The Inhalation DNEL-Challenge

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Rome, October 1, 2010

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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*

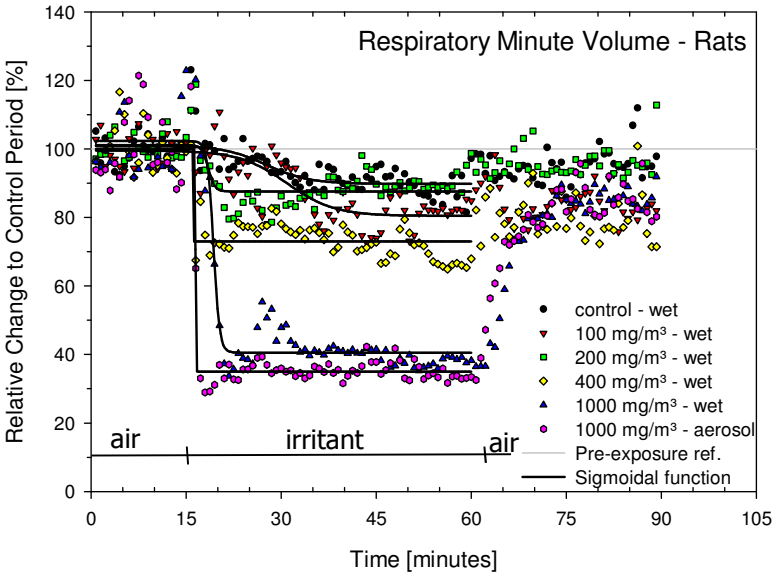
- "expresses an exposure level corresponding to a low risk"
- "excess lifetime risk: how many excess cases in absolute terms will result from a given relative estimate of risk."
- "cancer risk levels of 10^{-5} and 10^{-6} could be seen as indicative tolerable risk levels when setting DMELs for workers 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

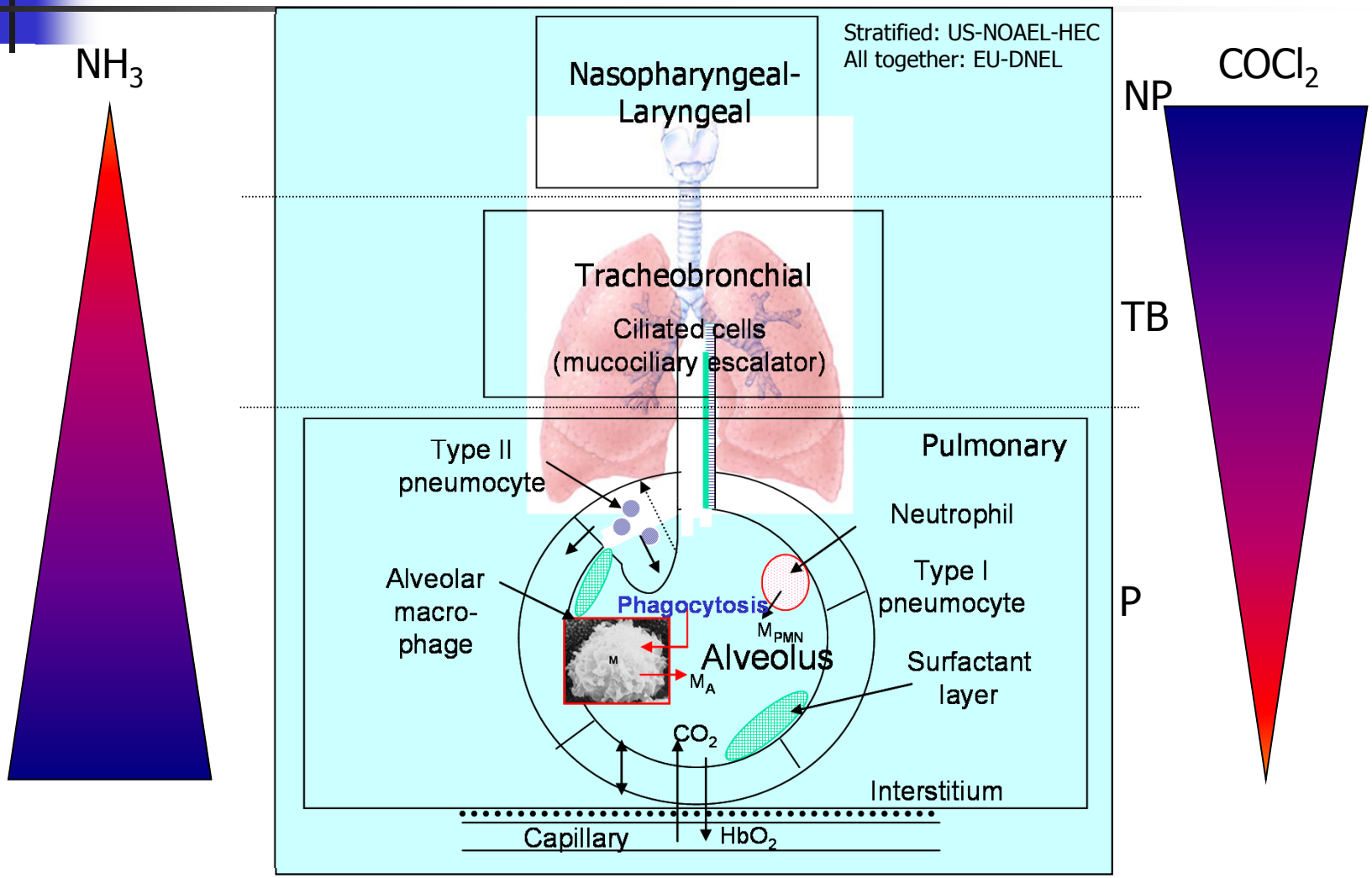
Diversity of Inhalation Toxicity not appreciated

