Executive Summary: Evaluating, Testing, and Reporting of Alternative Risk Assessment Methods (ARAM) Phase II — Risk Assessment Decision Framework

Report of Findings: Tasks 1-3

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[Note: MDH staff have made limited revisions to this report for the sake of clarity, correction, or formatting. This report does not represent official agency policy but may be used to inform future work.]

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List of Abbreviations

Abbreviation	Description
ADI	Acceptable Daily Intake
AIM	Analog Identification Methodology
AhR	Aryl hydrocarbon receptor
AHTN	6-Acetyl-1,1,2,4,4,7-hexamethyl-1,2,3,4-tetrahydronaphthalene (synthetic musk)
AR	Androgen receptor
ARAM	Alternative risk assessment methods
ATSDR	Agency for Toxic Substances and Disease Registry
B/B	Benigni and Bossa
BAF	Bioaccumulation factor
BCF	Bioconcentration factor
CalEPA	California Environmental Protection Agency
CASRN	Chemical Abstracts Service Registry Number
CEC	Contaminant of emerging concern
ChE	Cholinesterase
ClO_4	Perchlorate
DEET	*N,N*-Diethyl-*m*-toluamide (topical insect repellent)
DEHP	Di-2-ethylhexyl phthalate
DSSTox	Distributed Structure Searchable Toxicity Database
E	Endocrine activity
EADB	Endocrine Activity Database
ECETOC	European Center for Ecotoxicology and Toxicology of Chemicals
EDC	Endocrine disrupting chemical
EF	Extrapolation factor
EFSA	European Food Safety Authority
EPA	U.S. Environmental Protection Agency
ER	Estrogen receptor

Abbreviation	Description
ETU	Ethylene thiourea
FDA	U.S. Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
GM	Geometric mean
GR	Glucocorticoid receptor
HBG	Health Based Guidance
HBV	Health Based Value
HED	U.S. EPA Health Effects Division
HHBP	Human Health Benchmarks for Pesticides
HRL	Health Risk Limits
HSDB	Hazardous Substances Data Bank
ICH	The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Intake rate
IRIS	Integrated Risk Information Service
IUCLID	International Uniform Chemical Information Database
LD50	Lethal dose 50 (dose required to kill 50% of a population of test animals)
LOAEL	Lowest observed adverse effect level
log K_{OW}	Octanol-water partition coefficient
LTD	Lowest therapeutic dose
MDH	Minnesota Department of Health
METI	Japanese Ministry of Economy, Trade, and Industry
MPCA	Minnesota Pollution Control Agency
MSDS	Material safety data sheet
MTD	Maximum tolerated dose
NCCT	National Center for Computational Toxicology
NCI/NTP	National Cancer Institute/National Toxicology Program

Abbreviation	Description
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NOAEL	No observed adverse effect level
NOEL	No observed effect level
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
OEHHA	Office of Environmental Health Hazard Assessment (a division of CalEPA)
OP	Organophosphate
OWC	Organic wastewater compound
PFBA	Perfluorobutyric acid
PFBS	Perfluorobutane sulfonate
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctane sulfonate
PHG	Public Health Goal (CalEPA)
PPARγ	Peroxisome proliferator-activated receptor gamma
PXR	Pregnane X receptor
QSAR	Quantitative structure-activity relationship
RAA	Risk Assessment Advice
REACH	Registration, Evaluation, Authorisation, and Restriction of Chemicals
RSC	Relative source contribution
SA	Structural alert
SAR	Structure activity relationship
SMARTS	SMILES arbitrary target specification
SMILES	Simplified molecular-input line-entry system
RfD	Reference dose
TCE	Trichloroethylene

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Abbreviation	Description
TCEQ	Texas Commission for Environmental Quality
TD50	Median toxic dose (the dose at which toxicity occurs in 50% of cases)
TDCPP	Tris(1,3-dichloropropan-2-yl) phosphate
T.E.S.T.	Toxicity Estimation Software Tool
TNT	2,4,6-Trinitrotoluene
TTC	Threshold of toxicological concern
UV	Ultraviolet
VSD	Virtually safe dose
USGS	U.S. Geological Survey
WHO	World Health Organization
µg/d	Micrograms per day
µg/kg-d	Micrograms per kilograms per day
µg/L	Micrograms per liter
mg/kg/day	Milligrams per kilograms per day
L/kg-d	Liters per kilogram per day

