WORKSHOP at SOT 2023

Shedding Light on Population Variability and Susceptibility: New Approach Methods to Inform Risk Assessment

Empirical Data Describing Interindividual Variability: Comparison with Intraspecies Assessment Factors Used for Deriving Health-Based Guidance Values

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Interindividual variability and health-based values

- However, despite similar definitions, values for one substance sometimes deviate substantially in numbers
- One important reason, among many, is the lack of information on interindividual variability

Content

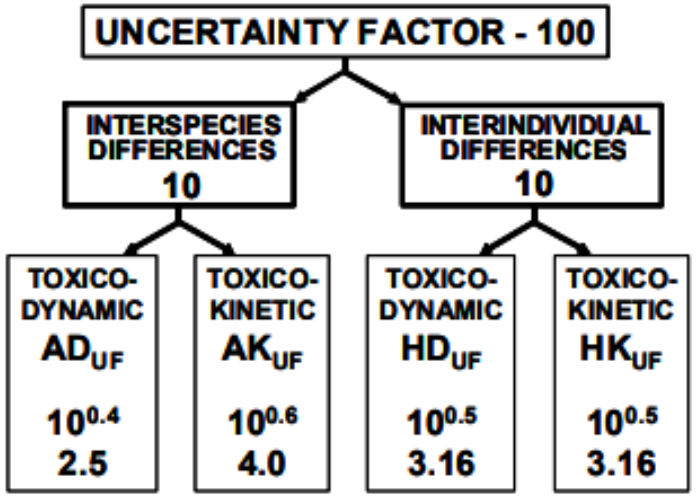
- Regulatory toxicology perspective and historical background
- Project F2437:
  - Empirical data on toxicokinetic variability
  - Empirical data on toxicodynamic variability
  - Distribution for intraspecies extrapolation and comparison with assessment factors used
- Conclusions and outlook

Historical background

In 1954 Lehman and Fitzhugh (US FDA) proposed to apply factors 10 x 10 to account for uncertainty regarding inter- and intraspecies extrapolation

Lehman, AJ; Fitzhugh, OG; 1954; 100-fold margin of safety
Quarterly Bulletin. Association of Food & Drug Officials of the United States, ISSN: 0004-5721

Historical background



AD_{UF} = Uncertainty factor for animal to human differences in toxicodynamics
AK_{UF} = Uncertainty factor for animal to human differences in toxicokinetics
HD_{UF} = Uncertainty factor for human variability in toxicodynamics
HK_{UF} = Uncertainty factor for human variability in toxicokinetics

Figure S-1. Subdivision of the usual uncertainty factor of 100 used in setting guidance values for the exposure of the general population, such as ADIs, TDIs or RfDs. Different numerical values could be derived if the usual total default uncertainty factor were not 100 — for example, in the risk assessment of occupational exposures (based on IPCS, 1994).

Taken from WHO (2005) Harmonization Project Document No. 2 CHEMICAL-SPECIFIC ADJUSTMENT FACTORS FOR INTERSPECIES DIFFERENCES AND HUMAN VARIABILITY: GUIDANCE DOCUMENT FOR USE OF DATA IN DOSE/CONCENTRATION–RESPONSE ASSESSMENT
https://apps.who.int/iris/bitstream/handle/10665/43294/9241546786_eng.pdf;sequence=1

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Assessment factors for intraspecies exptrapolation used for OELs in Europe

Regulatory system	Intraspecies factor used
EU REACH Regulation (inhalation DNELs workers) (ECHA guidance)	5
EU Plant Protection Products Directive	10
EU Biocidal Products Regulation	10
(former) Scientific Committee on Occupational Exposure Limits	>= 1
ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) (inhalation DNELs workers)	3
German OELs (Ausschuss für Gefahrstoffe)	Combined inter- and intraspecies factor: 5
German MAK Commission	Combined inter- and intraspecies factor: 2

Where we started from

- Dale Hattis and colleagues, Clark University Worcester, MA
  (https://www2.clarku.edu/faculty/dhattis/)


