Application of the QSAR Toolbox for Ecological Priority Setting and Risk Assessment of Organic Chemicals in Canada

Presentation Series:

OECD QSAR Toolbox Applications for REACH and Beyond

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Historical Context

- Environment and Climate Change Canada (ECCC) has been a core member of the OECD QSAR Management Group supporting the development of the Toolbox since its inception in 2006
- ECCC has had an evolution with the application of the OECD QSAR Toolbox that has seen its increased use by ECCC scientists (both regulatory and research)
  - The main uses of the Toolbox have been for prioritization and ecological assessment of organic chemicals
  - Other specific applications of the Toolbox have been very important to ECCC (e.g., model integration, science development, chemical profiling for research)
- ECCC has donated Canadian-based bioaccumulation databases (BCF/BAF/BMF, metabolism rate) to the QSAR Toolbox as a means to increase the dissemination of this science

Applications of the Toolbox

- The Toolbox has and continues to serve as core software for gathering empirical and predicted data for both target chemicals as well as finding data for analogues for new and existing substances
- Other applications of the Toolbox at ECCC can be summarized as:
  - Category building
  - Read-across
  - Chemical profiling for prioritization and risk assessment
  - Endpoint vs. endpoint correlations
  - QSAR development and trend analysis
  - Integration with ECCC software platforms
  - Contributing science to improve the Toolbox (bioaccumulation, mode of action)

Building Chemical Categories

- Grouping of ~1300 organics was performed for Phase III of the Chemical Management Plan (CMP) through a number of iterations involving the Toolbox (e.g., using clustering tool) and manual verification and sorting by chemists
  - Initially resulted in many “fragmented” sub-groups that required assimilation into a larger grouping suitable for assessment (e.g., amines, acids, alkanes, etc..)
  - Primarily based on structural similarity but some groups are based on functional use (e.g., pharmaceuticals)
  - 76 Organic Groups (i.e., N>1)
  - 55 Individual Organic Substances

Read-Across Example

- The Toolbox was one of a select set of *in silico* tools used in an analogue case study that examined the robustness of two halogenated analogues of the chemical Dechlorane Plus (an organic flame retardant)
- These detailed case studies were presented to the CMP Science Committee (Topic 7b) as background documentation for its 2nd meeting on the use of read-across for risk assessment
- Documentation from the CMP SC can be found at:
  - https://www.canada.ca/en/environment-climate-change/services/evaluating-existing-substances/science-committee-first-term-report.html#toc23

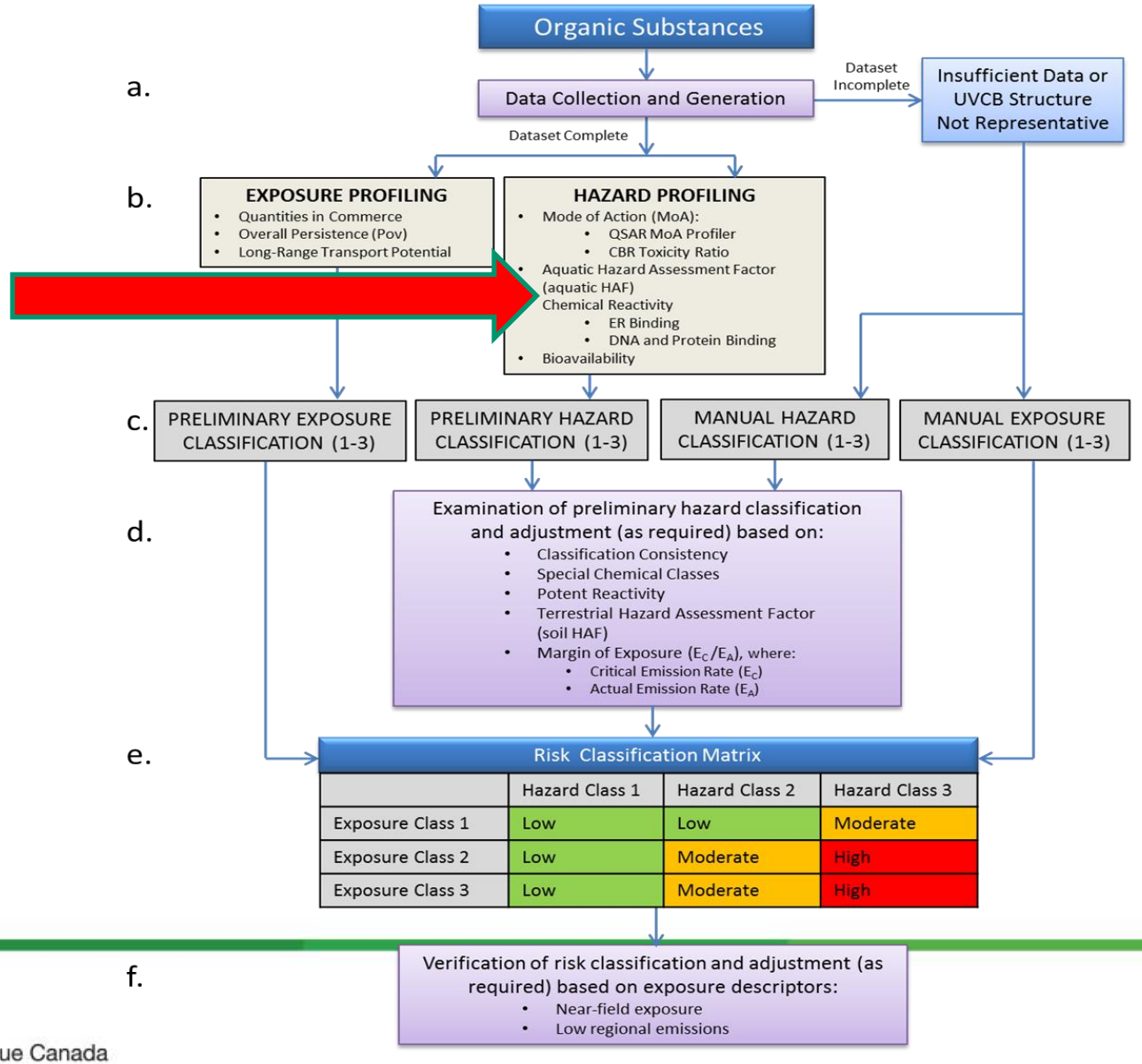
Chemical Profiling for Prioritization of Organic Chemicals: 2014-16

