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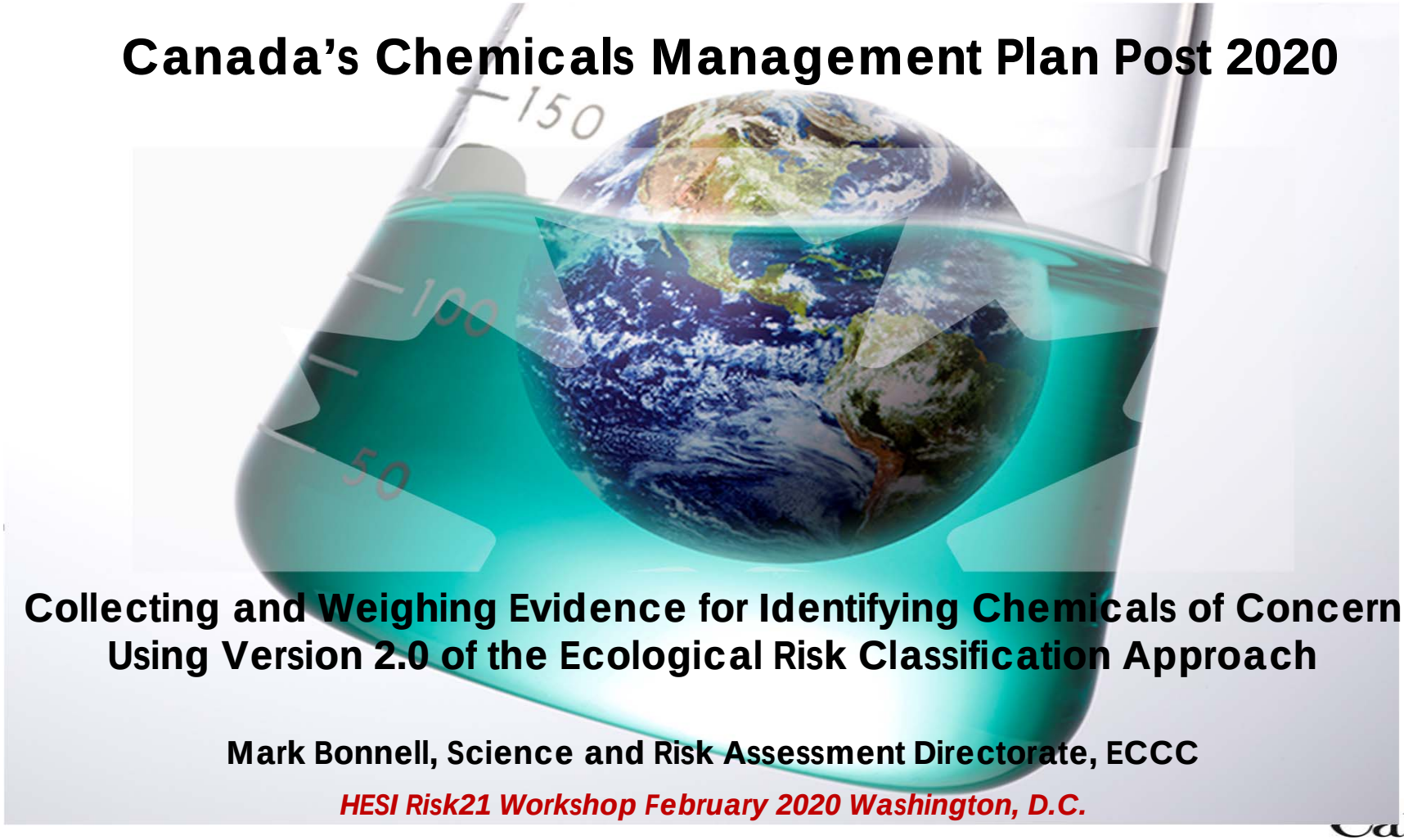
Canada's Chemicals Management Plan Post 2020



Collecting and Weighing Evidence for Identifying Chemicals of Concern Using Version 2.0 of the Ecological Risk Classification Approach

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Canada

Main Objective

- Give a basic overview of the main concepts of version 2.0 of ECCC's Ecological Risk Classification Approach (ERC2)
- Focus on how ECCC can make prioritization decisions from the output of ERC2 using eco-genotoxicity as an example

Ecological Risk Classification

- In 2016 ECCC successfully developed and published a 21st century science approach to re-prioritizing 640 organic chemicals for the third phase of the Chemicals Management Plan known as the Ecological Risk Classification (ERC)[1]
- ERC has been reviewed and published in the third cycle of OECD IATA (*Integrated Approaches to Testing and Assessment*) case studies[2]

[1]https://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=a96e2e98-1
[2]http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2018)27&docLanguage=En

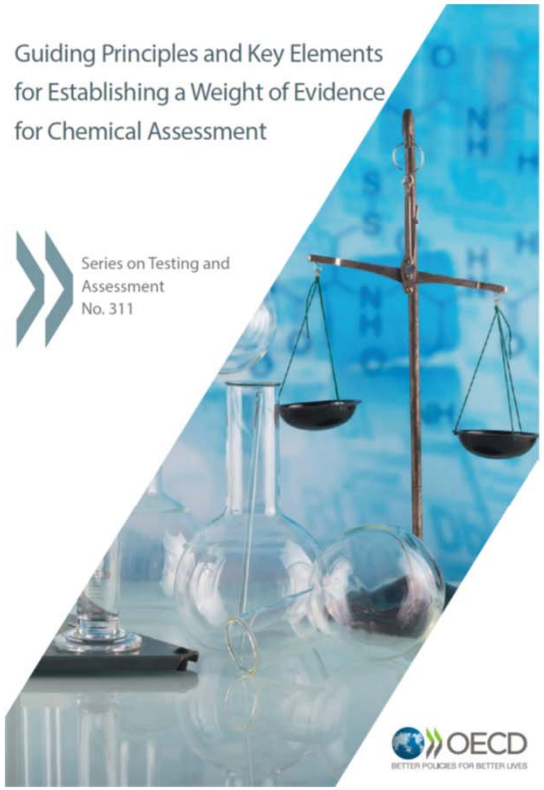
Version 2 of the ERC Organics for Post 2020