Human Interindividual Variability in
Parameters Related to Susceptibility
for Toxic Effects

General Interindividual Variability Database | Snaw Man Database and Papers, Including Price et al. (2002) Interspecies Paper and Data | Old General Interindividual Variability Database | Interspecies and Interindividual Variability in In Vitro Enzyme Measurements for Input to PBPK Models | Child/Adult/Elderly Databases and Acrylamide PBPK | Particle Variability Database | Age-Related Differences in Carcinogenesis | Chloroquine Pharmacokinetics and Pharmacodynamics

Web Site Description (Back to Top)

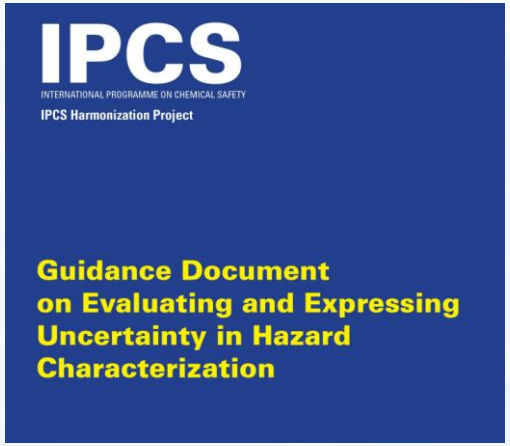
This web site allows you to download either summary data/analyses or detailed individual data sets that we used to derive our estimates of interindividual variability for various publications and ongoing work. The files below are organized into four groups:

- Andrew Renwick, Jean-Luce Dorne and colleagues

  e.g. publications on pathway-related assessment factors

- WHO IPCS Harmonization project 2014:

  Guidance document on Evaluating and Expressing Uncertainty in Hazard Characterisation



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Variability in toxicokinetics (TK): Database

- We identified:
  - 74 published toxicokinetic studies with adult humans:
  - 68 quantifiable datasets; 33 oral, 31 inhalation, 4 other routes
- Evaluation of kinetic parameters:
  - Area under curve (AUC)
  - Plasma concentration (Cmax)
  - Or others (e.g. urinary excretion, clearance)
- Variation characterised by:
  - Mean and standard deviation (SD)
  - Quantiles or
  - Coefficient of variation

Example 1: Toxicokinetic study with styrene

- Wenker, M. A., et al. (2001). "Metabolic capacity and interindividual variation in toxicokinetics of styrene in volunteers." Human and Experimental Toxicology **20**(5): 221-228.

- Styrene: industrial chemical and solvent
- Inhalation study with 20 male volunteers: young healthy adults
- 1 hour inhalation at 104 mg/m^3
- AUC: mean 673 (SD +/- 142) µmol min/L
- Standard deviation characterizes variability within the group of volunteers