Summary

Overview

The State of Minnesota monitors drinking water for contaminants of emerging concern (CECs) such as pharmaceuticals, personal care and household products, and unregulated industrial chemicals. The Minnesota Department of Health (MDH) is tasked with determining human health risks from exposure to contaminants in drinking water. Traditional risk assessment methods require chemical-specific toxicity data to develop numerical health-based guidance values for drinking water. However, many CECs have little to no available toxicological data, making it difficult to sufficiently evaluate potential public health risks associated with the chemical. Sometimes, all that may be available is the chemical structure.

With funding provided through the State of Minnesota Clean Water Fund of the Clean Water, Land and Legacy Amendment, MDH has been exploring ways to integrate established, evolving, and potentially novel approaches to assist in assessing potential human health risks associated with CECs. MDH's goal is to develop a scientifically robust decision process and risk assessment approach to help provide defensible risk context in a timely manner when CECs are detected in drinking water.

Developing a risk assessment decision framework has been an iterative process. Initiated in 2010, Phase I of the project, supported by an outside consultant under contract with MDH, involved a comprehensive review, assessment, and preliminary testing of viable alternative risk assessment methods to consider when empirical toxicity data for CECs might be sparse or non-existent. Phase I was completed in July 2012 and resulted in a series of recommendations and an initial risk assessment framework. Since that time, Phase II of the project has involved MDH conducting additional "crude" testing of candidate risk assessment methods and drafting a decision tree that integrated the most viable risk assessment methodologies identified in Phase I.

In October 2013, MDH contracted with Eastern Research Group, Inc. (ERG) to further support Phase II explorations. The project scope included (1) reviewing Phase I findings; (2) expanding the examination and testing of candidate risk assessment methods; (3) evaluating chemical categories/health endpoints warranting separate tracking; and (4) assisting in refining the decision tree framework—reassessing the overall logic and flow and integrating viable methods and tools where possible. ERG's Phase II work focused on evaluating the practical utility of candidate risk assessment methods and mapping a workable decision tree framework, and is the subject of this summary report.

The full report is organized as follows:

- Section 1: Introduction and background.
- Section 2: Description of the candidate alternative risk assessment methods considered and retained to support the decision tree framework, including the expanded testing results of candidate methods, the further examination of critical toxicological endpoints, and the rationale for retaining selected methods. The outcome of this effort supplements Phase I findings.
- Section 3: Outline of the decision tree structure, elements, and decision points—including the rationale for the framework and suggested approaches and tools for each decision point.

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- Sections 4 and 5: Literature cited and literature consulted, respectively.

This Executive Summary provides an overview of the Phase II report findings. Figure ES-1 shows the decision tree framework that culminated from this effort. The framework is based largely on chemical-specific structural alerts and associated toxicological endpoints and also incorporates open-access computational toxicology resources where possible. The framework is intended to assist MDH in conducting relatively rapid assessments to answer questions such as:

- Does the CEC pose a potential harm at detected concentrations, including risks associated with the most sensitive endpoints and receptors (e.g., developing fetuses, infants, and young children)?
- What is a reasonably "safe" CEC-specific level of exposure?
- Should the CEC be prioritized for further evaluation?

The decision tree framework integrates methods that performed well during Phase II testing, is methods which produced values equally or more protective (conservative) than values derived using traditional risk assessment methods. The general basis and logic for the current framework are highlighted below.

Decision Tree Criteria

Core criteria for developing a scientifically defensible and implementable framework included:

- Compatibility and consistency with existing MDH risk assessment methodologies as well as principles and practices being used by the larger risk assessment community. Special consideration was given to:
    - Vetted methods and open-access tools
    - Identification and protection of susceptible populations (e.g., highly exposed or highly sensitive)
- Robustness over a wide range of substances and adverse health endpoints
- Ability to support a rapid assessment (e.g., require limited time, resources, data, and expertise)

Candidate Alternative Risk Assessment Methods

A range of alternative risk assessment methods were considered under this project, including "generic" screening methods (e.g., percentile approach, threshold of toxicological concern [TTC]), chemical-specific methods including extrapolation methods (e.g., using acute toxicity or 90-day maximum tolerated doses) and computational toxicology methods/tools (e.g., expert systems, grouping tools, and quantitative structure-activity relationship [QSAR] models). The Phase II evaluation of candidate methods (review of Phase I findings, expanded methods testing, and review of activities/advancements in the area of computational toxicology) revealed that a limited set of methods and tools are immediately available to meet the defined needs of this project.

