Overview of the
QSAR Application Toolbox

Environment Health and Safety Division,
Environment Directorate, OECD

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Recognizing the Need for the QSAR Application Toolbox

- Required data for risk assessments are available for a small percentage of chemicals.
- QSAR methods offer the only non-testing alternative to fill data gaps and set priorities.
- Most QSAR methods are computer-based but are viewed too complex for assessments.
- A Toolbox will reduce complexity in the use of QSAR methods for reliable estimates.
Goals for the Pilot Version of the QSAR Application Toolbox
-Proof-of-Concept-

- Demonstrate that the Toolbox concept will make most QSAR methods readily accessible
- Apply QSAR methods to the formation of chemical categories and filling data gaps
- Illustrate the importance of the domain of application in making reliable QSAR estimates
- Integrate existing data, expert knowledge and QSAR models to facilitate risk assessments
Outline of the QSAR Application Toolbox

- The QSAR Toolbox will house QSAR models, databases and regulatory application chassis
- The Toolbox chassis is a flexible simulator of the normal workflow of experts and specialists
- The chassis will link needed tools to speed information/options to the application experts
- User interfaces will be designed by the application experts to reduce complexity
Typical Queries included in the QSAR Application Toolbox

- Describe the chemical(s) of Interest
- Is the chemical are included in regulatory inventories or categories?
- Has the chemical already been assessed by other agencies/organisations?
- Would you like to search for available data on assessment endpoints for each chemical?
Typical Queries included in the QSAR Application Toolbox

- Would you like structural alerts for each chemical?

- Examples:
  - Acetolactate Inhibitors (herbicides)
  - Acetylcholine analogs (spasmolytics)
  - Acyl-ureas (sedatives)
  - Anthroquinone, 1,4-dihydroxy (intercalating anti-neoplastics)
  - Benzhydryl, alpha-hydroxy (anticholinergics)
  - Benzopyran, 2,2-dimethyl (K channel openers)
  - Benzothiadiazine, dihydro, 1,1-dioxide (diuretics)
  - Beta-blocker (oxime type)
  - Chrysanthemic acid esters (insecticides)
  - Formamido oxime (antifungal; antihypertensive)
Typical Queries included in the QSAR Application Toolbox

- Explore a chemical list for possible analogues for each chemical?
  - select analogue searches engines
  - customize chemical list of inventory

- Group chemicals based with molecular similarity analysis?

- Prune chemicals with anomalous metabolic pathways or toxicity mechanisms?
Computer Simulated Pathways

Indicates observed metabolites
Identifying Plausible Metabolic Activation

indicates possible activation

X = H, OH, CO
Typical Queries included in the QSAR Application Toolbox

- Include estimated values in the categories data matrix using read-across, trend analysis or QSAR models?
- Design the data matrix for printing/exporting results (harmonized templates default)
### One Logical Workflow Sequence

<table>
<thead>
<tr>
<th>Substance input</th>
<th>Profiling</th>
<th>Selecting SIDS endpoints</th>
<th>Category Definition</th>
<th>Filling data gap</th>
<th>Report</th>
</tr>
</thead>
</table>

#### User Alternatives for Chemical ID

- Name
- CAS#
- SMILES
- Drawing

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- Create List
- Use Existing List
- Use Entire Inventory
### General characterization of chemical

- **Inventory Affiliation**: HPVC, LPVC, TSCA, DSL, etc.
- **Substance Type**: inorganic/organic, discrete, mixture, polymers, hydrolyzing compound, etc.
- **Chemical Class/Category**: nitro, aldehyde, phenol, etc.
- **Hazard/Risk Assessments**
- **Profile from Structural Alerts**
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Select SIDS and Other Properties

- Toolbox Data Summary
  - Measured Data Summaries
  - Estimated Data Summaries
- Toolbox Links to High Quality Databases
- Metabolism Assessment Review
Category formation

- Grouping chemicals into categories:
  - OECD Categories
  - Other Established Categories
  - AIM (EPA)
  - Super-fragments (Al Leo)
  - Atom-centered fragments (AMBIT, etc.)

- Pruning chemicals with anomalous behaviour:
  - Mechanisms
  - Metabolism
Chemical input | Profiling | Selecting SIDS endpoints | Category Definition | Filling data gap | Report

Data gaps filling approaches
- Read-across
- Trend analysis
- QSAR models
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Report the results
- Harmonised Templates
- C&L Summaries
- SIDS Dossiers
- User-Defined Reports, etc.