- 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



Misconception: neuronal efferents are flux-dependent; however injury is concentration x time – dependent.

Local Effects: Irritation of the Respiratory System



DNEL: Related Approaches

- US-Iris-RfC concept (general public)

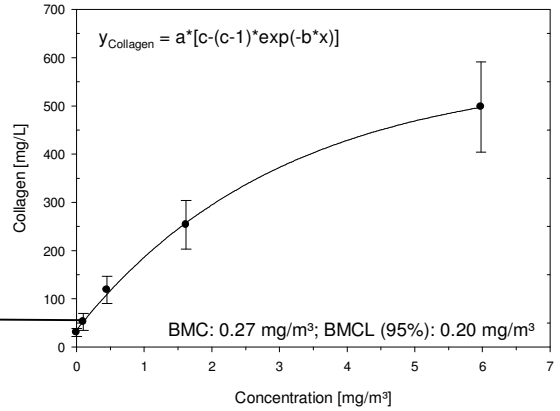
$$NOAEL_{HEC}(POD_{HEC}) = NOAEL_{ADJ}(POD_{ADJ}) \times \frac{DAF}{UF_H \times UF_A \times UF_S \times UF_L \times UF_D}$$

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

$NOAEL_{ADJ}$ = adjustment of exposure durations study & population

POD	Benchmark
UF_H	10
UF_A	3
UF_S	3
UF_L	1
UF_D	1

NOAEL
LOAEL
BMDL (POD)



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

DNEL: Default Approach for Workers (OELs)

$$DNEL(POD) = NOAEL_{ADJ}\,(POD_{ADJ}) \times \frac{Systemic\,or\,Local\,(\pm metabol.)}{AF_H \times AF_A \times AF_S \times AF_L \times AF_D}$$

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

POD	Benchmark
UF_H	5
UF_A	2.5
UF_S	$2_{13\text{-wk}}$ $(6)_{4\text{-wk}}$
UF_L	1
UF_D	1

