The BfR Decision Support System (DSS) for Local Lesions

Matthias Herzler
The BfR Decision Support System (DSS) is...

...a system to predict the presence or absence of a chemical's potential to cause skin and/or eye irritation/corrosion following acute topical exposure...

...in terms of EU classification criteria (Dir. 67/548/EEC)/OECD TG.

Right from the start the DSS was designed as an ITS building block.
Component 1: Physico-Chemical Exclusion Rules

- To predict the **ABSENCE** of an irritant/corrosive potential

- Straight-forward, **UNAMBIGUOUS** IF...THEN NOT... logic:

Rules appropriate for all groups of chemicals

<table>
<thead>
<tr>
<th>Basis</th>
<th>Evaluation of data for 1627 chemicals with purity ≥ 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>If</strong> melting point &gt; 200°C</td>
<td>Then not (skin corrosion R34 or R35) (true for 245/252 chemicals tested)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>If</strong> log ( P_{ow} ) &gt; 9</td>
<td>Then not (desions R34, R35, R36 or R41) (true for 32/32 chemicals tested)</td>
</tr>
<tr>
<td><strong>If</strong> log ( P_{ow} ) &lt; -3.1</td>
<td>Then not (skin corrosion R34 or R35) (true for 53/53 chemicals tested)</td>
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<tr>
<td><strong>If</strong> lipid solubility &lt; 0.01g/kg</td>
<td>Then not (skin corrosion R34 or R35) (true for 58/58 chemicals tested)</td>
</tr>
<tr>
<td><strong>If</strong> aqueous solubility &lt; 0.00002g/l</td>
<td>Then not (eye irritation R41) (true for 109/109 chemicals tested)</td>
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<tr>
<td><strong>If</strong> aqueous solubility &lt; 0.000005g/l</td>
<td>Then not (eye irritation R36) (true for 38/38 chemicals tested)</td>
</tr>
<tr>
<td><strong>If</strong> molecular mass &gt; 650g/Mol</td>
<td>Then not (eye irritation R36) (true for 139/139 chemicals tested)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>The seven skin corrosive substances are organic salts which release strong inorganic acids or bases when in contact with aqueous substrates/organic media.

<sup>b</sup>Chemicals with molecular mass > 650g/Mol may elicit severe tissue damage resulting in local corrosion (labelled R41).

(Gerner et al. (2005), ATLA 33, 215–237)
Component 2: Structural alerts

- To predict the **PRESENCE** of an irritant/corrosive potential
- Based on reactive substructures

**Chemical substructures indicative of skin corrosion:**

1) **Substituted benzoic acid halogenides**
   - Halogen = Cl or F
   - $R_1-R_4$ = any substituent
   ![Substituted benzoic acid halogenides](image)

2) **Aliphatic iso(thio)cyanates**
   - $R$ = aliphatic chain
   ![Aliphatic iso(thio)cyanates](image)

3) **Chlorosilanes**
   - $R_1-R_8$ = any (for example, further halogen)
   ![Chlorosilanes](image)

4) **Mixed Oxy-Carboxy-silanes**
   ![Mixed Oxy-Carboxy-silanes](image)

*(Gerner et al. (2005), ATLA 33, 215–237)*
Mining existing knowledge – Step 1: Data collection
Mining existing knowledge – Step 2: Generating a Hypothesis

Data collection → Mechanistic hypothesis → Data collection
Mining existing knowledge – Step 3: Formalisation
Mining existing knowledge – Step 4: Validation

- Data collection
- Mechanistic hypothesis
- Formalisation (rules/alerts)
- Validation
Mining existing knowledge – Step 5: The Reality Test

- Data collection
- Mechanistic hypothesis
- Formalisation (rules/alerts)
- Validation
- Reality
Data collection – The BfR ESTOFF Database

<table>
<thead>
<tr>
<th>Identity</th>
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<tbody>
<tr>
<td>Phys.-chem.</td>
</tr>
<tr>
<td>Acute Toxicity</td>
</tr>
<tr>
<td>Irritation/corrosion</td>
</tr>
<tr>
<td>Sensitisation</td>
</tr>
<tr>
<td>Add. Information</td>
</tr>
</tbody>
</table>

- 1992 entries, ca. 1400 for DSS training set, 200 for validation test set

Quality-controlled, peer-reviewed data; uniform evaluation criteria
Mechanistic Hypothesis – Two-step process