Table ES-1 summarizes the alternative risk assessment methods evaluated. Based on Phase II testing, the following methods were retained and integrated into the draft decision tree framework. Testing results that informed the framework are summarized in Table ES-2. Candidate methods testing approaches and results are detailed in Section 2.2 and Appendix A of the full report and accompanying

MS Excel workbooks, which are available from MDH upon request by emailing health.legacy@state.mn.us.

Generic screening methods

- Percentile approach: This approach uses a conservative statistic (e.g., 5th percentile) from a distribution of existing health-based drinking water guidance values as a screening benchmark. For the purposes of this project, calculated percentile values are based on existing drinking water guidance values from MDH (2008–2014) and the California Environmental Protection Agency (CalEPA) as well as those derived using the U.S. Environmental Protection Agency (U.S. EPA) Integrated Risk Information System (IRIS) and Human Health Benchmarks for Pesticides (HHBP) program toxicity values and MDH risk assessment methodologies. This approach assumes that the CEC being assessed is representative of a random draw from the "test" datasets. Testing revealed that this method was more protective and inclusive than the generic TTC method, also evaluated during Phase I and Phase II.

Chemical-specific methods

- LD50 extrapolation: This method is based on the premise that high-dose acute toxicity data (i.e., LD50 values) can be used to set chronic drinking water guidance values. The method assumes a correlation between gross acute toxicity potency at high doses and chronic toxic endpoints, using an extrapolation factor of 17,000 (as proposed by Kramer et al., 1996) to estimate a chronic no observed adverse effect level (NOAEL) from an LD50, which in turn is used to generate a reference dose by applying an uncertainty factor of 100. The method was tested across chemicals, established toxicity databases, and specific non-cancer endpoints of special interest (e.g., cholinesterase [ChE] inhibition, endocrine system disruption). Testing revealed that the method provides a reasonable results in the absence of other chemical-specific toxicity data. The method generally errs on the side of over-protectiveness (capture rate over 90%), with more than about half of the estimated LD50-based values greater than an order of magnitude lower than the actual drinking water values.

- Computational toxicology tools and methods: Advancements in *in silico* (computational toxicology) offer some promise for current MDH CEC assessment needs. These largely include research efforts supported by U.S. EPA and applications related to the Organisation for Economic Co-operation and Development's (OECD's) Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH) program. However, researchers and regulatory toxicologists acknowledge that no single off-the-shelf, vetted tool is currently available to allow an assessor to query computational data using a single structure or alert. Moreover, available tools generally require a moderate level of expertise in chemistry and toxicology. For this project we reviewed and identified computer-based tools (e.g., expert systems and chemical grouping tools) that could be used for predicting toxicity endpoints (structural alerts), and filling data gaps (e.g., read-across approaches) in the context of MDH's decision tree framework.

Chemical Categories and Endpoints Evaluated

A key factor considered in framing the decision tree was the extent to which different chemical classes or "critical" toxicity endpoints might merit separate tracking or assessment in the decision process. Considerations included:

- Chemical grouping schemes proposed in Phase I.
- Types of chemicals and degradates anticipated based on existing CEC occurrence data.
- Toxicity endpoints of historic and/or growing concern in MDH drinking water risk assessments and drinking water guidance values tied to those endpoints (e.g., cancer, endocrine disruption, developmental/reproductive system toxicity, neurotoxicity).
- Chemical classes and endpoints considered in TTC approach applications and critiques.
- Reasonable expectations that a specified endpoint could be predicted through a weight-of-evidence and/or structure-activity analysis.

Phase II testing evaluated method performance across cancer and non-cancer endpoints and specifically examined endocrine activity and neurotoxicity (as defined by ChE inhibition). Based on risk assessment method testing conducted during Phase II, it was determined that carcinogenicity and ChE inhibition endpoints should be examined separately where possible via structural alerts.

Decision Tree Components

Key decision points in the framework (numbered boxes in Figure ES-1) are described in the sections that follow.

