What are the differences in susceptibility between human individuals in the adult population?

Less than two-fold or ten-fold?

WORKSHOP ON BAUA-RESEARCH PROJECT F2437

TOPIC 6: Intraspecies extrapolation

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

Klaus Schneider - FoBiG, Forschungs- und Beratungsinstitut Gefahrstoffe GmbH, www.fobig.de

FoBiG
Forschungs- und Beratungsinstitut Gefahrstoffe GmbH

History

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

In 1994 the World Health Organisation split the factor 10 for intraspecies extrapolation in subfactors for toxicokinetics (3.16) and toxicodynamics (3.16)

Intraspecies factors used for deriving OEL or analogue values vary from >1 to 10 – without empirical justification

Variability in toxicokinetics (TK): Database

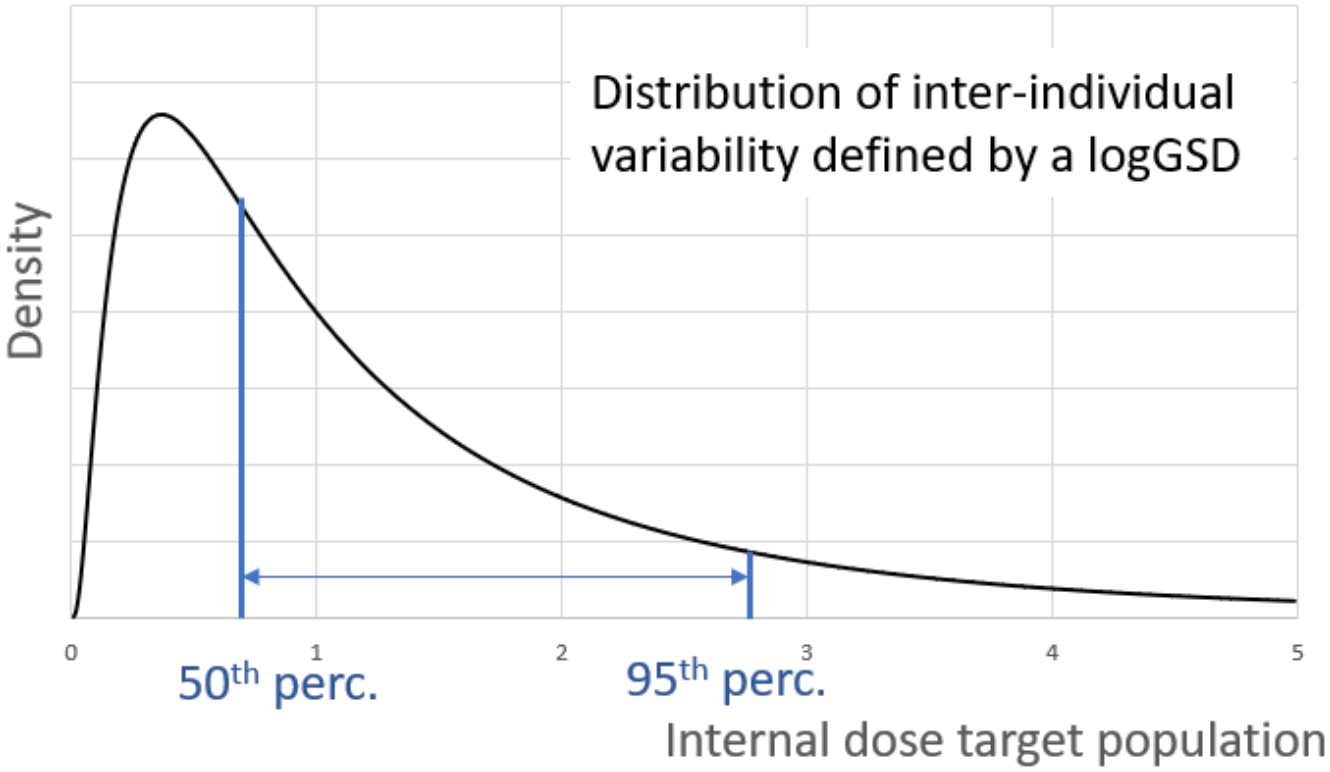
- We identified:
  - 74 published toxicokinetic studies with adult humans:
  - 68 quantifiable datasets; 33 oral, 31 inhalation, 4 other routes
- Evaluation of kinetic parameters:
  - Area under curve (AUC)
  - Plasma concentration (Cmax)
  - Or others (e.g. urinary excretion, clearance)
- Variation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

Variability in toxicokinetics (TK): Approach

- Variability in toxicokinetic parameters expressed as **log GSD**, assuming lognormal distributions
- Log GSD is the SD of 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): logGSD

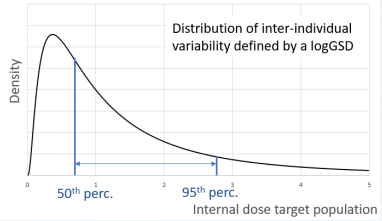
Specific dataset:



