A comparison of safety margins - DNELs and IOELVs

Gunnar Johanson
Professor, Head of Unit
Work Environment Toxicology
Institute of Environmental Medicine
Karolinska Institutet
Unit of work environment toxicology

Research
- Controlled chamber exposure of volunteers: acute effects, inhalation TK
- Dermal uptake
- Computer modeling: TK, PBPK, nanoparticles, dermal uptake, dose-response modeling
- Setting of limit values
- Receptor mechanisms (AhR)

Education
- Toxicologists, physicians, occupational health, PhD students

Committee work
- SCOEL
- Nordic Expert Group
- Swedish Criteria Group for OELs
- US AEGL Committee
- EU-LCI working group
Layout

1. OELs

2. DNELs

3. Comparison of OELs by SCOEL and DNELs by us
   - Calculation of OEL Implicit Safety Margins
   - Calculation of DNEL Dose Adjustments
   - Choice of DNEL Assessment Factors
   - Calculation of DNEL Total Adjustment and Assessment Factor
   - Comparisons

4. Comparison of DNELs by industry and by us

5. Personal thoughts
OEL setting of today

- **Similar scientific principles and procedures**
  - Independent expert committee
  - Appointment procedure
  - Transparency, objectivity
  - Declaration of conflict of interest and bias
  - Defined document format
  - Focus on dose-response, dose-effect and critical effect
  - Statements corroborated by references
  - Only refer to international peer-reviewed publications (?)
  - Circulate for comments before final decision

- **Different legislative frameworks**
  - Health-based guidance (tex European IOELV)
  - Administrative / pragmatic / binding (e.g. Sweden)
  - ACGIH TLV: intended as som guidance for occupational hygiensists, but implemented in the national legislation in many countries
SCOEL Key document

✓ How to evaluate animal and human data
✓ Seriousness of critical effect, especially nuisance and irritation
✓ No-health based OEL (⇒ no IOELV) for genotoxic carcinogens and airway sensitizers (no effect threshold)
✓ Criteria for skin notation
✓ Use of uncertainty factors
✓ Biological limit values and guidance values

No quantitative guidance, only qualitative

Emphasis on case by case, expert judgement
SCOEL on uncertainty factors

OEL = POD / (UF1 x UF2 x UF3…)

✓ In practice, the data base is less than ideal to set an OEL
✓ Reflected by use of UFs, the less confidence in data, the higher the UF
✓ No generally agreed approach to the application of UFs in setting OELs
✓ For several reasons often appropriate to apply lower UFs for workers
✓ UFs set on a case-by-case basis, cannot be established in advance
✓ The rationale should include…the reasons for the numerical value of the OEL in relation to the NO(A)EL(s), including a note on the choice of UFs
Chapter R.8: Characterisation of dose [concentration]-response for human health

APPENDIX R. 8-13  Deriving DNELs, when a community/national occupational exposure limit (OEL) is available

The following guidance applies in situations where

- an EU indicative occupational exposure limit (IOEL) has been adopted
- an EU binding occupational exposure limit (BOEL) has been adopted
- a national occupational exposure limit has been adopted

**EU Indicative Occupational Exposure Limit (IOEL)**

A registrant is allowed to use an IOEL as a DNEL for the same exposure route and duration, unless new scientific information that he has obtained in fulfilling his obligations under REACH does not support the use of the IOEL for this purpose. This could be because the information obtained is more recent than the information that was used to support setting the IOEL at EU level and because it leads to another value being derived which requires different risk management measures (RMMs) and operational conditions (OCs).

determining and assessing risks, e.g. in accordance with Article 4 of Directive 98/24/EC. IOELs are adopted at EU level by Commission Directives.

IOELs have been set for around 100 substances. Information on the setting of the IOELs and the recommendations of scientific committee on occupational exposure limits (SCOEL) are available on the website of Directorate General for Employment, Social Affairs and Equal Opportunities (DG EMPL): http://ec.europa.eu/employment_social/health_safety/index_en.htm
DNEL derivation is an important part in the REACH safety assessment process

- RMM/OC library
- DNELs/PNECs
- Exposure assessment
- Exposure scenario (safe use proven)
- eSDS
- Chemical safety report

Use descriptors and exposure determinants

Measurement data and models

Iterations

Risk Characterization Ratio < 1
(estimated exposure / DNEL)

RMM - risk management measure
OC - operational condition
PNEC - Predicted No Effect Concentration
eSDS – extended Safety Data Sheet

Adapted from van Hemmen J J Occup Environ Med 66 (2009) 561-568
DNEL derivation

DNEL = POD / TAAF

 POD = Point Of Departure
     = dose or exposure level for the leading effect

 POD is dose-adjusted for route (if not inhalation) and exposure duration (if not 8 h)

