Overview of the QSAR Application Toolbox

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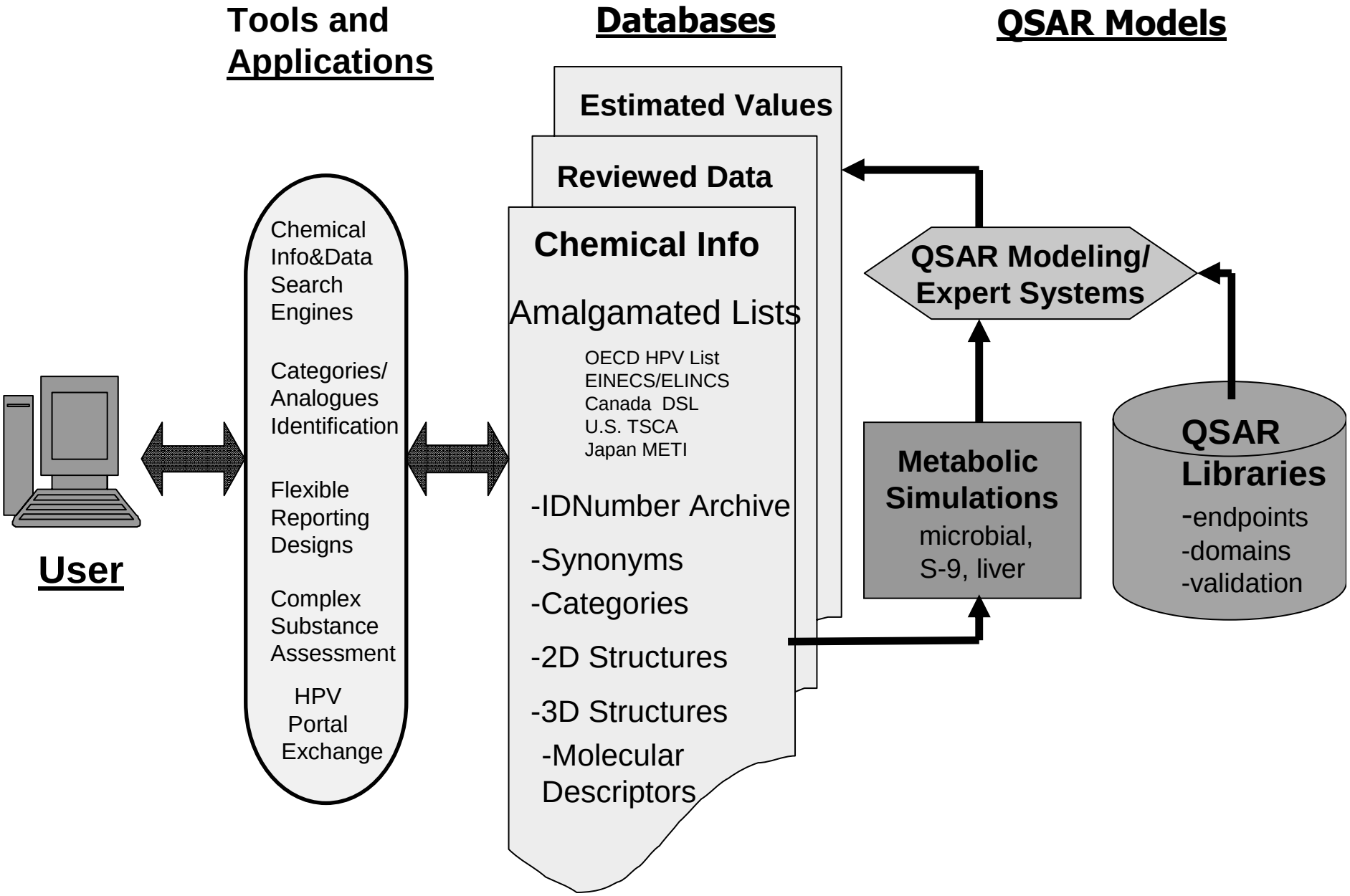
Recognizing the Need for the QSAR Application Toolbox