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

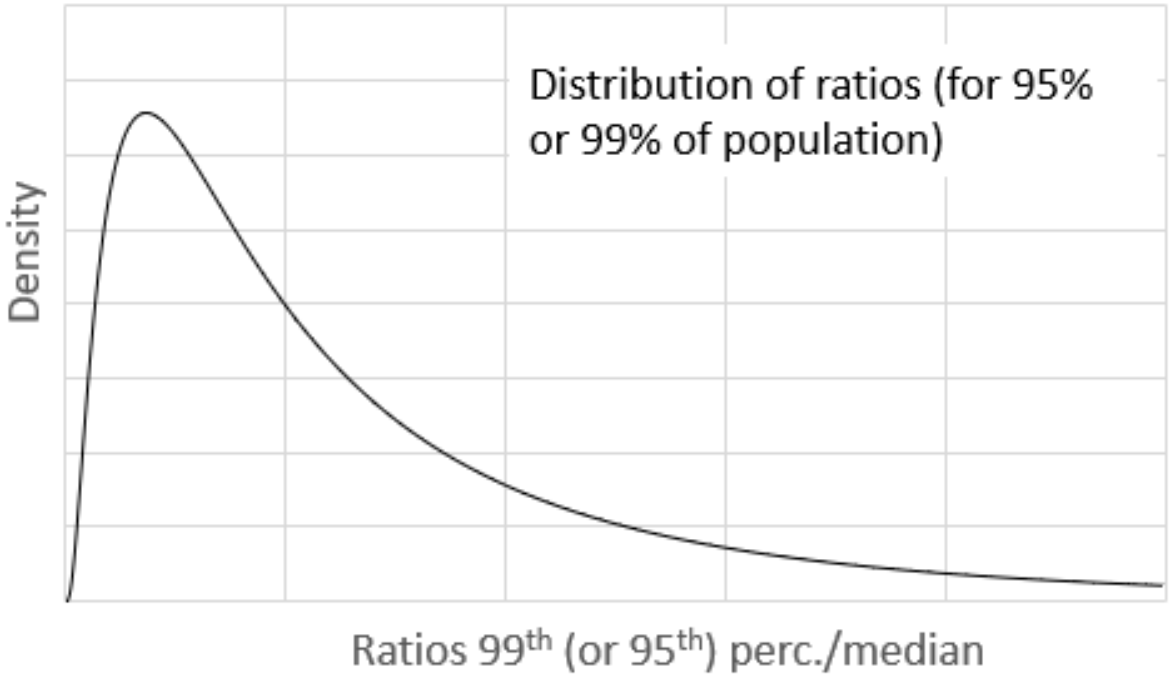
Variability in toxicokinetics (TK): logGSD

Specific dataset:



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

Evaluation of sets of chemicals:



FoBiG
Forschungs- und Beratungsinstitut Gefahrstoffe GmbH

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

Variability in toxicodynamics (TD): Database and approach

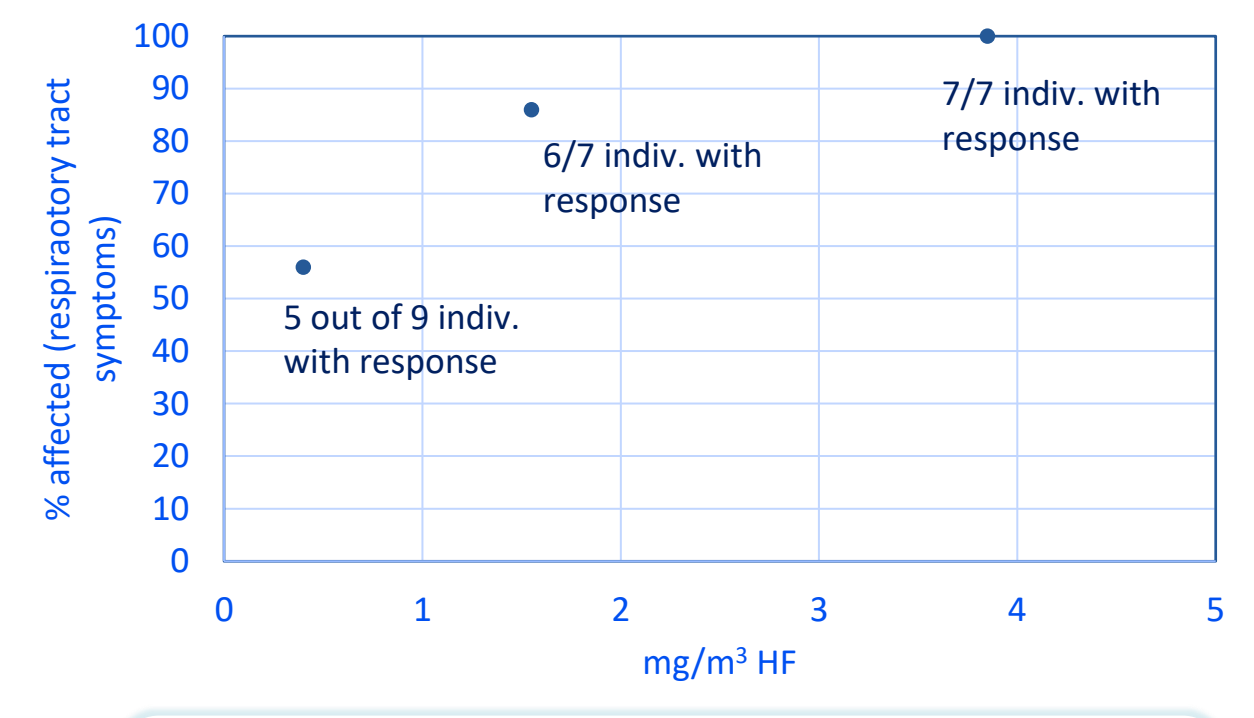
- Database:
  - 25 published studies with adult humans
  - 12 inhalation, 5 oral exposure, 8 with parenteral administration

