Cost Effective Way to Generate Data for Registration- (Q)SAR

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Data Requirements for REACH

- Technical Dossier
- Chemical Safety Report
- Risk Reduction
  - Physico-Chemical
  - Environmental
    - Persistent, Bioaccumulative, Toxic (PBT)
    - Very Persistent, Very Bioaccumulative(vPvB)
- Risk Assessment

Obtaining Data for REACH

- Laboratory Testing
  - In vivo test (animal tests)
  - In vitro test (cell cultures
  - Analytical measurements

REACH – Article 25

ECHA's approach towards collecting hazard information

REACH Regulation Article 25, paragraph 1

"In order to *avoid animal testing, testing on vertebrate animals for the purposes of this Regulation shall be undertaken only as a last resort*. ..."

Obtaining Data for REACH

- Laboratory Testing
  - In vivo test (animal tests)
  - In vitro test (cell cultures
  - Analytical measurements
- Estimation Methods
  - Qualitative
    1. Structure-Activity Relationship (SAR)
    2. Read-Across
    3. Categorization
  - Quantitative
    1. QSAR

Non-test method to collect information

Refer to Annex XI

- Use existing data
- Weight of evidence
- *In vitro*
- Grouping of substances and Read-across
- (Q)SAR

Information retrieved from ECHA website

What is (Q)SAR

- Quantitative Structure – Activity Relationship
- *In silico*
- Mathematical model
- Relates a quantitative measure of chemical structure (e.g. physicochemical property) to a physical property or biological effect (e.g. a toxicological endpoint)

Mathematical form

Activity = *f* (physiochemical properties and/or structural properties)

- Activity means biological effect
- Physiochemical properties like hydrophobic, electronic effect, and steric effect

Why We Need QSAR?

- You do not need QSAR if you have lot's of data
- Only if data gaps exist, you can either have the hazard assessment or use QSAR

10,000 chemicals have been tested

World Inventory of produced chemicals exceeds 160,000

Advantages of using (Q)SAR

- Reduce animal tests and use of animals
- Huge cost saving potential
  - Estimated €940million savings*
- Collect data in a short period of time

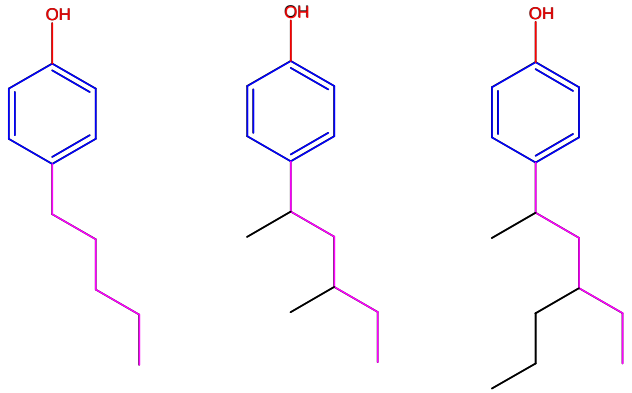
* EC Joint Research Centre Data, 2003

QSAR Methods

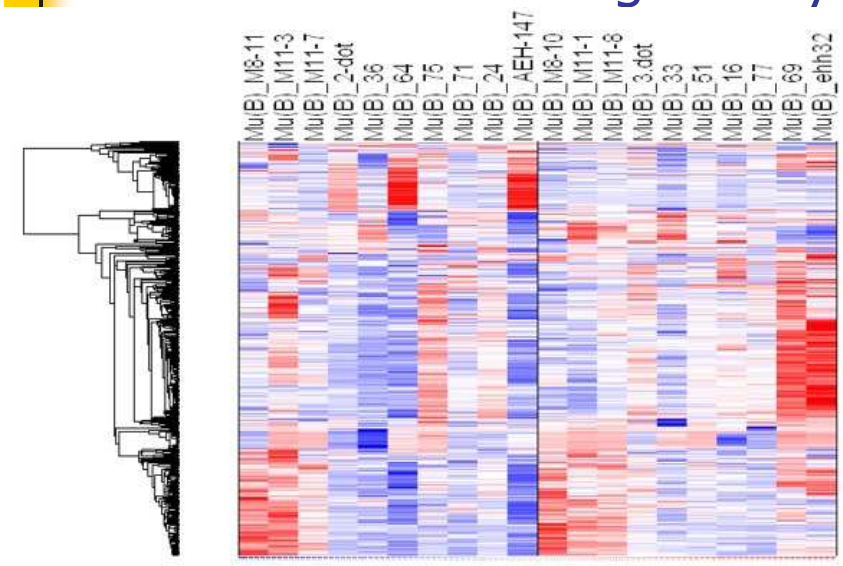
- Fills data gaps by first grouping chemicals
- Use existing data within a group to estimate missing values
- When the chemical group is identified by a common mechanism
- QSAR models accurately describe the trends