- ECCC has developed version 2.0 of the ERC (ERC2) for re-prioritizing ~12000 organics on the DSL which were not 'categorized' as a concern using P or B and T metrics in 2006
- ERC2 includes discrete organics, organic moieties of metal salts, UVCBs with known structure
- This will provide information to feed into the main themes for ECCC's post 2020 chemicals management thinking
- ERC is big data (>10 million data points; 405K files)
- ERC2 is always "in development" and morphing to accommodate new science

Core Concepts of ERC2

1. Classifies risk (hazard and exposure) using a chemical profiling approach
2. Profiles parent and metabolites for some hazard endpoints
3. Is weight of evidence driven (consensus within and among *in silico*, *in chemico*, *in vitro*, and *in vivo* datasets
4. Incorporates biological extrapolation assuming a sufficient degree of cross species susceptibility*
5. Finds plausible mechanisms to explain causality (adverse effects) using the AOP framework
   - linking chemistry with biology
6. Determines the likelihood of exposure at varying temporal and spatial scales

Regulatory Acceptance of ERC2: OECD Weight of Evidence Principles

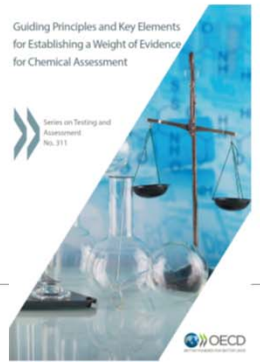


- Include a ***Hypothesis*** which involves a clear formulation and statement of the problem for which evidence is needed and possible alternative hypotheses
- Be ***Systematic and Comprehensive*** in design by documenting a step-wise procedure integrating all evidence and indicating how evidence was collected, evaluated and weighed
- Include a ***Treatment of Uncertainty*** arising from available data (knowns) and data and/or knowledge gaps (unknowns)
- Consider the ***Potential for Bias*** during collection, evaluation and weighing of evidence
- Be ***Transparent*** by including clear documentation to assist the communication of WoE decisions so that they can be understood, reproduced, supported or questioned by all interested parties.

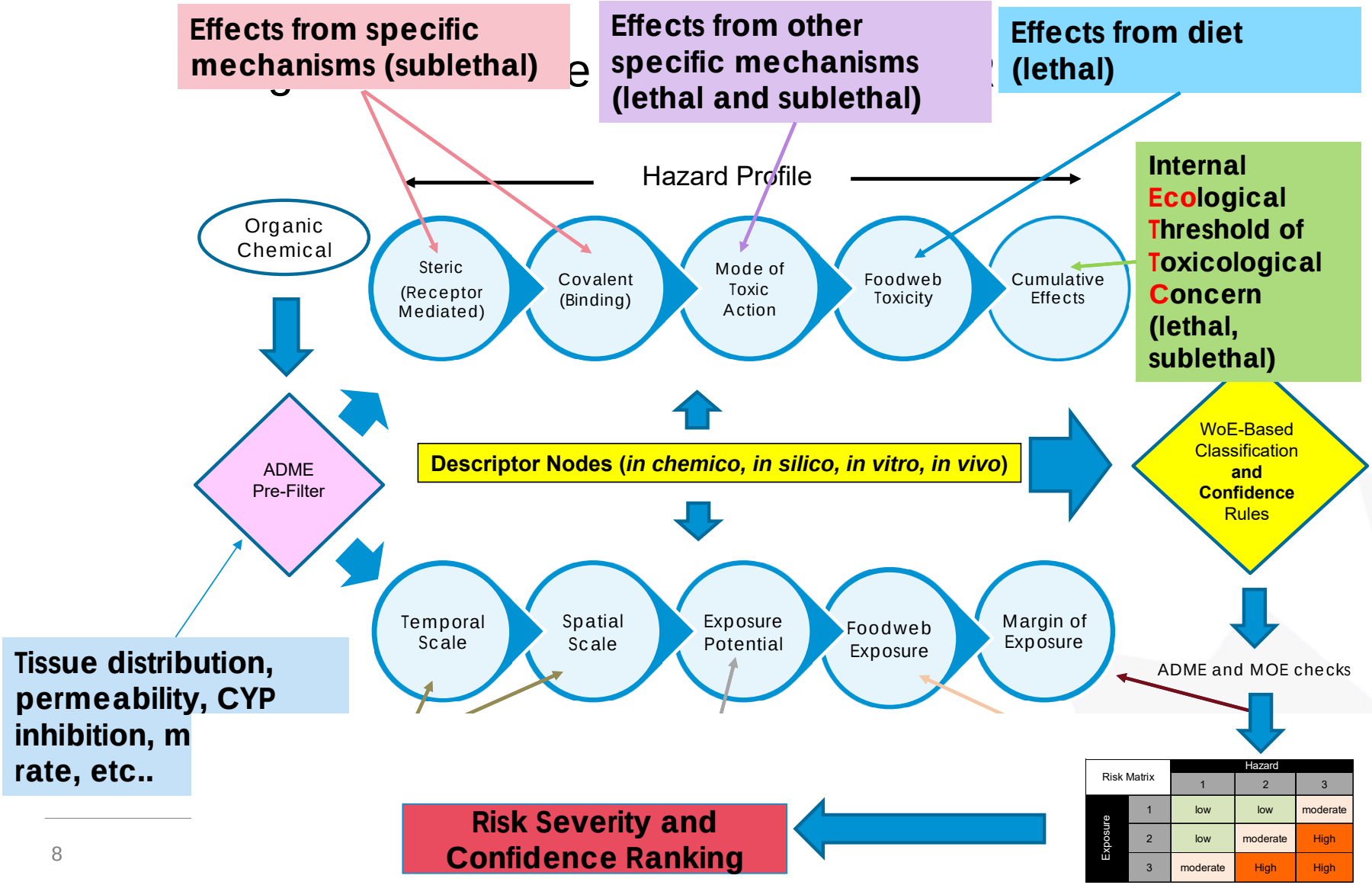
- **Hypothesis**: endpoint specific and overall risk questions
- **Systematic and Comprehensive**: rule based logical classification
- **Potential for Bias:** precaution only when justified
- **Treatment of Uncertainty**: Confidence and severity scoring included
- **Transparency**: All data will be publically available and decision rules traceable

