Computational Toxicology – Objective 2: Developing Approaches for Prioritizing Chemicals for Subsequent Screening and Testing

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The Challenge for Program Offices

Given finite resources and time to generate and evaluate data, which chemicals should be evaluated first when confronted with a large number of chemicals to assess for a number of potential adverse outcomes?

TSCA Programs:

Pre-Manufacture Notification (PMN) Program

- ~ 2,500 new PMN chemicals/yr

High Production Volume (HPV) Chemical Challenge Program

- ~2,800 HPV Chemicals that are produced or imported at levels of one million lbs/yr
- Screening Information Data Sets (SIDS) required for physicochemical properties, environmental fate, ecotoxicity and health effects to allow screening-level hazard identification

FIFRA Programs:
Active and Inert Pesticide Ingredients

- Identifying lower risk active ingredients
- Backlog in assessing 700 inert ingredients by 2006
- Scarce assessment resources

The Challenge to ORD's Computational Toxicology Research Program

- Provide Predictive Models/Tools for Hazard Identification and Prioritization for Further Testing

QSAR and Other Computational Approaches

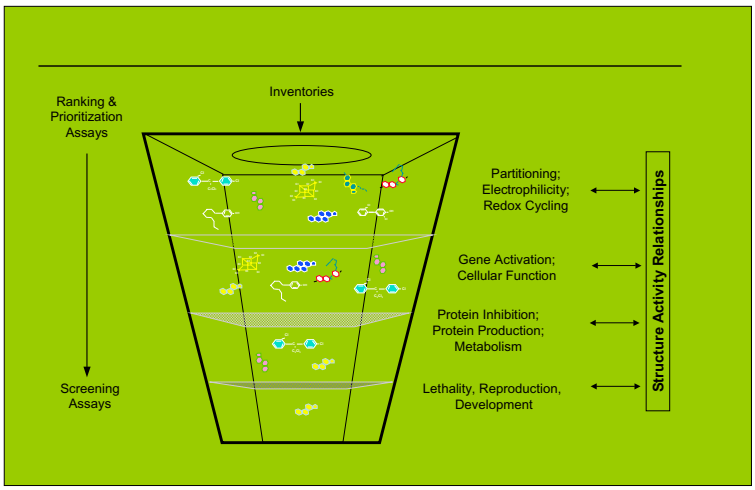
- Quantify physical-chemical parameters to predict fate/metabolism
- Identify potential hazard in absence of empirical data
- Estimate missing parameters for untested chemicals
- Provide framework for optimized use of "omic data"

Pollution Prevention Strategies

- Methods for estimating potential impact after release into the environment
- Provide final impact indicators

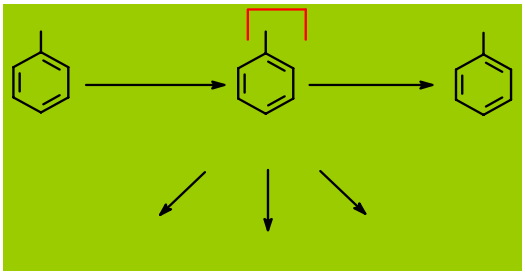
High Through-Put Screening

- Rapid, efficient means to provide preliminary data
- Recommended for Endocrine Disruptors



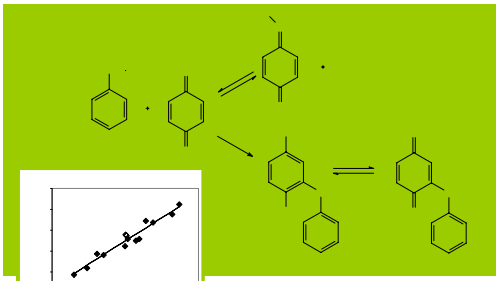
Screening-Level Models for Hazard Identification:

Transformation/Metabolic simulators are required because many toxic effects do not arise from nor can they be forecasted directly from the parent chemical.

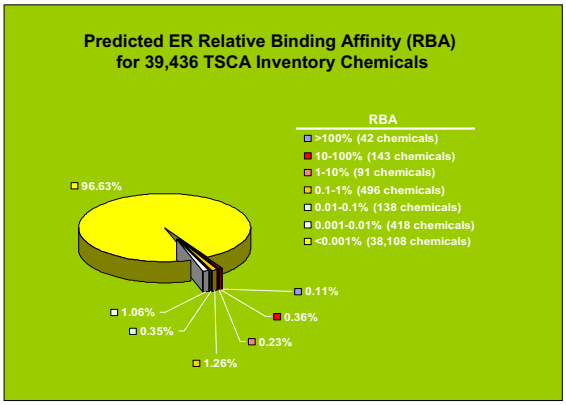


Subsequent QSAR analysis based on appropriate molecular descriptors (e.g., one-electron reduction potentials for nitroaromatic reduction) provides ability to sort parent chemicals into user-defined bins of high, medium and low reactivity for the purpose of ranking.

QSAR analysis also provides user information concerning the reactivity/toxic effect of the transformation products/metabolites. For example, aromatic amines can bind irreversibly to biomolecules through nucleophilic addition to carbonyl groups (see below).



Example of Prioritization Process Using Computational Tools: Screening of TSCA Inventory Chemicals for Endocrine Disrupting Properties



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