(Box 1) Chemical Name/CASRN/Structure

This is the starting point. The decision tree is intended for CECs determined to have insufficient or no data based on MDH's established CEC screening process. As such, proceeding through the framework relies largely on the structure of the CEC.

(Box 2) Identifying Exclusion Chemicals

The decision tree is designed to assess organic compounds, however, there are compounds for which the decision tree methods are not adequate. The following substances are excluded: metals, nanomaterials, polymers (esp. with high molecular weight), radionuclides, compounds specifically designed to exhibit hormonal activity, and highly bioaccumulative compounds. For the purposes of this framework, a highly bioaccumulative compound is defined as a chemical with a known (experimental) or predicted bioconcentration factor (BCF) ≥5,000 or a log K_{OW} ≥5. Tools for acquiring bioconcentration factors include EPI Suite™, CAESAR BCF model, U.S. EPA T.E.S.T, and U.S. EPA PBT Profiler, which are searched as part of MDH's established CEC screening process.

(Box 3) Structural Alerts/Evidence of Carcinogenicity

Here the assessor would conduct a broad evaluation of the chemical structure using rules, alerts, and "black box" QSAR, and compile information and data to evaluate whether the CEC should be categorized and tracked as a potential carcinogen. The primary tool considered for identifying structural alerts for carcinogenicity/mutagenicity is Toxtree, which can be downloaded or accessed online. The OECD QSAR

Toolbox also now incorporates Toxtree plug-ins, rule-bases, and data. A CEC would be flagged for carcinogenic potential if Toxtree output contains one or more of the following alerts:

- At least one positive structural alert for micronucleus assay
- Structural alert for *S. typhimurium* mutation
- Potential structural alert for *S. typhimurium* mutation based on QSAR
- Benigni/Bossa: Structural alert for genotoxic carcinogenicity
- Benigni/Bossa: Structural alert for nongenotoxic carcinogenicity
- Benigni/Bossa: Potential carcinogen based on QSAR

Testing and documentation of Toxtree sensitivity and specificity illustrates some limitations with this widely-used expert system (see Section 2.3.1 and Appendix B). For completeness, it is recommended that other expert systems/tools also be consulted (see Table 2-7), to corroborate Toxtree output. Discrepancies should be documented, with a general rule to err on the side of over-inclusion.

(Box 4) Compare to Cancer Screening Value

A screening value for predicted carcinogens is proposed to be set at 0.006 µg/L. Selection of this value is based on the assessment of the alternative approaches described in Section 2 of the report. The selected value reflects the 5th percentile screening drinking water value estimate across "test" datasets (see Table ES-2 and report Table 2-3), which included chemicals that met the exclusion criteria. No appreciable risk of harm is anticipated for potentially carcinogenic CECs detected at concentrations below 0.006 µg/L. CECs detected at concentrations above the screening value will require further evaluation, which entails further structure analysis and read-across approaches (Box 11). In the next phase of the project, MDH will remove chemicals that meet the exclusion criteria from the dataset prior to calculating a final generic screening value for potential carcinogens.

(Box 5) Consider Testing Options

If the structural alert exercise (Box 3) is unable to yield a result (e.g., Toxtree returns "Error when applying decision tree"), MDH may consider pursuing *in vitro* screens for carcinogenicity.

(Box 6) Identify LD50 Data

For those CECs found to have no structural alerts for carcinogenicity (genotoxic or nongenotoxic), the LD50 extrapolation method was selected for use in the absence of other toxicity data in generating a reasonably protective screening drinking water value. If LD50 data are available, continue to Box 7. If no LD50 data are available, structural alerts for ChE inhibition are explored (Box 8).

(Box 7) LD50 Extrapolation

Screening drinking water values can conceivably be derived using the "LD50 extrapolation" methods described in Section 2.1.2.1 and Appendix A of the report, and as summarized below.

Derivation method:

- Find the lowest rat oral LD50. Sources used in testing include the Hazardous Substances Data Bank (HSDB) and ChemID Plus. Review the study source and quality of the study. If multiple oral LD50 values are identified, evaluate possible outlier values before selecting one to use. In the

absence of a rat oral LD50, use a mouse oral LD50. In the absence of an experimental oral LD50, consider using estimated LD50s (e.g., T.E.S.T)—further reliability testing of models used in deriving an LD50 is warranted before adopting this practice, however.