- ECCC developed its first version of the Ecological Risk Classification of organic substances (ERC), a 21st century IATA-based approach, which was used to re-examine 640 organic chemicals originally prioritized as persistent OR bioaccumulative AND inherently toxic (PiT, BiT)
- The ERC approach was the subject of an OECD IATA case study 3rd cycle
- The OECD QSAR Toolbox featured prominently in the chemical profiling of hazard in ERC v1

Application of the QSAR Toolbox for Re-examining 640 Organic Substances in CMP Phase III Using ERC Version 1.0

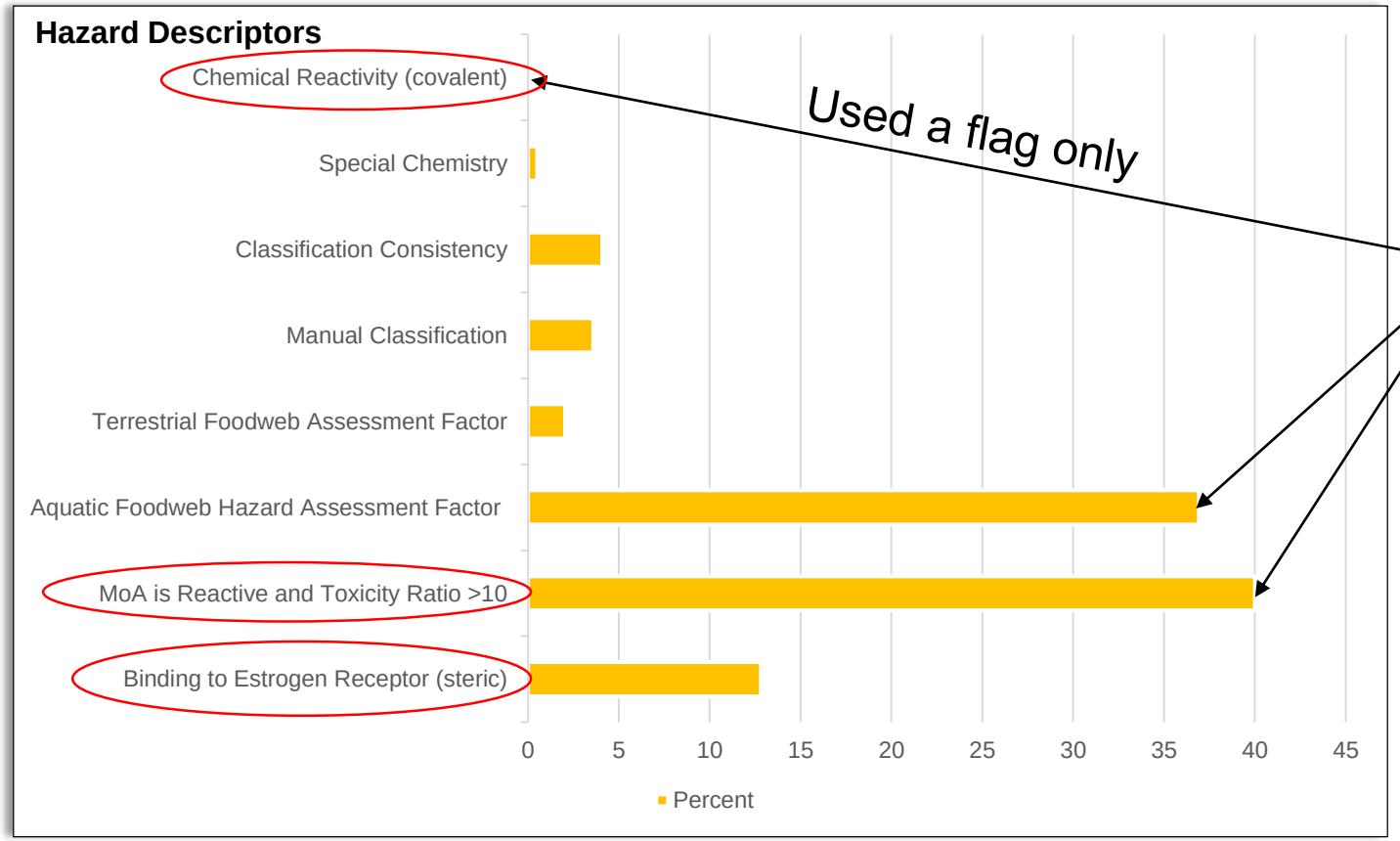
Chemical profiling using v3.3 and v3.4 of the OECD QSAR Toolbox for

- MoA
- Chemical reactivity
- Estrogen receptor binding



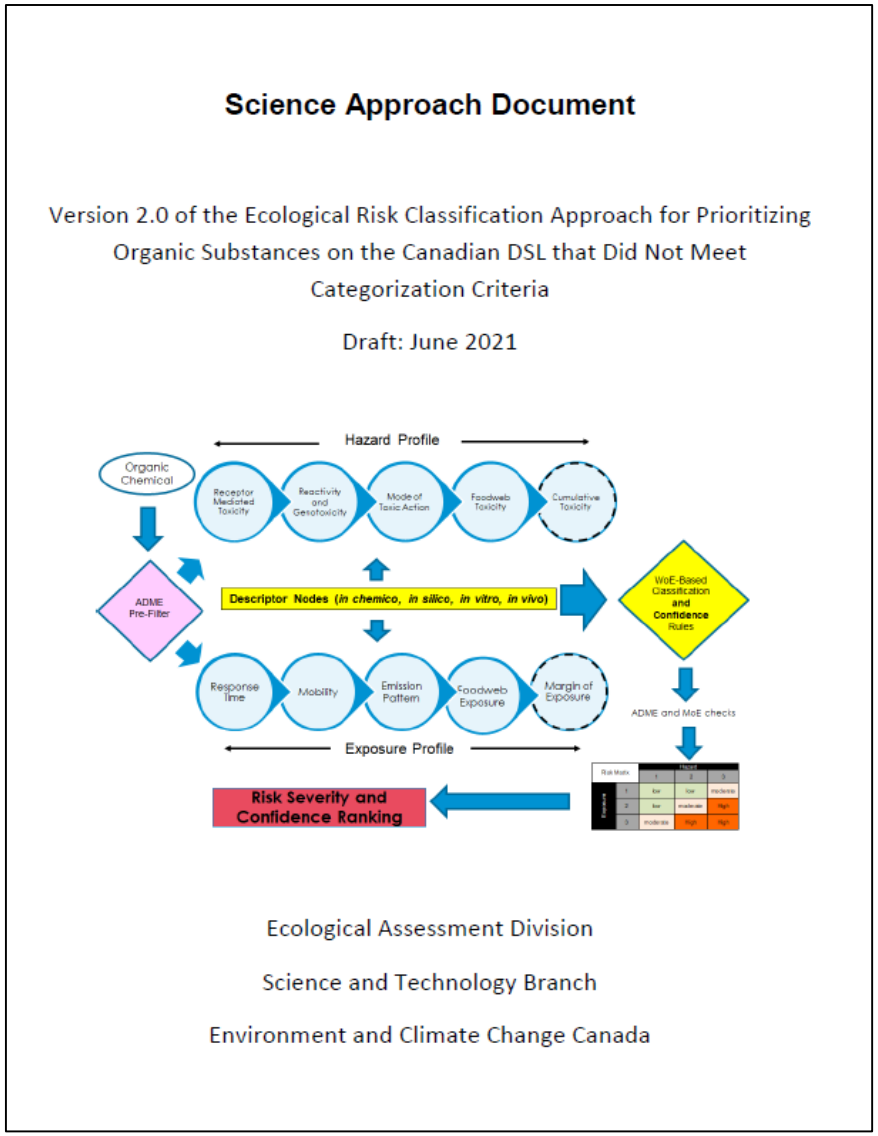
Impact of ERC Hazard Descriptors on High Hazard Classification

