Read Across, SARs and QSARs for Acute Inhalation Toxicity

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Problem Formulation

- Many chemicals have little or no toxicological data
- Concern regarding potential toxicity of chemicals
- Newer legislation regarding chemical safety
- Need to derive toxicity factors for limited toxicity data (LTD) chemicals
- Sustainable methods and reduced animal testing
  - Generic approaches
  - Read across or extrapolations
  - SAR/QSAR
TCEQ Approaches for LTD Chemicals

- Structural Surrogate
- Tiered Approach
- Route-to-Route Extrapolation
- N-L Ratio
  - Calculate LC50 by N-L (NOAEL-LC₅₀ Ratio)
  - Grant et al., 2007
TCEQ Approaches for LTD Chemicals

- **Tier I**
  - Emission Controls
  - (Best-Available-Control Technology)
  - Threshold of Regulation
  - Default ESL = $2 \mu g/m^3$

- **Tier II**
  - Use LC$_{50}$ Data
  - Generic ESL
  - N to L Ratio
  - Surrogate

- **Tier III**
  - Relative Toxicity/Potency Approach
  - Generic ESL
  - Read Across SAR/QSAR

**Former Case Study**
<table>
<thead>
<tr>
<th>Structure</th>
<th>CAS #</th>
<th>Name</th>
<th>Physiochemical Properties</th>
<th>LC50 (rat) 4 h (experimental data)</th>
<th>LD50 (rat) (TEST-experimental data)</th>
<th>TEST Software- Nearest Neighbor (LD50 rat)</th>
<th>TEST Software- Hierarchical Clustering (LD50 rat)</th>
<th>RD50 (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Structure" /></td>
<td>624-83-9</td>
<td>methyl isocyanate</td>
<td>MW = 57.05, VP = 531 mm Hg 25°C</td>
<td>7 ppm</td>
<td>51.56 mg/kg</td>
<td>381.65 mg/kg</td>
<td>62.02 mg/kg (24-162)</td>
<td>ND</td>
</tr>
<tr>
<td><img src="image2" alt="Structure" /></td>
<td>822-06-0</td>
<td>hexamethylene diisocyanate</td>
<td>MW = 168.22, VP = 0.05 mm Hg 25°C</td>
<td>18.2 ppm</td>
<td>737.7 mg/kg</td>
<td>4129.3 mg/kg</td>
<td>1054.17 mg/kg (810-1371)</td>
<td>0.35 (1h, mice)</td>
</tr>
<tr>
<td><img src="image3" alt="Structure" /></td>
<td>584-84-9</td>
<td>2,6 - toluene diisocyanate</td>
<td>MW = 174.15, VP = 0.05 mm Hg 25°C</td>
<td>13.9 ppm</td>
<td>5793.93 mg/kg</td>
<td>5065.71 mg/kg</td>
<td>3913.86 mg/kg (2471-6200)</td>
<td>0.39 (1h, mice)</td>
</tr>
<tr>
<td><img src="image4" alt="Structure" /></td>
<td>101-68-8</td>
<td>4,4’ diphenyl methane diisocyanate</td>
<td>MW = 250.25, VP = 0.0003 mm Hg 25°C</td>
<td>16.5-18 ppm</td>
<td>9191.97 mg/kg</td>
<td>6291.33 mg/kg</td>
<td>10298.44 mg/kg (6478-16370)</td>
<td>4.8 (1h, mice)</td>
</tr>
<tr>
<td><img src="image5" alt="Structure" /></td>
<td>51944-41-3</td>
<td>4-Cyanodiphenyl-methane diisocyanate</td>
<td>MW=291.26, VP = 0 mm Hg 25°C</td>
<td>ND</td>
<td>20012.93 mg/kg</td>
<td>5942.61 mg/kg</td>
<td>18895.13 mg/kg (11684-30558)</td>
<td>ND</td>
</tr>
</tbody>
</table>

- **MW**: Molecular Weight
- **VP**: Vapour Pressure
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<th>LD50 (rat) (TEST-experimental data)</th>
<th>TEST Software- Nearest Neighbor (LD50 rat)</th>
<th>TEST Software- Hierarchical Clustering (LD50 rat)</th>
<th>RD50 (ppm) 10 minute exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Structure" /></td>
<td>50-00-0</td>
<td>formaldehyde</td>
<td>MW = 30 VP = 3890 mm Hg</td>
<td>83.5 ppm</td>
<td>ND</td>
<td>1594.25 mg/kg</td>
<td>190.19 mg/kg (23.35-1548.86)</td>
<td>3 ppm (rat)</td>
</tr>
<tr>
<td><img src="image2" alt="Structure" /></td>
<td>75-07-0</td>
<td>acetaldehyde</td>
<td>MW = 44 VP = 902 mm Hg</td>
<td>13344 ppm</td>
<td>660.76 mg/kg</td>
<td>1044.83 mg/kg</td>
<td>433.38 mg/kg (4.13-45451.06)</td>
<td>13.8 ppm (rat)</td>
</tr>
<tr>
<td><img src="image3" alt="Structure" /></td>
<td>123-38-6</td>
<td>propionaldehyde</td>
<td>MW = 50 VP = mm Hg</td>
<td>3250 ppm</td>
<td>1409.62 mg/kg</td>
<td>134.1 mg/kg</td>
<td>458.01 mg/kg (236.60-886.63)</td>
<td>2932 ppm (rat)</td>
</tr>
<tr>
<td><img src="image4" alt="Structure" /></td>
<td>123-72-8</td>
<td>butyraldehyde</td>
<td>MW = 72 VP = 72 mm Hg</td>
<td>7500 ppm</td>
<td>2489.18 mg/kg</td>
<td>859.12 mg/kg</td>
<td>2078 ppm (rat)</td>
<td>4946 ppm (rat)</td>
</tr>
<tr>
<td><img src="image5" alt="Structure" /></td>
<td>110-62-3</td>
<td>valeraldehyde</td>
<td>MW = 86 VP = 50 mm Hg</td>
<td>ND</td>
<td>4584.11 mg/kg</td>
<td>2116.36 mg/kg</td>
<td>1532 ppm **</td>
<td>2078 ppm (rat)</td>
</tr>
</tbody>
</table>

By definition from the Haz Map page, RD50 Concentration producing a 50% decrease in respiratory rate in experimental animals following a 10-minute exposure.