- Derive an LD50-based NOAEL, by applying an extrapolation factor of 17,000 (Kramer et al., 1996).
- Apply an uncertainty factor to the LD50-based NOAEL to estimate a reference dose (RfD) (mg/kg/day).
- Calculate a screening drinking water value in µg/L using MDH's "short-term" risk assessment algorithm.

(Box 8) Structural Alert/ChE Inhibition

As noted above, based on alternative risk assessment testing and exploration, ChE inhibition was flagged as an endpoint that warranted special tracking due to observations that established or estimated drinking water values for chemicals exhibiting ChE inhibition activity were an order of magnitude lower than non-cancer drinking water values overall. Currently, Toxtree plug-ins for organophosphates offer the most viable option for flagging CECs with potential ChE inhibition activity (see Section 2.3.1 and Appendix C in the report).

(Box 9) Compare to ChE Screening Values

A screening value for CECs with potential ChE inhibition is proposed at 0.05 µg/L. Selection of this value is based on the assessment of the alternative approaches described in Section 2. The selected value reflects the 5th percentile screening drinking water value distribution across "test" datasets looking at those chemicals for which ChE inhibition was reported as the critical effect (see Table ES-2 and report Table 2-3). For CECs detected at concentrations below 0.05 µg/L, no appreciable risk of harm is anticipated. CECs detected at concentrations above the screening value will require further evaluation, which entails further structure analysis and read-across approaches (Box 11).

(Box 10) Compare to "Generic" Non-cancer Screening Value

If no structural alerts are identified for carcinogenicity or ChE inhibition, then a CEC would land in this box ('other' non-carcinogen). A screening value for non-carcinogens is proposed at 0.2 µg/L. The selected value reflects the 5th percentile screening drinking water value distribution across "test" datasets (see Table ES-2 and report Table 2-3), which included chemicals that met the exclusion criteria. For non-cancer CECs detected at concentrations below 0.2 µg/L, no appreciable risk of harm is anticipated. CECs detected at concentrations above the screening value will require further evaluation, which entails further structure analysis and read-across approaches (Box 11). In the next phase of the project, MDH will remove chemicals that meet the exclusion criteria from the dataset prior to calculating a final generic screening value for non-carcinogens.

(Box 11) Read-across Evaluations

The goal of this step is to use available methods/tools to predict the toxicity of the CEC of concern. That is, to develop a health-based guideline by selecting analog(s) with similar structural and functional features and deriving a drinking water guidance value based on reliable toxicity data identified for the

"best" analog. While general implementation frameworks for read-across are available (see report Table 2-8), experts agree that the process requires a moderate to high level of toxicology and chemistry expertise. The OECD Toolbox, along with other vetted tools (see report Section 2.3.2), offer means to complete the assessment via read-across.

Summary/Future Needs

The Phase II exploration process revealed that a relatively limited number of tools and approaches meet the established project criteria and MDH CEC risk assessment needs. Nonetheless, this report provides the justification and rationale for pursuing a risk assessment decision framework that proposes defensible CEC screening benchmarks; identifies a protective method for deriving non-cancer screening drinking water values if oral LD50 data are available; and calls for the application of "read-across" techniques in all other cases where CECs are at concentrations above the recommended screening benchmarks proposed in the framework.

Additional testing of the framework using the recommended approaches and tools outlined in this report will further evaluate the ease and efficacy of implementing the proposed methods. For example, the available frameworks for conducting read-across (analog or category selection) are not prescriptive by any means. The ability to derive reproducible results utilizing a core set of computer-based tools and expert judgment requires further assessment.

Active areas of ongoing research that attempt to better integrate chemical structure (e.g., alerts and classifications) and activity (e.g., genotoxicity) hold promise for the future development, testing, and validation of more robust toxicity prediction tools. Continued monitoring and evaluation of said efforts is therefore recommended to identify additional tools to support MDH's risk assessment needs as defined under this project.

