Celebrating 80 Years of Improving Human and Planet Health

Application of the threshold of toxicological concern (TTC) in the evaluation of drinking water contact chemicals

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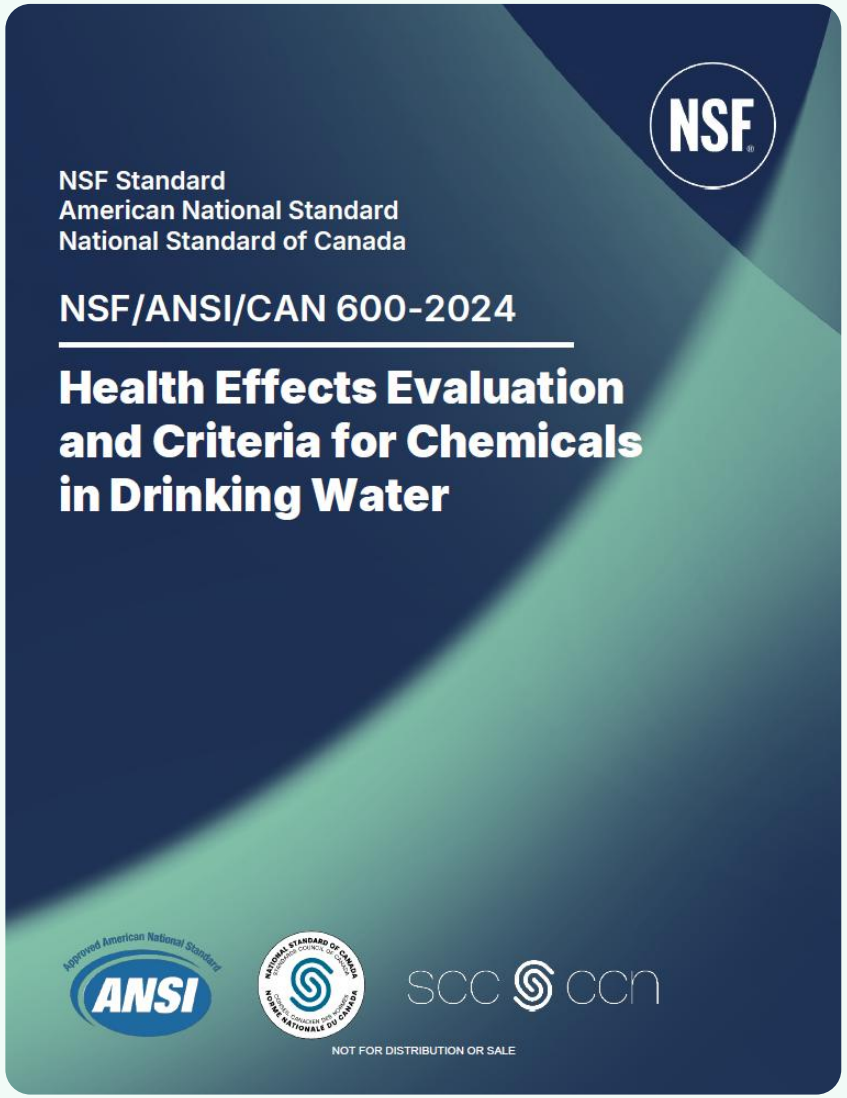
NSF – Who We Are

- Develop and maintain public health standards and conduct third-party product certification.
- Relevant standards include:
  - Drinking water treatment chemicals (Std 60)
    - Chemicals for coagulation, flocculation, disinfection, oxidation, corrosion control, etc.
  - Drinking water system components (Std 61)
    - (e.g., cements, coatings, valves, filters, pipes, hoses, faucets, drinking fountains)
- These all reference Std 600*: Health Effects Evaluation and Criteria for Chemicals in Drinking Water* (NSF 600).
  - List of health-based criteria for DW additives and extractants
  - Evaluation procedures used to establish those criteria.

NSF/ANSI/CAN 600

- Over 2000 chemicals listed with health-based criteria:
  - Existing drinking water regulatory criteria established by authoritative body (U.S. EPA MCL, U.S. EPA Health Advisories, Health Canada MAC, U.S. EPA IRIS)
  - Quantitative risk assessment developed by NSF or other certification body, conducted according NSF/ANSI/CAN 600.
  - “Qualitative” health-based criteria based on screening values.
    - Consensus with JPRSC
    - Non-genotoxic substances



NSF/ANSI/CAN 600 – Quantitative vs. Qualitative Criteria

- **Quantitative Criteria:**
  - Require an externally peer-reviewed risk assessment, with minimum data requirements
    - Gene mutation assay, micronucleus and/or chromosomal aberration assay (*in vitro*), 90-day assay in rodent species (oral)
  - Peer review body, the Health Advisory Board (HAB), meets 2x/year.
  - Longer turnaround time, more costly, finite resources.
- **Qualitative criteria:**
  - Health-protective screening values that do not require HAB review
  - Implemented quickly
  - New qualitative criteria based on TTC, implemented in 2024 and currently in use
  - Old qualitative criteria, implemented in 1999 and used until 2023

NSF/ANSI/CAN 600 – Health Based Criteria

Total Allowable Concentration (TAC): The maximum concentration of a nonregulated contaminant allowed in a public drinking water supply.