Grouping (Molecular Similarity)

- By inspection of the common substructures



Hierarchical Clustering on Keys



Grouping (Molecular Similarity)

- Chemistry is based on the premise that similar chemicals will behave similarly
- The behavior of a chemical is derived from its structure
- Chemical behavior in biological system is described as biological activity of chemicals

Selection of Endpoint

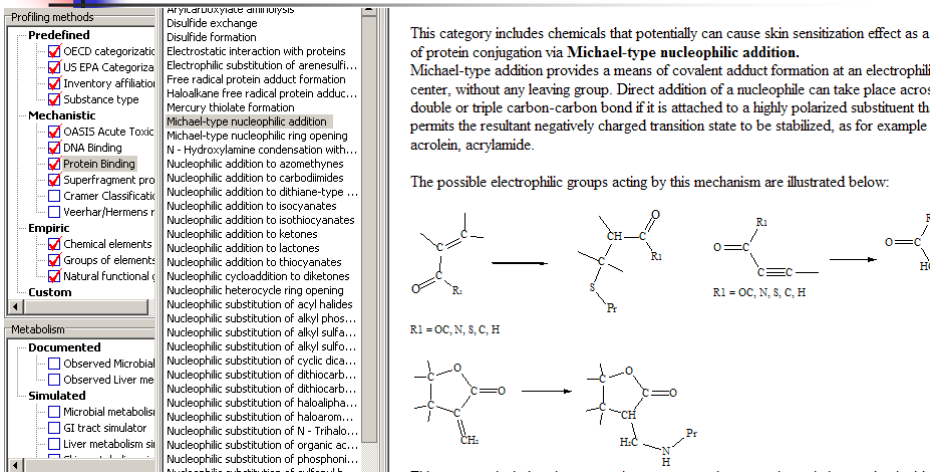
- The measure of a biological effect, for example, LC50 or EC50
- QSAR always associated with endpoint and a toxicity mechanism
- Only chemicals causing common toxicity mechanisms lead to a reliable QSAR
- In QSAR, chemical behavior is grouped in terms of toxicity mechanisms

Mechanistic Interpretation

General characterization by the following grouping schemes:

- Substance information
- Predefined
- Mechanistic
  - •Acute Toxicity MOA (OASIS)
  - •Protein binding (OASIS)
  - •DNA binding (OASIS)
  - •Electron reach fragments (Superfragments) BioBite
  - •Cramer Classification Tree (ToxTree)
  - •Veerhar/Hermens reactivity rules (ToxTree)