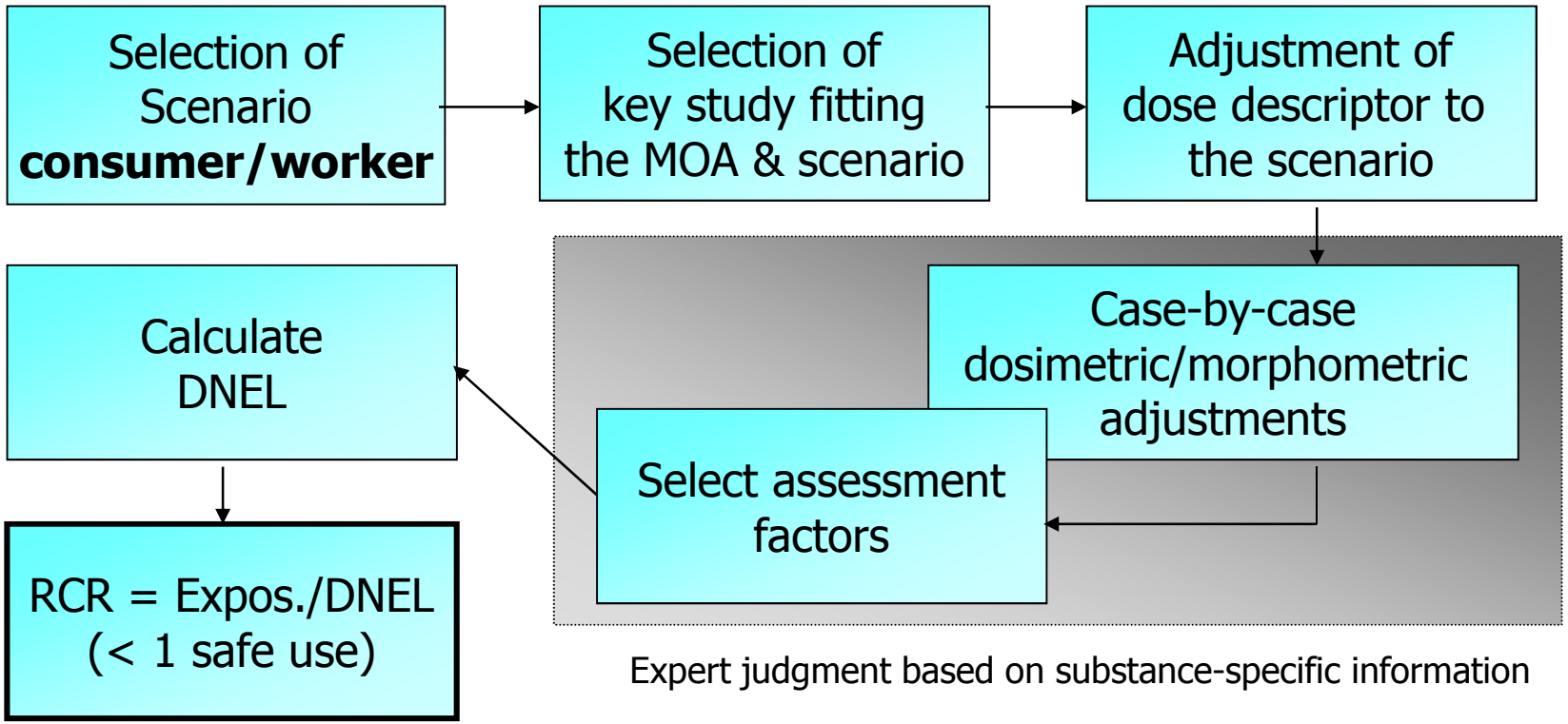
Inhalation: local

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

Default AF_{tot}-local irritant/4 wk rat study: 75

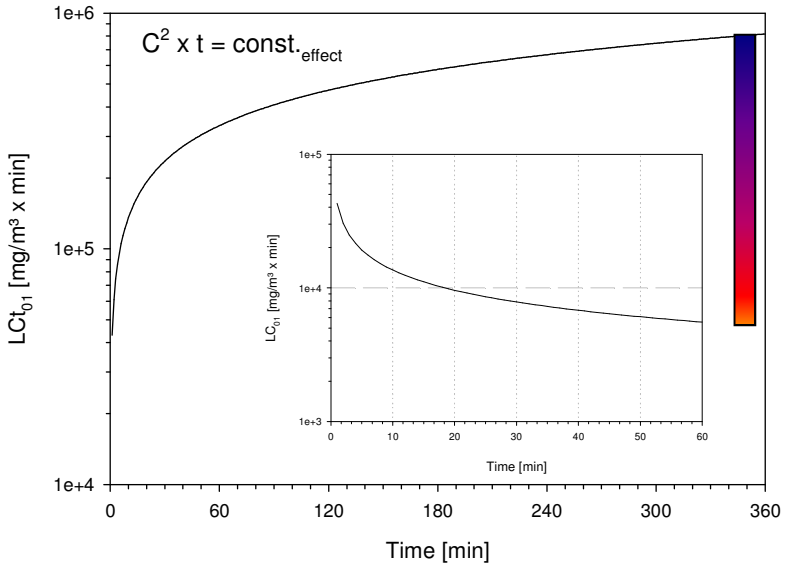
D*erived* **N***o* **E***ffect* **L***evel*: The Purpose is to derive an OEL