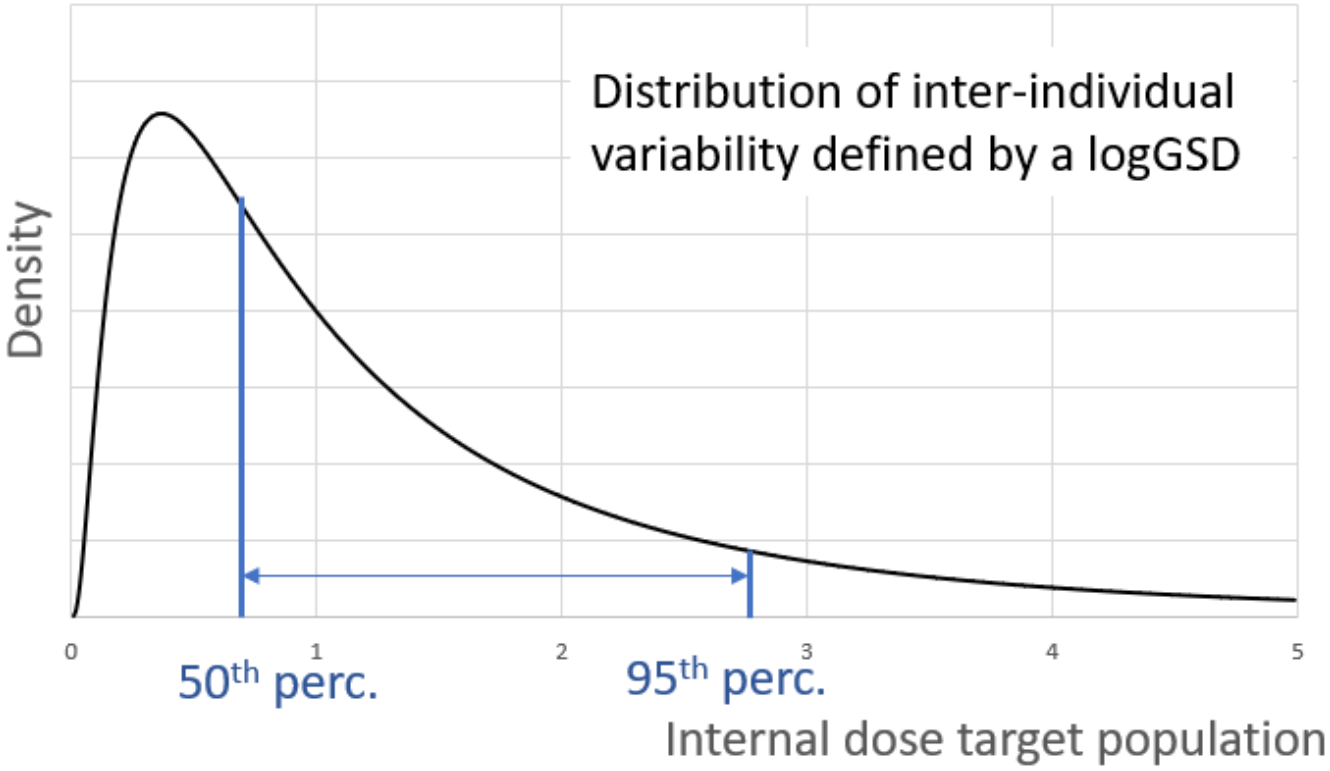
As this kind of data are restricted on the left side (values cannot be <0), distributions are typically shifted to the right

→ Assumption: lognormal distribution suitable approximation

→ Log GSD (SD of logarithmized values) used to characterize variability

Variability in toxicokinetics (TK): logGSD

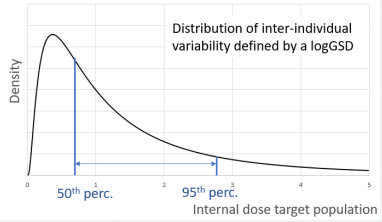
Specific dataset:



For each dataset: two values representing the ratios of the 95th (or 99th) percentile versus median

