OELs protect against adverse effects

Even the most susceptible individuals?
Under all circumstances?
What level of protection do we strive to achieve?

WORKSHOP ON BAUA-RESEARCH PROJECT F2437

TOPIC 7: Protection levels

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

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Protection levels

- Which percentage of the target population do we aim to protect?
- How do we deal with uncertainties in our assessment? What probability do we want to obtain that the values are conservative enough?

Use of deterministic assessment factors

- Deterministic assessment factors (AFs) as currently used are (partly) based on empirical data
  - At which percentile of the underlying distributions should we set AFs?
  - What results from combining such AFs?
  - What is the consequence for the final OEL?

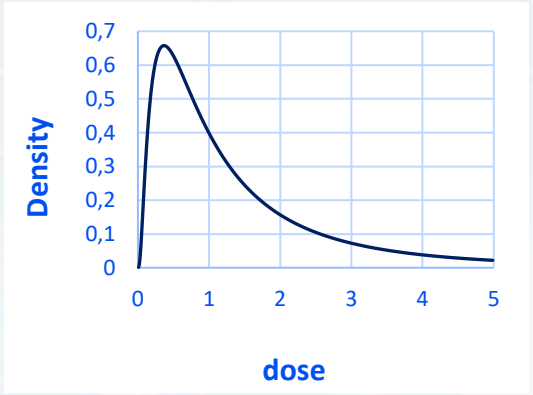
- These questions can be answered by a probabilistic approach

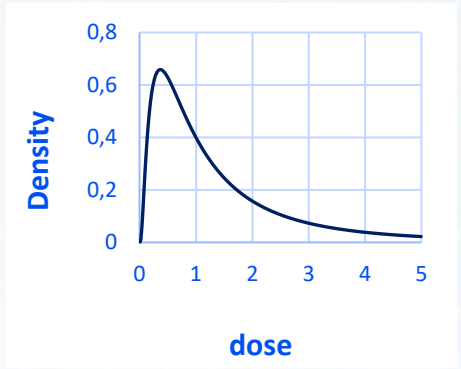
As asked for by ECETOC (2020)
(Technical Report No. 136)

Determinstic OELs

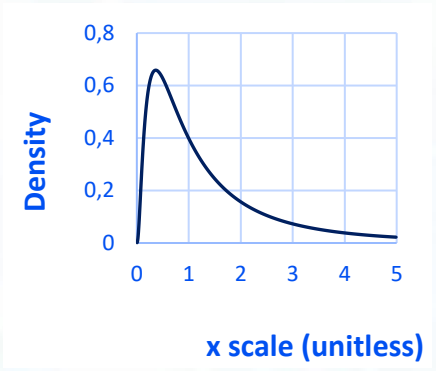
$$OEL = \frac{POD}{AF_1 * AF_2 * AF_3 * \cdots}$$

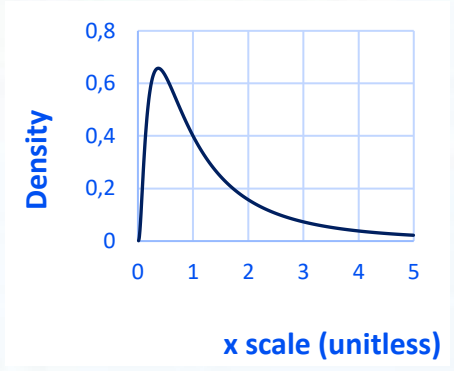
Probabilistic approach

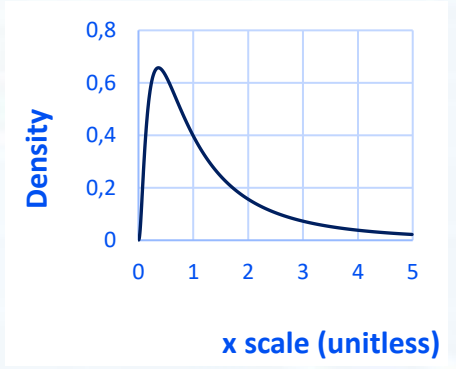




$$OEL = \frac{POD}{AF_1 * AF_2 * AF_3 * \cdots}$$







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Probabilistic OEL distribution

