DNELs and OELs

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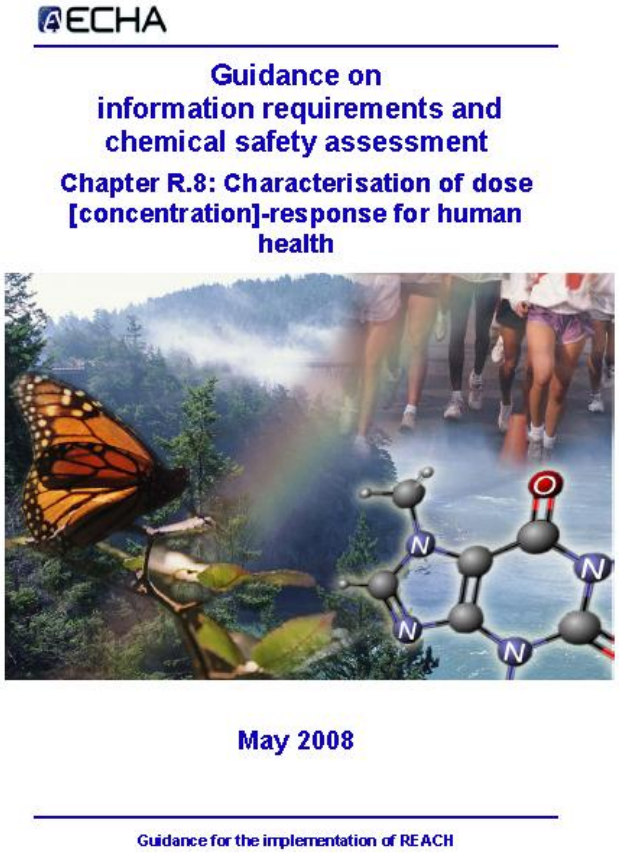
DNELs and OELs

- What is a DNEL?
- NOAEL and LOAEL
- What is an OEL? IOELV?
- OEL as a replacer of DNEL
- Assessment factors
- Default assessment factors in the REACH Guidance
- Use of uncertainty factors by SCOEL
- Comparison between IOELVs and DNELs
- Conclusion

What is a DNEL?

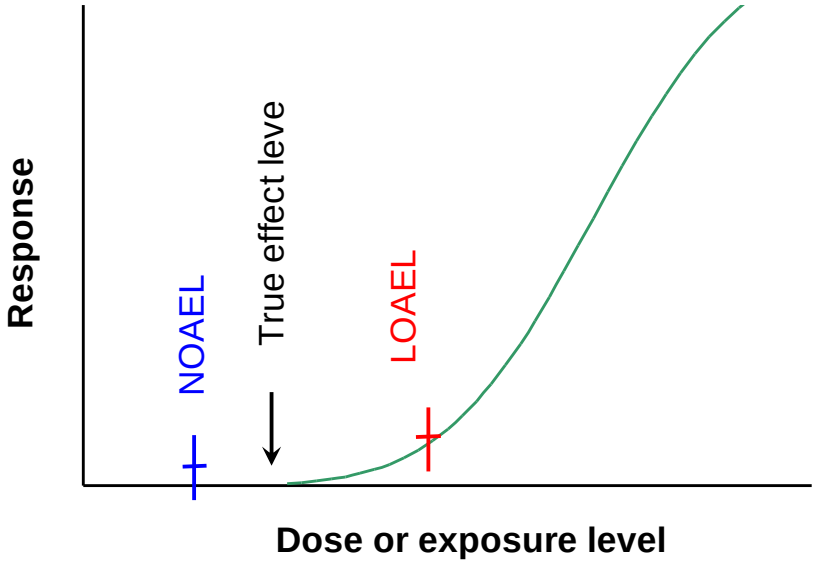


- "DNEL is a level of exposure which should not be exceeded, indicating control "
- "DNEL can be considered as an 'overall' No-(Adverse-)Effect-Level (N(A)EL) for a given exposure (route, duration, frequency)"

?

NOAEL and LOAEL

- NOAEL
  - → No Observed Adverse Effect Level
  - → Highest dose given without any observed adverse effect
- LOAEL
  - → Lowest Observed Adverse Effect Level
  - → Lowest dose given with an observed adverse effect
- NOAEL < “true” effect level < LOAEL



What is an OEL?