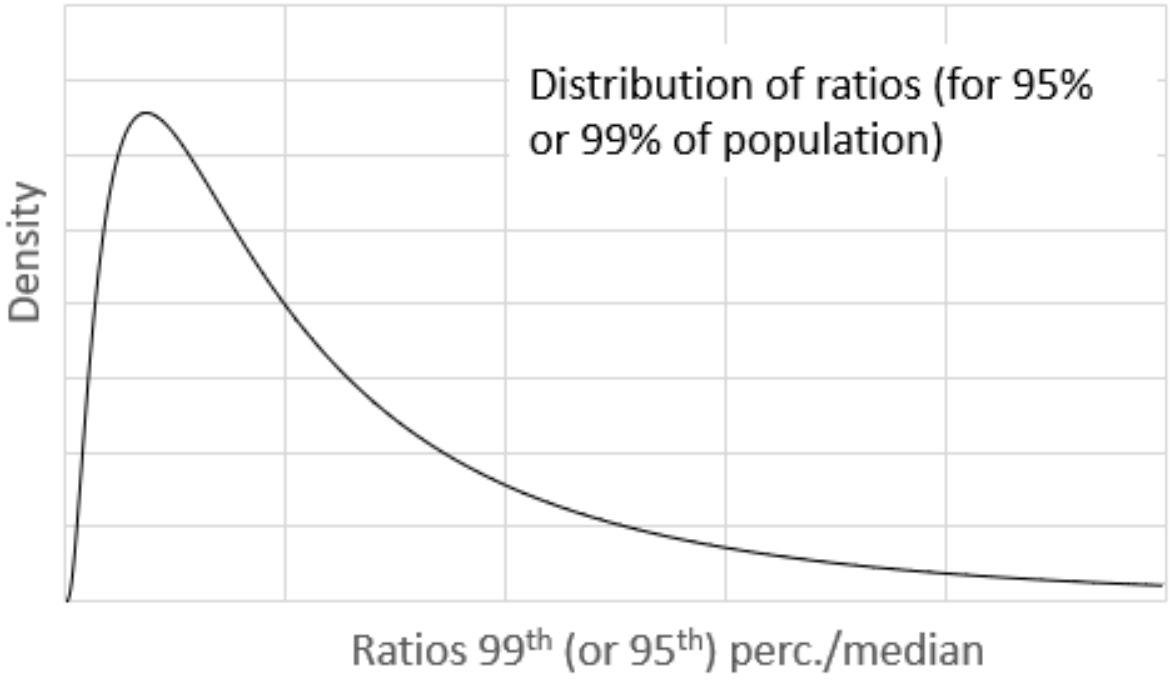
Variability in toxicokinetics (TK): logGSD

Specific dataset:



From these values: two distributions are obtained over all substances evaluated

Evaluation of sets of chemicals:



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Variability in toxicokinetics (TK): Approach

- Variability in toxicokinetic parameters expressed as **log GSD**, assuming lognormal distributions
- Log GSD is the SD of the logarithmic values - a measure of the spread of the distribution
- From each dataset one can calculate the factor required to cover 95% or 99% of the population – two values per dataset
- Two distributions are obtained describing the uncertainty over the set of chemicals studied for the values describing variation in 95% or 99% of the population

Variability in toxicokinetics (TK): Results

Source	N	Probability	Factor covering 95% of population	Factor covering 99% of population
Hattis database as used by WHO (2014)*	37	50%	1.88	2.45
		95%	4.67	8.85
Our evaluation**	68	50%	1.74	2.19
		95%	3.84	6.7

*mainly pharmaceuticals (mostly oral exposure)

**Pharmaceuticals (mostly oral data) and chemicals (mostly inhalation)

Our data indicate lower variability for inhalation data (chemicals)

Variability in toxicodynamics (TD): What are we looking for?

- NOTE:
  - This is about differences between internal doses leading to the same effect in different individuals
  - IT IS NOT about variation in endpoint measures, because internal dose and endpoint measures are not necessarily linearly correlated