Acceptable Level (Tolerance) for Uncertainty

hypothesis question(s). Brunk (2007) has noted, in scientific enquiry the "*standard of proof*" required to reject a null hypothesis is typically high (i.e., "greater than 95% confidence" or equivalently "beyond reasonable doubt"). However in risk assessment, as in some legal contexts, the "standard of proof" may be lower – e.g., "a preponderance of evidence" or "greater than 50% confidence" (Krimsky 2005). The level of confidence required to accept or reject a hypothesis formed during problem formulation can be associated with the acceptable level of uncertainty given the context in which the question is being asked. Acceptance of the level of uncertainty is directly linked to the protection goal(s) outlined during problem formulation and may differ between the human receptor (single species, higher specificity often required) and ecological receptors (multiple species, lower specificity is inherent). It may also vary according to the level or tier of evaluation undertaken depending on the decision context. It should also be noted that in



Pg. 14 OECD Guiding Principles and Key Elements for Establishing a Weight of Evidence for Chemical Assessment


Effects from specific mechanisms (sublethal)
Effects from other specific mechanisms (lethal and sublethal)
Effects from diet (lethal)
Hazard Profile
Organic Chemical
Steric (Receptor Mediated)
Covalent (Binding)
Mode of Toxic Action
Foodweb Toxicity
Cumulative Effects
Internal Ecological Threshold of Toxicological Concern (lethal, sublethal)
ADME Pre-Filter
Descriptor Nodes (in chemico, in silico, in vitro, in vivo)
WoE-Based Classification and Confidence Rules
Temporal Scale
Spatial Scale
Exposure Potential
Foodweb Exposure
Margin of Exposure
ADME and MOE checks
Tissue distribution, permeability, CYP inhibition, m rate, etc..
Risk Matrix
Hazard
Exposure
1 2 3
1 low low moderate
2 low moderate High
3 moderate High High
Risk Severity and Confidence Ranking

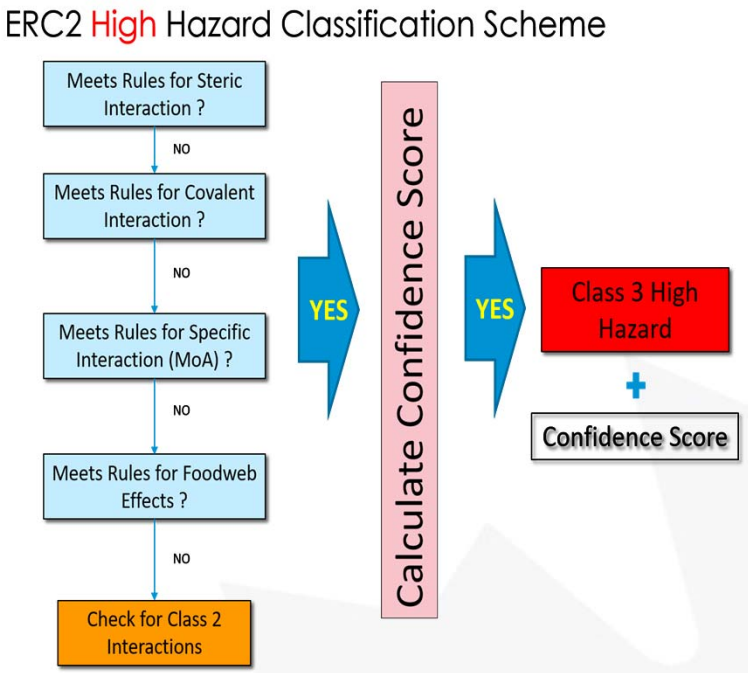
Core Output of ERC2

For each CAS#, ERC2 provides:

- Classification scores (hazard, exposure, risk)
- Confidence scores (hazard, exposure risk)
- Severity scores (hazard, exposure, risk)