 TAAF = Total adjustment and assessment factor

 TAAF = dose-adjustment x AF1 X AF2 X AF3…
Comparison of OELs and DNELs

1. Calculation of OEL Implicit Safety Margins

- Use OELs as proposed by SCOEL, not IOELV (more substances can be included)
- All SCOEL sumdocs available at the time were included
- 90 substances with info on:
  - Exposure conditions
  - Exposure route
  - Species
  - NOAEL or LOAEL (POD)
  - UF (if used)
- Calculate implicit safety margin as
  \[ ISM = \frac{POD}{OEL} \]
Comparison of OELs and DNELs

2. Calculation of Total Adjustment and Assessment Factor

- Worker-DNEL long-term inhalation

- Use same dose descriptor as in SCOEL sumdoc *
  (although REACH guidance says one should identify several dose descriptors and select the one resulting in lowest DNEL)

- Make dose adjustment according to REACH guidance

- Choose AFs according to REACH guidance

- Calculate Total Adjustment and Assessment Factor

\[ \text{TAAF} = \text{Dose-adj} \times \text{AF}_1 \times \text{AF}_2 \times \text{AF}_3 \ldots \]
Comparison of OELs and DNELs

Adjustment of dose descriptor

- Different exposure routes
  - E.g. from oral to inhalation
  -Accounts for differences in abosrption

- Different species
  - Allometric scaling
  - Accounts for differences in biotransformation
  - Not needed for inhalation (test species) → inhalation (man)

- Different durations
  - Haber's law: $C^n \times t = k$ (n=1 or 3)

- Different work loads/ventilation rates
  - Rest 6.7 m$^3$/8h, light work 10 m$^3$/8h
### Comparison of OELs and DNELs

#### Adjustment of dose descriptor

<table>
<thead>
<tr>
<th></th>
<th>1,1,1-trichloroethane</th>
<th>2-(2-methoxy ethoxy)ethanol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical effect</td>
<td>Behavior</td>
<td>Reprotox</td>
</tr>
<tr>
<td>Dose descriptor</td>
<td>LOAEL 175 ppm</td>
<td>NOAEL 50 mg/kg bw</td>
</tr>
<tr>
<td>Duration</td>
<td>3.5 h</td>
<td>Gestation days 7-18</td>
</tr>
<tr>
<td>Route</td>
<td>Inhalation</td>
<td>Dermal</td>
</tr>
<tr>
<td>Art</td>
<td>Human</td>
<td>Rabbit</td>
</tr>
</tbody>
</table>

#### Adjustment

| Different routes          | -                      | 50% dermal, 100% inhalation |
| Allometric scaling       | -                      | 2.4                         |
| Duration \( C^n \times t = k \) | \((175\text{ppm}^1 \times 3.5\text{h}) / 8\text{h} = 76.6 \text{ ppm} \) | -                           |
| Inhaled volume           | 76.6 ppm \( \times (6.7 \div 10) = 51.3 \text{ ppm} \) | \( \text{bw=70 kg, ventilation=}10 \text{ m}^3/8\text{h} \) |
| Modified dose (POD)      | 51.3 ppm               | 72.91 \text{ mg/m}^3        |

#### Adjustment factor

- 1,1,1-trichloroethane: \( 175/51.3 = 3.41 \)
- 2-(2-methoxy ethoxy)ethanol: \( (50/25) \times 2.4 = 4.8 \)
Comparison of OELs and DNELs
Choice of AFs and TAAF calculation

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<td>Rabbit</td>
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<table>
<thead>
<tr>
<th>Assessment factors</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Interspecies</td>
<td>1</td>
<td>2,5</td>
</tr>
<tr>
<td>Intraspecies</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>LOAEL-NOAEL</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Exposure duration</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>(additional support</td>
<td>(relevant gestation</td>
</tr>
<tr>
<td></td>
<td>from subchronic data</td>
<td>period)</td>
</tr>
<tr>
<td>Quality of data base</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total Assessment Factor</td>
<td>1x5x3x3x1 = 30</td>
<td>2.5x5x1x1x1 = 12.5</td>
</tr>
</tbody>
</table>
### Comparison of OELs and DNELs