- 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


Tools and Applications
Databases
QSAR Models
Estimated Values
Reviewed Data
Chemical Info
Amalgamated Lists
OECD HPV List
EINECS/ELINCS
Canada DSL
U.S. TSCA
Japan METI
-IDNumber Archive
-Synonyms
-Categories
-2D Structures
-3D Structures
-Molecular Descriptors
Chemical Info&Data Search Engines
Categories/ Analogues Identification
Flexible Reporting Designs
Complex Substance Assessment
HPV Portal Exchange
User
QSAR Modeling/ Expert Systems
Metabolic Simulations
microbial, S-9, liver
QSAR Libraries
-endpoints
-domains
-validation

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?

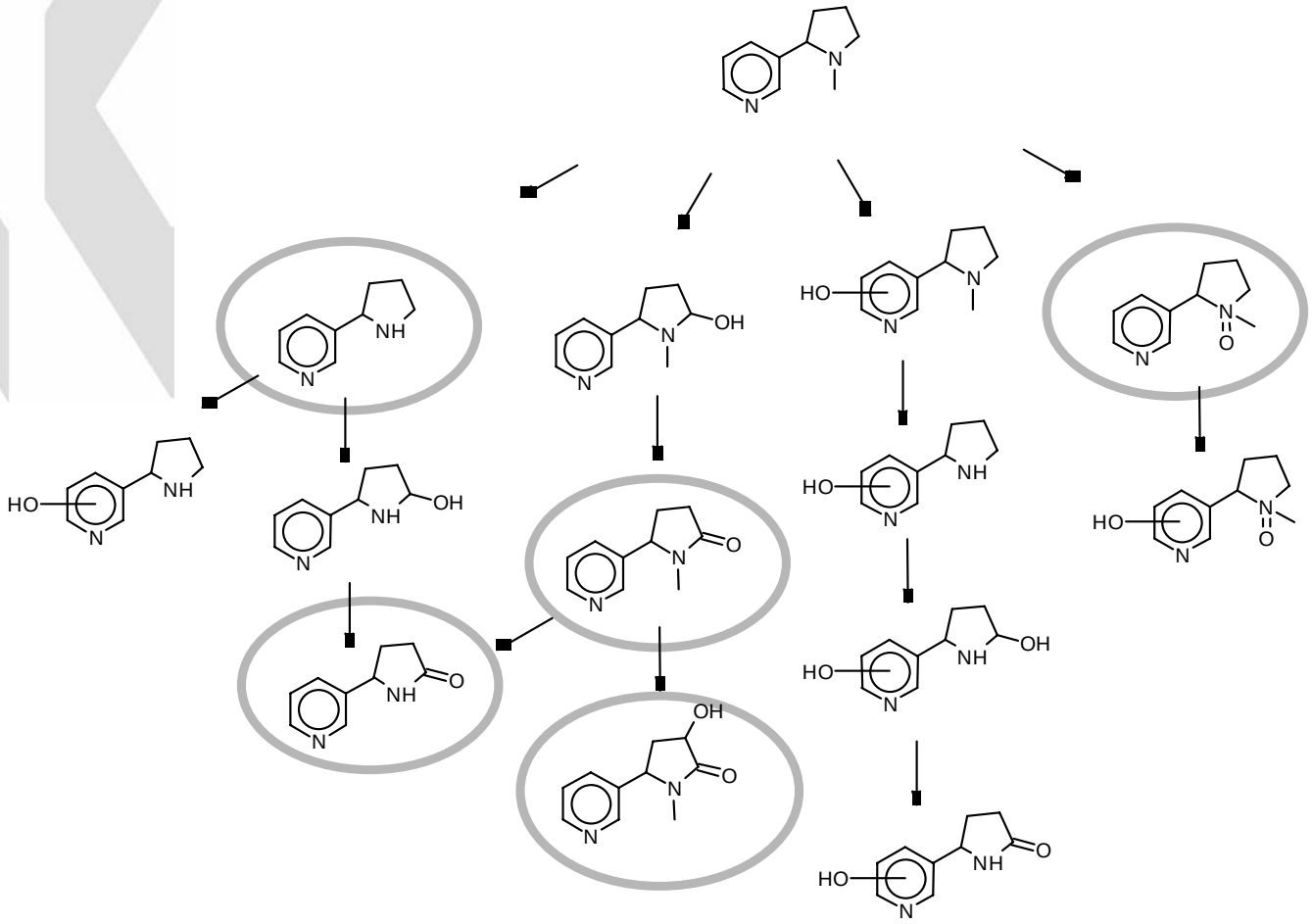
Typical Queries included in the QSAR Application Toolbox