Classification Scoring

- Classification of hazard, exposure and risk is conducted according to **rules** based on potency indices (hazard) probability (exposure)
  - Many of these are scientifically established (e.g., ER/AR binding, protein binding)
- Classification rules have been established at:
  - The data level (in silico to in vivo)
  - Final classifications of hazard, exposure, risk
- The classifications are used to determine the risk matrix



Confidence Scoring

- Where possible and appropriate, each descriptor for ADME, hazard and exposure will be associated with a confidence score ("data level confidence")
- In addition to each descriptor, overall classification will have a confidence score based on concordance of in silico, in vitro and in vivo data ("final classification confidence")
- Confidence ranking is intended to give transparency to the impact of uncertainty in accordance with weight of evidence principles

Example *in silico* Confidence Rules and Scoring for Covalent Interactions

Rule Description	Rule No.	Confience Class	Confidence Score
>6 models agree	1	very high	5
4 to 6 models agree	2	high	4
4 models agree	3	moderate	3
<4 models agree	4	low	2
Models are equivocal	5	equivocal	1
3 or more models indicate metabolite is positive	6	high	4

Severity Scoring

- Chemicals can cause effects from more than one pathway and organisms can be exposed at different temporal and spatial scales
- Hazard and exposure severity scores are based on the number of descriptor rules triggered
  - e.g., one Class 3 hazard rule triggered = moderate, all Class 3 rules triggered = very high
- Risk severity is the sum of the hazard and exposure severity scores and ranges from very low to very high
- Severity can be viewed as an integrated measure of “risk scale”

ECO-GENOTOXICITY AND VULNERABLE ECOLOGICAL POPULATIONS

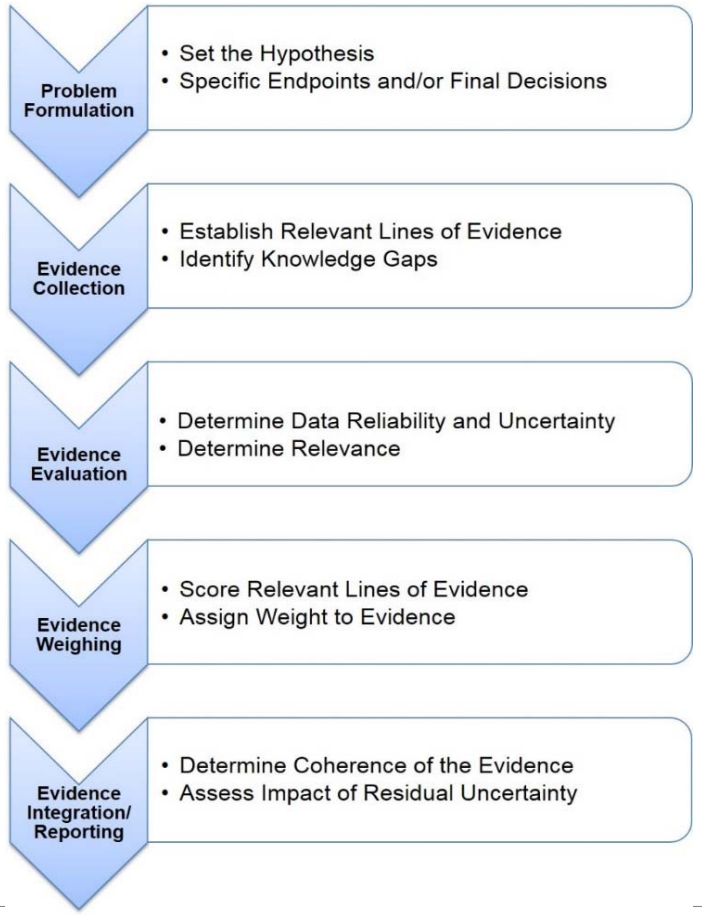
Ecological Relevance of Genotoxicity Profiling

- For non-human organisms, we are mainly interested in genotoxic responses related to developmental and reproductive effects and thus mainly mutagenic responses
- Most non-human organisms are less likely to develop carcinogenic outcomes due to much shorter lifespans (exceptions exist such PFOA tumors in turtles)
- Issue of exposures to epigenetic chemicals with wide environmental distribution and long residence time in the environment
  - Transmissible population level impacts continue even after emissions are stopped and “safe levels” are reached (e.g., based on chronic PNEC)

What Does Vulnerable Mean Ecologically?

- Not defined for CMP for ecological receptors
- For this case study we can consider Vul-Pop to include:
  - **Sensitive and or early life stage(s) or sex (e.g., developmental stages in females)**
  - Populations exposed to multiple stressors in highly disturbed ecosystems (e.g., areas of human development, natural disasters)
  - Populations under stress from the impacts of climate change
  - **Populations highly and continuously exposed to chemicals including chemical mixtures (red zones)**
  - Species used as a major food source for humans
  - Species threatened or at risk

ERC2 and OECD Key Elements for Weight of Evidence



Are vulnerable ecological populations at risk from eco-genotoxic chemicals?