195 ERC High Hazard Substances



ERC Version 2: 2018-2021

- In 2020-1, ECCC completed the development of version 2.0 of the ERC (ERC2) which expands the toxicological and exposure space from ERC1 while providing a more transparent WoE approach
- ERC2 was applied to ~12200 non-PBT substances on the Canadian Domestic Substances List (DSL) identified during ECCC's 2006 categorization process
- Almost all *in vivo* empirical data and many in silico, in chemico and *in vitro hazard* data points were collected or generated using v4.2-4.4 of the QSAR Toolbox
- ERC2 approach and results for ~12200 organic chemicals will be published for 60 day public comment in February 2022



DESCRIPTOR ENDPOINTS
ER RBA
AR RBA
Thyroid TPO, alpha-beta binding
AhR
DART (mammalian/aquatic)
Repeated Oral Dose
Teratotoxicity

DESCRIPTOR ENDPOINTS
Chromosome aberration
Gene mutation I, II
DNA and protein damage
DNA damage and repair
in vitro/in vivo Micronucleus I, II
Ames
DNA and Protein Binding
Protein Binding Potency
GHS RC50
DART (mammalian/aquatic)
Repeated Oral Dose
Teratogenicity

DESCRIPTOR ENDPOINTS

6 MoA QSARs
7 Body Residue models (equations)

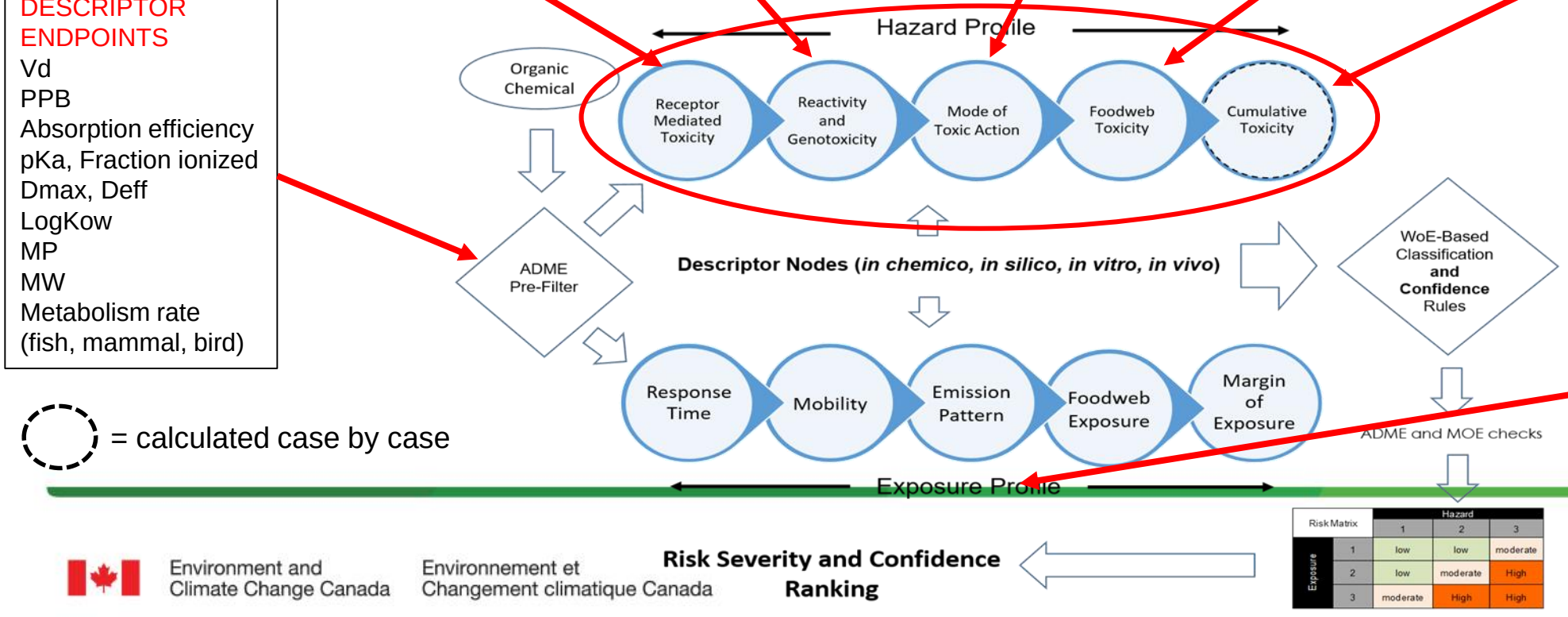
DESCRIPTOR ENDPOINTS

Integrated foodweb PBT factor
(Aquatic/Terrestrial)

DESCRIPTOR ENDPOINTS

MoA-based internal eco-TTC (mmol/kg)