- 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

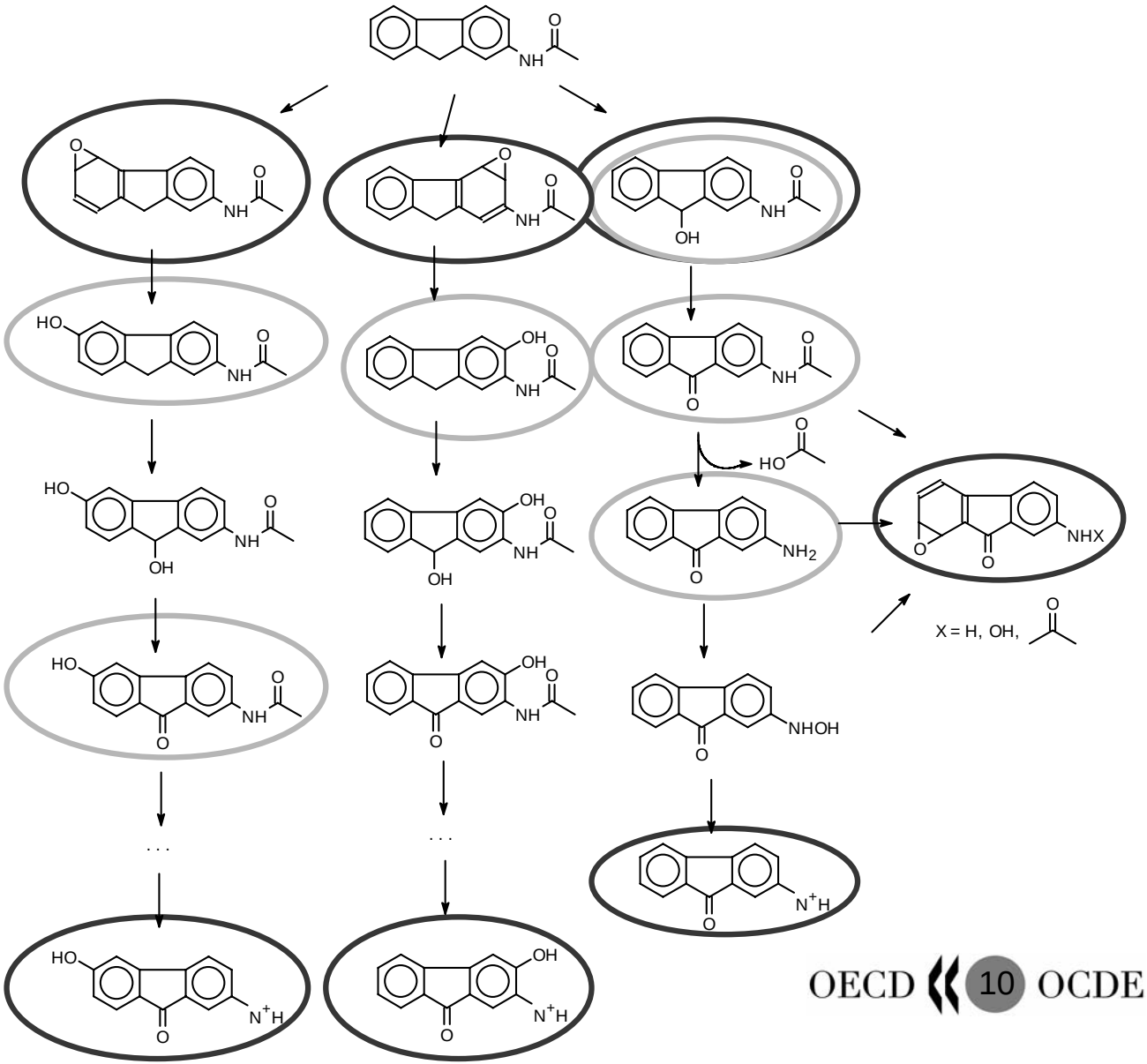
- Explore a chemical list for possible analogues for each chemical?
  - select analogue searches engines
  - customize chemical list of inventory
- Group chemicals based with molecular similarity analysis?
- Prune chemicals with anomalous metabolic pathways or toxicity mechanisms?