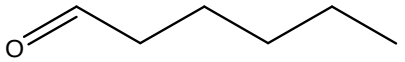
Mechanistic Interpretation



Example

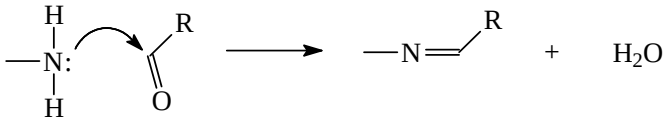
Target chemical: hexanal

Target endpoint: Acute Toxicity to Ciliate

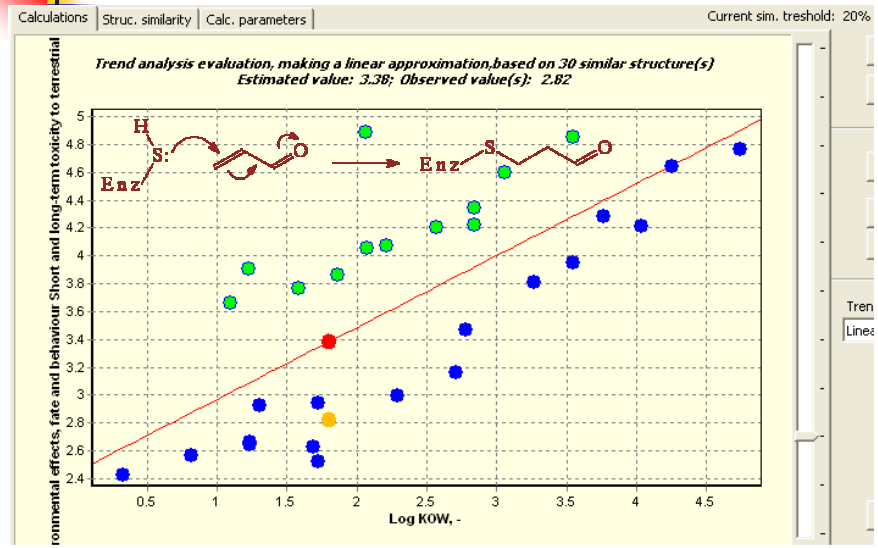


Monoaldehydes

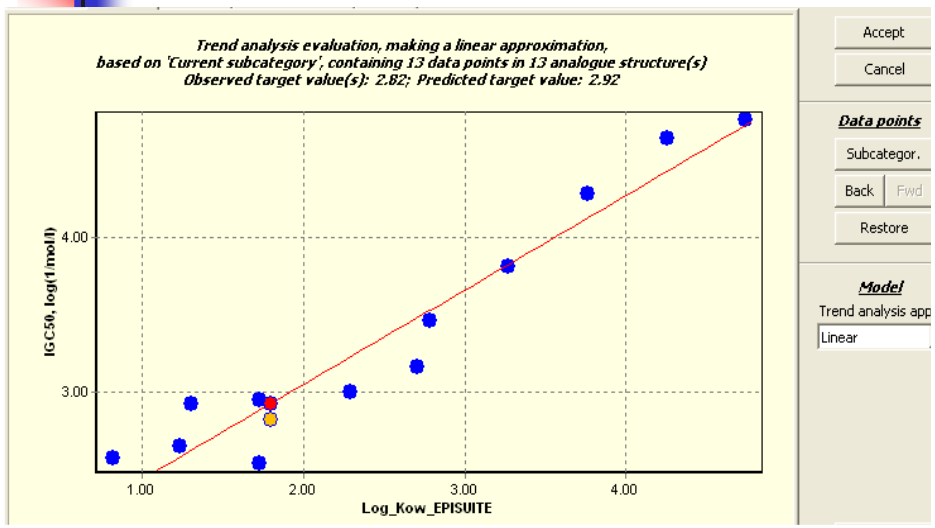
Formation of Schiff bases with amino groups



Elimination Outliners of Different Interaction Mechanism



Apply Trend Analysis



Possible applications of QSARs

Supplement to testing

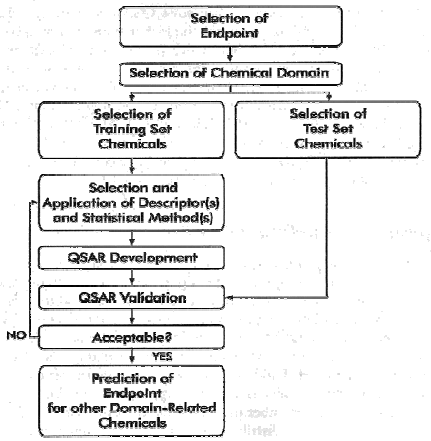
- To support priority settings of chemicals
- To guide experimental design
- To provide mechanistic information

