The Inhalation DNEL-Challenge

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First Step of Risk Characterization: Reference Concentration for Workers

**DNEL = derived no effect level**
- “the level of exposure above which humans should not be exposed”
- “DNELs are for **threshold effects**”
- the basis of derivation is a NEL or a POD.
  - When no DNEL can be obtained (non-threshold effect or no threshold is identifiable) a DMEL should be derived. Limited operational guidance is given.

**DMEL = derived minimal effect level**
- “expresses an exposure level corresponding to a low risk”
- “excess lifetime risk: how many **excess cases** in absolute terms will result from a given relative estimate of risk.”
- “cancer risk levels of $10^{-5}$ and $10^{-6}$ could be seen as indicative **tolerable risk levels** when setting DMELs for workers and the general population, respectively”
The Principles of Derivations of NOAEL_{HEC}, POD_{HEC} and DNEL

- **Analysis of data base and selection of most appropriate study to fit the purpose**
  - Most relevant species & study design
  - Lowest dose descriptor from all studies accessible
  - Substance-specific data allow modified procedure

- **Purpose**
  - Protection of pre-defined population (consumer, workers)
  - Most apt exposure regimen and route
  - Most critical and relevant mode of action (MOA: local, systemic with or without metabolism/toxicophoresis)

- **Selection of dose descriptor**
  - NEL/NOAEL from default study
  - MOA-based specialized study
Diversity of Inhalation Toxicity not appreciated

- Categorization ‘irritants’ vs. ‘corrosives’ (‘similar as eyes and skin’)
  - too simple / clarification needed
- Differentiation between ‘sensory’ and ‘cytotoxic’ irritants
  - too simple / clarification needed
- ‘No tests available for respiratory tract irritation’
  - too simple / clarification needed
  - OECD-GD#39 (2009) provides a great deal of guidance
- Compartmentalization of respiratory tract
  - REACH: Respiratory system
  - All other: differentiation into NP-, TB- and P-region

**Respiratory Minute Volume - Rats**

<table>
<thead>
<tr>
<th>Time [minutes]</th>
<th>Relative Change to Control Period [%]</th>
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<tbody>
<tr>
<td>0</td>
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</tr>
<tr>
<td>15</td>
<td>20</td>
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<tr>
<td>90</td>
<td>120</td>
</tr>
<tr>
<td>105</td>
<td>140</td>
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</table>

- control - wet
- 100 mg/m³ - wet
- 200 mg/m³ - wet
- 400 mg/m³ - wet
- 1000 mg/m³ - wet
- 1000 mg/m³ - aerosol

Misconception: neuronal efferents are flux-dependent; however injury is concentration x time – dependent.
Local Effects: Irritation of the Respiratory System

Stratified: US-NOAEL-HEC
All together: EU-DNEL
DNEL: Related Approaches

- US-Iris-RfC concept (general public)

\[
NOAEL_{HEC}(POD_{HEC}) = NOAEL_{ADJ}(POD_{ADJ}) \times \frac{DAF}{UF_H \times UF_A \times UF_S \times UF_L \times UF_D}
\]

DAF: Dosimetric adjustment factor, which differ for vapors and aerosols and is dependent on the substance-specific mode of action (MOA)

\[
NOAEL_{ADJ} = \text{adjustment of exposure durations study & population}
\]

<table>
<thead>
<tr>
<th>POD</th>
<th>Benchmark</th>
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<tbody>
<tr>
<td>UF_H</td>
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</tr>
<tr>
<td>UF_A</td>
<td>3</td>
</tr>
<tr>
<td>UF_S</td>
<td>3</td>
</tr>
<tr>
<td>UF_L</td>
<td>1</td>
</tr>
<tr>
<td>UF_D</td>
<td>1</td>
</tr>
</tbody>
</table>

- Key study:
  90-day inhalation study on rats with borderline NOAEL

\[y_{\text{Collagen}} = a\cdot(\text{c-1}\cdot\exp(-b\cdot x))\]

- Benchmark: 0.27 mg/m³; BMCL (95%): 0.20 mg/m³
DNEL: Default Approach for Workers (OELs)

\[ \text{DNEL}(POD) = \text{NOAEL}_{\text{adj}}(POD)_{\text{adj}} \times \frac{\text{Systemic or Local (±metabol.)}}{AF_H \times AF_A \times AF_S \times AF_L \times AF_D} \]

**RfC:** Regional-specific dosimetric adjustments
**DNEL:** Entire respiratory system with distinction of sensory/cytotoxic irritation
**Dose expression:** C, effect-based C x t and cumulative C x t ill-addressed
**Route to route:** unclear and inconsistent with all other regulations, e.g. pharmaceuticals
**Read-across:** regulatory acceptance yet unclear