Computer Simulated Pathways



Indicates observed metabolites

Identifying Plausible Metabolic Activation



indicates possible activation

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)

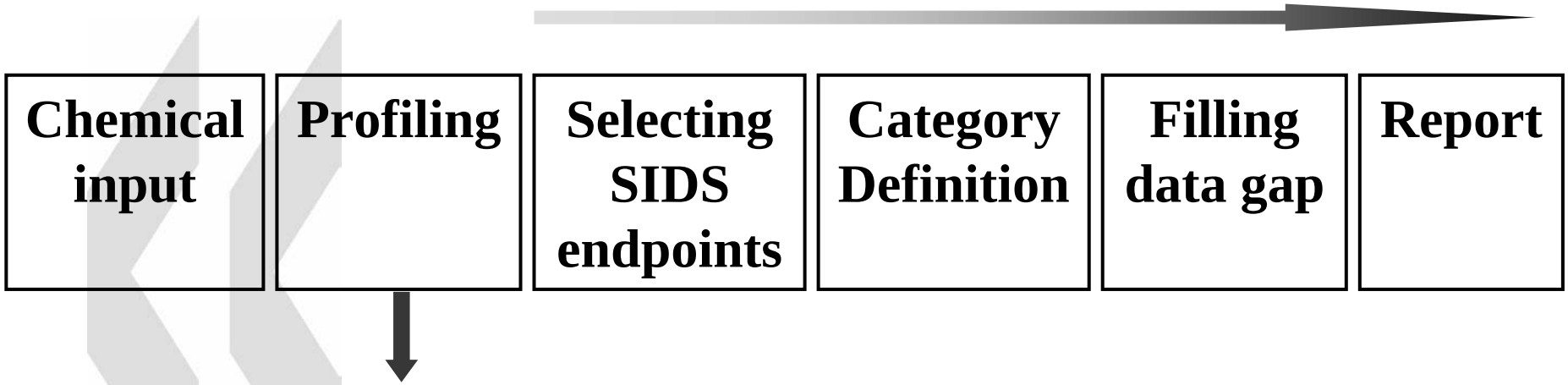
One Logical Workflow Sequence

Substance input	Profiling	Selecting SIDS endpoints	Category Definition	Filling data gap	Report