Single Product Allowable Concentration (SPAC): The maximum concentration of a contaminant in drinking water that a single product is allowed to contribute

$$\text{TAC} = \frac{\text{RfD (mg/kg per day)}}{\text{Intake Rate (L/kg per day)}} \text{ x RSC}$$

$$\text{SPAC} = \frac{\text{TAC}}{10}$$

Intake rate usually based on adult DW intake rate in the US EPA Exposure Factors Handbook (Chapter 3)

Basis of the TTC Approach

- Cramer et al. (1978) developed a decision tree approach to categorize chemicals into three classes:
  - Class I: Compounds with structures/data suggestion low oral toxicity
  - Class II: Compounds with structures of intermediate concern
  - Class III: Compounds with structures suggesting more significant toxicity
- TTC dataset of 613 chemicals developed by Munro et al. (1996) covering food, consumer, and agricultural chemicals.
  - 137 Class I, 28 Class II, 448 Class III.
  - TTC values derived from the distributions of NOAEL values from oral studies (5^{th} percentile)
  - 100-fold UF applied, 3x if from a subchronic study.

Basis of the TTC Approach

- Kroes et al. (2004): Additional “genotoxic” threshold of 0.0025 µg/kg-day proposed.
  - Based on linear extrapolation of TD50 values from 730 chemicals in the cancer potency database (Gold et al., 1989) and a cancer risk of 10^{-6}.
- Critically reviewed in many subsequent publications. Determined to be sufficiently protective of:
  - Neurotoxic and reproductive/developmental endpoints
  - Non-genotoxic carcinogens

- Existing criteria for 752 chemicals listed in NSF Standard 600 were compared to TTC-derived TAC.
  - TTC-derived TAC was adequately protective for >95% of these chemicals.

NSF/ANSI/CAN 600 – Current Qualitative Paradigm (Based on TTC)