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



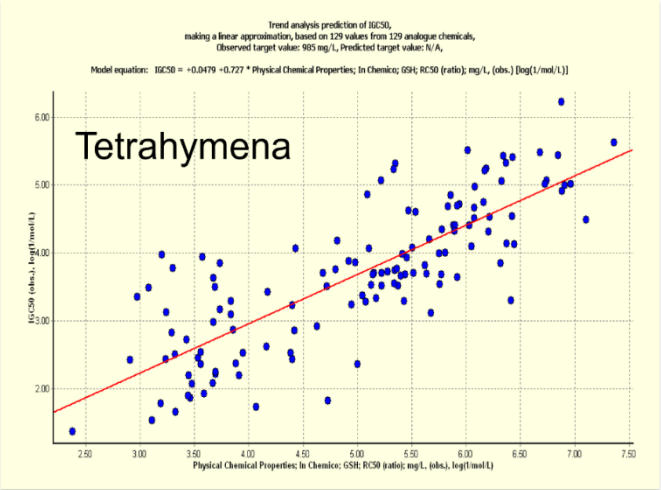
= calculated case by case

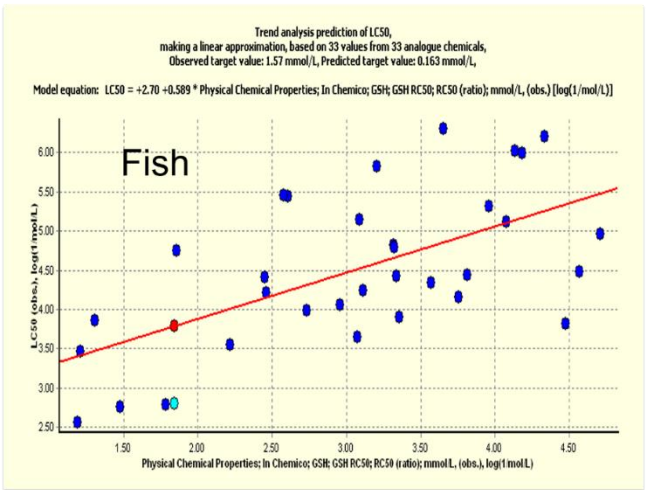
EXPOSURE PROFILE DESCRIPTOR ENDPOINTS

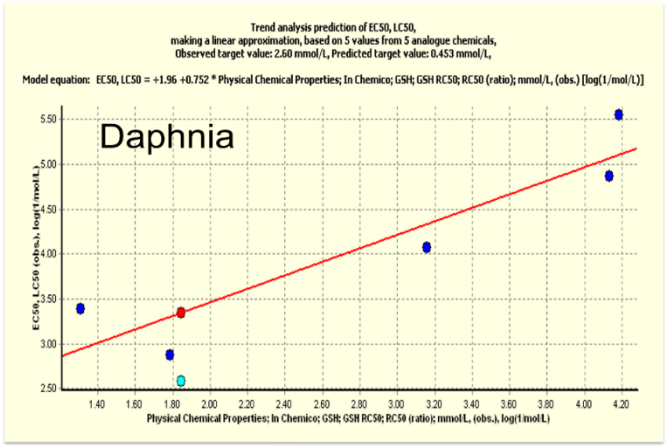
Quantity (estimated and reported)
Use Pattern (known/predicted)
Mode of Entry
Emission Rate (known/predicted)
Overall persistence
Characteristic travel distance (water/air)
Critical emission rate
Tissue residues (terrestrial/aquatic)
Fish BERs

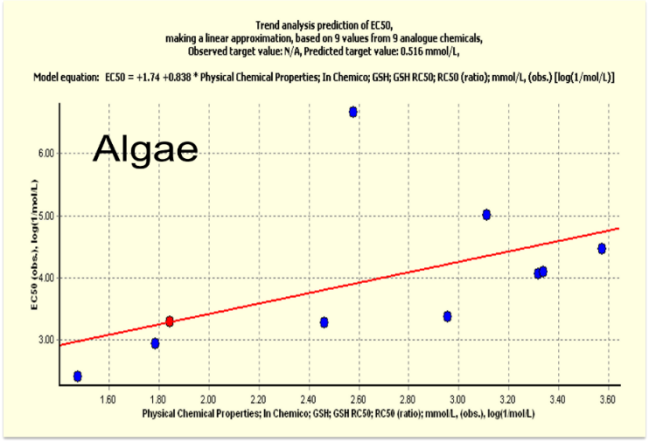
Endpoint vs. Endpoint Correlation: Protein Binding in ERC2

- Using endpoint vs. endpoint correlation in the OECD QSAR Toolbox for *in chemico* RC50 protein binding vs growth inhibition increased toxicity from increased binding potency is correlated across species
- Data for a chemical must be contained in both the protein binding RC50 and ecotox database and thus varies from species to species
- Scales log(1/mol/L)