User Alternatives for Chemical ID

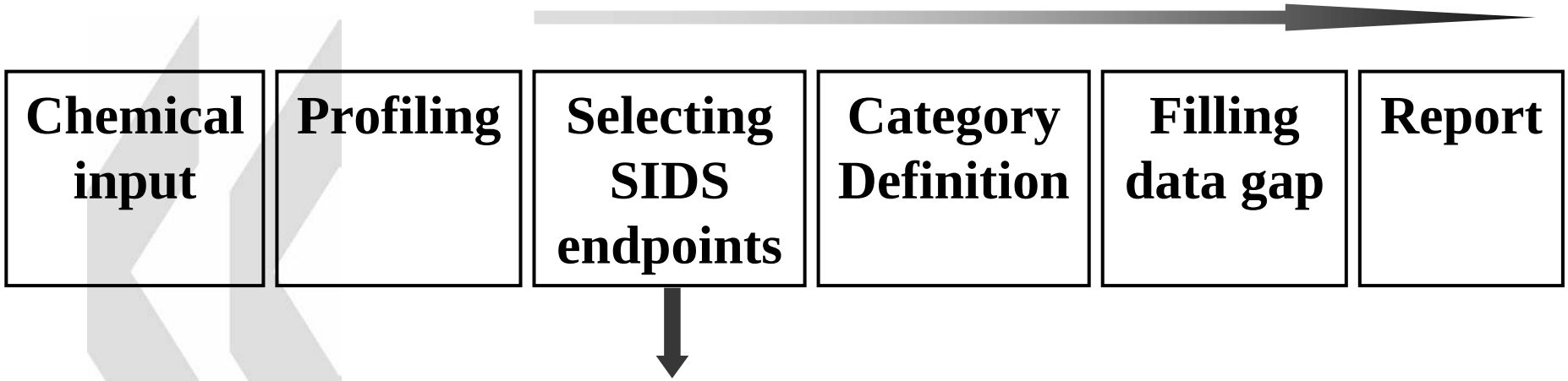
- **Name**
- **CAS#**
- **SMILES**
- **Drawing**

