All OELs and OEL-analogue values aim to protect against adverse effects

How can values for the same substance differ numerically?

WORKSHOP ON BAUA-RESEARCH PROJECT F2437

TOPIC 4: Analysis of Methods

Derivation of occupational exposure limits for airborne chemicals - Comparison of methods and protection levels

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Frameworks investigated

Abbreviation	Framework
REACH	Regulation & guidance for deriving DNELs
RAC	Now responsible for deriving OELs at EU level
SCOEL	Formerly responsible for deriving OELs at EU level
AGS	Responsible for deriving legally binding OELs (AGW) in Germany
MAK Commission	Responsible body for deriving MAK values
ECETOC	Methodological proposal for deriving DNELs
PPP	Directive & guidance for deriving AOELs
BPR	Regulation & guidance for deriving AELs

EU REACH Registration, Evaluation, Authorisation and Restriction of Chemicals
RAC Committee for Risk Assessment,
SCOEL Scientific Committee on Occupational Exposure Limits,
AGS Ausschuss für Gefahrstoffe,
MAK DFG Ständige Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe,
ECETOC European Centre for Ecotoxicology and Toxicology of Chemicals,
EU PPP Plant Protection Products,
EU BPR Biocidal Products Regulation

Preliminary remarks

- The analysis is based on available documentation of the methodology (additional comments, beyond written documentation, received from MAK Commission)
- The need for detailed written methodology is different for OEL committees compared to e.g. REACH (DNEL derivation by many independent actors)
- Project aims at increasing transparency and harmonisation:
  All frameworks have written guidance (although in varying granularity) –
  allows transparent comparison

Definition and scope of values

AELs/AOELs (biocides/pesticides): for workers and other exposed groups

STEL values (15 min) or exceedance factors for OELs, short-term DNELs and similar values in other

OELs and analogue valu
Health-based guidanc
values protecting against adverse effects

Example diglyme
German AGW: 5.56 mg/m³ plus notation Z
RAC DNEL: 1.68 mg/m³

AELs/AOELs

Example diisocyanates
MAK: 3.4 µg NCO groups/m³ (irritation) and notation Sa
RAC: ERR 5% at <1 µg NCO groups/m³ (allergic asthma)
The Netherlands: 0.1 µg NCO groups/m³ (allergic asthma)

developmental toxicity: German AGW/MAK: addressed by notations, values do not necessarily provide protection

Respiratory sensitisation: addressed by many with notations, quantitatively considered by some if data allow

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Key steps of OEL derivation

Data search and evaluation

Differences observed regarding
- Requirements to update with new data
- Requirements for data searches
- Assessment of data quality
- Weighing of human versus experimental data
- Definition of adversity
- Identification of key study/endpoint

can be reduced by more detailed guidance

Determination of the point of departure (POD)

BMD/BMDL or NOAEL or LOAEL?
Limited guidance on use of benchmark approach

Key steps of OEL derivation

Adaptation for exposure conditions

Example for differences:
REACH guidance R.8: „(POD) modifications only apply when there is evidence that … not the concentration drives the appearance of the effect”

Assessment factors

Major source of numerical differences – examples in following slides (time, inter- and intraspecies)
Differences in further factors (e.g. severity of effect, LOAEL-NOAEL) noted

Differences in assessment factors

Time extrapolation for substances acting locally in the respiratory tract

REACH Guidance, AGS, MAK, BPR
Factor
subacute to chronic: 6
subchronic to chronic: 2

ECETOC
Factor 1

Factor 1 is based on the assumption that local irritating effects are purely concentration-driven
Reason for large numerical differences for this class of effects/substances