- Probabilistic modelling by Monte-Carlo simulation
- Ready-to-use tools, e.g. by EFSA (https://r4eu.efsa.europa.eu/)
- Intraspecies extrapolation:
  - two different distributions (for covering 95% or 99% of the population) result in two final distributions for the OEL, associated with different definitions

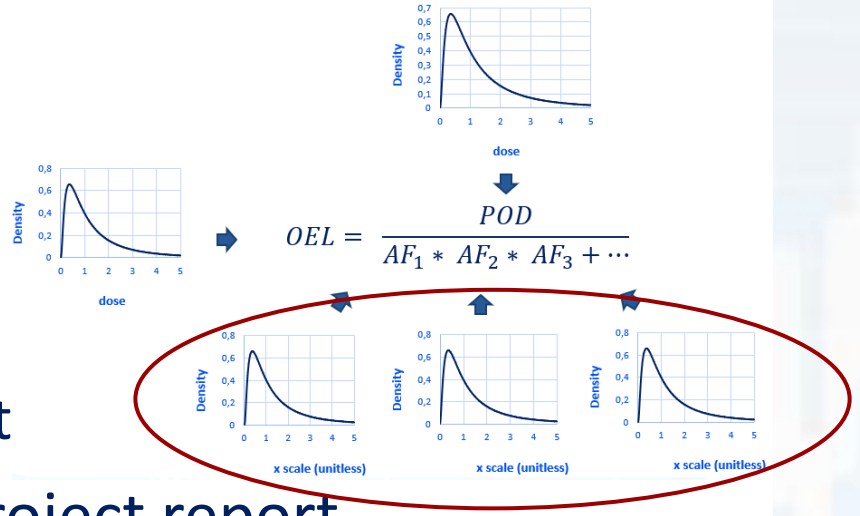
OEL distribution for 99% of population:

describes the probability that the effect as defined by the POD is not exceeded in 99% of the exposed population