- **ACGIH TLV booklet:**
  "…these values are not fine lines between the safe and dangerous conditions and should not be used by anyone who is not trained in the discipline of industrial hygiene. TLVs® are not regulatory or consensus standards…"

- **Swedish statute book on OEL values:**
  "…An OEL value indicates the maximum concentration of an air contaminant below which a person exposed to that contaminant is regarded as protected from ill-health. However…
- …an effort should be made to keep concentrations of all air contaminants as far as possible below the OEL value. .. ?
- …particularly essential if multiple exposures or heavy work…"
- Swedish OELs are legally binding administrative norms

Indicative Occupational Exposure Limit Values (IOELV)

- … health-based, non-binding values, derived from the most recent scientific data available and taking into account the availability of measurement techniques

- …threshold levels of exposure below which, in general, no detrimental effects are expected for any given substance after short term (15-min STEL) or daily exposure (8-h TWA) over a working life time

- Developed by SCOEL, an independent expert group appointed by the Commission

- Public consultation → Tripartite committee → Commission → EU Directive

Member state implementaion of OELs

- When an indicative value (IOELV) has been established, member states must establish a national OEL in accordance with national legislation and practices
- The national OEL can be higher or lower than the IOELV
- When a binding value (BOELV) has been established, Member States must establish a corresponding national OEL
- The national OEL can be lower than the BOELV, but not higher.
- Member States may also set national OELs for additional substances
- National legislation and approcahes differ
  - → in some cases the OELs are purely health based values
  - → in other cases they take into account feasibility factors
- ~ 100 IOELVS in the EU, plus ~ 70 draft proposals
- 600 national OELs in total in the member states

OEL as a replacer of DNEL

- When an IOELV exists the registrant may use it in place of developing a DNEL
- Alternatively the registrant should, in accordance with the requirements of REACH, derive a DNEL
- A registrant is allowed to use an IOELV as a DNEL for the same exposure route and duration, unless new scientific information does not support the use of the IOELV. This could be because

  → the information obtained is more recent than the information that was used to support setting the IOELV

  → it leads to another value being derived which requires different risk management measures and operational conditions

How do OELs compare with DNELs derived according to the REACH guidance?

Assessment factors

- Assessment factors (AF) are used to derive a DNEL, guidance value or limit value departing from toxicological data such as the NOAEL (or LOAEL)

Limit value = NOAEL / AF

- Also called safety factors or uncertainty factors

- Different AFs are used depending on the type of the extrapolation, e.g.
  → from animals to humans
  → from a small group to the general or working population

Default assessment factors in the REACH Guidance

- For workers, default assessment factor of 5 is to be used, based on the fact that this subpopulation does not cover the very young, the very old, and the very ill

Variability among workers, AF = 5

- Default AFs may be replaced by higher or lower AFs if specific information exists

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]

Subacute: 28 d study

Subchronic: 90 d study

Chronic: 1.5-2 y study

Allometric scaling factors

- From animal to man, assuming a 70-kg man
- Not applicable when inhalation animal study

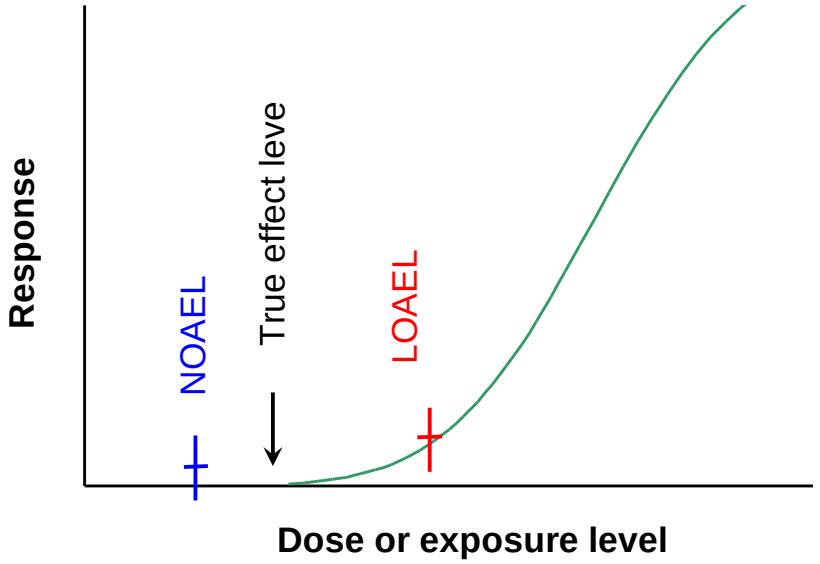
Species	Body weight (kg)	AS factor[b]
Rat	0.250	4
Mouse	0.03	7
Hamster	0.11	5
Guinea pig	0.8	3
Rabbit	2	2.4
Monkey	4	2
Dog	18	1.4

