BAuA project F 2437:
Derivation of occupational exposure limits for airborne chemicals - Comparison of methods and protection levels

Institutetreffen „Grenzwertsetzung” 2021

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Project output - reports

- **10 reports**
  - Comparison of methods for deriving OELs
  - Benchmark dose modelling (with seperate report on examples)
  - Probabilistic hazard assessment
  - Route-to-route extrapolation
  - Time extrapolation
  - Interspecies extrapolation
  - Intraspecies extrapolation
  - Human equivalent concentration and kinetic modelling of aerosols in the lower respiratory tract
  - Synthesis report: Modelling of distributions of assessment factors, comparison with current methods and discussion of protection goals
- Available at https://www.baua.de/EN/Tasks/Research/Research-projects/f2437.html

Overall objectives

- Analyse and compare existing frameworks for deriving occupational exposure limits (OELs)
- Discuss differences between methods and protection levels achieved
- Improve empirical database for extrapolations
- Contribute to transparency and harmonisation of approaches

Major project steps

- Detailed analysis and comparison of methods to derive
  - German OELs (AGS and MAK)
  - EU OELs (RAC – DG Employment)
  - EU OELs (SCOEL – DG Employment)
  - AOELs and AELs (EU Plant Protection Products and Biocidal Products Regulation)
  - DNELs (ECHA - REACH)
  - DNELs (ECETOC - REACH)
- Analyse empirical datasets:
  - NTP studies and REACH data → time, interspecies extrapolation
  - Literature data → intraspecies extrapolation
- Develop (new) distributions for extrapolation steps and compare with literature
- Analyse protection levels achieved by organisations with probabilistic methods
- Develop recommendations for increasing transparency and harmonisation

Key characteristics and differences

	REACH Regulation (DNELs for workers)	RAC OEL metho-dology (OELs at EU level)	SCOEL (OELs at EU level)	AGS (German OELs)	DFG MAK (German OELs)	ECETOC (DNELs for workers)	Plant Protection Products Directive (AOELs for opera-tors, bystanders and residents)	EU Biocidal Products Regulation (AELs for prof. and non-prof. users)
Target populations	Workers only	Workers only	Workers only	Workers only	Workers only	Workers only	Workers (operators) and others	Workers (professional users) and others
Unit	mg/m³ or ppm	mg/m³ or ppm	mg/m³ or ppm	mg/m³ or ppm	mg/m³ or ppm	mg/m³ or ppm	mg/kg bw/day	mg/kg bw /day
Developmental toxicity considered?	yes	yes	(yes)*	No – pregnancy group notation	No – pregnancy group notation	?	yes	yes
Respiratory sensitis. considered?	only qualitative	Yes, plus sensitisation notation	If data allow, plus sensitisation notation	No, , sensitisation notation	No, , sensitisation notation	Not mentioned	Not mentioned	only qualitative

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Default AF for time extrapolation	sa** – c: 6 sa – sc: 3 sc – c: 2	sa** – c: 6 sa – sc: 3 sc – c: 2	No	sa** – c: 6 sa – sc: 2 sc – c: 2	In practice, same factors applied as AGS	sa** – c: 6 sa – sc: 3 sc – c: 2 for local effects: all factors = 1	sc** – c: 2	sa** – c: 6 sa – sc: 3 sc – c: 2
Allometric scaling for interspecies extrapolation	Yes, exponent 0.75	Yes, exponent 0.75	Yes, exponent 0.75	Yes, exponent 0.75	Yes, exponent 0.75	Yes, exponent 0.75	No	No, but can be used to replace default AF
Default AF for interspecies extrapolation	2.5	2.5	No default provided	Inter + Intra = 5	Inter + Intra = 2	1	10	10
Default AF for intraspecies extrapolation	5	5	>=1	see above	see above	3	10	10

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Distributions for extrapolations