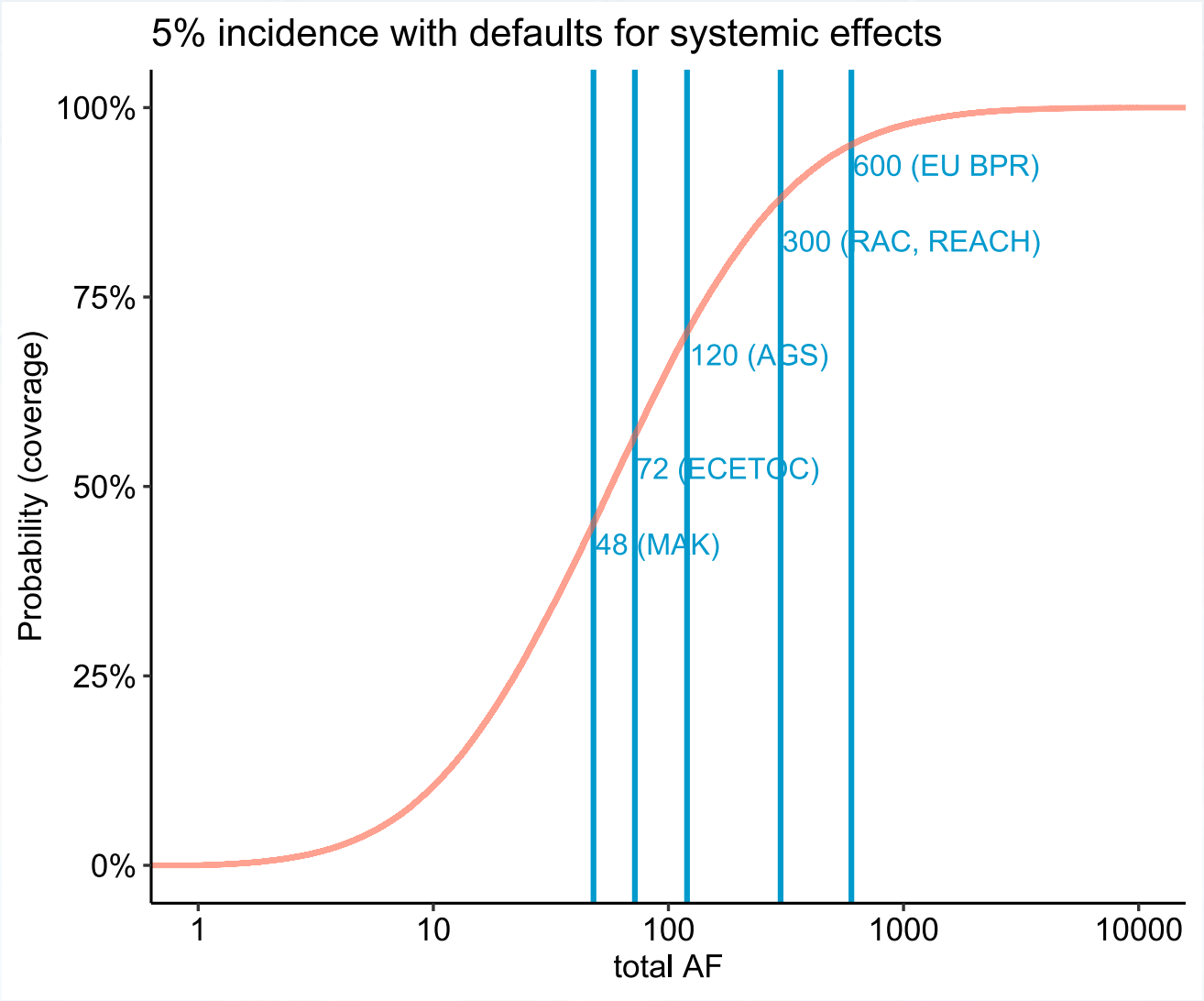
Combinations of AFs

- With what probability the combined AF of a certain framework is large enough to cover the uncertainty (i.e. substance-to-substance variability)?

- Case for illustration:
  - Starting point is a subacute rat study
  - Coverage of 95% of target population
  - With systemic or local effects as the critical endpoint
- Results for other starting points are given in the project report



POD subacute oral rat study – systemic effects



BPR AF 600:
6 (time extrapolation)
10 (interspecies)
10 (intraspecies)

MAK AF 48:
6 (time extrapolation)
4 (allometric scaling)
2 (inter- and intraspecies)