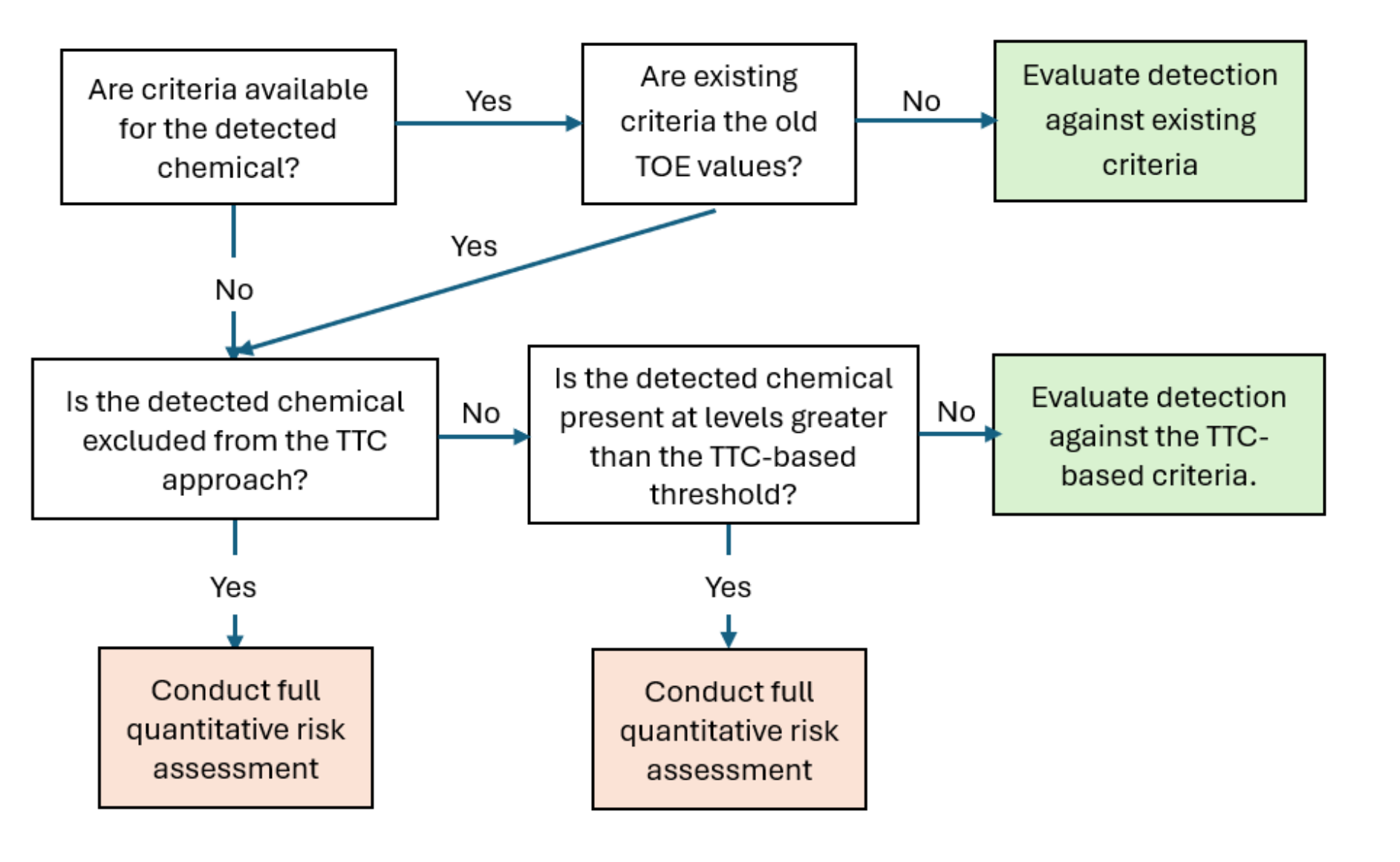
Classification	5th percentile NOAEL (mg/kg-day)	TTC (µg/kg-day)	TAC (µg/L)[a]	SPAC (µg/L)[b]
Genotoxic (highest concern)	Not applicable	0.0025	0.3[c]	0.03
Cramer Class III (high concern)	0.15	1.5	8.8 (10, rounded)	0.88 (1, rounded)
Cramer Class II (intermediate concern)	0.91	9	53 (50, rounded)	5.3 (5, rounded)
Cramer Class I (low concern)	3.0	30	176 (200, rounded	17.6 (20, rounded

[a]Based on a drinking water intake rate of 0.034 L/kg-day and a relative source contribution of 20%

[b]Assuming 10 point sources of the contaminant

[c]Based on 10^{-5} cancer risk level, assuming intake of 0.034 L/kg-day with lifestage adjustment (2.3 factor) for mutagenic MOA.

NSF/ANSI/CAN 600 – General Evaluation Procedure



Steps in the TTC evaluation

1. Verify the chemical is not within an excluded class of compounds
2. Conduct evaluation of genotoxicity potential
    - Consider empirical data on target chemical or analogue
    - Consider evidence from QSAR-based predictions
3. Identify the appropriate Cramer class if non-genotoxic
    - Apply the genotoxic TTC-based threshold if predicted to be genotoxic
4. Derive a comparative POD to ensure TTC threshold is protective

Steps in the TTC evaluation

Identifying Excluded Classes

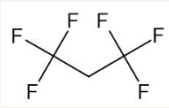
Genotoxicity Evaluation

Cramer Class Designations & Conflicts

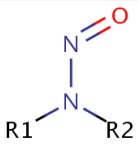
Calculating cPOD

TTCs for the following chemical categories were determined not to be protective due to high potency, endocrine disruption, or bioaccumulation potential and include:

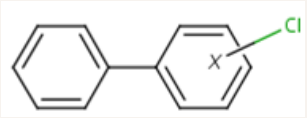
- High potency carcinogens
- Polycyclic aromatic hydrocarbons
- Polyhalogenated dibenzodioxins, -dibenzofurans, -biphenyls, and other bioaccumulating compounds that have a bioaccumulation factor or bioconcentration factor ≥ 500 (e.g., perfluoroalkyl substances)
- Steroids, and other known endocrine disruptors
- Polyhalogenated organics and terminal alkenes are also excluded



Polyfluorinated compounds



N-nitroso compounds



Polyhalogenated biphenyls

Steps in the TTC evaluation

Identifying Excluded Classes

Genotoxicity Evaluation

Cramer Class Designations & Conflicts

Calculating cPOD

Chemical categories, where the database of compounds to establish the TTCs was not inclusive and thus not applicable, include the following:

- Inorganics
- Metals and organometallics
- Proteins
- Nanomaterials
- Radioactive substances
- Polymers
- Undefined mixtures
- Organophosphate and carbamate pesticides