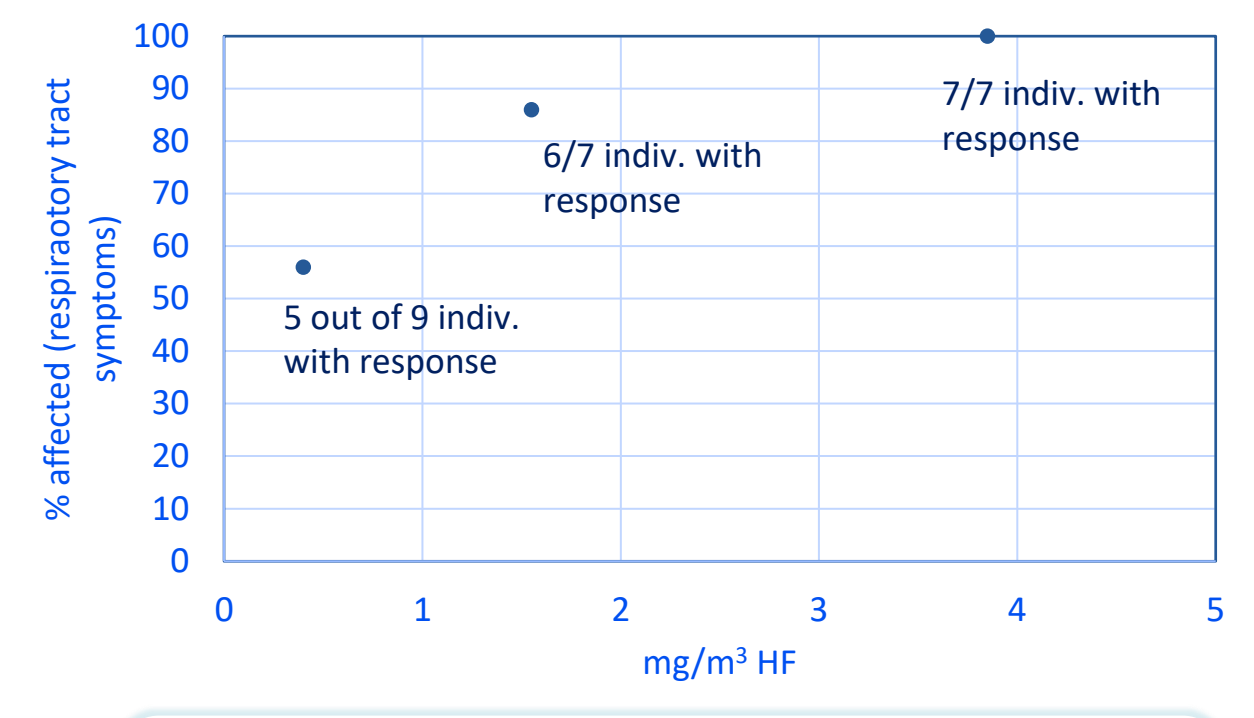
Example lead:

X-fold increase in blood lead does not induce x-fold increase in blood pressure

- WHAT IS REQUIRED:
  - Human studies with large variation in dose or concentration reporting individual responses at these doses/concentrations
  - So far, Hattis and colleagues were the only ones providing a quantitative proposal

In vivo studies investigating differences in toxicodynamics

Lund, et al., 1997: Exposure to hydrogen fluoride: an experimental study in humans of concentrations of fluoride in plasma, symptoms, and lung function. *Occupat. & Envir. Med*, 54, 32-37



0.4 mg/m³: 5 out of 9 indiv. **with** response
1.55 mg/m³: 1 out of 7 indiv. **without** response
→ Factor between most and least sensitive: > 4

- Difficulties/uncertainties
  - Such studies are difficult to find
  - Most often group mean exposures are reported, not individual data
  - High uncertainty in quantifying effects at the individual level
  - Investigated dose or concentration ranges too narrow
  - Toxicokinetic variability is difficult to exclude in in vivo studies

→ differences observed ranged from 3 to 201

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Variability in toxicodynamics (TD): Database and approach

- Database:
  - 25 published studies with adult humans
  - 12 inhalation, 5 oral exposure, 8 with parenteral administration

- Variation characterised by:
  - Difference between **highest dose without response** in individual subjects and **lowest dose with response**

- Results:
  - Broad range observed (from 3 to 201), several severe uncertainties

Alternative: *in vitro* data by Abdo et al. 2015*

- *In vitro* cytotoxicity dose-response data for 179 chemical substances
- Tested in lymphoblastoid cell lines from 1086 human individuals from from five continents and nine populations ("1000 Genomes project")
- Effective concentration 10% (EC10) for each combination of substance and cell line
- Replicates allow correction for measurement uncertainty
- For each substance: factor for difference between median and
  - 5^{th} percentile or
  - 1^{st} percentile of EC10 values
- From data values provided by the authors we established two distributions over all substances for covering 95 and 99% of the population

*N. Abdo, M. Xia, C. C. Brown, O. Kosyk, R. Huang, S. Sakamuru, et al.; EHP 2015, **123** (5), 458-66; DOI: 10.1289/ehp.1408775