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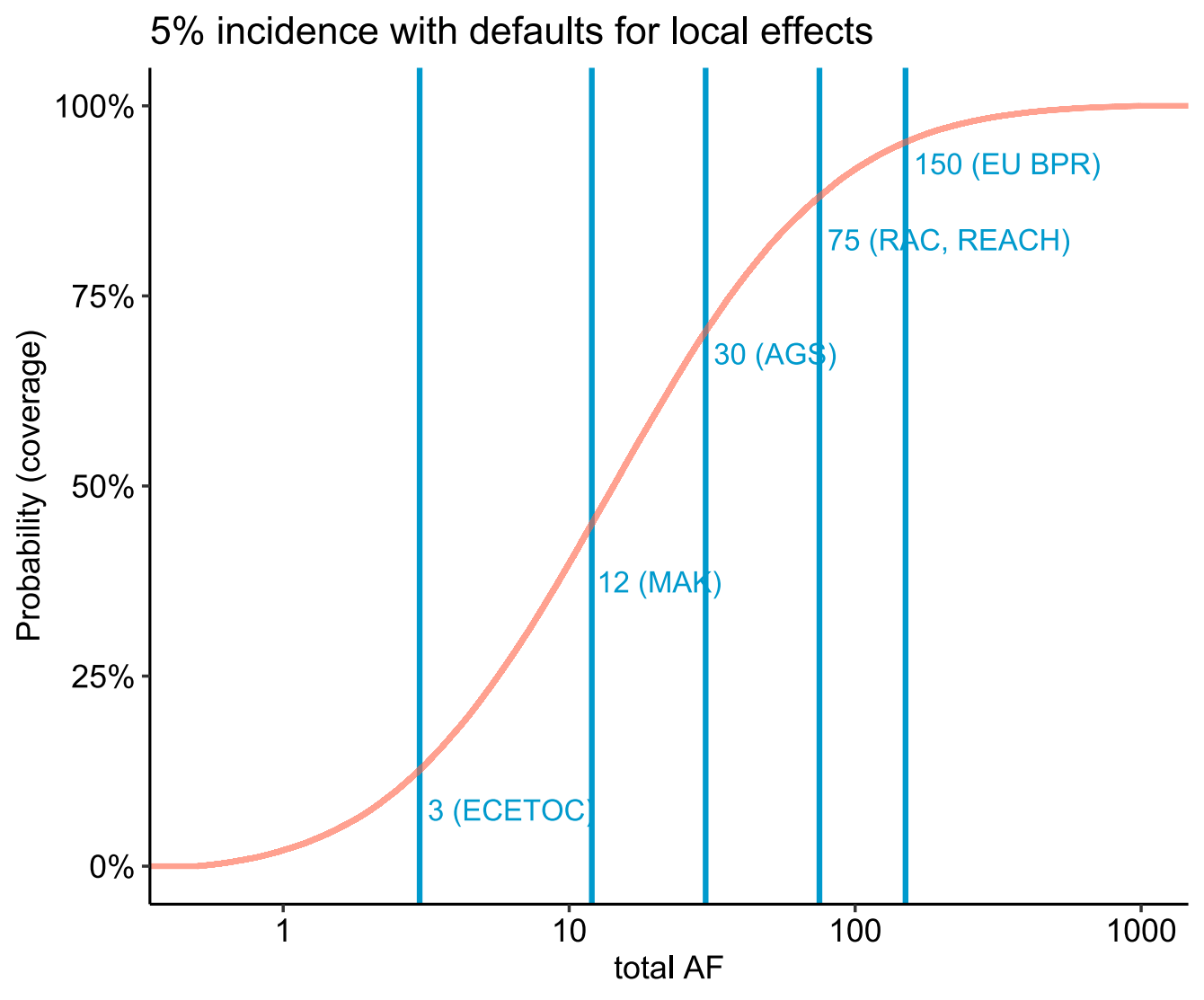
POD subacute inhalation rat study – local effects



REACH AF 75:
6 (time extrapolation)
2.5 (interspecies)
5 (intraspecies)

ECETOC 3:
1 (time extrapolation)
1 (interspecies)
3 (intraspecies)