Table ES-1. Summary of Alternative Risk Assessment Methods Evaluated

Method	Description	Status	Comments
Generic Methods			
Percentile	Uses a conservative statistic (e.g., 5th percentile) from a distribution of existing health-based drinking water guidance values as a screening benchmark. For the purposes of this project, drinking water values derived by MDH and CalEPA were considered, as well as screening drinking water values derived from U.S. EPA IRIS and HHBP toxicity data (cancer and non-cancer endpoints) using MDH risk assessment methodologies. Assumes that the chemical for assessment is a random draw from "test" datasets.	Retained for expanded testing in Phase II	Provides a reasonably protective value against which to compare ("screen") CEC detections. Database outliers would be expected to meet decision tree exclusion criteria (e.g., highly bioaccumulative chemicals). (*See Sections 2.1.1 and 2.2.2*)
Threshold of Toxicological Concern (TTC)	Establishes generic human exposure levels for chemicals below which there is a low probability of risk to human health based on the known toxicity of chemicals with similar structural characteristics (Munro et al., 1996; Kroes et al., 2004).	Eliminated after verification texting in Phase II	Despite fairly widespread use within the global risk assessment community, testing revealed that TTC values are not adequately protective when compared to a subset of MDH-derived drinking water guidance (cancer and non-cancer) values. (*See Sections 2.1.1 and 2.2.2, and Appendix A*)
Chemical-Specific Methods			
As Low As Reasonably Achievable	Technology-based approach that identifies "best practices" to remediate a contaminant.	Eliminated in Phase I	Not health-based. Does not achieve project objective to provide risk context for detected CECs.
LD50 Extrapolation	Uses a published extrapolation factor of 17,000 (Kramer et al., 1996) to calculate a chronic no observed adverse effect level (NOAEL) for a chemical from its oral LD50 value combined with an uncertainty factor of 100 to produce an LD50-based reference dose.	Retained for expanded testing in Phase II	Method testing revealed a relatively high capture rate using this method. That is, screening drinking water values derived using oral LD50-based reference doses were equal to or lower than those generated using chronic toxicity data. (*See Section 2.2.2 and Appendix A*)

Method	Description	Status	Comments
Lowest Therapeutic Dose (LTD)	Exclusively for pharmaceuticals, applies a series of uncertainty factors based on reported chemical-specific characteristics available from the drug label.	Evaluated under separate MDH project	A viable method, but not described in detail here because MDH is deriving screening level benchmarks for pharmaceuticals using a simplistic LTD approach as part of a separate project (relying on drug label data).
Margin of Exposure	Provides a ratio between a toxicological benchmark (e.g., known or predicted NOAEL, lowest observed adverse effect level [LOAEL]) and a calculated or measured exposure metric for a chemical.	Eliminated in Phase I	Not practical in current MDH context where sufficient toxicity data are presumed to be unavailable and the absence of vetted tools to predict toxicity points of departure such as a LOAEL.
Percent Sample Mass	Simply represents an 'acceptable' level of the unidentified chemical mass in a sample, expressed as a percent of the total chemical mass in the sample, e.g., 10%.	Eliminated in Phase I	Not health-based.
Toxicology-based Structure-Activity Relationship (SAR) and Quantitative Structure-Activity Relationship (QSAR) Models	Represents a variety of techniques for predicting activities and properties of untested chemicals based on their structural similarity to chemicals with known activities and properties.	Retained for further evaluation in Phase II	A number of evolving tools that integrate SAR/QSAR principles offer promise in supporting CEC assessments. Few are fully ready to meet direct needs of this project, but several can be used in concert to predict a likely toxicity endpoint or to aid in the selection of analogs for use in read-across. They have a relatively steep learning curve and require a moderate level of expertise in toxicology/chemistry. (*See Section 2.3*)
Analog and Category Read-Across	Integrated process of computer analysis and expert decision that uses chemical hazard data from one chemical to predict hazard of another based on structural similarities (substructural features) relevant to risk assessment.	Retained for further evaluation in Phase II	A number of evolving tools that integrate SAR/QSAR principles offer promise in supporting CEC assessments. Few are fully ready to meet direct needs of this project, but several can be used in concert to predict a likely toxicity endpoint or to aid in the selection of analogs for use in read-across. They have a relatively steep learning curve and require a moderate level of expertise in toxicology/chemistry. (*See Section 2.3*)