Default assessment factors in the REACH Guidance

- When the starting point is a LOAEL, use AF between 3 (majority of cases) and 10 (exceptional)

  LOAEL to DNEL, AF = 3 (to10)

  depending on the:
  - → dose spacing in the experiment,
  - → shape and slope of the dose-response curve,
  - → extent and severity of the efect seen at the LOAEL



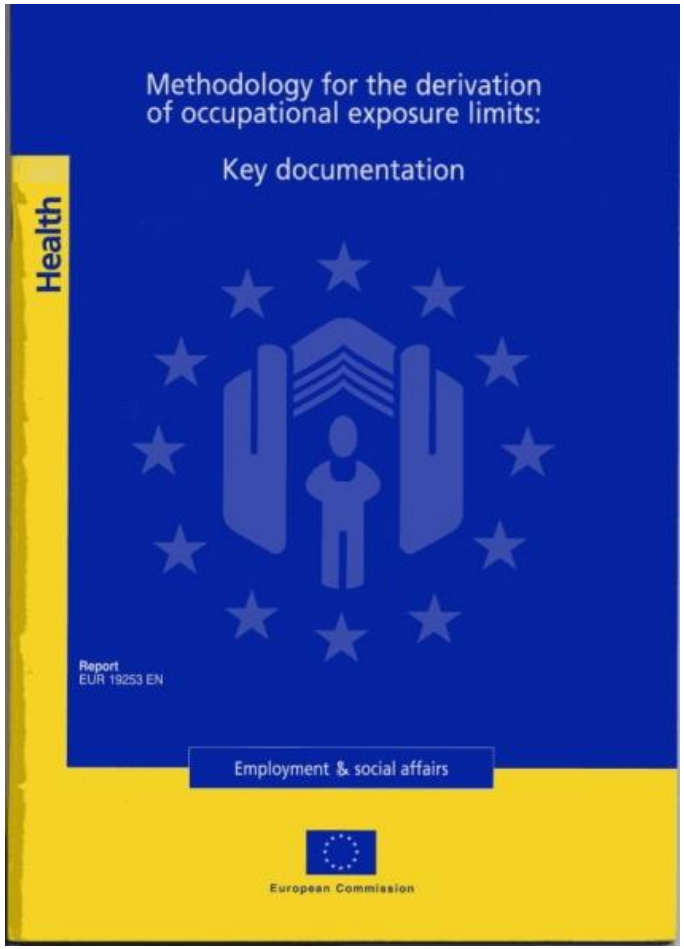
- In absence of specific info, use default AF of 2 for oral to inhalation extrapolation

  Oral to inhalation, AF = 2

Default assessment factors in the REACH Guidance

- Additional AF considerations discussed in the Guidance, e.g.
  - → Use of Benchmark Dose calculations
  - → Use of PBPK models
  - → Only acute tox data (LC50 / LD50) available
  - → Read-across from chemically related substances
  - → Etc.