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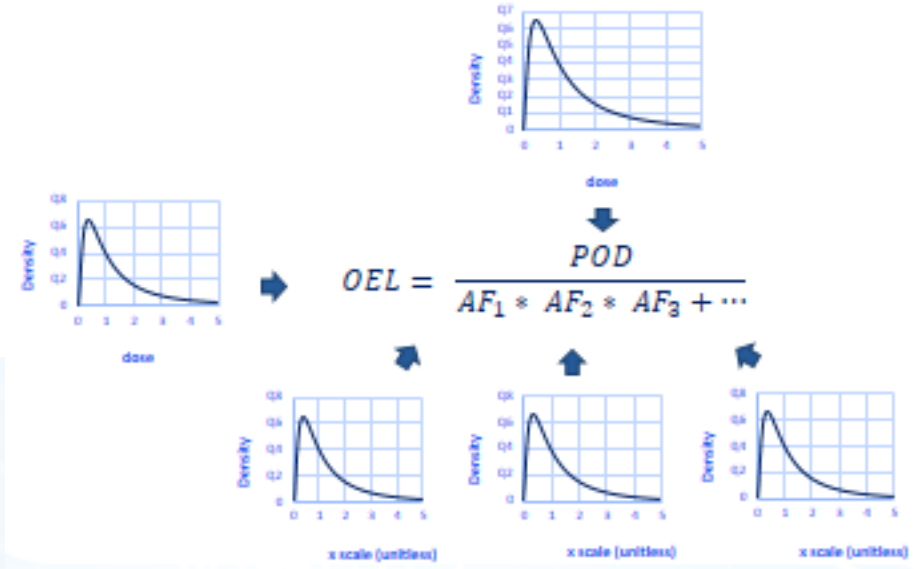
Ranking according to probability for covering uncertainty