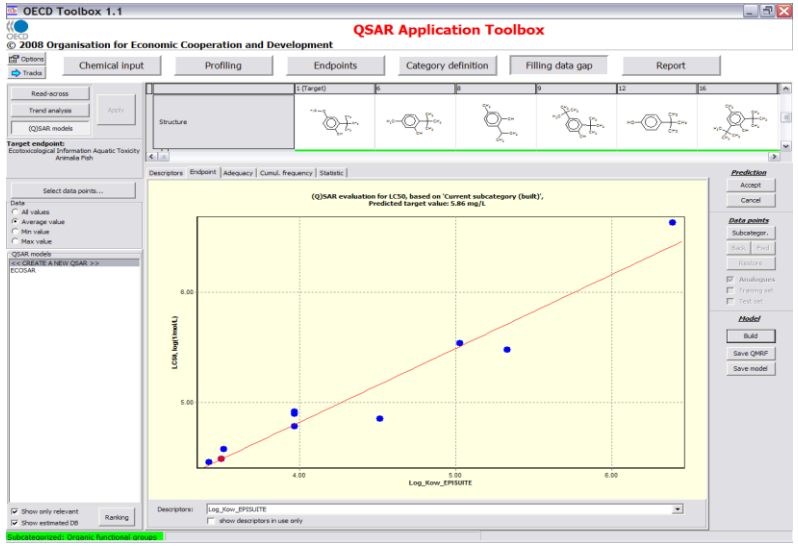


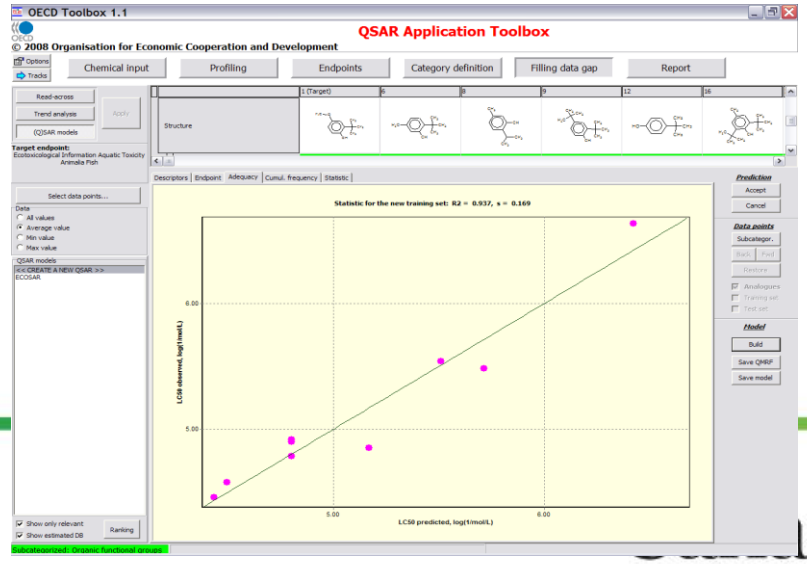




Building QSARs and Trend Analysis

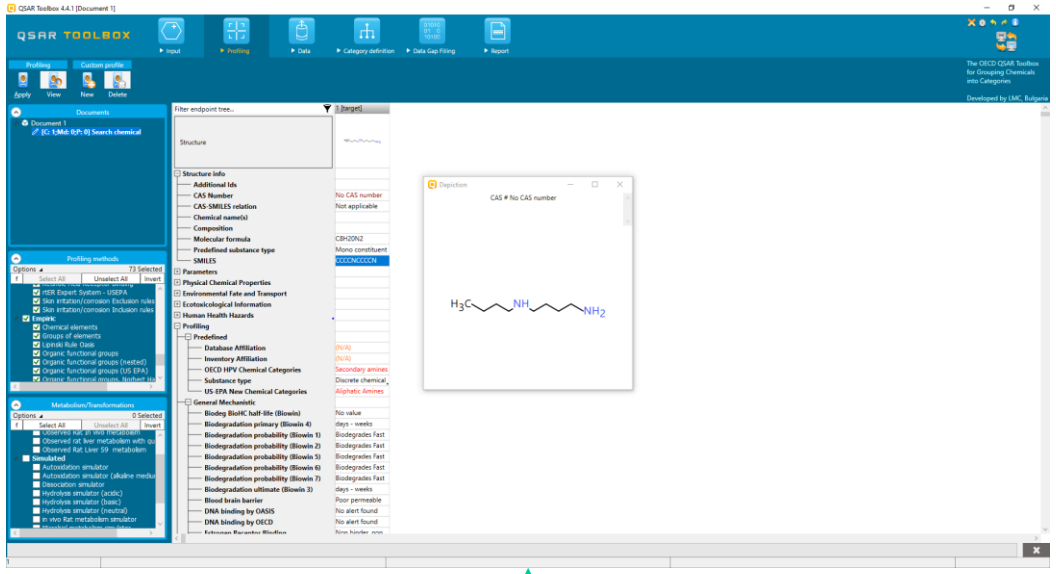
- Some QSARs have been built for certain chemical categories chemicals (e.g., alkyl phenol category)
  - Daphnia magna 48hr EC50
  - Medaka higheye 96hr LC50
- But these functions in the Toolbox are perhaps under utilized by ECCC in part due to the use of other external QSAR tools or approaches that meet the same need
- There is also a need to re-conduct internal training on these Toolbox functionalities using existing OECD Toolbox guidance



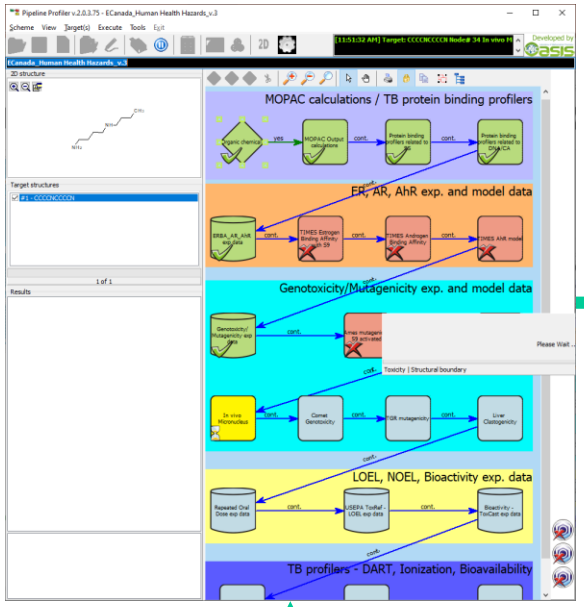


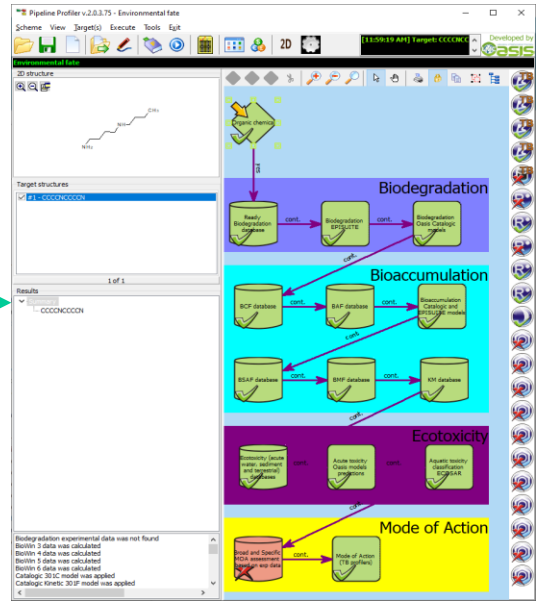
Connecting the QSAR Toolbox to Other Platforms