Use mechanistic understanding to identify LoEs relevant to hypothesis – data and knowledge gaps identified

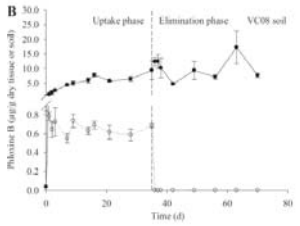
Data consensus and confidence scoring

ERC2 scoring systems - weight given to according to confidence score

Coherence of data from in silico to in vivo **(strength of evidence) – final confidence** ranking for assessing uncertainty

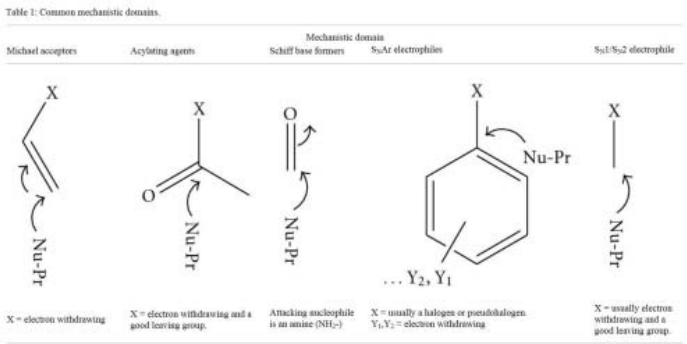
ERC2 and Eco-genotoxicity

Goal: Identify specific toxicological endpoints of concern and the plausible mechanisms that can be linked to adverse outcomes (causality)



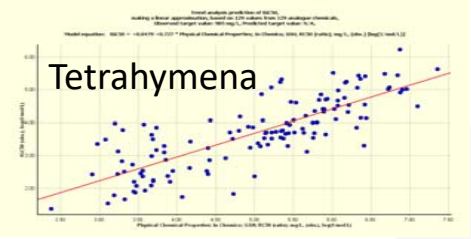
Binding Leads to Different Tissue Distribution (Princz et al. 2014)

Example Protein and DNA Binding Mechanisms

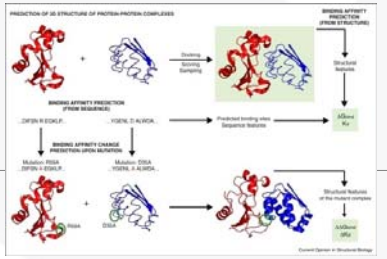


GHS RC50 Binding Potency; in vitro DNA damage, chrom. abb.

Dermal Effects (~sensitization)



Developmental Effects (mutation)



Conceptual Model of ERC2

STERIC DESCRIPTOR ENDPOINTS
ER RBA
AR RBA
Thyroid TPO, Binding
AhR
DART in vivo toxicity
Chronic aquatic toxicity
Acute Aquatic Toxicity

COVALENT DESCRIPTOR ENDPOINTS
Chromosome aberration
Gene mutation I, II
DNA and protein damage
DNA damage and repair
Micronucleus I, II
Ames
DNA and Protein Binding (7 profilers from Toolbox)
Protein Binding Potency
GHS RC50
DART
Repeated Oral Dose
Teratogenicity

ADME DESCRIPTOR ENDPOINTS
Vd
PPB
Ka intestine
pKa, Fraction ionized
Dmax, Deff
LogKow
MP
MW
Metabolism rate (fish, mammal, bird)

All EXPOSURE DESCRIPTOR ENDPOINTS
Tonnage
RAIDAR Pov
RAIDAR CTD water
RAIDAR CTD air
RAIDAR EAF
RAIDAR critical emission rate
RAIDAR tissue residue terrestrial
RAIDAR tissue residue aquatic
Fish BERs