BPR (≈ PPP) > RAC/REACH > AGS > MAK ≈ ECETOC

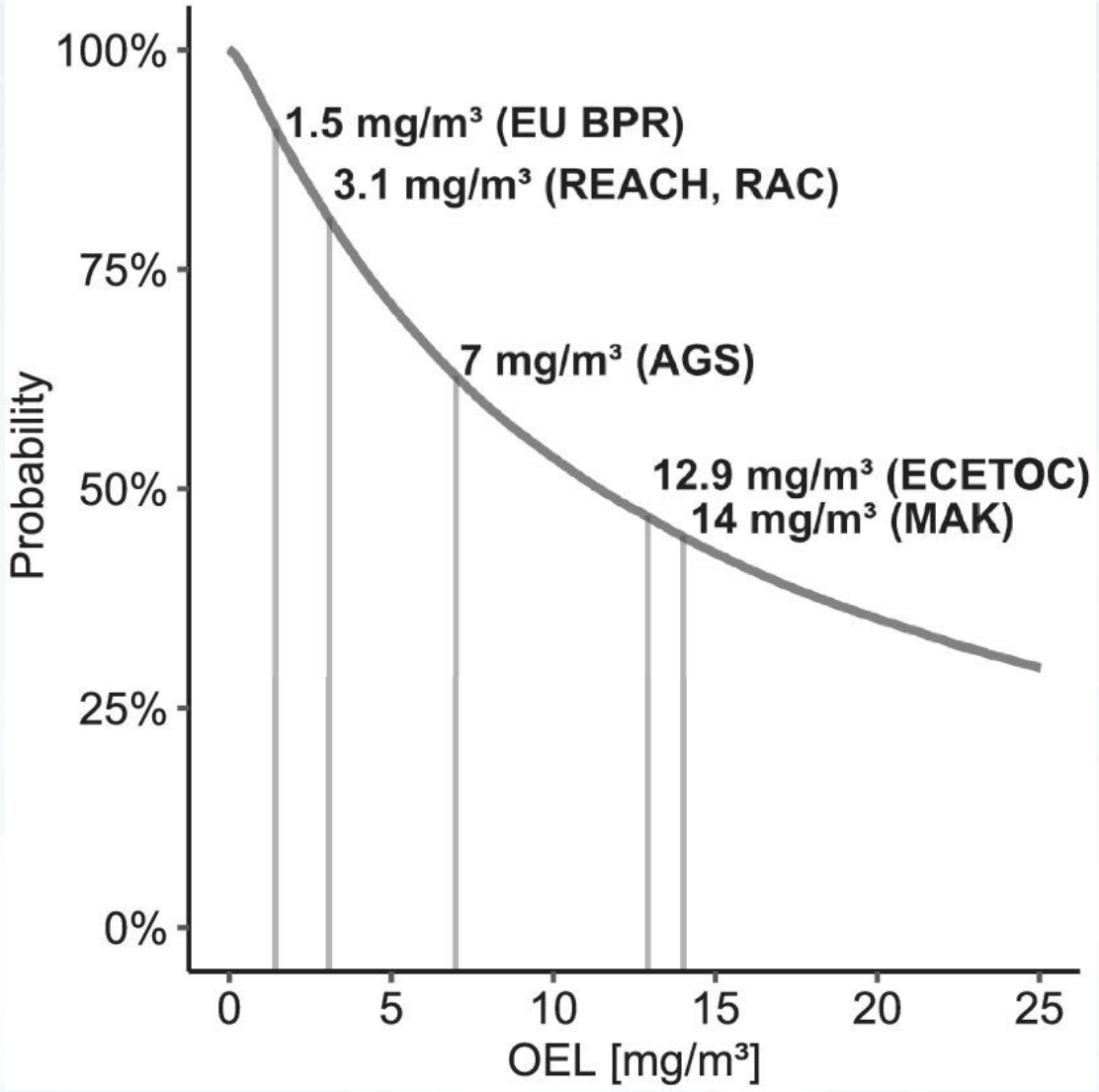
Complete probabilistic assessment

- All input variables described as distributions
- Convert BMD result in distribution (with BMDL and BMDU, assume lognormal distribution)
- Combine all distributions by Monte-Carlo simulation
- Two examples
  - 1,1,2,2-tetrachloroethane – subchronic oral rat study, continuous data: liver weight
  - Benzoic acid – subacute rat inhalation study

    quantal data: lung inflammation



Example 1,1,2,2-tetrachloroethane



Probability for covering 99% of the target population

Note:

BMDL higher than NOAEL

(49.3 versus 20 mg/kg bw/d)

→ Leads to higher probabilities for deterministic OELs

Schneider et al., 2022; J. Appl. Tox., DOI: 10.1002/jat.4307

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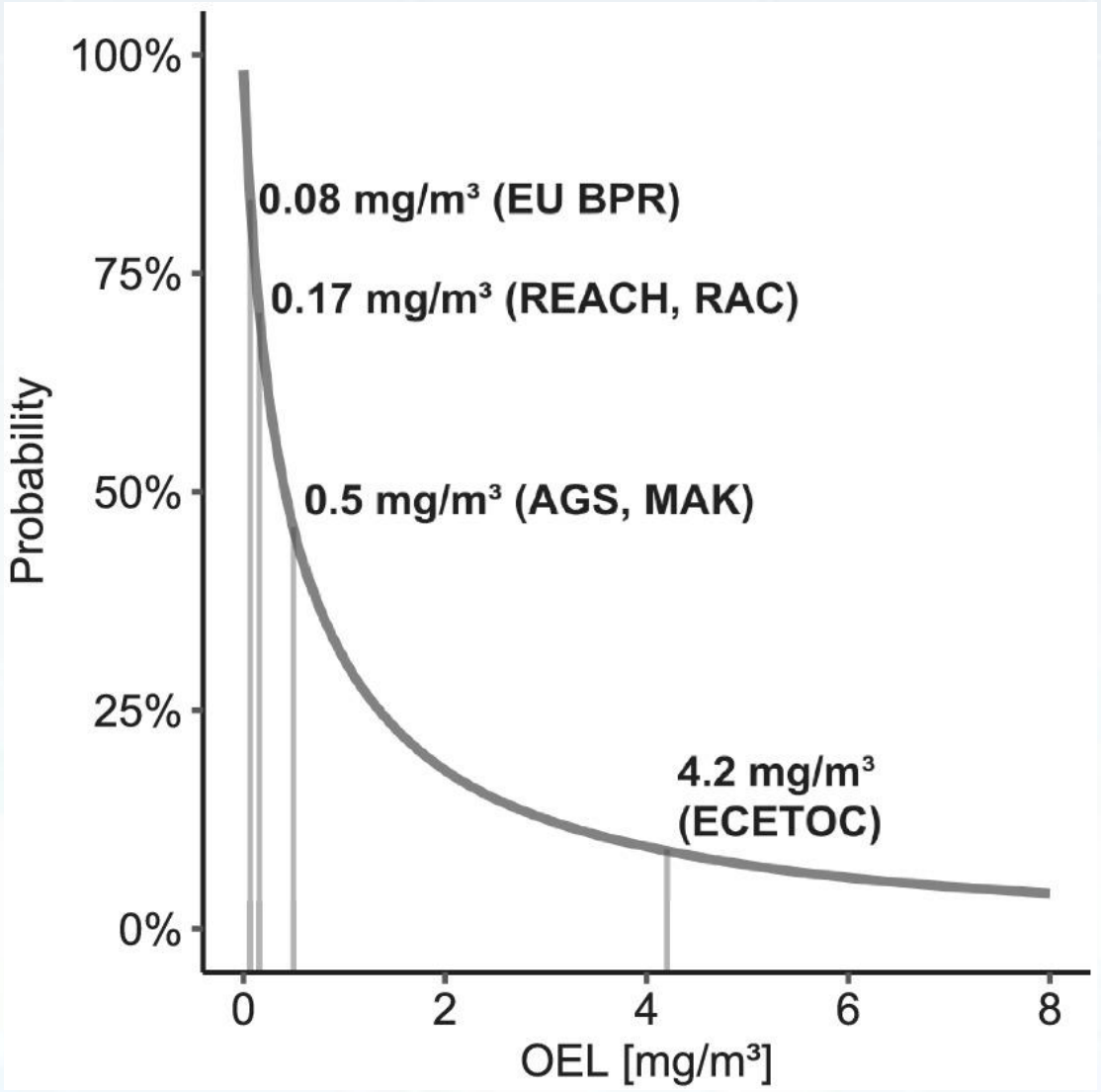
Example benzoic acid