OECD Toolbox v4.4.1



ECCC's Chemical Pipeline Profiler for Hazard and Fate





QSAR Toolbox exports empirical data and profiler results to ECCC Pipeline Profiler according to Pipeline queries for specific workflows

Both the Toolbox and ECCC's Pipeline Profiler will be a core component of the future automated version of ERC2

Partnering to Add New Science and Tools to the Toolbox

Development of an Enhanced Mechanistically Driven Mode of Action Classification Scheme for Adverse Effects on Environmental Species

Maria Sapounidou, David J. Ebbrell, Mark A. Bonnell, Bruno Campos, James W. Firman, Steve Gutsell Geoff Hodges, Jayne Roberts, and Mark T. D. Cronin*

Cite This: https://dx.doi.org/10.1021/acs.est.0c06551 Read Online

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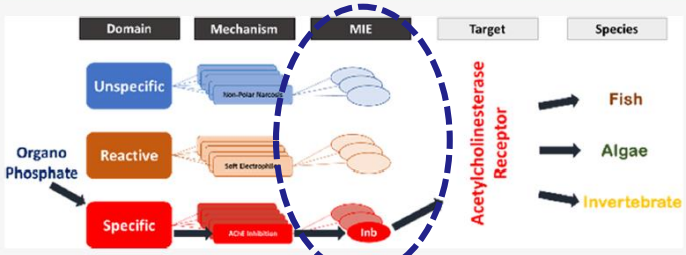
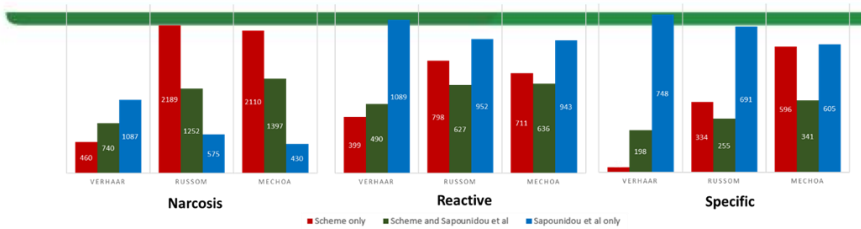


The aim of this investigation was to provide a unified, mechanistically driven scheme across a broad range of species for the classification of environmental toxicants, bringing together and enhancing current knowledge. The updated

- The main development comes from connecting verified molecular initiating events (MIEs) existing MechoA knowledge to find support for cross-species susceptibility to adverse effects associated with an MIE and broad MoA

- "*This approach also allows for the taxonomic diversity of MIEs to be expanded, captured and applied…the most comprehensive published so far in terms of coverage of mechanisms and species*."



- Classified compounds
- Species coverage
- Chemical coverage
- Unique information particularly for the reactive and specific domains

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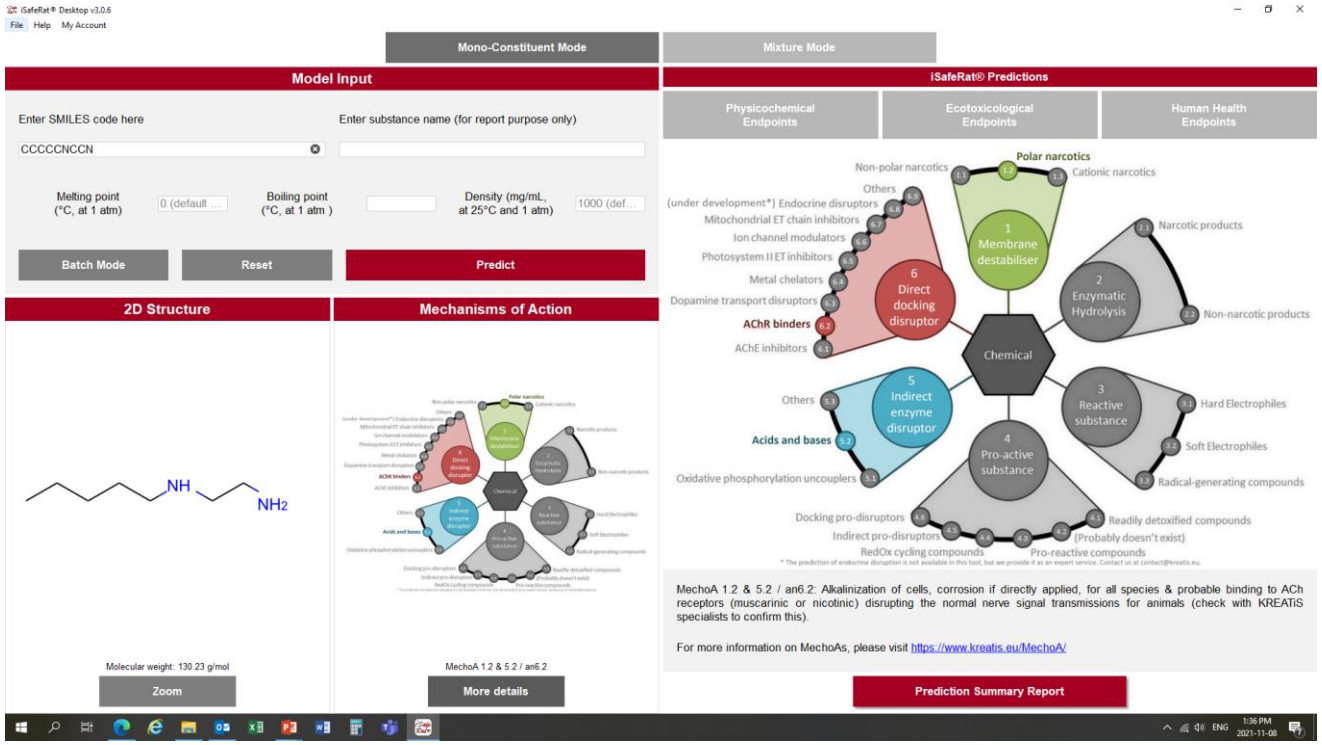
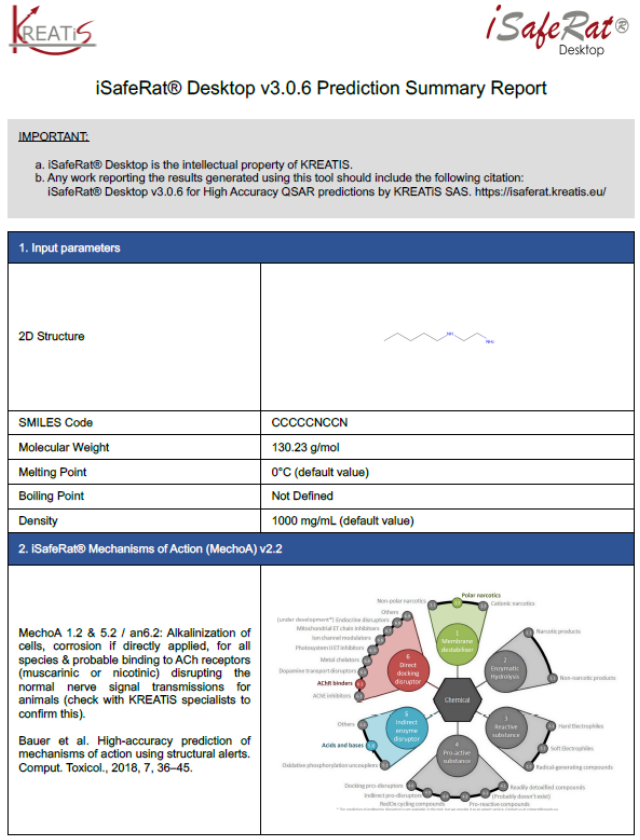
Updating MechoA Profiling in iSafeRat with New Scheme