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



Time Adjustments & Mode of Action

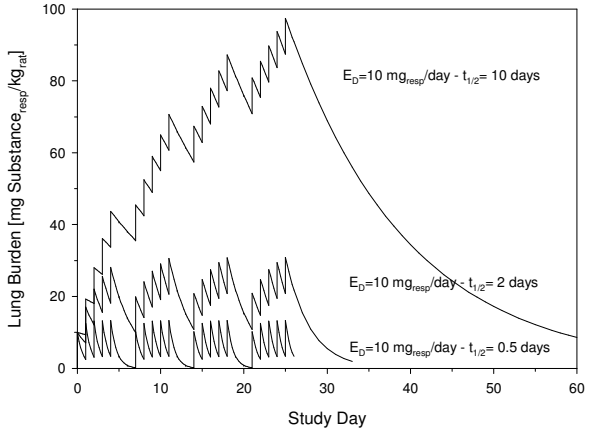
Exposure adjustment: short-term

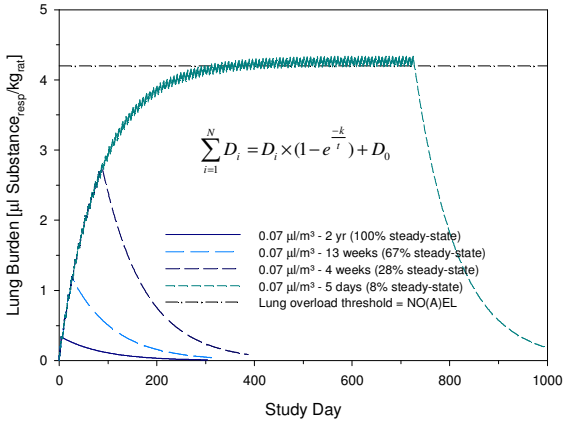


Dose required to elicit a constant effect vs. exposure frequency related accumulation of dose.

Acute-on-chronic effects important to consider.

Exposure adjustment: long-term





Local acute alveolar Irritation: Example 'Phosgene'

Key study

Worker -DNEL:

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

default

$$= 0.004\,mg/m^3(0.001\,ppm)$$

13-week rat inhalation study

Worker –OEL / weight of evidence:

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

$$= 0.4\,mg/m^3(0.1\,ppm)$$

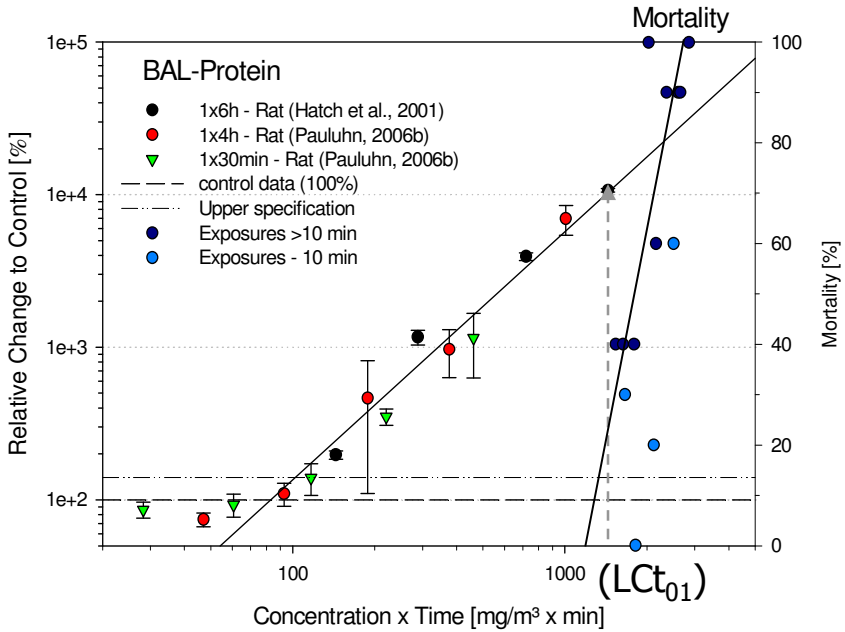
1x30 min dog MOA inhalation study
+
13-week rat inhalation study