Genotoxicity Evaluation

Identifying Excluded Classes

Genotoxicity Evaluation

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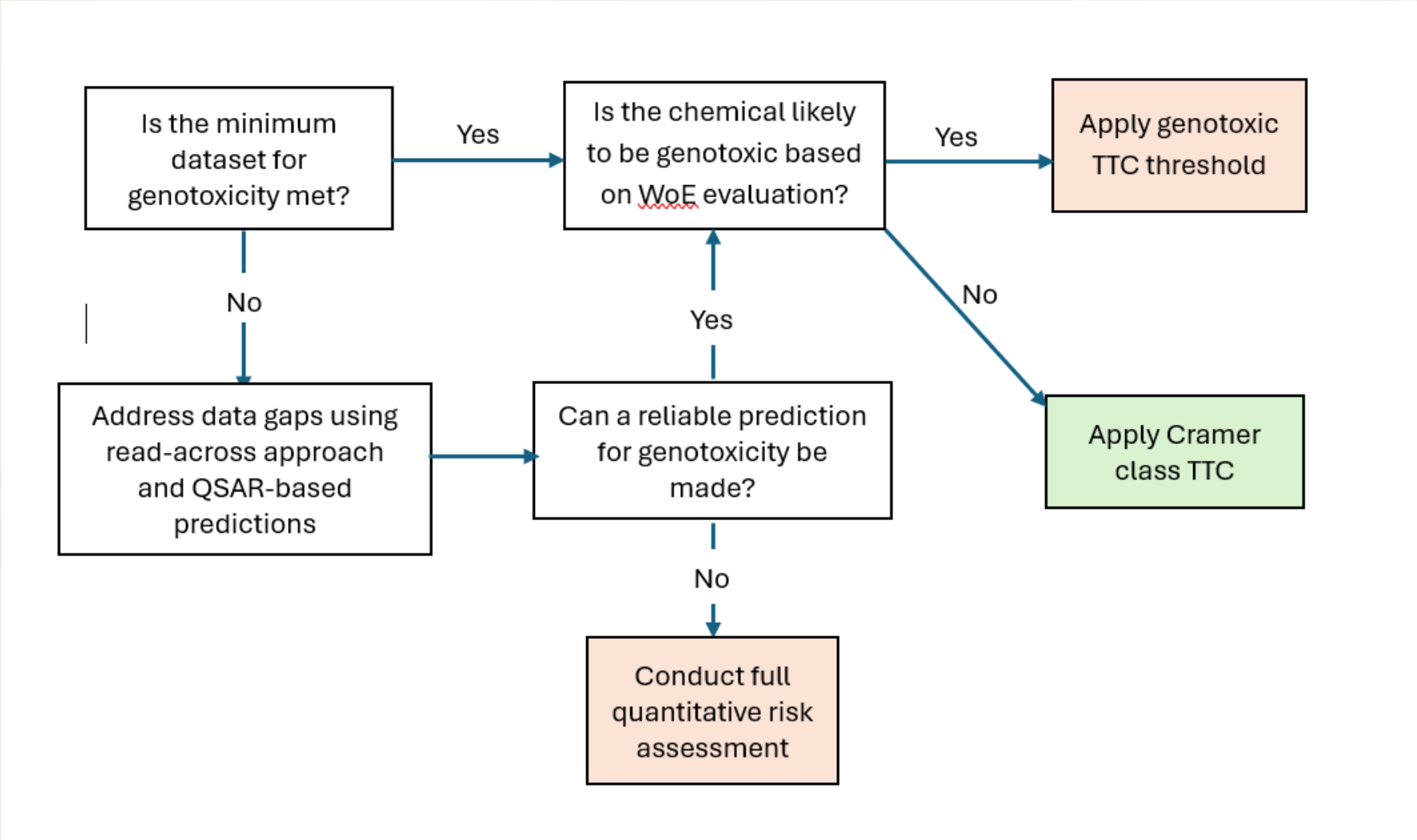
Calculating cPOD



Genotoxicity Evaluation

Identifying Excluded Classes

Genotoxicity Evaluation

Cramer Class Designations & Conflicts

Calculating cPOD

Minimum dataset:

- Mutagenicity: Bacteria reverse mutation assay or cell gene mutation assay
- Clastogenicity: In vitro chromosome aberration study, in vitro micronucleus test, and/or in vivo micronucleus test.