Step 1: Active destruction (corrosion) or passive transport through protective biolayers

Step 2: Reaction/interference with biological structures/processes
Mechanistic Hypothesis – Factors Influencing Irritation Potential

- Charge / ~ distribution
- Molecular geometry
- Intra- and Intermolecular Interaction forces
- Diffusion
- Partitioning
- Transport through biolayer
- Chemical reactivity
- Structural features / Functional Groups
- Melting/bolling point...
  ...Log K_{ow}...
  ...Vapour pressure...
  ...Molecular weight...
  ...Aqueous/Epid solubility

New Chemicals Notification data

Irritation
Creating Physico-Chemical Exclusion Rules

**Example**: Exclusion rule for corrosion for group CHal \((C_xH_yO_z\text{Halogen}_d)\) based on m.w.

\[ \text{Deduced rule:} \quad \text{IF m.w.} > 280 \text{ g/mol THEN NOT corrosion R34 or R35} \quad \text{(CHal)} \]
Creating Structural Alerts

### Full Papers

#### Skin

- Hulzebos et al. (2005), QSAR Comb. Sci. 24, 332-342

### Structural Alerts for the Prediction of Serious Damage to Eyes

1. **Aliphatic monoalcohols**
   - C₃–C₁₁: eye damage
   - C₁₂–C₁₄: eye irritation
   - \( R = \) aliphatic chain
   - \( R_1/R_2 = H \) or aliphatic chain

2. **Aliphatic monooxenones**
   - \( R = \) aliphatic chain
   - \( R_1/R_2 = H \) or aliphatic chain

3. **Derivatives of halogenated benzoic acids and corresponding aliphatic esters**
   - \( R = R_1 = H \), aliphatic chains or halogen

### Eye

- Gerner et al. (2005), ATLA 33 (3), 215-237

(Source: Gerner et al. 2005)
Validation (2005-today)
Validation – Summary of Results

**P.-C. rules**: good agreement with OECD (Q)SAR validation principles

- predictivity (NPV) > 87 % (eye) and > 95 % (skin) upon external validation
- exclude > 40 % EU NONS from skin and ca. 10 % for eye irritation testing

**Structural Alerts**:  

- predictivity (PPV) between 80-100 % upon internal validation (training set)
- low to no coverage of the test set chemical space

Considerable relevance for pesticide active ingredients
Use of the DSS: REACH ITS for irritation/corrosion

1. P.-C. PROPERTIES
2. EXISTING HUMAN DATA
3. EXISTING DERMAL TOXICITY / SENSITISATION STUDIES
4. (Q)SAR AND READ-ACROSS

WoE

More data

C & L decision
How to interpret the outcome of a DSS prediction

There can be no general recommendation.

The decision depends on

- the purpose of the prediction
- the degree of reliability required
- the costs of a negative vs. a positive prediction
- WoE of other available data: supportive/equivocal/contradictory?
Availability of the DSS

TOXTREE

TOXTREE is a flexible and user-friendly open-source application that places chemicals into categories and predicts various forms of toxic effect by applying decision tree approaches. The following decision tools are currently implemented:

- The Catalyst classification scheme
- The ARAMIS decision tree
- The Venkataraman scheme for aquatic modes of action
- The EHC keys for skin and eye irritation and corrosion
- The Benchmark capacity for mutagenicity and carcinogenicity
- The OECD criteria for the in vivo micronucleus test
- Structural alerts for identification of Michael Acceptors
- The Snyder categories for persistence and biodegradation

TOXTREE was developed by the Commission of the European Union (DG ENV) under the terms of a JRC contract. The software is made freely available as a service to scientific researchers and anyone with an interest in the application of computer-based estimation methods in the assessment of chemical toxicity.


OECD (Q)SAR TOOLBOX

http://www.oecd.org
Outlook

- Combined validation (rules+alerts, ITS)
- RIVM work:  
  - Distributions and error probability  
  - Using DSS with calculated phys.-chem. properties
- Multivariate analysis of descriptors/p.c. properties
- Work on p.-c. properties and dermal absorption
- Skin sensitisation
  - alerts have been derived
  - similar mechanistic concept
  - combining LLNA database with alerts/p.c. rules
Credits

Ingrid Gerner (BfR)

Emiel Rorije and Etje Hulzebos (RIVM)

JRC (Ex-ECB) Computational Toxicology Team
Thank you for your attention

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