MOA DESCRIPTOR ENDPOINTS

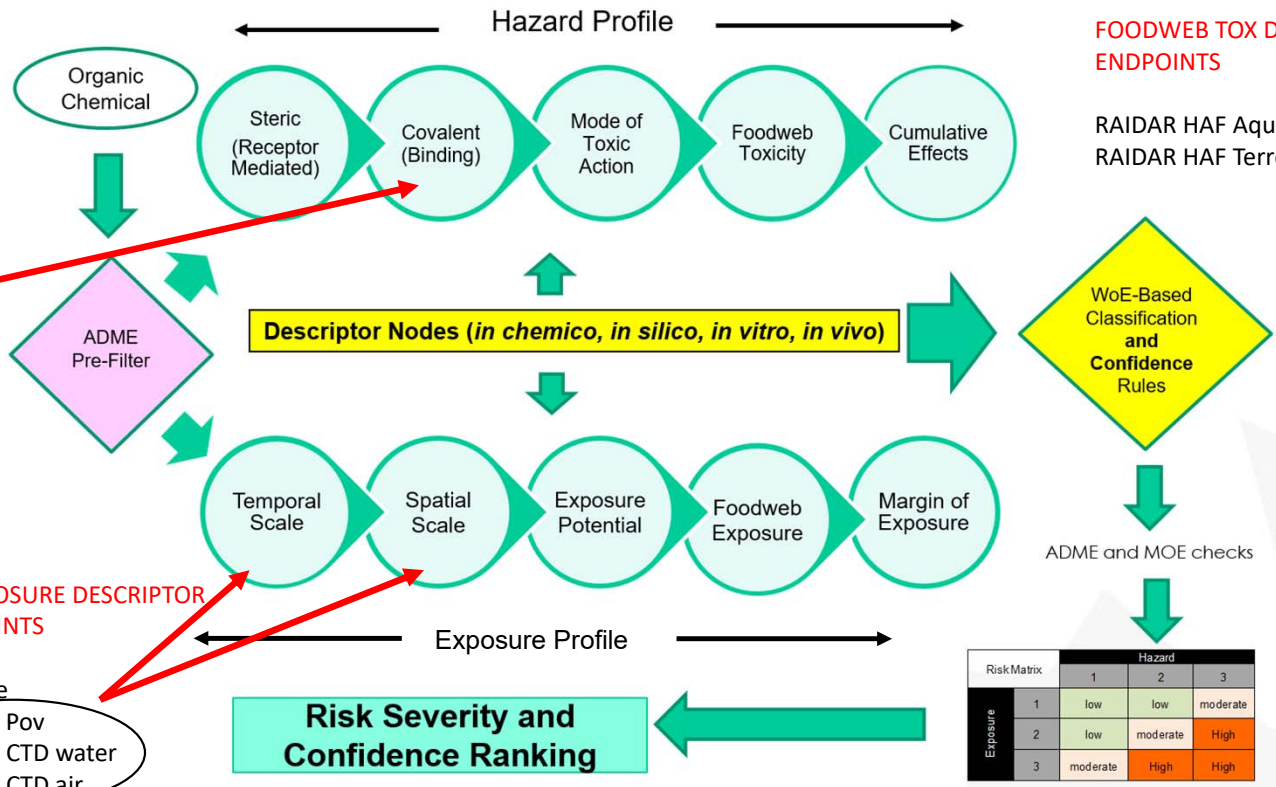
6 MoA QSARs
7 Tissue Residue models

FOODWEB TOX DESCRIPTOR ENDPOINTS

RAIDAR HAF Aquatic
RAIDAR HAF Terrestrial

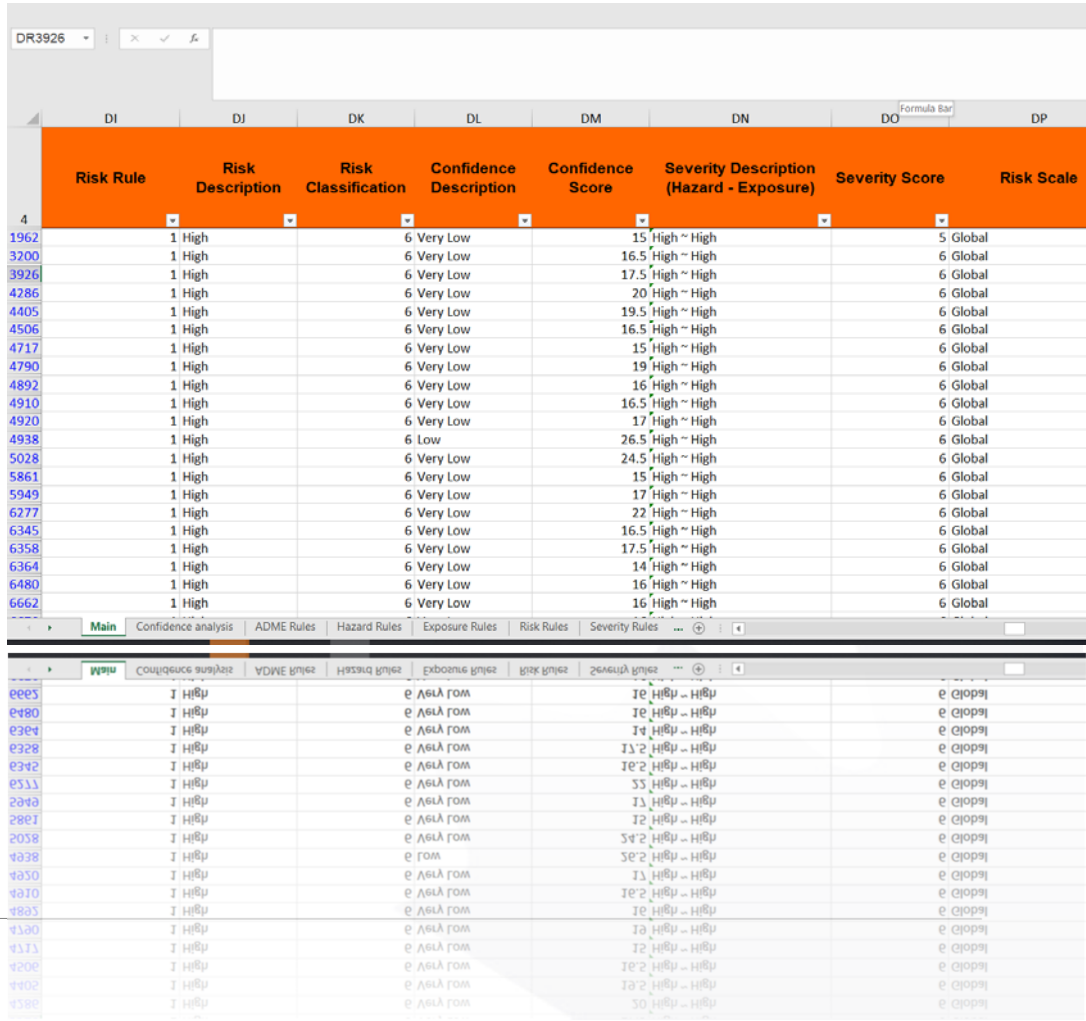
CUMM. DESCRIPTOR ENDPOINT

MoA Based CBR50



Preliminary ERC2 Eco-genotoxicity Results

- There are almost 200 chemicals that meet the hypothesis question posed (~1.5% of ERC2 list) - most are ionogenic (multiprotic)
- All of these chemicals have a low or very low confidence score (<40), meaning that all hazard and exposure classifications have relied almost solely on *in silico* evidence
- Points to significant data gaps in testing at all biological levels
- The high severity score suggests several other mechanisms of action (e.g., endocrine, uncoupling, neurotoxicity) coupled with very long clearance time (up to decades) and high mobility in water = monitoring needed
- The **regulatory decision** on the priority of these chemicals is now related to the acceptable level of uncertainty given the regulatory context