QSAR approaches:

- OECD QSAR Toolbox version 4.8 (rules-based)
- VEGA QSAR models (statistical based)
- ToxTree version 3.1.0 (rules based)
- EPA TEST Model version 5.1.2 (statistical based)
- Oncologic version 9.0 (rules-based)

Assignment of Cramer class

Identifying Excluded Classes

Genotoxicity Evaluation

Cramer Class Designations & Conflicts

Calculating cPOD

Cramer class assignments made using two software tools

- OECD QSAR Toolbox v. 4.8
  - Based on original Cramer (1978) publication, including 33 questions
- ToxTree v. 3.1.0.
  - “Cramer rules with extensions” decision tree
  - Based on original Cramer (1978) 33 questions, plus five additional questions addressing functional groups such as phosphates, benzene-like substances, divalent sulphurs and unsaturated heteroatom moieties.

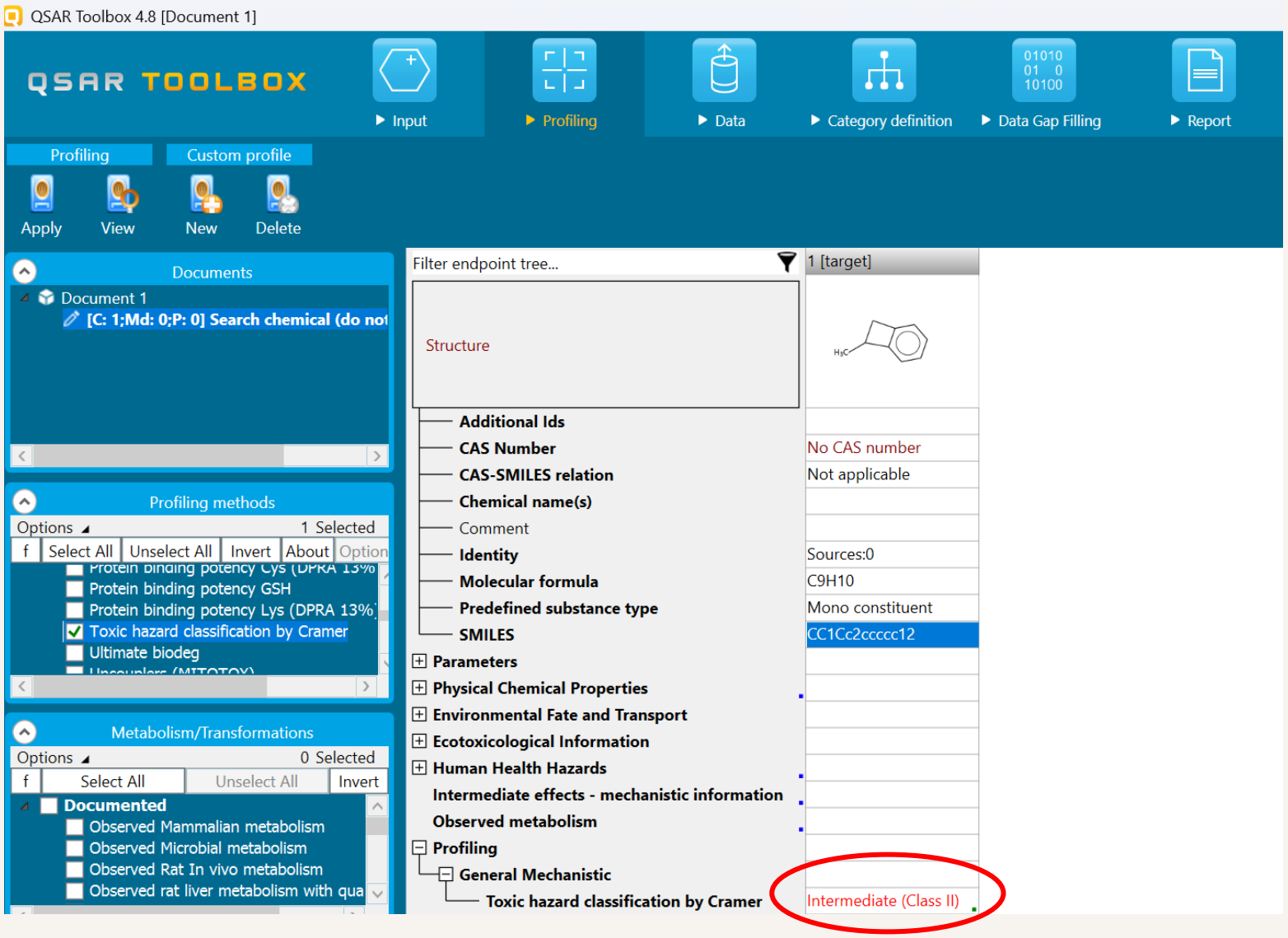
Informative Annex

Identifying Excluded Classes

Genotoxicity Evaluation

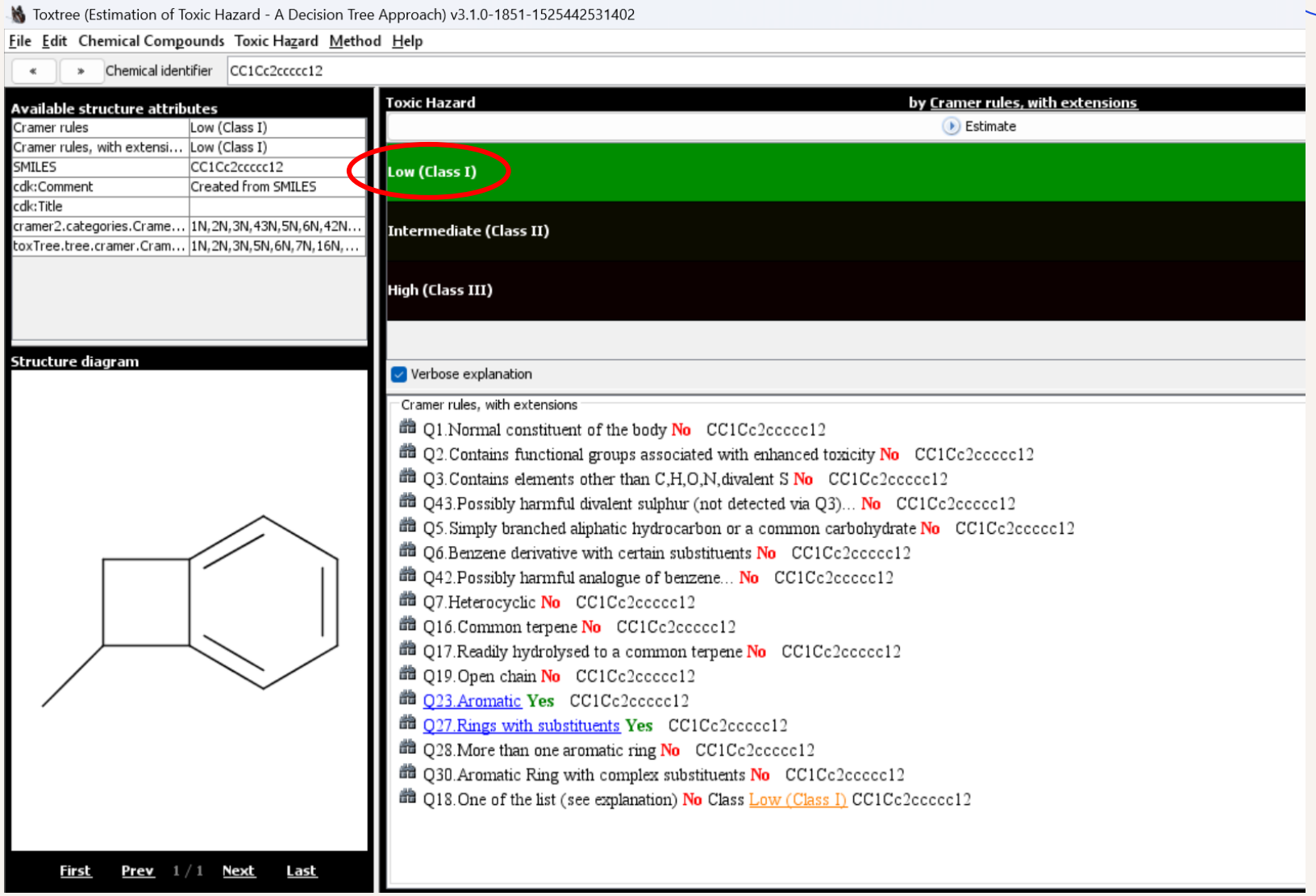
Cramer Class Designations & Conflicts

Calculating cPOD



Assignment of Cramer class

- Identifying Excluded Classes
- Genotoxicity Evaluation
- **Cramer Class Designations & Conflicts**
- Calculating cPOD



Assignment of Cramer class

Identifying Excluded Classes

Genotoxicity Evaluation

Cramer Class Designations & Conflicts