#### 3. Compare DNEL and OEL

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#### Calculation of DNEL

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</thead>
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<tr>
<td>Adjusted POD</td>
<td>51.3 ppm</td>
<td>72.91 mg/m³</td>
</tr>
<tr>
<td>Total Assessment Factor</td>
<td>30</td>
<td>12.5</td>
</tr>
<tr>
<td>DNEL</td>
<td>1.71 ppm</td>
<td>5.8 mg/m³</td>
</tr>
<tr>
<td>OEL given by SCOEL</td>
<td>100 ppm</td>
<td>50 mg/m³</td>
</tr>
<tr>
<td>Ratio OEL/DNEL</td>
<td>100/1.71 = 58.5</td>
<td>50/5.8 = 8.6</td>
</tr>
</tbody>
</table>
DNEL versus OEL safety margins

- 90 substances with SCOEL sumdoc and OEL proposal
- TAAF 0.3 - 60 (median 5) times higher than corresponding ISM or
- DNEL 0.3 - 60 (median 5) times lower than corresponding OEL
DNEL versus OEL safety margins

<table>
<thead>
<tr>
<th></th>
<th>Min</th>
<th>Max</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>REACH DNEL TAAF</td>
<td>5</td>
<td>234</td>
<td>16.3</td>
</tr>
<tr>
<td>SCOEL OEL ISM</td>
<td>0.9</td>
<td>71.4</td>
<td>2.5</td>
</tr>
<tr>
<td>TAAF/ISM ratio</td>
<td>0.33</td>
<td>58.6</td>
<td>5 (gm=6)</td>
</tr>
</tbody>
</table>

Graph showing safety margins for different animal and human LOAEL and NOAEL values.
Discussion
DNEL versus OEL safety margins

- DNELs 0.3 – 60 times “safer” than OELs
- Difference may be larger (or smaller) in practice, depending on how the REACH guidance is interpreted and applied
- Huge variability for several reasons:
  - Missing or unreliable data
    = difficult to interpret
  - Different opinions on how to interpret data
  - Different opinions on how to apply AFs
  - Different opinions on how to interpret the REACH guidance
DNEL by industry and by us

- Pilot study – preliminary data

- 15 substances for which
  1. worker DNEL long-term inhalation values are given at the ECHA website, and
  2. Worker-DNEL ≠ SCOEL-OEL, and
  3. a scientific basis for OEL has been published by the Swedish Criteria Group within the last 15 years

- DNELs:
  - Industry DNELs as given in ECHA database
  - Our DNELs calculated according to our interpretation of the REACH guideline, using the Swedish OEL basis
  - Our PODs may differ from industry’s

- TAFs:
  - Implicit industry TAFs calculated from PODs and DNELs given at the ECHA website
  - Our TAFs obtained using industry PODs and our interpretation of the REACH guideline
  - Same PODs
DNELs by industry and by us

<table>
<thead>
<tr>
<th>Chemical</th>
<th>By industry (mg/m³)</th>
<th>By us (mg/m³)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimethylamine</td>
<td>1.04</td>
<td>0.25</td>
<td>4.2</td>
</tr>
<tr>
<td>Gamma-butyrolactone</td>
<td>130</td>
<td>1.17</td>
<td>110</td>
</tr>
<tr>
<td>Meta-cresol</td>
<td>3.5</td>
<td>0.135</td>
<td>26</td>
</tr>
<tr>
<td>Molybdenum</td>
<td>11.2</td>
<td>0.01</td>
<td>1100</td>
</tr>
<tr>
<td>Naphtalene</td>
<td>25</td>
<td>0.35</td>
<td>71</td>
</tr>
<tr>
<td>N-butylacetate</td>
<td>480</td>
<td>48.6</td>
<td>9.9</td>
</tr>
<tr>
<td>Ortho-cresol</td>
<td>3.5</td>
<td>1.02</td>
<td>3.4</td>
</tr>
<tr>
<td>Ortho-dichlorobenzene</td>
<td>59</td>
<td>1.47</td>
<td>40</td>
</tr>
<tr>
<td>Para-cresol</td>
<td>3.5</td>
<td>0.29</td>
<td>12</td>
</tr>
<tr>
<td>Pentfluoroethane</td>
<td>16 400</td>
<td>5 010</td>
<td>3.3</td>
</tr>
<tr>
<td>Styrene</td>
<td>85</td>
<td>1.43</td>
<td>59</td>
</tr>
<tr>
<td>Tin</td>
<td>11.8</td>
<td>0.016</td>
<td>730</td>
</tr>
<tr>
<td>Triethanolamine</td>
<td>5</td>
<td>1.68</td>
<td>2.9</td>
</tr>
<tr>
<td>Trifluoroethane</td>
<td>38 800</td>
<td>2 810</td>
<td>14</td>
</tr>
<tr>
<td>Trimellitic anhydride</td>
<td>17.5</td>
<td>0.000 067</td>
<td>260 000</td>
</tr>
</tbody>
</table>

Our DNELs 2.9 – 1100 times lower than industry’s except trimellitic anhydride (260 000 times)
TAFs by industry and by us