- The KREATiS iSafeRat MechoA profiling software will be updated to include new mechanisms from the Sapounidou et al. paper





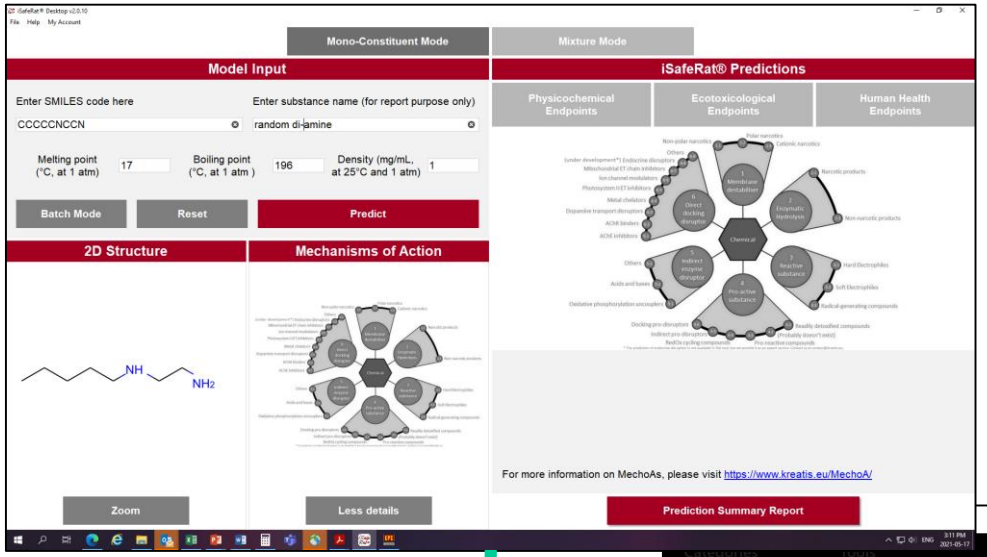
iSafeRat® Desktop v3.0.6 Prediction Summary Report

IMPORTANT:

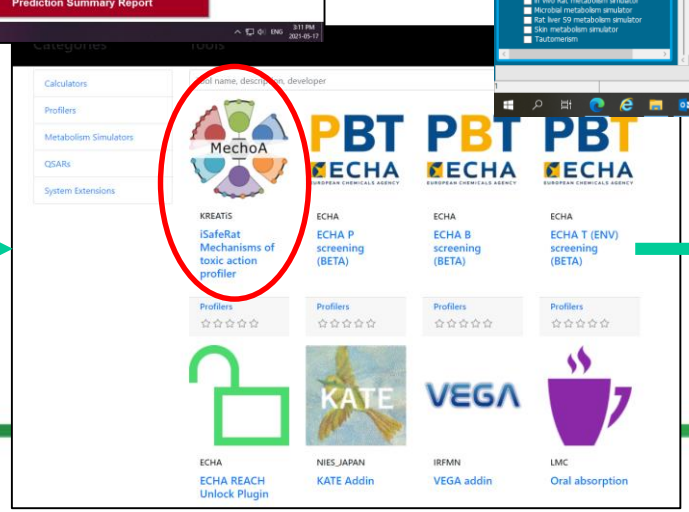
a. iSafeRat® Desktop is the intellectual property of KREATIS.
b. Any work reporting the results generated using this tool should include the following citation: iSafeRat® Desktop v3.0.6 for High Accuracy QSAR predictions by KREATiS SAS. https://isaferat.kreatis.eu/