- **Create List**
- **Use Existing List**
- **Use Entire Inventory**



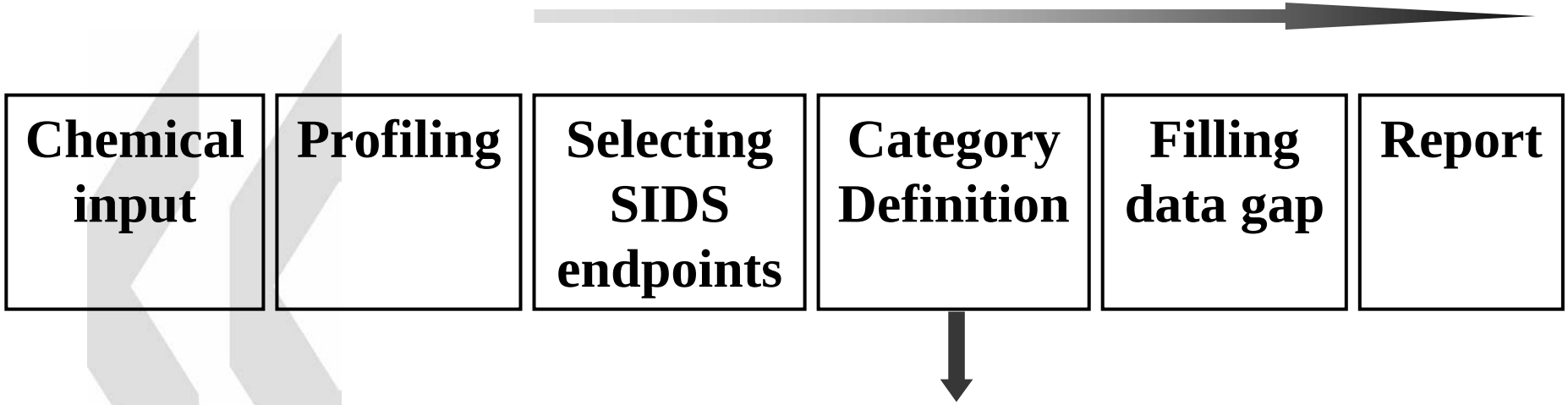
General characterization of chemical

- **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**



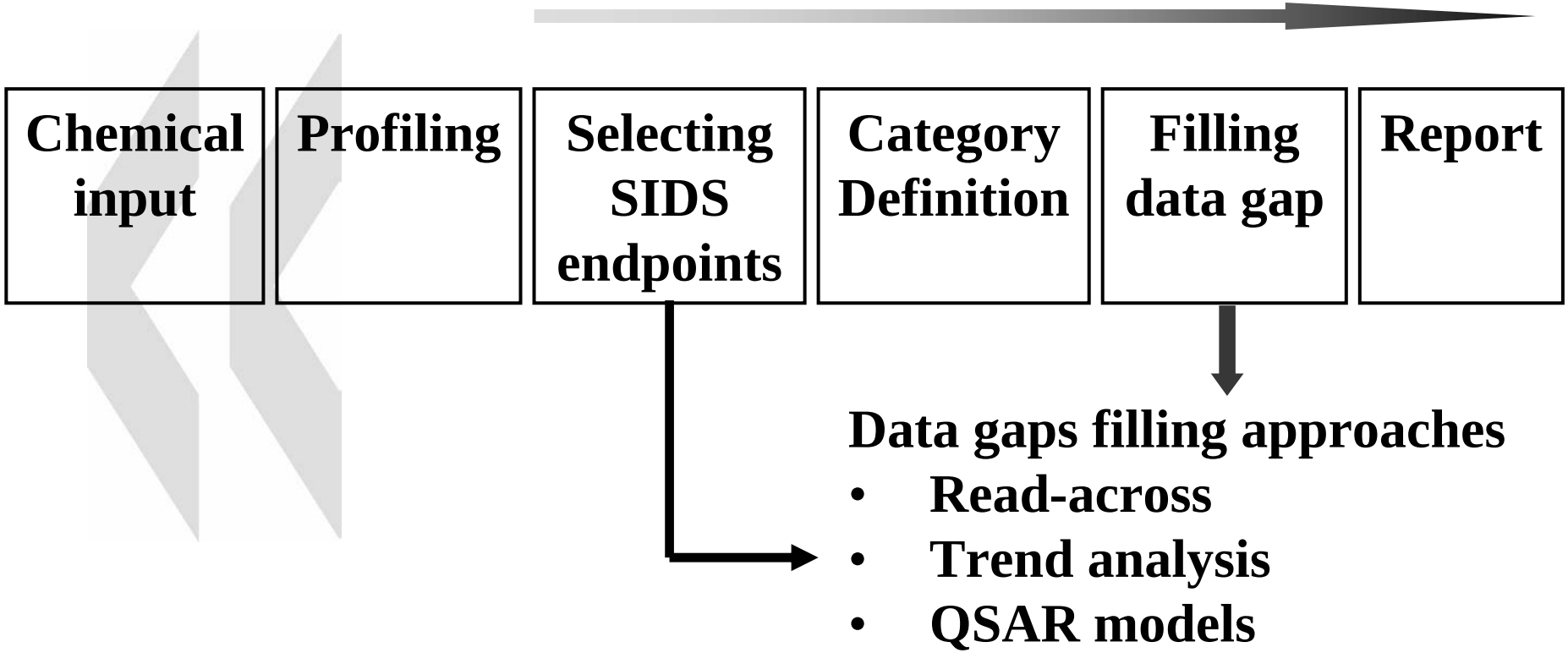
Select SIDS and Other Properties

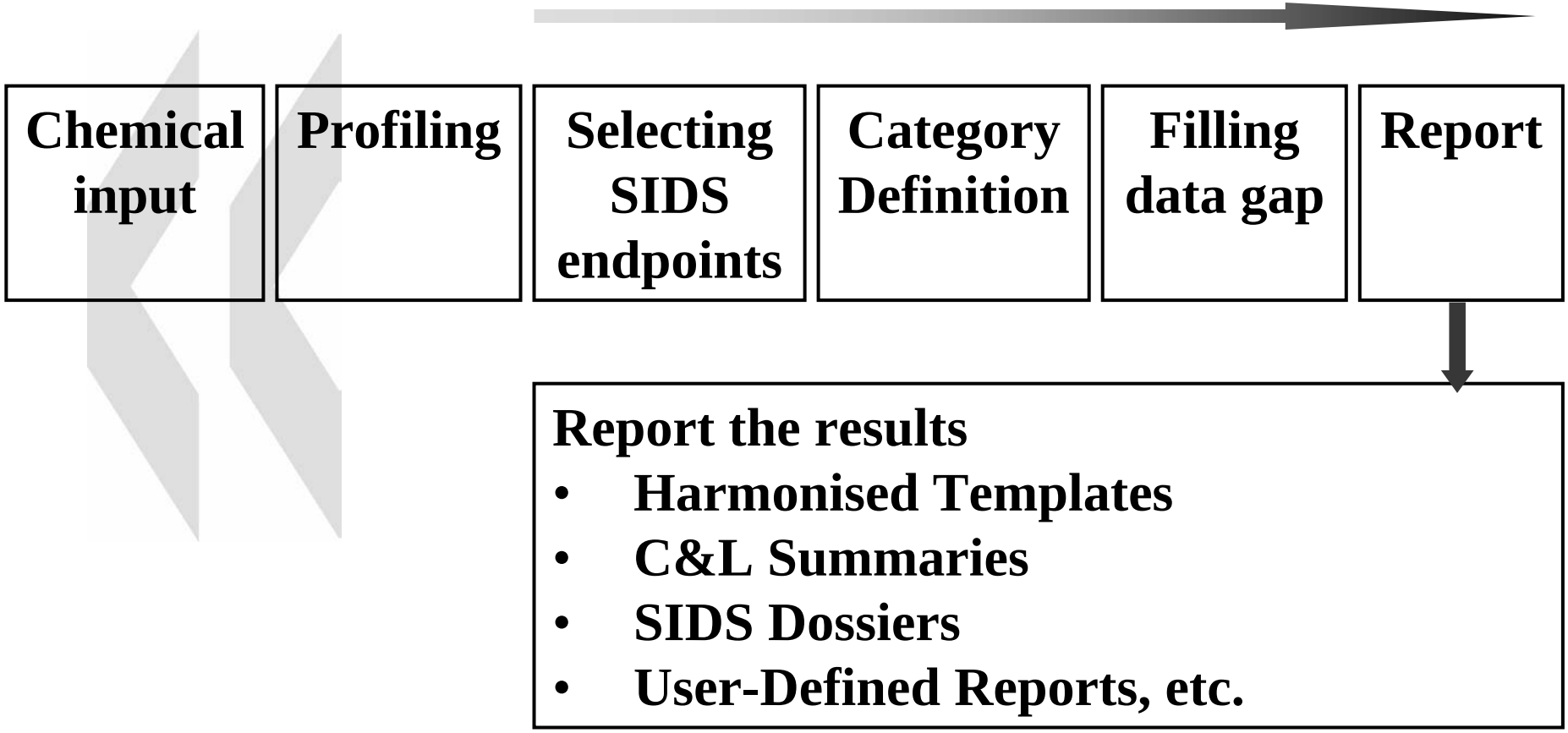
- **Toolbox Data Summary**
  - ✓ **Measured Data Summaries**
  - ✓ **Estimated Data Summaries**
- **Toolbox Links to High Quality Databases**
- **Metabolism Assessment Review**



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


Chemical input
Profiling
Selecting SIDS endpoints
Category Definition
Filling data gap
Report
Report the results
• Harmonised Templates
• C&L Summaries
• SIDS Dossiers
• User-Defined Reports, etc.