Use of uncertainty factors by SCOEL



1. In practice, the scientific data base (to set an OEL) is not ideal. SCOEL deals with this by using UFs
2. No generally accepted method to derive UFs when setting OELs
3. For several reasons, lower UFs can be used for OELs than for limit values for the general population
4. UFs are set on a case by case basis
5. …Generally, less reliable data leads to a higher UF
6. SCOEL should motivate the choice of UF in the recommendation

IOELV vs DNEL: Toluene

- SCOEL 1999

The data from performance studies suggest that the first effects are found at concentrations of about 75 ppm (237 mg/m^3) (LOAEL); this applies for short-term effects (Echeverria *et al.*, 1989) and long-term effects (Foo *et al.*, 1990). Ørbaek and Nise (1989) reported about first effects at levels below 50 ppm (191 mg/m^3). However, the higher toluene concentrations to which those printers had been exposed in the long term had not been assessed individually. In this context, the absence of reproducible effects found in repeated performance tests with persons exposed long-term to higher concentrations (62 ppm - 237 mg/m^3) in spite of simultaneous noise exposure (Kempe *et al.*, 1980) must be taken into account. The data available for subjective effects of toluene (effects on how the persons feel) suggest that the LOAEL is about 60 ppm (230 mg/m^3).

Overall, a great deal of human data are available, which produce no reliable evidence of effects at or below toluene concentrations of 50 ppm (192 mg/m^3). Therefore the SCOEL considers 50 ppm (192 mg/m^3) to be an appropriate level for the 8 hour TWA.

Overall UF = 1.2

- DNEL derivation

LOAEL to DNEL x Variability among workers

Overall AF = 3 x 5 = 15

IOELV vs DNEL: N,N-Dimethylacetamide

- SEG 1994

The study of Horn (1961), establishing a LOAEL of 40 ppm (145 mg/m³) for slight irritation of the respiratory tract of rats and dogs, was considered to be the best available basis for proposing occupational exposure limits. An uncertainty factor of 5 was considered appropriate because of the absence of a NOAEL. Taking into account the preferred value approach, and the minimal nature of the effects, the recommended 8-hour TWA is 10 ppm (36 mg/m³).

Overall UF = 5 (or 8)

- DNEL derivation

LOAEL to DNEL x Animal to human x Variability among workers

Overall AF = 3x2.5 x 5 = 37.5

IOELV vs DNEL: 2-(2-Methoxyethoxy)ethanol (DEGME)

- SEG 1994

… In the developmental study with rabbits and dermal application a NOEL of 50 mg/kg bw. was obtained. Assuming a similar (100%) absorption after oral, inhalative and dermal exposure and a 8 h inhalation volume of 10 m3 at the workplace 50 mg/kg bw. correspond to 70 ppm. For interspecies extrapolation regarding systemic effects it should be noted that presumably the metabolites of DEGME have a longer half-live in humans than in animals. As shown for 2-ethyoxyacetic acid the half-live is 6-fold longer in humans than in rats. As a worst-case approach it is assumed that the effects of DEGME are governed by the time-concentration product. The dose per kg bw for workers should therefore be accordingly lower than the NOEL of 50 mg/kg bw obtained in the animal experiment. Considering the difference in the DEGME metabolite between animals and man a factor of 5 is applied resulting in an OEL of 10 ppm.