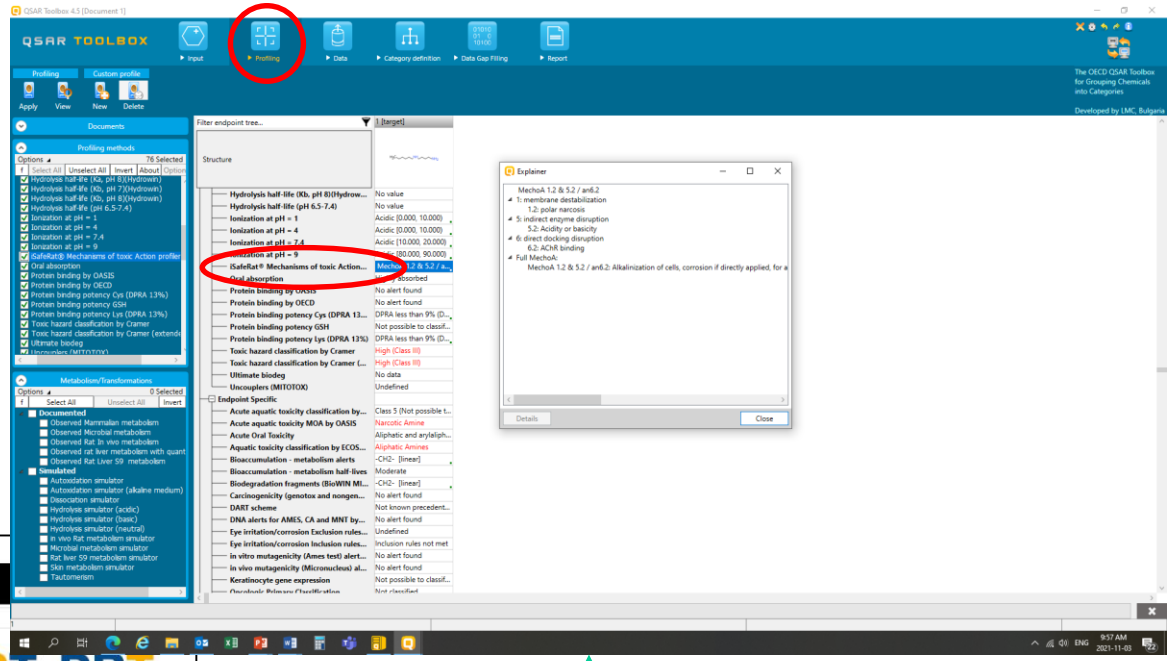
1. Input parameters	
2D Structure	
SMILES Code	CCCCCNCCN
Molecular Weight	130.23 g/mol
Melting Point	0°C (default value)
Boiling Point	Not Defined
Density	1000 mg/mL (default value)
2. iSafeRat® Mechanisms of Action (MechoA) v2.2	
MechoA 1.2 & 5.2 / an6.2: Alkalinization of cells, corrosion if directly applied, for all species & probable binding to ACh receptors (muscarinic or nicotinic) disrupting the normal nerve signal transmissions for animals (check with KREATiS specialists to confirm this).	
Bauer et al. High-accuracy prediction of mechanisms of action using structural alerts. Comput. Toxicol., 2018, 7, 36–45.	

Update of iSafeRat in OECD QSAR Toolbox v4.5 with New Scheme



KREATIS
iSafeRat
MechoA Profiler





Existing iSafeRat MechoA Toolbox Profiler will be updated with new scheme

Q3 2022

OECD Toolbox Repository Plugin
https://repository.qsartoolbox.org/

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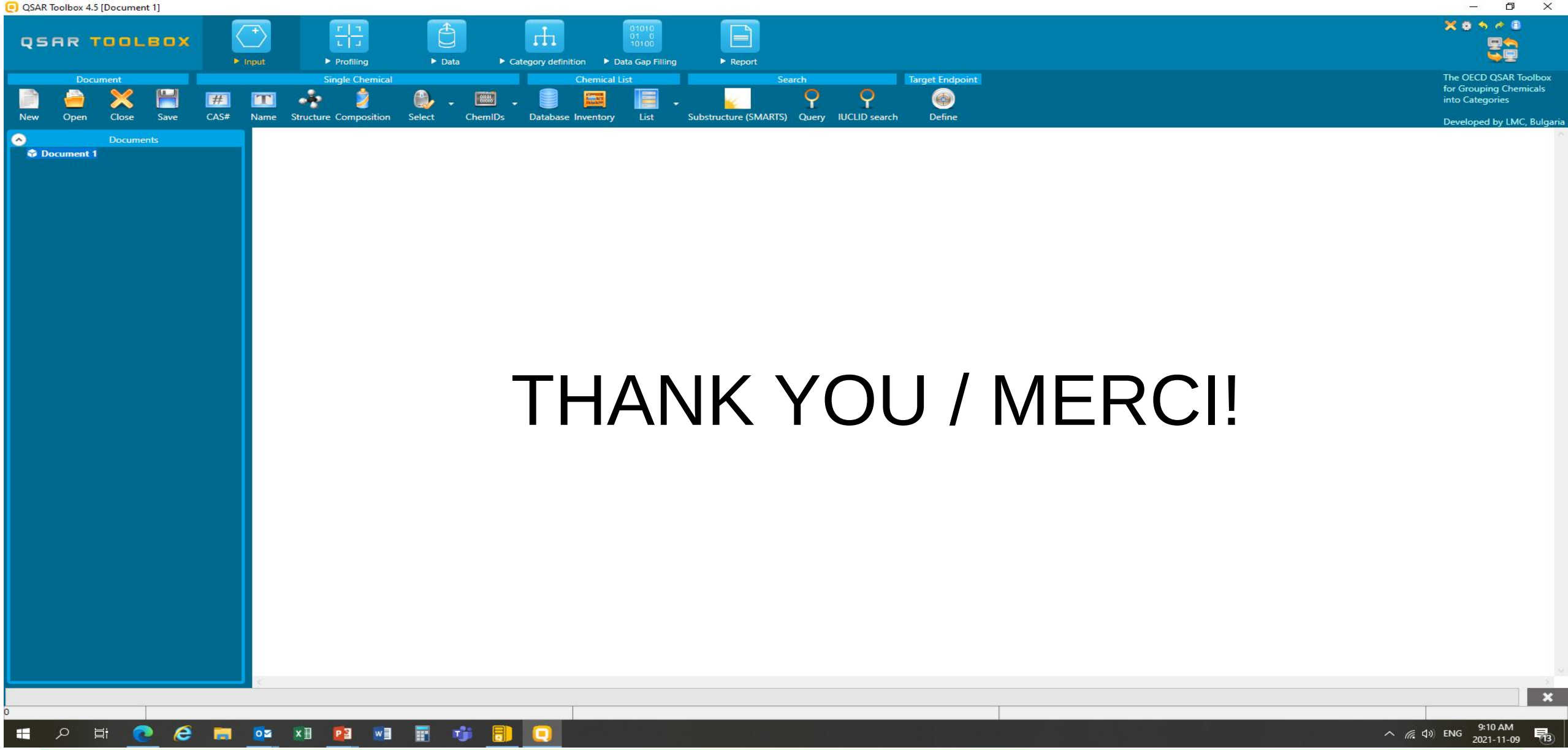
QSAR Toolbox 4.5 [Document 1]
QSAR TOOLBOX
Input
Profiling
Data
Category definition
Data Gap Filling
Report
Document
Single Chemical
Chemical List
Search
Target Endpoint
New
Open
Close
Save
CAS#
Name
Structure
Composition
Select
ChemIDs
Database
Inventory
List
Substructure (SMARTS)
Query
IUCLID search
Define
The OECD QSAR Toolbox for Grouping Chemicals into Categories
Developed by LMC, Bulgaria
Documents
Document 1
THANK YOU / MERCI!
ENG
9:10 AM
2021-11-09