Our study: toxicodynamics (TD)

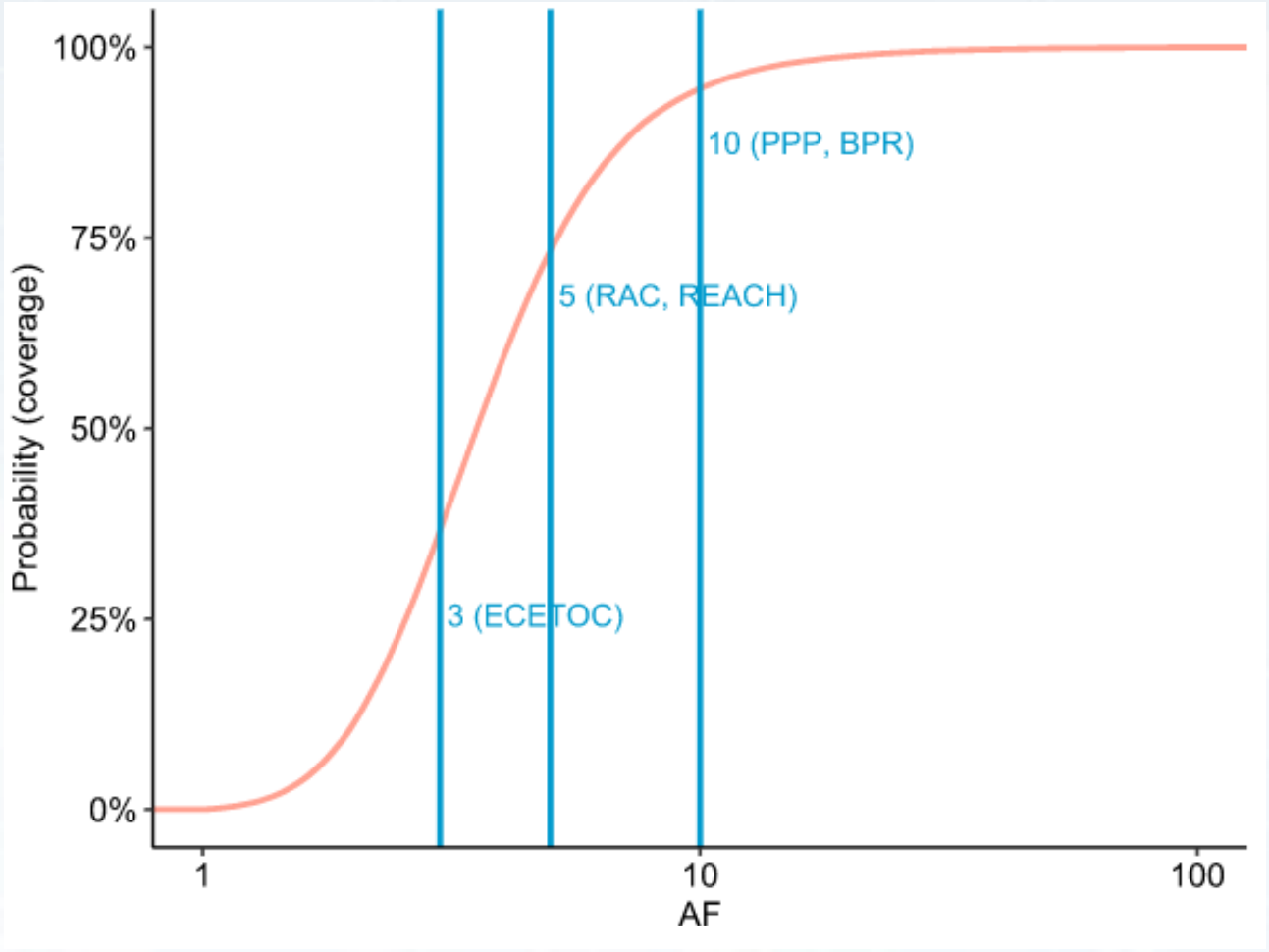
Source	Probability	Factor to cover 95% of population	Factor to cover 99% of population
Hattis database, *in vivo*	50%	2.31	3.27
	95%	10.91	29.37
Abdo et al (2015), *in vitro,* our evaluation	50%	1.95	3.04
	95%	4.67	10.32