Replacement of testing

- To group chemicals into chemical categories
- To fill in data gaps for Classification and Labelling
- To fill in data gaps for risk assessment

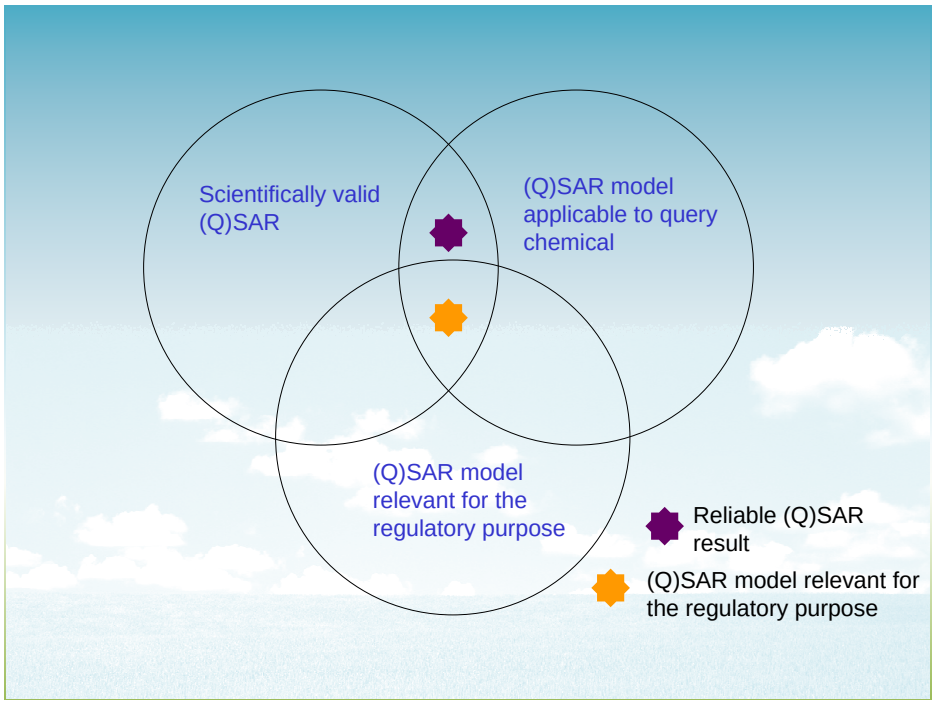
Does not imply a single QSAR replaces a single test

Process for Developing and Validating QSARs



Use of QSARs under REACH

- Acceptance of QSAR results only if
  - Models have been validated;
  - The substances falls within the applicability domain of the (Q)SAR model
  - Models are adequate for the purpose of classification and labelliing and/or risk assessment and
  - Adequate and reliable documentation of the applied method is provided



Expert Systems

- TOPKAT
- Toxtree
- Derek
- Castox
- Molcode
- Sarchitect
- Leadscope

Toxicological properties accessible via QSARs

- Skin irritation or corrosion
- Eye irritation
- Skin sensitization
- Mutagenicity
- Acute toxicity
- Reproductive toxicity
- Carcinogenicity

Human Health Hazard Assessment

- Toxicokinetics (absorption, metabolism, distribution and elimination)
- Acute toxicity
- Irritation
  - Skin
  - Eye
  - Respiratory tract
- Corrosivity
- Sensitization

Human Health Hazard Assessment (Con't)

- Skin
  - Respiratory system
  - Repeated dose toxicity
- Mutagenicity
- Carcinogenicity
- Toxicity for reproduction
  - Effect on fertility
  - Developmental toxicity
- Derivation of DNEL(s)

QSAR & IUCLID 5

What is IUCLID 5?

- IT tool
- To facilitate data exchange, maintenance, storage and submission
- Export standardized report format

Project Deliverables

- Purchase yearly license of (Q)SAR operating system
- (Q)SAR models in eco-/toxicology

The End

Thanks for your attention