Differences in assessment factors

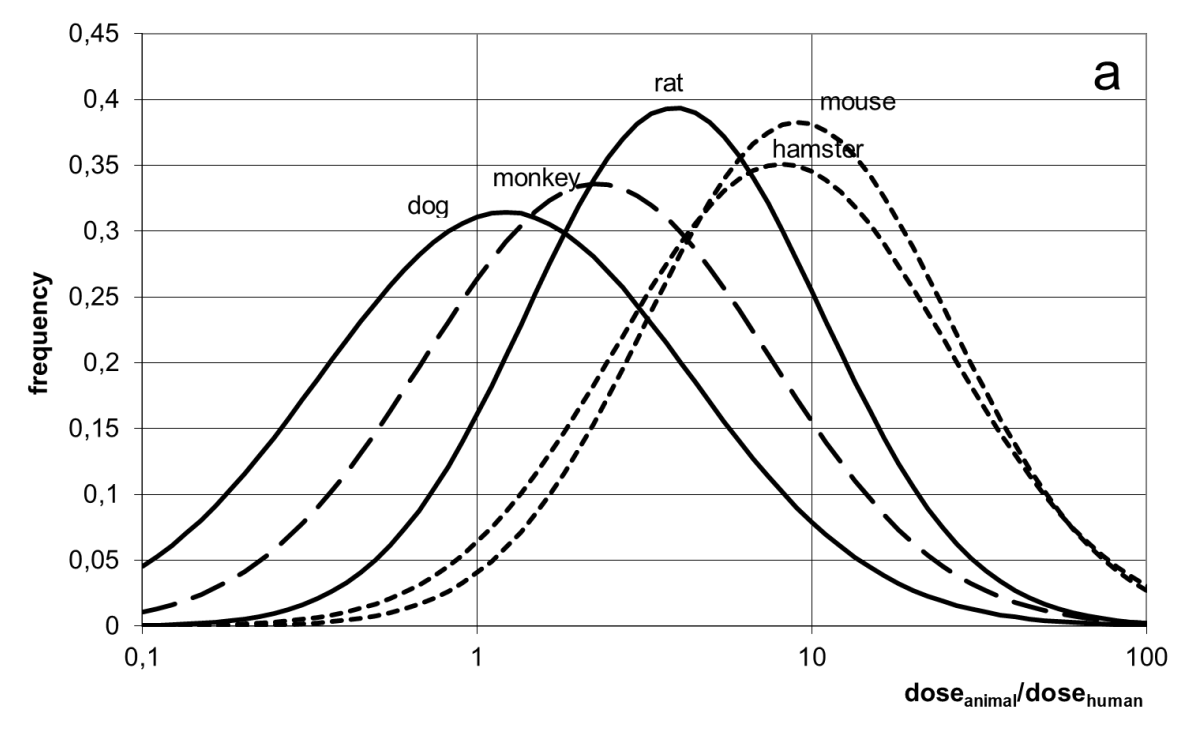
Interspecies extrapolation: allometric concepts or default assessment factor

REACH/RAC, SCOEL, AGS, MAK, ECETOC
Caloric demand scaling +
factor for remaining uncertainties (1–2.5)

PPP, BPR
Factor 10

Convincing theoretical and empirical evidence for allometric scaling
Factor 10 still used in food safety (WHO)
BPR guidance recommends scaling as a second tier approach

Allometric scaling in risk assessment



Species	Body weight (kg)	Scaling factor
Mouse	0.03	7
Hamster	0.11	5
Rat	0.25	4
Guinea pig	0.8	3
Rabbit	2	2.4
Monkey	4	2
Dog	18	1.4

Ratios toxic doses of anti-neoplastic agents in humans versus animals (Schneider et al., 2004; Reg. Tox. Pharm., 39, 334-347)

REACH Guidance on IR and CSA, R.8

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Differences in assessment factors

Intraspecies extrapolation (interindividual differences in susceptibility)

PPP, BPR	REACH/RAC	ECETOC	AGS, MAK	SCOEL
Factor 10	Factor 5	Factor 3	combined inter-intra factor 5 or 2	Factor ≥1

Large range from 1 to 10
Values are not based on empirical data

Further observations

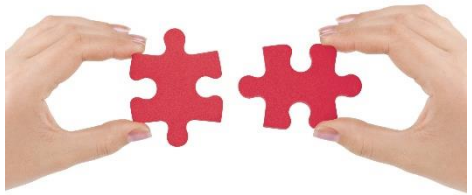
- OEL committees tend to give more priority to human data

Example hydrogen peroxide:
MAK: 0.5 ppm (0.71 mg/m³) (human data)
BPR assessment report: AEL 0.9 ppm (1.25 mg/m³) (90-d rat study)
Both use the other data as supporting evidence

- OEL committees prefer inhalation data and give more attention to local irritative effects, including sensory irritation
- Detailed methodology how to deal with sensory irritation published by Brüning et al. (2014) used in Germany (sensory irritation: effects caused by stimulation of peripheral nerves, e.g., trigeminus)
- Detailed procedure to model deposition of particles in the lower respiratory tract used in Germany („Human equivalent concentration“, MPPD model) – not used as a standard approach by the other frameworks studied

Conclusions and recommendations

- Descriptions of methodology (with varying level of detail) are available for all frameworks
- For increasing transparency further guidance documents should address in detail
  - Requirements for data searches
  - Assessment of data quality
  - Identification of key studies and endpoint
  - Definition of adversity (with examples)
  - Modifications of the POD to adjust to the workers‘ scenario
  - Requirements to update assessments with new data
  - Weighing of human versus experimental data
- The guidance should explicitly address how the benchmark dose approach should be used:
  - Preferred POD: BMD, BMDL
  - Setting of the adequate benchmark response for continuous and quantal data
  - Applicability for various situations/datasets



Key aspects asking for harmonisation

- Definition and scope of values, esp. regarding specific endpoints such as developmental tox and respiratory sensitisation

- Size of assessment factors

- Further aspects:
  - Use of the benchmark dose approach
  - Application of allometric scaling
  - Approach for local effects in the respiratory tract (incl. sensory irritation)
  - Approach for considering interspecies differences in deposition and clearance of particles in the respiratory tract (HEC, „Human equivalent concentration“)