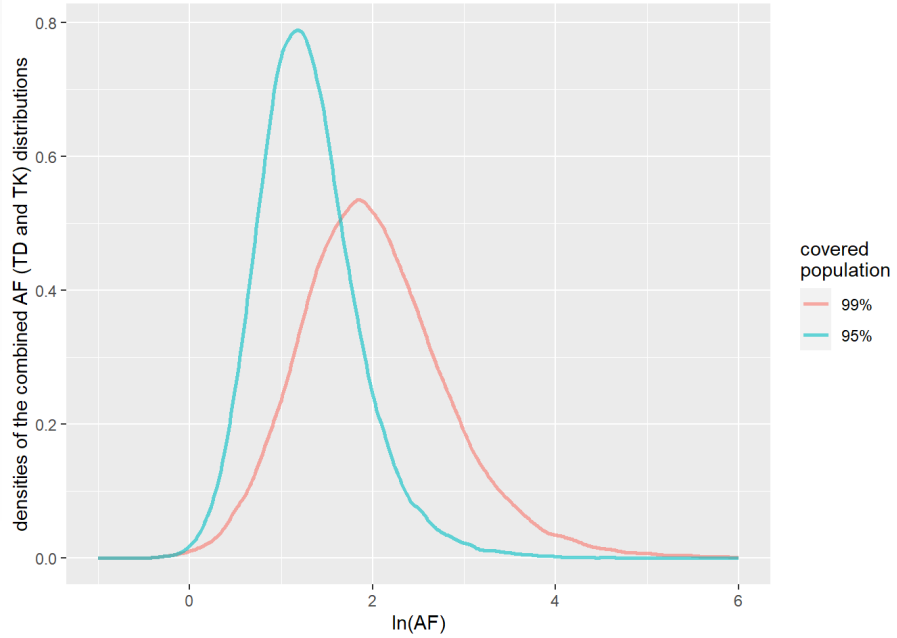
- Existing knowledge and size of extrapolation factors (time, interspecies) largely confirmed
- Improved database regarding local effects in the respiratory effects:

  No differences between local and systemic effects regarding time and interspecies extrapolation
- Differences between species according to allometric scaling confirmed
- New datasets and new distributions proposed for intraspecies extrapolation

Distributions for intraspecies extrapo

Slightly lower variability, but not clear enough for deriving separate distributions, should be further investigated

- Separate data analysis for toxicokinetics and –dynamics
- Toxicokinetics: 68 datasets from human studies, 31 for inhalation
- Toxicodynamics: based on analysis of in vitro data by Abdo et al. (2015) (“1000 Genomes Project”): in vitro cytotoxicity for 179 chemicals in 1086 human lymphoblastoid cell lines from individuals from five continents and nine populations
- Both distributions combined:



Incidence	GM	GSD	5%	Median	75%	95%
1 %	7.8	2.4	2.3	7.3	12.5	34.3
5 %	3.8	1.8	1.7	3.6	5.2	10.4

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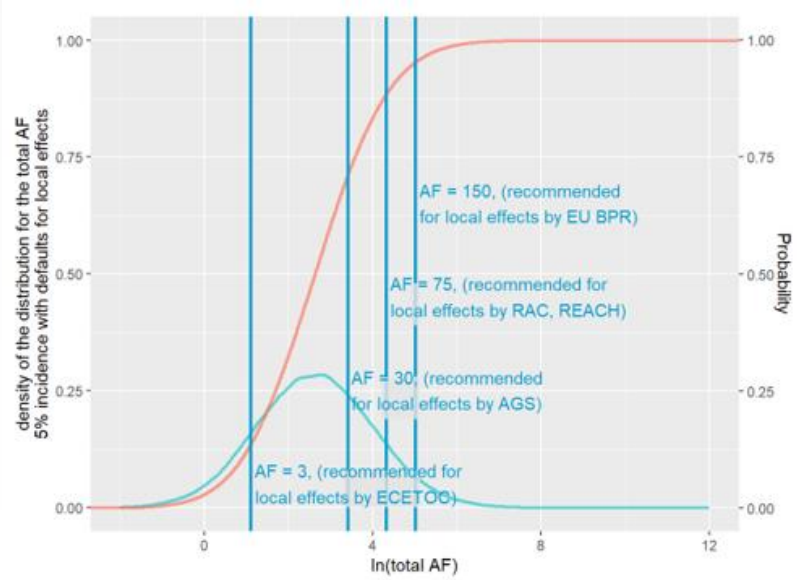
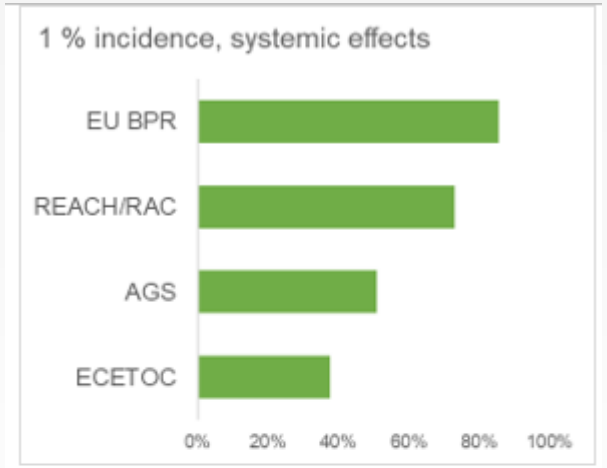
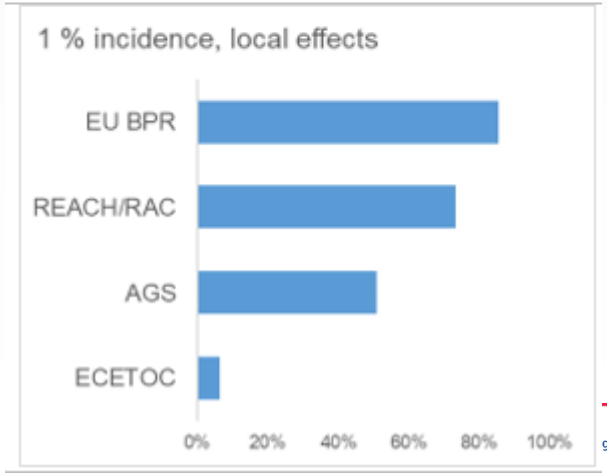
Protection levels