<table>
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<th>POD</th>
<th>Benchmark</th>
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<tr>
<td>UF_H</td>
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</tr>
<tr>
<td>UF_A</td>
<td>2.5</td>
</tr>
<tr>
<td>UF_S</td>
<td>2_{13-wk (6)}_{4-wk}</td>
</tr>
<tr>
<td>UF_L</td>
<td>1</td>
</tr>
<tr>
<td>UF_D</td>
<td>1</td>
</tr>
</tbody>
</table>

**Inhalation:** local

**Key study:**
- 90-day inhalation study on rats
- MOA-studies of short duration
- Acute-on-chronic effects
- Accumulation
- Allometric scaling (oral→inhalation)

Default \( AF_{\text{tot}} \)-local irritant/4 wk rat study: 75
Derived No Effect Level: The Purpose is to derive an OEL

- Newly developed health benchmark for risk management decisions (RCR):

  - Selection of Scenario: consumer/worker
  - Selection of key study fitting the MOA & scenario
  - Adjustment of dose descriptor to the scenario
  - Case-by-case dosimetric/morphometric adjustments
  - Select assessment factors
  - Expert judgment based on substance-specific information

  Calculate DNEL

  RCR = Expos./DNEL (< 1 safe use)
Time Adjustments & Mode of Action

Dose required to elicit a constant effect vs. exposure frequency related accumulation of dose.

Acute-on-chronic effects important to consider.
Local acute alveolar Irritation: Example ‘Phosgene’

Worker -DNEL:

$$DNEL = 0.3 \text{ mg/m}^3 [8h/d, POD] \times \frac{1}{5_H \times 2.5_A \times 2_S \times 3_L \times 1_D} \text{ default}$$

$$= 0.004 \text{ mg/m}^3 (0.001 \text{ ppm})$$

Worker –OEL / weight of evidence:

$$DNEL = 9 \text{ [mg/m}^3 - 30 \text{ min}] \times \frac{270}{480} \times \frac{1}{1_H \times 1_A \times 1_S \times 1_L \times 1_D}$$

$$= 0.4 \text{ mg/m}^3 (0.1 \text{ ppm})$$

Current workplace standards:

- MAK/TLV: 0.4 mg/m$^3$ (0.1 ppm)
- Ceiling (MAK): x2

100-times higher than the DNEL$^{\text{default}}$

Key study

- 13-week rat inhalation study
- 1x30 min dog MOA inhalation study

+ 13-week rat inhalation study
Acute and (sub)chronic Effects: Example Phosgene Gas

Mode of action:
- $C^{n-1} x t = \text{const.}$
- Acute on chronic effect (this means the chronic NOAEL is driven by acute P-irritation)
- Dog data supersede rat data
Route-to-Route Extrapolation

Example R. 8-2 Workers

oral

\[
\text{Dose} = \text{RMV} \times C \times t
\]

RMV-rat young-adult nose-only exposure: 0.8 L/(min x kg) or 0.29 m³/kg-day → 172 mg/m³

RMV-human working day 10 m³/70 kg: 0.14 m³/kg-day → 25 mg/kg

Algorithms suggested by REACH R.8 are at variance with all other guidelines, e.g. inhalation pharmaceuticals
Systemic acute Methemoglobinemia: Example ‘Aniline’

Oral: 5-times more toxic than by inhalation
Aniline – Route & Time Dependence of MetHb-Formation

Steady-state attained at 30 mg/m³
- 4 hrs exposure (< 1% MetHb)
Aniline

**Worker -DNEL:**

- Feeding study: \( \frac{7 \times 7}{4} \times \text{AF} \times (2.5 \times 5 \times 3_L) = 0.3 \text{ mg/m}^3 \)
- Feeding study: \( \frac{7}{0.29} \times \text{AF} \times (2.5 \times 5 \times 3_L) = 0.6 \text{ mg/m}^3 \)
- Feeding study: \( \frac{7}{0.29 \times 5} \times \text{AF} \times (2.5 \times 5 \times 3_L) = 3.2 \text{ mg/m}^3 \)
- 2-wk inhalation study: \( \frac{9.2 \times 6}{8} \times \text{AF} \times (2.5 \times 5 \times 6 \times 2) = 0.05 \text{ mg/m}^3 \)
- 2-wk inhalation study: \( \frac{9.2}{\text{AF}} \times (2.5) = 3.7 \text{ mg/m}^3 \)