Approaches for LTD Chemicals: Conclusions

• Derivation of a toxicity factor for an LTD chemical is dependent on available resources
• Approaches are designed to be conservative and produce generic toxicity factors that are health protective
• Inhalation can be highly variable
• Oral toxicity trend do not necessarily inform inhalation exposure concerns
• Available QSAR models are not particularly predictive of inhalation toxicity
Intrinsic properties:
- molecular volume
- connectivity
- charge distribution
- molecular weight

Molecular structure

Physico-chemical properties:
- pKa
- log Kow
- solubility
- stability

Biological activity:
- reactivity
- biotransformation
- pharmaco-dynamics
Area = the calculated molecular planarity, which is an indication for the three dimensional structure

ΔE = measure for the oxidative activation potential by P450 system

Ke = electrophilicity parameter, indicative for directly acting carcinogens
SARs/QSARs: Strengths and Limitations

• **Estimate toxicity**
  – Select least toxic chemical suitable for industrial use
  – Estimate toxicity in case of emergency
  – Determine whether emissions would be a potential risk

• **Direct toxicity testing**
  – What data is missing? Prioritization?

• **End point specific**
  – Does a QSAR based on LD50 or LC50 data inform other endpoints?
  – Inhalation endpoints?

• **Inaccuracy in model**
  – Oral data not predictive of inhalation toxicity
  – Is the model predictive?
  – Database used to generate QSAR model:
    - Limited, heterogeneous data points
    - Representativeness of database to chemical of concern/interest
Data for QSAR Development

• Based on quality data
  – Systematic evaluation
  – Applicability
  – Heterogeneity

• Well chosen set of chemicals

• Best categorization of data
  – Structural, physicochemical, or MOA?

• What is a well-balanced training set?
  – Range of chemicals
  – High quality studies
  – Validated by comparing experimental data to predicted data

• Uncertainty
Exploratory ATSDR Models
for Inhalation Health Guidance Values

**ATSDR MRLs**

- Estimated log(MRL) vs. Experimental log(MRL)
- \( R^2 = 0.82, N = 24 \)

**DOE TEELs**

- Estimated log(PAC) vs. Experimental log(PAC)
- \( R^2 = 0.47, N = 396 \)

**EPA AEGLs**

- Estimated log(AEGL-3) vs. Experimental log(AEGL-3)
- **Train:** \( R^2 = 0.85, N = 175 \)
  **Test:** \( R^2 = 0.60, N = 14 \)

**Data Quantity:**
- **few** (ATSDR MRLs)
- **ample** (DOE TEELs)
- **sufficient** (EPA AEGLs)

**Data Quality:**
- **high** (ATSDR MRLs)
- **poor** (DOE TEELs)
- **high** (EPA AEGLs)
Exploratory ATSDR Models
for Acute Exposure Guidelines Levels at 8 hour duration of exposure

AEGL-1

Train: $R^2 = 0.84$, $N = 121$, Test: $R^2 = 0.72$, $N = 12$

AEGL-2

Train: $R^2 = 0.82$, $N = 176$, Test: $R^2 = 0.69$, $N = 18$

AEGL-3

Train: $R^2 = 0.85$, $N = 175$, Test: $R^2 = 0.60$, $N = 14$
ATSDR: Conclusions

- Available inhalation health guidance values can be modeled using QSAR methods.
- The quality of QSAR estimates can not be better than the quality of experimental data using which the models were built.
- AEGLs/ERPGs represent the most promising source of data for modeling.
ATSDR/TCEQ: Future Directions

• Parameters of the models need to be optimized to achieve the best performance
• The chemical domain of model applicability needs to be explored and additional data recruited to improve coverage, as needed
• Confidence and prediction intervals for the estimates need to be derived
• Mode-of-action, species, and uncertainty-factor stratification of the data needs to be explored
• HGV cross-extrapolation dependencies need to be determined, e.g. exposure durations and severity levels
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ATSDR Computational Toxicology Group
EPA (TEST Software)
TERA
Questions/Comments??
EXPOSURE  TRANSPORT  METABOLISM  RECEPTOR BINDING  EFFECT

Chemical agent → Enzyme → Ultimate reactant → Biological endpoint

DNA or protein receptor

SAR PROPERTIES
partition coefficients, size, shape parameters
reactivity parameters: energies, 3D structures, functional groups, steric parameters, electronic properties

CARCINOGENICITY
GENOTOXICITY
TERATOGENICITY
NEUROTOXICITY
CYTOTOXICITY

CHEMICAL CLASSES
Alcohols
PAHs
halocetic acids
chlorofluoromethanes
nitrosoamines
dioxins
PAHs
PCBs
steroids

RIVM report 601516.001
QSAR Modeling Methods: Choices, Choices, Choices