<table>
<thead>
<tr>
<th>Chemical</th>
<th>By industry</th>
<th>By us</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimethylamine</td>
<td>9</td>
<td>37.5</td>
<td>4.2</td>
</tr>
<tr>
<td>Gamma-butyrolactone</td>
<td>1.53</td>
<td>25</td>
<td>16</td>
</tr>
<tr>
<td>Meta-cresol</td>
<td>12.6</td>
<td>25</td>
<td>1.9</td>
</tr>
<tr>
<td>Molybdenum</td>
<td>4.87</td>
<td>25</td>
<td>5.1</td>
</tr>
<tr>
<td>Naphthalene</td>
<td>0.11</td>
<td>25</td>
<td>230</td>
</tr>
<tr>
<td>N-butylacetate</td>
<td>2.53</td>
<td>25</td>
<td>9.9</td>
</tr>
<tr>
<td>Ortho-cresol</td>
<td>12.6</td>
<td>25</td>
<td>1.9</td>
</tr>
<tr>
<td>Ortho-dichlorobenzene</td>
<td>1.5</td>
<td>25</td>
<td>17</td>
</tr>
<tr>
<td>Para-cresol</td>
<td>12.6</td>
<td>25</td>
<td>1.9</td>
</tr>
<tr>
<td>Pentfluoroothane</td>
<td>7.61</td>
<td>25</td>
<td>3.3</td>
</tr>
<tr>
<td>Styrene</td>
<td>3.8</td>
<td>75</td>
<td>19</td>
</tr>
<tr>
<td>Tin</td>
<td>75</td>
<td>75</td>
<td>1</td>
</tr>
<tr>
<td>Triethanolamine</td>
<td>50.25</td>
<td>75</td>
<td>1.5</td>
</tr>
<tr>
<td>Trifluoroethane</td>
<td>1.81</td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td>Trimellitic anhydride</td>
<td>No key study</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Our TAAF 1 – 230 times higher than industry
DNEL by industry and by us

- Our DNELs 2.9 – 1100 times lower than industry’s for 14 substances and 260 000 times lower for trimellitic anhydride

- Some of the discrepancy is explained by different choice of key studies and/or PODs

- However, TAFs also differ markedly, ours being 1 – 230 times higher

- Although the REACH guidance is relatively detailed, many arbitrary choices remain that will influence AFs, TAAFs and DNELs

- A major problem is that little advice is given on when and how to depart from defaults
  We tended to stick to default AFs
  Industry more deviations
Personal thoughts on OELs

- Long experience, well established OEL committees and procedures

- Inexplicit and inconsistent use of UF values
  OEL committees should strive to clearly state the UF values and the reasoning behind

- Indicative OEL proposal should be purely health based but always a risk that economy and technology is brought in
  OEL committees should have a system to deal with conflict of interest and bias (now implemented in SCOEL)

- Much of the OEL (and DNEL) work cannot be subordinated to rules set up in advance, must rely on expert judgement
  Continued need for SCOEL and other independent OEL committees
Personal thoughts on DNELs

- REACH guidance R8, including advice on AFs, is a good step forward
- However, advice on when and how to deviate from defaults is lacking
- Obvious risk that deviations from default AFs varies between chemicals and assessors/consortia => DNELs will be inconsistent
- More strict guidance might not help – every chemical is unique
- Obvious risk for conflicting interests between health and economy
- Industry-derived DNELs do not replace independent expert committee judgements
Personal thoughts on DNELs

- DNELs are not intended to replace OELs…

- …but what will happen in practice?
  - Many DNELs
  - Very few OELs

- “DNELs will be regarded as OELs”,
  Susan Ripple, Science and Technical Manager, Global Industrial Hygiene Expertise Center, Dow Chemical,
  at IOHA-2010 in Rome
Acknowledgments

Linda Schenk
PhD thesis at the Royal Institute of Technology, Stockholm
Now postdoc at the Unit of Work Environment Toxicology

Uriell Deng
Pharmacy student in Paris
Internship at the Unit of Work Environment Toxicology

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Swedish Work Environment Authority (SWEA)

New funding from the
Swedish Council for Working Life and Social Research (FAS)
A Quantitative Comparison of the Safety Margins in the European Indicative Occupational Exposure Limits and the Derived No-Effect Levels for Workers under REACH

How consistent are the Derived No-Effect Levels (DNELs) in the European REACH Legislation?

Schenk L, Deng U, Johanson G. Karolinska Institutet, Institute of Environmental Medicine, Stockholm, Sweden

The new European REACH regulation places more responsibility than hitherto on manufacturers and importers of chemicals.