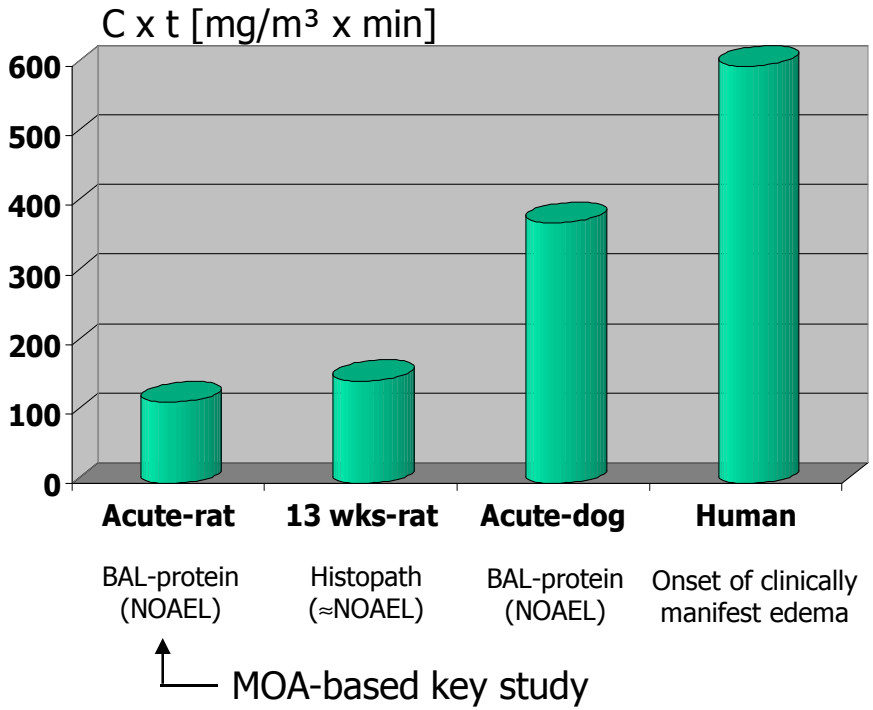
Current workplace standards:

MAK/TLV: 0.4 mg/m³ (0.1 ppm)
Ceiling (MAK): x2

100-times higher than the $DNEL_{default}$

Acute and (sub)chronic Effects: Example Phosgene Gas

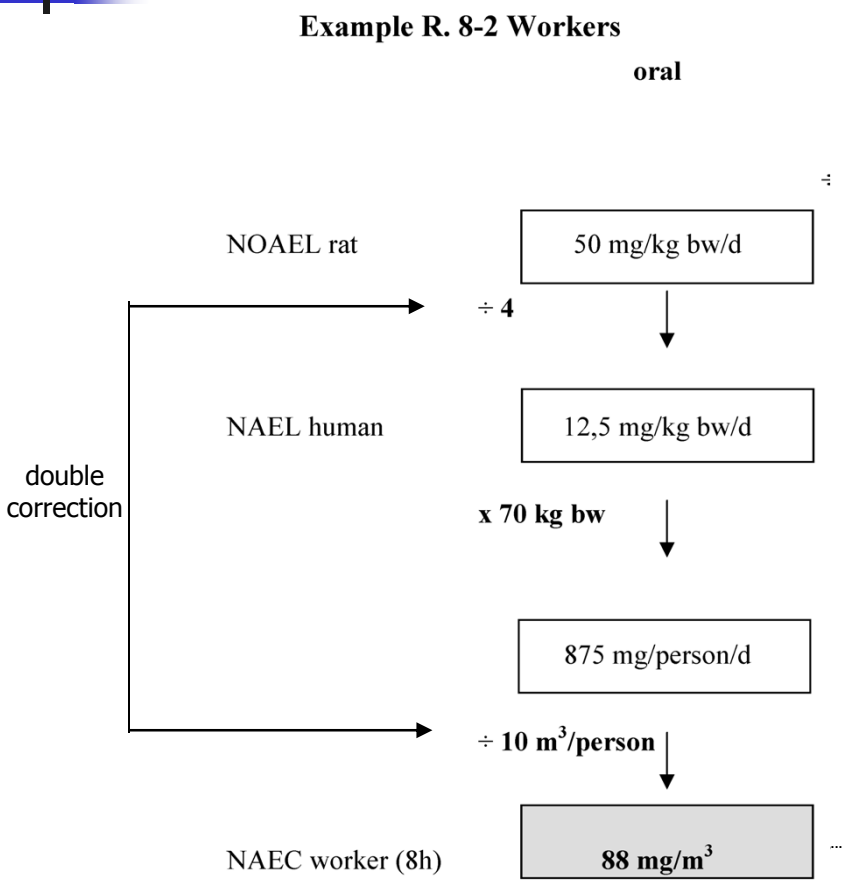




Mode of action:

- $C^{n=1} \times t = const.$
- Acute on chronic effect (this means the chronic NOAEL is driven by acute P-irritation
- Dog data supersede rat data

Route-to-Route Extrapolation



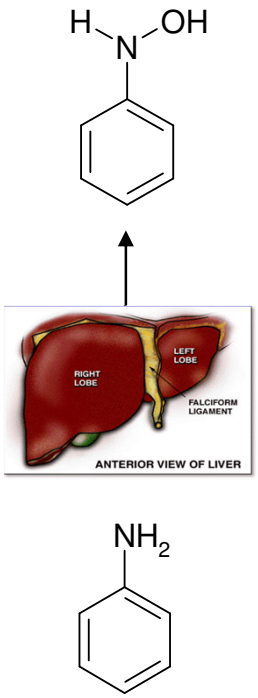
Dose = RMV x C x t

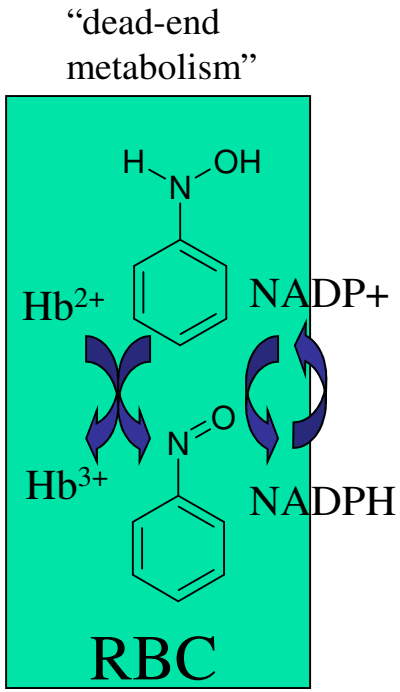
RMV-rat young-adult nose-only exposure: 0.8 L/(min x kg) or 0.29 m³/kg-day →172 mg/m³

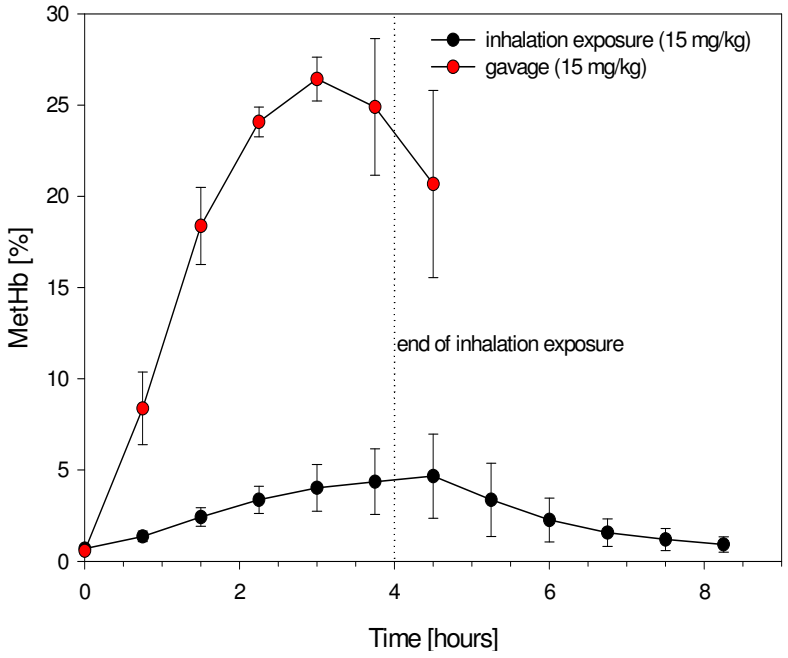
RMV-human working day 10 m³/70 kg: 0.14 m³/kg-day→25 mg/kg

Algorithms suggested by REACH R.8 are at variance with all other guide-lines, e.g. inhalation pharmaceuticals

Systemic acute Methemoglobinemia: Example 'Aniline'