- Sequence from high to low „coverage“ (probability that factors are high enough to achieve protection goal):
  - BPR/PPP > RAC/REACH > AGS > MAK > ECETOC
- Large differences regarding “Intraspecies extrapolation”
- ECETOC: no AF for time extrapolation in case of local effects

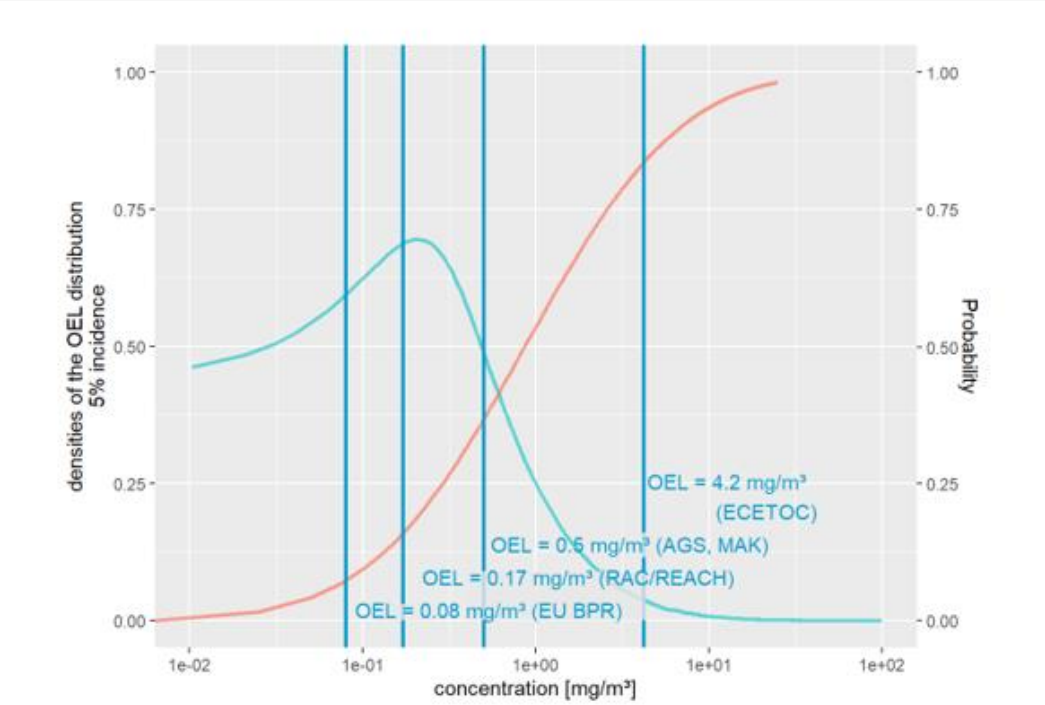






Two probabilistic examples

- 1,1,2,2-tetrachloroethane and benzoic acid, compared to recent evaluations performed in Germany by MAK and AGS
- Probabilistic modelling with EFSA Monte Carlo tool https://shiny-efsa.openanalytics.eu/app/montecarlo
- BMD distribution (log normal assumed)
- Similar conclusions with regard to AF
- BMDL can deviate substantially from NOAEL



Key recommendations

- **Recommendation 1:**
- All OEL derivation frameworks should clearly define their protection goals by stating:
  - The fraction of the exposed population covered by the OEL
  - The probability with which they intend to provide protection from adverse effects (as defined by the POD)

- **Recommendation 2:**
- Benchmark dose modelling should be used as the default procedure to derive a POD

- **Recommendation 3**:
- Probabilistic models should be further developed and used for benchmarking against deterministic methodologies to test them

- **Recommendation 4:**
- Increasing and improving the database on inter-individual variability in human inhalation studies might allow to establish route-specific distributions for intraspecies variability.

Ongoing activities

- Two publications in preparation
- Workshop presenting the project planned for beginning of next year

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THANK YOU FOR YOUR ATTENTION