Calculating cPOD

- 7-methylbicyclo[4.2.0]octa-1,3,5-triene is classified as a Cramer Class I compound by ToxTree v3.1.0 and a Cramer Class II compound by QSAR Toolbox v4.8
- The two profilers deviated at question 30, which is the criteria for aromatic rings with complex substituents.
- In order to satisfy this criteria, a compound must have at least one substituent other than a 1-5 carbon hydrocarbon, aldehyde, ketone, carboxylic acid, ester, hydroxyl, or methoxy group.
- The target chemical has one 3-carbon substituent fused to the aromatic ring and, thus, the criteria for aromatic rings with complex constituents is not satisfied.
- The Cramer Class I classification as identified by Toxtree v3.1.0 is the most appropriate classification, which corresponds to a TTC 5th% NOAEL of 3 mg/kg-day.

cPOD derivation

Identifying Excluded Classes

Genotoxicity Evaluation

Cramer Class Designations & Conflicts

Calculating cPOD

- **Objective: To verify that the assigned Cramer class criteria are adequately protective based on empirical data**

- Relevant studies (oral):
  - Repeated dose, ≥ 28 days
  - Prenatal developmental studies
  - Single generation reproduction studies
  - Screening studies, such as OECD 421 and 422

- Effect levels (NOAEL and LOAEL) assigned to each study.