**Key study**

- 2-yr rat chronic dietary study (NEL < 7 mg/kg/day)

**Worker –DNEL / weight of evidence:**

\[
\text{DNEL} = 30 \left[ \frac{\text{mg/m}^3 - 4h}{3_h \times 1_A \times 1_s \times 1_L \times 1_D} \right] = 10 \text{ mg/m}^3
\]

**Current workplace standards:**

- MAK/TLV: 8 mg/m\(^3\)
- Ceiling (MAK): x2

2 to 160-times higher than the default DNEL
## Default Assessment Factors

<table>
<thead>
<tr>
<th>Assessment factor – accounting for differences in:</th>
<th>Default value systemic effects</th>
<th>Default value local effects</th>
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</thead>
<tbody>
<tr>
<td><strong>Interspecies</strong></td>
<td><strong>AS&lt;sup&gt;a,b&lt;/sup&gt;</strong></td>
<td><strong>–</strong></td>
</tr>
<tr>
<td>- correction for differences in metabolic rate per body weight</td>
<td>2.5</td>
<td>1&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>- remaining differences</td>
<td></td>
<td>2.5&lt;sup&gt;g&lt;/sup&gt;</td>
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<tr>
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<tr>
<td>- worker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- general population</td>
<td>10&lt;sup&gt;c&lt;/sup&gt;</td>
<td>10&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Exposure duration</strong></td>
<td><strong>3</strong></td>
<td><strong>3&lt;sup&gt;h&lt;/sup&gt;</strong></td>
</tr>
<tr>
<td>- subacute to sub-chronic</td>
<td></td>
<td></td>
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<tr>
<td>- sub-chronic to chronic</td>
<td>2&lt;sup&gt;h&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>- subacute to chronic</td>
<td>6&lt;sup&gt;h&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Dose-response</strong></td>
<td><strong>1&lt;sup&gt;d&lt;/sup&gt;</strong></td>
<td><strong>1&lt;sup&gt;d&lt;/sup&gt;</strong></td>
</tr>
<tr>
<td>- issues related to reliability of the dose-response, incl. LOAEL/NAEL extrapolation and severity of effect</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Quality of whole database</strong></td>
<td><strong>1&lt;sup&gt;d&lt;/sup&gt;</strong></td>
<td><strong>1&lt;sup&gt;d&lt;/sup&gt;</strong></td>
</tr>
<tr>
<td>- issues related to completeness and consistency of the available data</td>
<td></td>
<td></td>
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<tr>
<td>- issues related to reliability of the alternative data</td>
<td>1&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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<sup>a</sup> AS = factor for allometric scaling (see Table R. 8-3).
<sup>b</sup> Caution should be taken when the starting point is an inhalation or diet study.
<sup>c</sup> Not always covering for very young children; see text for deviations from default.
<sup>d</sup> See text for deviations from default.
<sup>e</sup> Special consideration needed on a case-by-case basis.
<sup>f</sup> For effects on skin, eye and GI tract via simple destruction of membranes.
<sup>g</sup> For effects on skin, eye and GI tract via local metabolism; for effects on respiratory tract.
<sup>h</sup> For effects on respiratory tract.
Inhalation studies are triggered if local effects are expected to occur within the respiratory tract.

Inhalation studies probe specifically the localized site of injury. Modeling procedures available for rat→human dosimetric adjustments.

The diversity of the respiratory tract needs to be appreciated in regard to deposition/retained dose and resulting localized dose and effect.

Default time-adjustments irrelevant for acute-on-chronic effects.

Prorated C x t adjustments need thoughtful considerations in regard to cumulative dose and attainment of steady state.
Summary

- The NELs from MOA-based on short-term studies are more relevant for DNEL estimations than from ‘default guideline studies’.
- The prorated default time-adjustment does neither take into account the substance-specific MOA nor its kinetic profile.
- The variability and uncertainties of inhalation studies are lower than from non-inhalation studies. The study design is targeted to meet the exposure patterns of workers.
- The different locations of the respiratory tract need to be differentiated and thoughtfully adjusted to humans.
Conclusion

- The endpoint-specific guidance (R.7) needs to be adopted to the updated OECD guidance as of 2009.
- Risk characterization (R.8) does not adequately appreciate the highly targeted and MOA-driven design of inhalation studies.
- Most of the criteria given appear to match eye/skin or oral tests but not inhalation toxicity tests.
- Therefore, the default uncertainty factors articulated by R.8 have to be understood as trigger for undertaking a **substance**- and **MOA-specific** RC to arrive at more meaningful and science-based OELs or DNELs.