Schneider et al., 2022; J. Appl. Tox., DOI: 10.1002/jat.4307

Probability for covering 99% of the target population

Note:

different PODs were used for REACH/RAC, BPR, ECETOC (12.6 mg/m³) versus AGS, MAK (6.3 mg/m³)

"However, these modifications would only apply when there is evidence that the inhaled dose or duration of exposure, and not the concentration, drive the appearance of the effect" (ECHA Guidance R.8)

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Conclusions

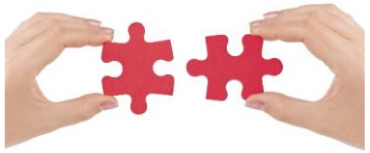
- Protection levels are described as the probability that a predefined percentage of the target population is covered by the OEL (effect as defined by POD)

  → Recommendation: frameworks should clearly define their protection goals

  Which fraction of the exposed population is intended to be covered by the OEL?

  With what probability the OEL intends to avoid adverse effects (as defined by the POD)?

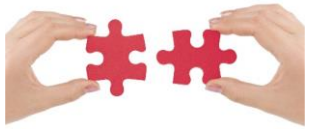
- Assessment factors as currently used in the investigated frameworks vary largely with regard to protection levels achieved, for example
  - for local effects:
    - from 6.5 to 85.6% (subacute study, 99% of target population),
    - from 13.3 to 95% (subacute study, 95% of target population),
  - for systemic effects:
    - from 28 to 85.6% (subacute study, 99% of target population)
    - from 45 to 95% (subacute study, 95% of target population)



Conclusions

- Probabilistic assessments of two examples show how distributions can be used to investigate protection levels and uncertainties of OELs. The probabilistic approach can be used for comparing existing methodologies

- Examples also show that selection and modification of POD can be important sources of differences of OELs



- The benchmark approach can be used to describe the uncertainty of the POD, which is a further advantage of the BMD as a POD