planning and Scoping; Problem Formulation with Conceptual Model and Analysis Plan) Draft to Work Group for revisions (revisions due by Web Jan 31)
✓	Feb 5, 2024	Outline and detailed Planning sections shared with group and revised/approved.
✓	Feb 12, 2024	Draft Exposure Assessment (parts 1 and 2), and Draft Effects Assessment outline/report due to WG for review
✓	Feb 19, 2024	Final Exposure Assessment shared with WG for approval; incorporated into full report
✓	Feb 19, 2024	Full Draft of Effects Assessment – Part 1 due to WG for review
✓	Feb 26, 2024	Final Effects Assessment shared with WG for approval and incorporated into full report. Meet with Risk Characterization Team to begin work and create outline
✓	Feb 29, 2024	Risk Characterization outline shared with WG for feedback
✓	March 15, 2024	Incorporate feedback into Risk Characterization
	April 5, 2024	Draft Risk Characterization shared with WG for review.
	April 11, 2024	Final Risk Characterization to WG for approval and incorporation into full report; share with NC SSAB.
	April 17, 2024	Final Draft Complete for DEQ and DHHS review
	May 1, 2024	Legislative Report and Presentation delivered to EMC by DEQ

1,4-Dioxane Report Timeline

Due Date	Task
April 5, 2024	Draft Risk Characterization shared with WG for review.
April 11, 2024	Final Risk Characterization to WG for approval and incorporation into full report; share with NC SSAB.
April 17, 2024	Final Draft Complete for DEQ and DHHS review
May 1, 2024	Legislative Report and Presentation delivered to EMC by DEQ