	DI	DJ	DK	DL	DM	DN	DO	DP
4	Risk Rule	Risk Description	Risk Classification	Confidence Description	Confidence Score	Severity Description (Hazard - Exposure)	Severity Score	Risk Scale
1962	1	High	6	Very Low	15	High ~ High	5	Global
3200	1	High	6	Very Low	16.5	High ~ High	6	Global
3926	1	High	6	Very Low	17.5	High ~ High	6	Global
4286	1	High	6	Very Low	20	High ~ High	6	Global
4405	1	High	6	Very Low	19.5	High ~ High	6	Global
4506	1	High	6	Very Low	16.5	High ~ High	6	Global
4717	1	High	6	Very Low	15	High ~ High	6	Global
4790	1	High	6	Very Low	19	High ~ High	6	Global
4892	1	High	6	Very Low	16	High ~ High	6	Global
4910	1	High	6	Very Low	16.5	High ~ High	6	Global
4920	1	High	6	Very Low	17	High ~ High	6	Global
4938	1	High	6	Low	26.5	High ~ High	6	Global
5028	1	High	6	Very Low	24.5	High ~ High	6	Global
5861	1	High	6	Very Low	15	High ~ High	6	Global
5949	1	High	6	Very Low	17	High ~ High	6	Global
6277	1	High	6	Very Low	22	High ~ High	6	Global
6345	1	High	6	Very Low	16.5	High ~ High	6	Global
6358	1	High	6	Very Low	17.5	High ~ High	6	Global
6364	1	High	6	Very Low	14	High ~ High	6	Global
6480	1	High	6	Very Low	16	High ~ High	6	Global
6662	1	High	6	Very Low	16	High ~ High	6	Global

2006 Categorization Decisions for ~200 ERC2 Eco-genotoxic Chemicals

- None of the ~200 substances in this case study were classified as PB(i)T or P or B and (i)T in 2006 thus they were not evaluated further under the Chemicals Management Plan until now
- All of the ~200 were categorized as persistent
- Only one of the ~200 was classified as bioaccumulative
- None were classified as inherently toxic using acute and or chronic lethality < 1 or 0.1 mg/L, respectively
  - Several iT results were deemed uncertain
- All of the categorization results were based on QSARs or category read-across due to lack of data at the time

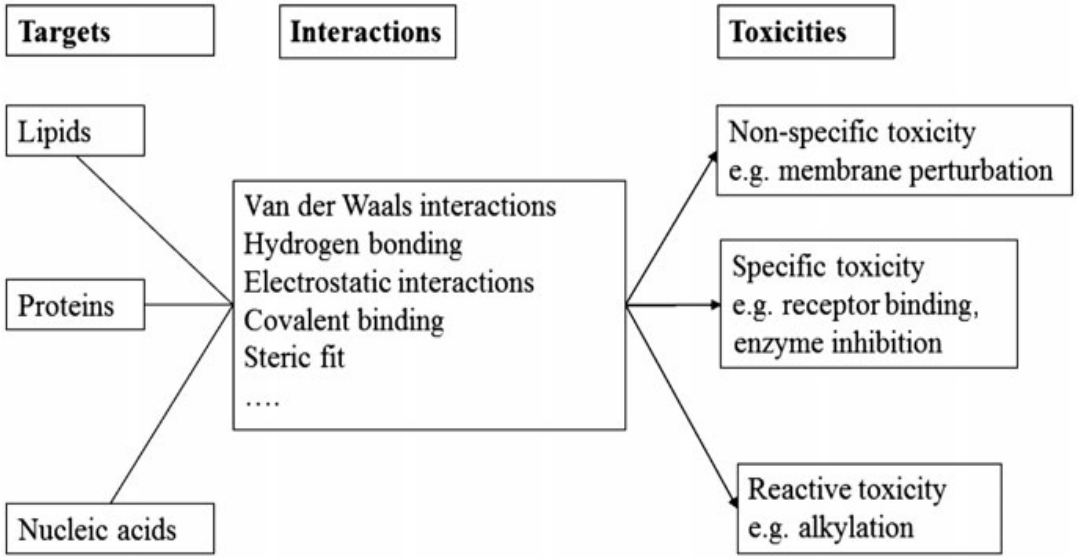
Thank You / Merci !

For more information on the Chemicals Management Plan:

https://www.canada.ca/en/health-canada/services/chemical-substances/chemicals-management-plan.html

ANNEX:

Defining Toxicological Space for Ecological Prioritization



SAR and QSAR in Environmental Research

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gsar20

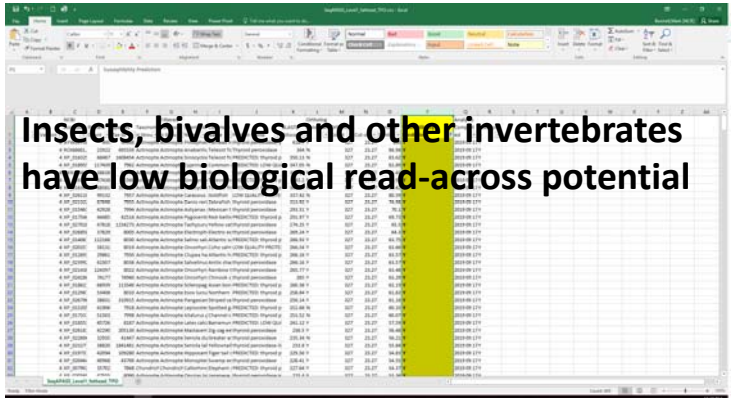
Discriminating toxicant classes by mode of action: 4. Baseline and excess toxicity