- The lowest POD, modified by appropriate uncertainty factor(s), should be higher than the corresponding TTC level.

cPOD derivation

- Identifying Excluded Classes
- Genotoxicity Evaluation
- Cramer Class Designations & Conflicts
- **Calculating cPOD**

cPOD Summary						
Study Type (Species)	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Critical Effect	Adjustment Factor[1]	cPOD (mg/kg-day)	Source
[Target Chemical]						
				1x (chronic, developmental or reproductive) **3x** (subchronic) **10x** (short-term) AND **3x or 10x** (LOAEL to NOAEL)		
[Analogue, if applicable]						

[1] Study types for application of the adjustment factor are as defined in Section 2 of NSF/ANSI/CAN 600
[# Insert footnote text here where alternative PODs are identified by the criteria author as compared to the original study author or as provided by the secondary source of the data]

- The lowest cPOD is selected for comparison to the TTC
- NOAEL/LOAEL values are consistent with those identified by the study author
- If no data available for the target compound, incorporate data from closest analogue compound.

cPOD derivation

Identifying Excluded Classes

Genotoxicity Evaluation

Cramer Class Designations & Conflicts

Calculating cPOD

28-Day Oral Study (rats) Similar to OECD TG 407	OECD 15 ECHA CHEM 50	OECD 50 ECHA CHEM 150	Hematology results consistent with hemolytic anemia with increased extramedullary hematopoiesis in the spleen.	**10x** (short-term)	5	Unpublished report by Hüls AG (1995) As cited by OECD (2004) ECHA CHEM (2023)
Extended One-Generation (rats)	50 (general toxicity)	150	P0 & F1 Adults Hematology consistent with hemolytic anemia. Histopathology of spleen and bone marrow consistent adaptations resulting from anemia. F1 Pups No developmental effects reported	**1x** (chronic, developmental or reproductive)	50	Unpublished report (2022) As cited by ECHA CHEM (2023)
Prenatal Developmental Toxicity Study	Maternal 45 Fetus >135	Maternal 135 Fetus >135	Maternal Decreased body weight gain (-15%) Fetus No effects at maximum dose tested	**1x** (chronic, developmental or reproductive)	45	Unpublished report by Aventis Pharma ProTox (2004) As cited by OECD (2004) ECHA CHEM (2023)

- The lowest study-specific value is 5 mg/kg-day and would be selected as the cPOD.