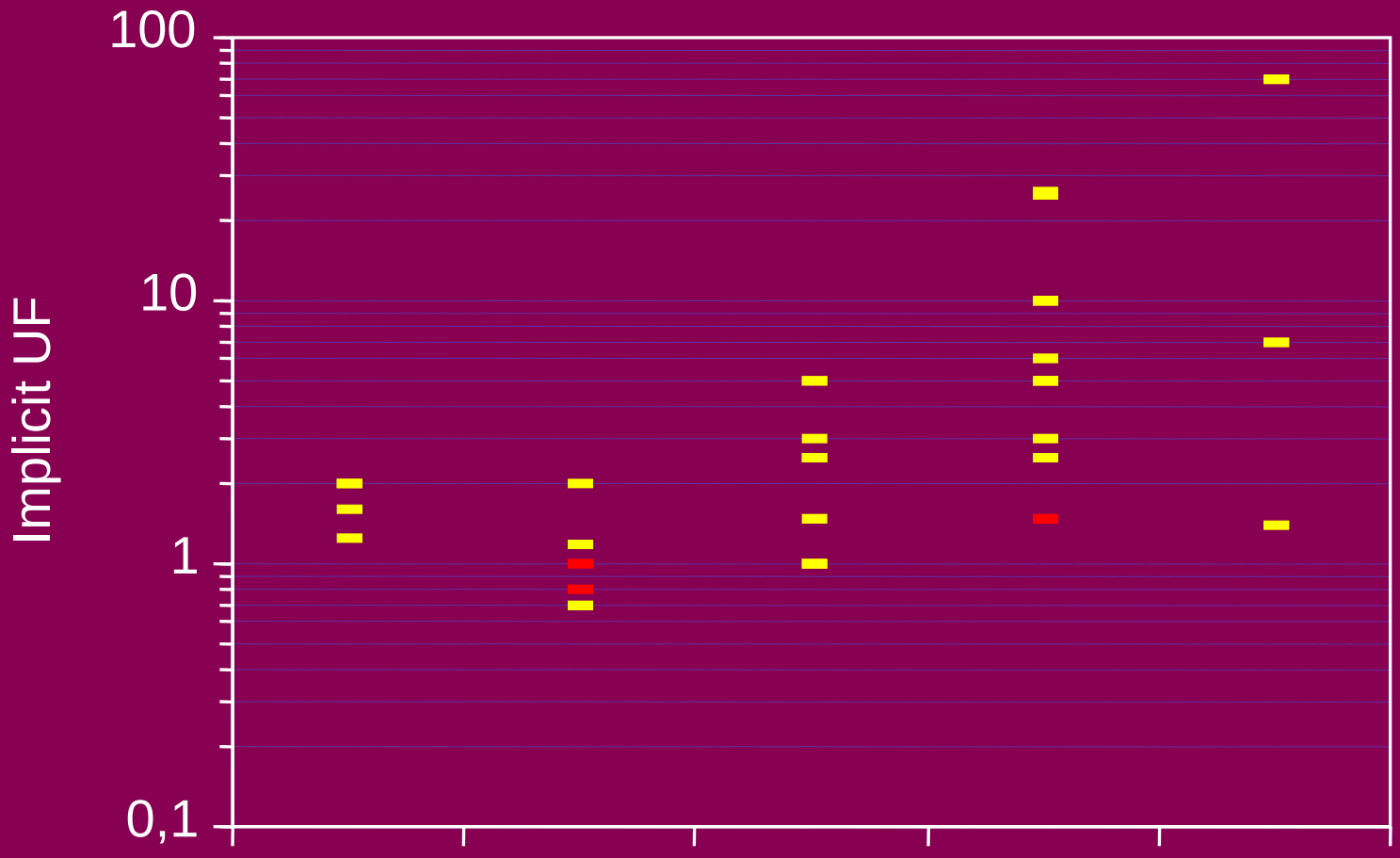
Overall UF = 5 (or 7)

- DNEL derivation

Oral to inhalation x Rabbit to human x Variability among workers

Overall AF = 2 x 2.4 x 5 = 24

Implicit uncertainty factors in some SCOEL summary documents (ratio between recommended OEL and effect level in key paper)



	Human Inhal NOAEL	Human Inhal LOAEL	Animal Inhal NOAEL	Animal Inhal LOAEL	Animal Oral NOAEL
DNEL overall assessment factor	**1-5**	**3-30**	**12-35**	**36-350**	**24-70**

Conclusion

- Different frameworks, but
- Same toxicology and RA principles
- DNEL derivation is dificult, practical experience needed
- Risk for confusion, when OEL ≠ DNEL

Conclusion:
DNEL and OELs - different frameworks but same toxicological principles

- **IOELVs**
  - → Based on EU minimum directives
  - → Derived via concensus expert judgement (SCOEL summary docment)
  - → Decided by the Commission
  - → To be implemented at national level
  - → Qualitative instructions how to derive OEL, case-by-case use of AF

- **National OELs**
  - → Based on different national legislations
  - → Some are derived via concensus expert judgement (e.g. MAK, DECOS, Sweden)
  - → Decided by national government or authority
  - → Used to check that employers comply with legislation and healthy work environment
  - → Some use AFs (e.g. DECOS)

- **DNELs**
  - → Based on REACH legislation
  - → Derived by importer/manufacturer
  - → Used for comparison with exposure scenarios
  - → Detailed ”semi-quantitative” instructions how to derive DNEL, including choice of AF
  - → Several DNELs may be derived for same chemical