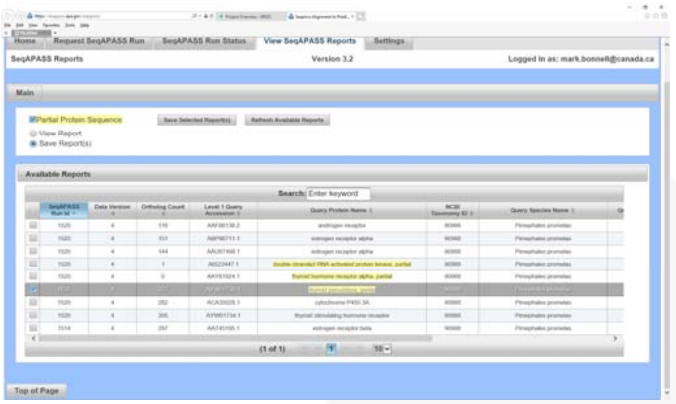
M. Nendza[a], M. Müller[b] & A. Wenzel[b]
[a] Analytisches Laboratorium, Luhnstedt, Germany
[b] Fraunhofer-Institute for Molecular Biology and Applied Ecology, Schmallenberg, Germany
Published online: 28 Apr 2014.

ERC2 and One Toxicology

- ERC uses a high amount of data that would traditionally be in the human health domain thus promotes the notion of “one health” via cross species susceptibility and can include human dietary exposures
- USEPA’s SeqAPASS* Tool can be used to verify the degree of cross species susceptibility to specific interactions (e.g., estrogen receptor, P450 inhibition) by checking the commonality of protein sequences

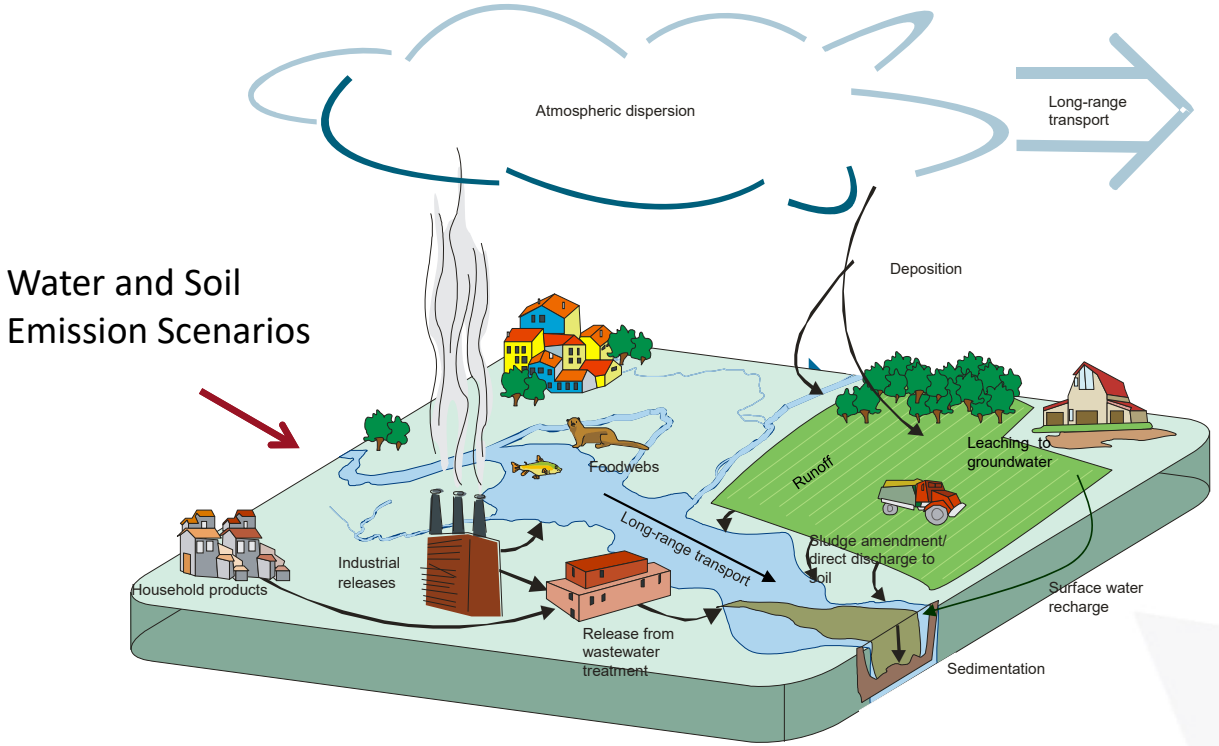
Example cross species alignment to thyroid peroxidase inhibition susceptibility





*Sequence Alignment to Predict Across Species Susceptibility

Exposure Scale Using Regional and Far Field Scenarios



Principle Models Used in ERC2

- OECD QSAR Toolbox v4.4 (profilers, empirical data)
- ECCC Chemical Pipeline Profiler (TIMES, CATALOGIC, OASIS ecotoxicity)
- EPIWIN
- ACD Labs *Percepta*
- IFS QSAR (metabolic half-lives fish, mammals)
- TEST,
- ASTER
- AIEPS
- Danish QSAR DB (Thyroid) (online)
- OPERA (ER/AR binding using CERAPP, COMPARA consensus models)
- RAIDAR v2.99 beta
- EXPOCAST (QSUR)