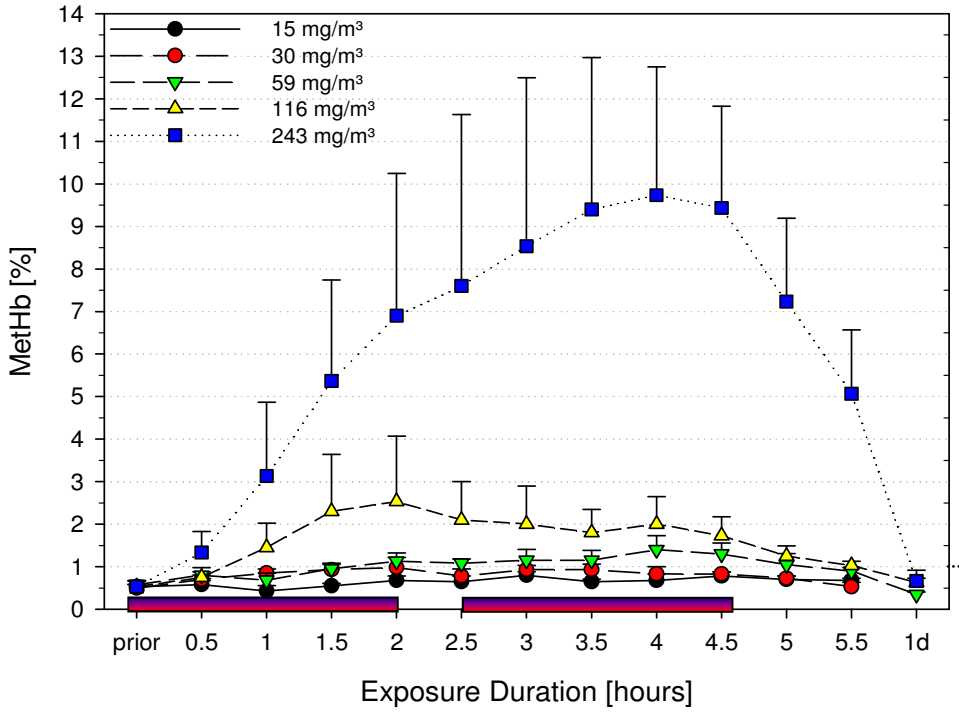






Oral: 5-times more toxic than by inhalation

Aniline – Route & Time Dependence of MetHb-Formation



No time-adjustment needed below or at effect threshold.

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

Aniline

Worker -DNEL:

Feeding study: (7x7/4)/AF (2.5 x 5 x 3_L) = 0.3 mg/m³	*default*
Feeding study: (7/0.29/AF (2.5 x 5 x 3_L) = 0.6 mg/m³	*default/modified*
Feeding study: (7/0.29x5)/AF (2.5 x 5 x 3_L) = 3.2 mg/m³	***expert***
2-wk inhalation study: 9.2x6/8/AF (2.5 x 5 x 6 x 2) = 0.05 mg/m³	*default*
2-wk inhalation study: 9.2/AF (2.5) = 3.7 mg/m³	***expert***

Key study

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

Worker –DNEL / weight of evidence:

$$DNEL = 30\,[mg/m^3 - 4\,h] \times \frac{1}{3_H \times 1_A \times 1_S \times 1_L \times 1_D} = 10\,mg/m^3$$

Single 4-hour dog MOA inhalation study

Current workplace standards:

MAK/TLV: 8 mg/m³
Ceiling (MAK): x2

2 to 160-times higher than the default DNEL

Default Assessment Factors

Assessment factor – accounting for differences in:		Default value systemic effects	Default value local effects
Interspecies	- correction for differences in metabolic rate per body weight	AS[a, b]	–
	- remaining differences	2.5	1[f] 2.5[g]
Intraspecies	- worker	5	5
	- general population	10[c]	10[c]
Exposure duration	- subacute to sub-chronic	3	3[h]
	- sub-chronic to chronic	2	2[h]
	- subacute to chronic	6	6[h]
Dose-response	- issues related to reliability of the dose-response, incl. LOAEL/NAEL extrapolation and severity of effect	1[d]	1[d]
Quality of whole database	- issues related to completeness and consistency of the available data	1[d]	1[d]
	- issues related to reliability of the alternative data	1[e]	1[e]

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

Expert-Based Assessment Factors

- 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 considera-tions 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 under-taking a **substance**- and **MOA-specific** RC to arrive at more meaningful and science-based OELs or DNELs.