Our study: toxicodynamics (TD)

- **Advantages of the Abdo et al. data:**
  - Clear separation from toxicokinetic variability
  - Clear definition of endpoint
  - Variability corrected for measurement error
  - Large number of individuals and populations

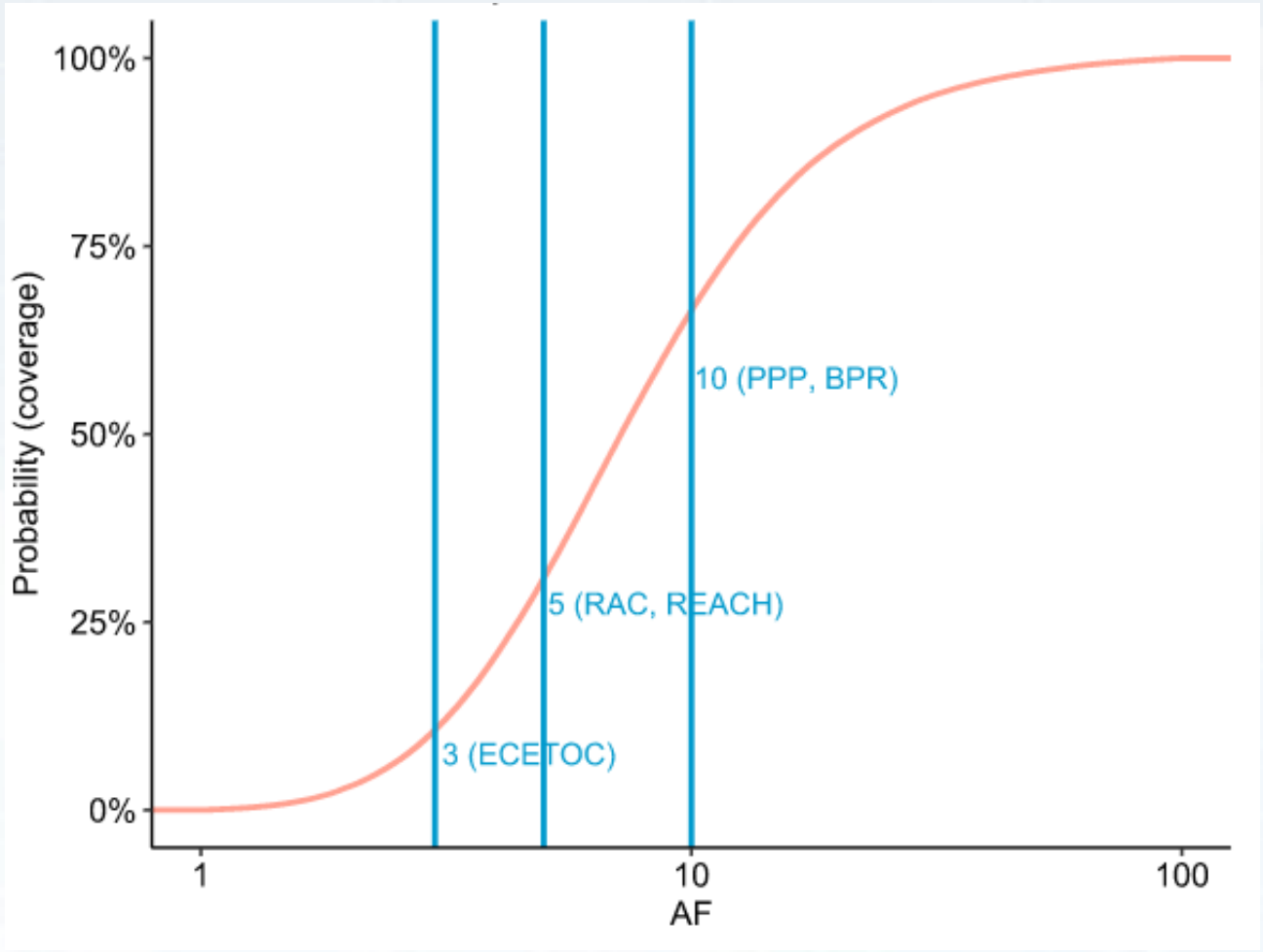
- **Disadvantages of the Abdo et al. data:**
  - Only cytotoxicity as endpoint
  - Established cell lines representative for humans in vivo?