TTC Approach

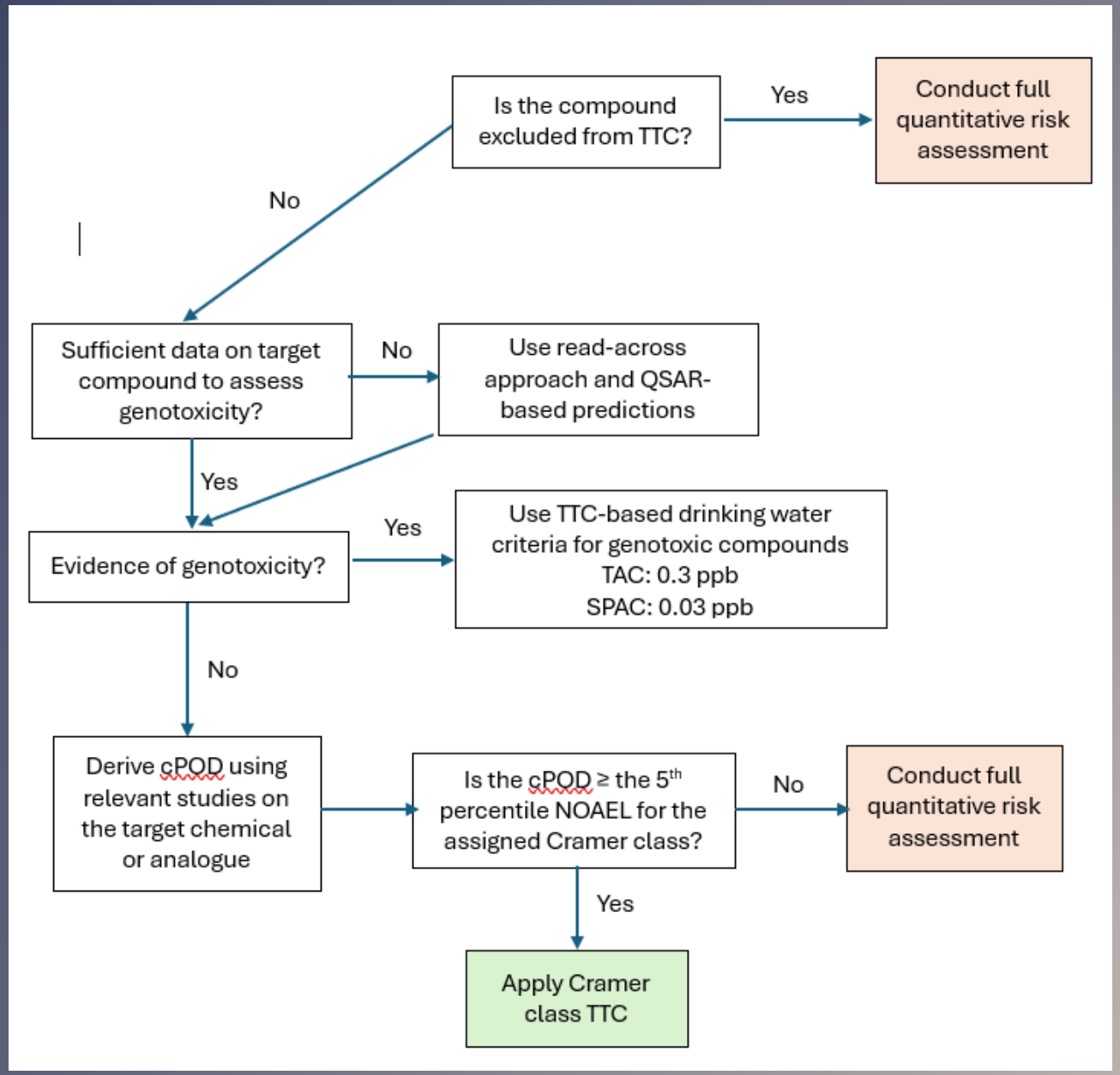
Comparative Point Of Departure (cPOD) Calculation

To confirm that the identified Cramer class TTC is health protective, a cPOD should be calculated to assess against the 5th percentile (%ile) NOAEL for the specified Cramer category

- If cPOD < 5th %ile NOAEL: quantitative risk assessment required
- If cPOD ≥ 5th %ile NOAEL: TTC-derived criteria may be applied
- If available toxicity data are insufficient to calculate cPOD: TTC-derived criteria may be applied

Classification	5th percentile NOAEL (mg/kg-day)
Genotoxic (highest concern)	Not applicable
Cramer Class III (high concern)	0.15
Cramer Class II (intermediate concern)	0.91
Cramer Class I (low concern)	3.0

TTC Paradigm



Further Reading

TOXICOLOGY MECHANISMS AND METHODS
https://doi.org/10.1080/15376516.2023.2279041

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REVIEW ARTICLE

Check for updates

Application of the threshold of toxicological concern (TTC) in the evaluation of drinking water contact chemicals

Kelly A. Magurany[a], J. Caroline English[b] and Kevin D. Cox[c]

[a]Toxicology, NSF, Ann Arbor, MI, USA; [b]NSF Health Advisory Board, ProTox Consulting, LLC, MI, USA; [c]Water Toxics Unit, Michigan Department of Environment, Great Lakes and Energy (EGLE), Lansing, MI, USA

TOXICOLOGY MECHANISMS AND METHODS
https://doi.org/10.1080/15376516.2023.2216289

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REVIEW ARTICLE

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Third party product certification for drinking water health effects

Kathryn Foster[a] and Kristin Licko[b]

[a]Water Division, NSF, Ann Arbor, MI, USA; [b]Product Certification- Toxicology, Water Quality Association, Lisle, IL, USA

TOXICOLOGY MECHANISMS AND METHODS
https://doi.org/10.1080/15376516.2025.2463487

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REVIEW ARTICLE

Check for updates

Quantitative methods for the risk assessment of drinking water contact chemicals following the NSF/ANSI/CAN 600 standard – part I: general methods

Bradley J. Lampe[a], Shannon Cousineau[a], J. Caroline English[b], Shannon Ethridge[c], Lynne T. Haber[d], Kristin Kerstens[e], Craig Rowlands[f] and Kelly A. Magurany[a]

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NSF Toxicology Staff

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Thank you!

Discussion, Comments, Questions, Recommendations?