Method	Description	Status	Comments
Virtually Safe Dose	Exclusively for carcinogens/genotoxins, applies an extrapolation factor (577,000) recommended by Gaylor and Gold (1995) to a 90-day study maximum tolerable dose (MTD), adjusted to equate to MDH's target 10^{-5} cancer risk level.	Eliminated after verification testing in Phase II	Testing of the method against MDH cancer guidance values revealed that only ~30% of the chemicals tested would be captured by this method. Availability/reliability of an MTD also is likely limited for target chemicals. (*See Section 2.1.2 and Appendix A*)

Table ES-2. Summary of Alternative Risk Assessment Method Testing

Method	Critical Endpoint	MDH Database (2008-2014)[a]	CalEPA PHGs[b]	EPA IRIS[c]	EPA HHBP[c]	EPA IRIS/HHBP/CalEPA Combined
Percentile approach (5th percentile)	Cancer	0.005 µg/L (n=17)	0.01 µg/L (n=36)	0.002 µg/L (n=82)	0.5 µg/L (n=40)	**0.006 µg/L (n=135)**
	Non-cancer	0.3 µg/L (n=66)	0.2 µg/L (n=57)	0.2 µg/L (n=365)	0.7 µg/L (n=363)	**0.2 µg/L (n=666)**
	ChE inhibition	0.03 µg/L (n=23)	NA	0.07 µg/L (n=22)	0.04 µg/L (n=31)	**0.05 µg/L (n=45)**
	Endocrine activity	5 µg/L (n=15)	1.1 µg/L (n=5)	0.06 µg/L (n=30)	4.9 µg/L (n=70)	0.3 µg/L (n=96)
TTC	Cancer	10^{-5} TTC value = 0.25 µg/L [d] 75% protective (12/16 MDH values >0.25 µg/L)	Not tested	Not tested	Not tested	Not tested
	Non-cancer (Cramer Class III)	TTC value = 1 µg/L [e] 88% protective (44/50 MDH values >1 µg/L)	Not tested	Not tested	Not tested	Not tested
	ChE inhibition	TTC value = 0.2 µg/L [e] 65% protective (15/23 pesticide values >0.2 µg/L)[f]	Not tested	Not tested	Not tested	Not tested
LD50 Extrapolation	Non-cancer	95% protective (n=57)	Not tested	92% protective (n=332)	Not tested	Not tested
	ChE inhibition	Not tested	Not tested	91% protective (n=47)	91% protective (n=47)	Not tested
Virtually Safe Dose (VSD)	Cancer	31% (n=16)	Not tested	Not tested	Not tested	Not tested

[a] MDH database represents drinking water guidance values published by MDH from 2008-2014.

[b] CalEPA drinking water Public Health Goals (PHGs); CalEPA cancer-based PHGs were adjusted to represent a 10^{-5} cancer risk.

[c] EPA IRIS and HHBP datasets (reference doses and oral slope factors) used to derive screening drinking water values using MDH short-term and cancer algorithms:

MDH short-term algorithm: RfD (mg/kg-d)*0.5 (RSC)*(1000 mg/µg)/0.289 L/kg-d

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MDH cancer algorithm which uses age-dependent potency adjustment factors: (0.00001 risk level*1000 µg/mg)/((Oral Slope Factor*10*0.137 [$IR_{<2yr}$]*2 yr)+(Oral Slope Factor*3*0.047[$IR_{2\text{-}16yr}$]*14yr)+(Oral Slope Factor*1*0.039[IR_{16+yr}]*54yr))/70 yr)

[d] TTC-based screening value generated based on MDH cancer algorithm.