Combined TK and TD intraspecies variability distribution



Probability for covering 95% of the population

Combined TK and TD intraspecies variablity distributions



Probability for covering 99% of the population

Conclusions

- There is sufficient empirical data to inform assessment factors for regulatory purposes
  - Info on kinetic variability can be derived from human pharmaco- and toxicokinetic studies
  - The distribution for toxicodynamic variability is based on *in vitro* data by Abdo et al. 2015
- There is considerable variability in the healthy adult human population
- We derived distributions for the coverage of 95% and 99% of the target population as examples (for both TK and TD and combined)
- Consideration of inter-individual variability for deriving health-based values requires
  - to define the percentile of the population (workers) to be covered
  - and a decision on the pursued probability
- Most existing assessment factors fail to provide protection with a high probability
- It is time to make use of the data!

Research project F2437

- 2018-2021 Research project for German Federal Institute for Occupational Safety and Health (BAuA) (https://www.baua.de/EN/Service/Publications/Report/F2437.html)

- Publications (open access)
  - Dilger et al. (2022), J Appl Tox, 42, 898-912, DOI: 10.1002/jat.4305
  - Schneider et al. (2022), J Appl Tox, 42, 913-926, DOI: 10.1002/jat.4307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RESEARCH ARTICLE
Journal of Applied Toxicology WILEY

Distributions for time, interspecies and intraspecies extrapolation for deriving occupational exposure limits

Marco Dilger[1] | Klaus Schneider[1] | Claudia Drossard[2] | Heidi Ott[2] | Eva Kaiser[1]


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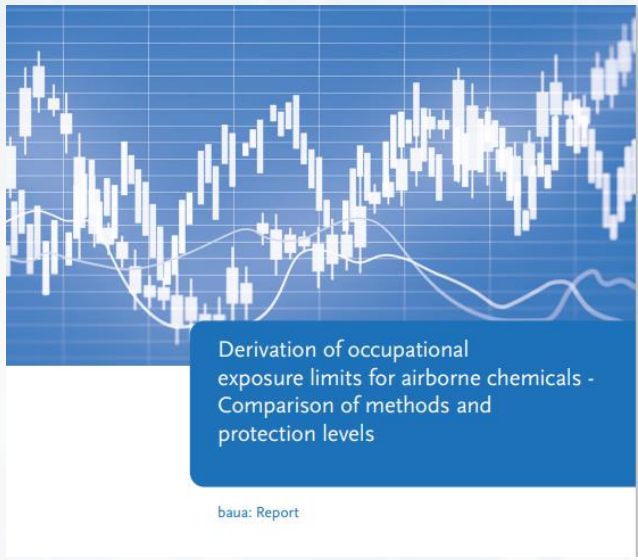
RESEARCH ARTICLE
Journal of Applied Toxicology WILEY

Derivation of occupational exposure limits: Differences in methods and protection levels

Klaus Schneider[1] | Marco Dilger[1] | Claudia Drossard[2] | Heidi Ott[2] | Eva Kaiser[1]



- International workshop on BAuA research project F 2437 on methods for derivation of occupational exposure limits on 05 April 2022 (https://www.baua.de/EN/Service/Events/Proceedings/Hazardous-substances/F2437-Workshop.html)

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And to the members of the Advisory Board accompanying the project

IN MEMORIAM Tom Gebel †

Thank you for your attention!

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