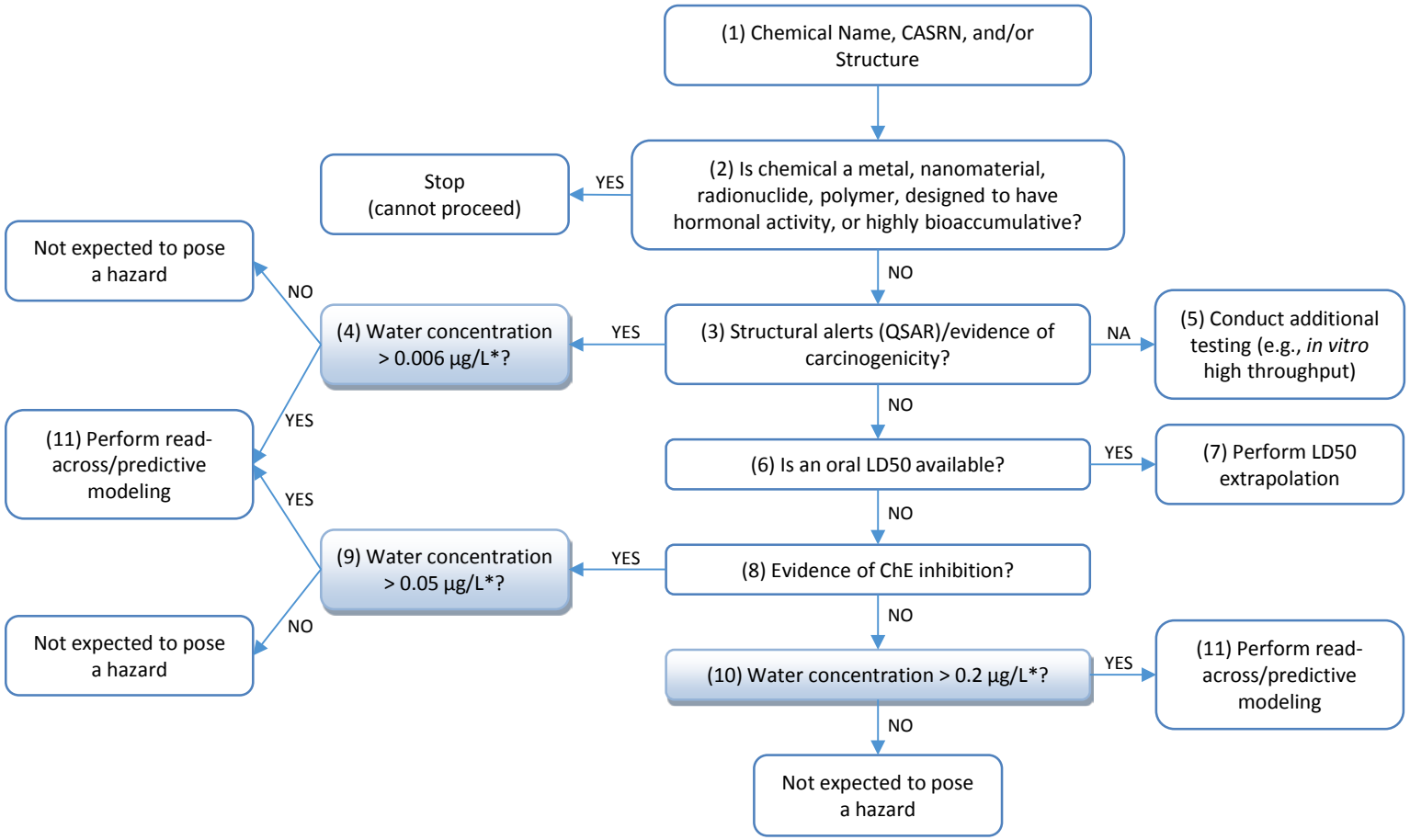
[e] TTC-based screening value generated based on MDH short-term algorithm: RfD (mg/kg-d)*0.2 (RSC)*(1000 mg/µg)/0.289 L/kg-d (see Appendix A, Section 2.2.2)

[f] Based on expanded testing of drinking water values derived under MDH's pesticide "rapid assessment" for chemicals and degradates with ChE inhibition listed as the critical effect (MDH, 2014).

NA: Not available
µg/L: micrograms per liter

Bolded values represent endpoint specific benchmark values considered for inclusion in the decision tree. Note: the "test" datasets included chemicals that met the exclusion criteria (e.g., highly bioaccumulative chemicals). In the next phase of the project, MDH will remove chemicals that meet the exclusion criteria from the dataset prior to calculating final generic screening values.

Figure ES-1. Preliminary Decision Tree Framework



Benchmark values used for high level decision-making or initial screening and are not intended to predict chemical-specific potency/toxicity. The framework can only provide risk context for detected chemicals whose detection limits are below the relevant screening values.
*In the next phase of the project, MDH will remove chemicals that meet the exclusion criteria from the dataset prior to calculating final generic screening values.

NA: Structural alerts or other scientific evidence not available

[Note: MDH staff have made limited revisions to this report for the sake of clarity, correction, or formatting. This report does not represent official agency policy but may be used to inform future work.]