- 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

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

FoBiG
Forschungs- und Beratungsinstitut Gefahrstoffe GmbH

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

Our study: toxicodynamics (TD)

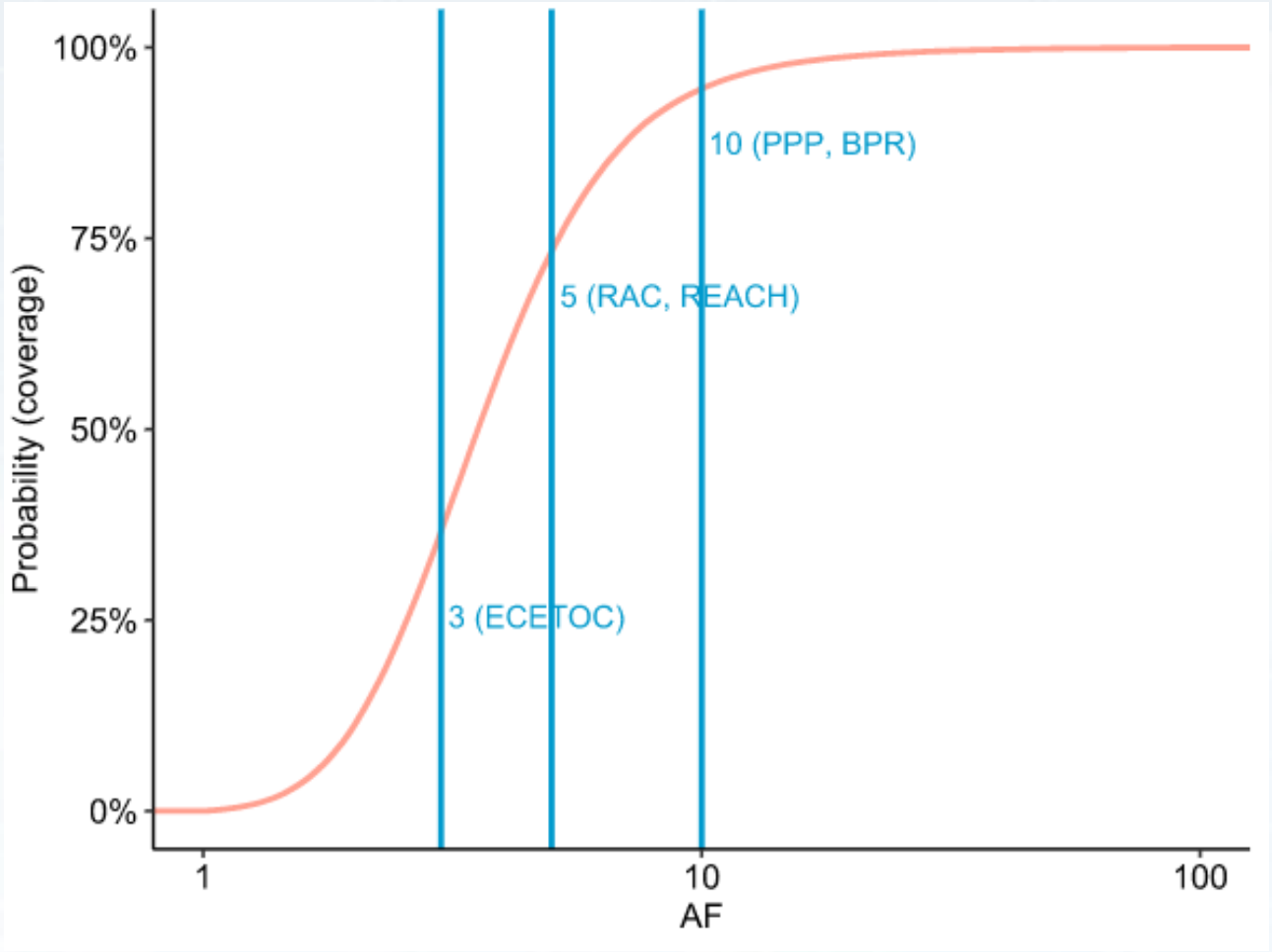
Source	Probability	Factor to cover 95% of population	Factor to cover 99% of population
Hattis database, *in vivo*	50%	2.31	3.27
	95%	10.91	29.37
Abdo et al (2015), *in vitro,* our evaluation	50%	1.95	3.04
	95%	4.67	10.32

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?

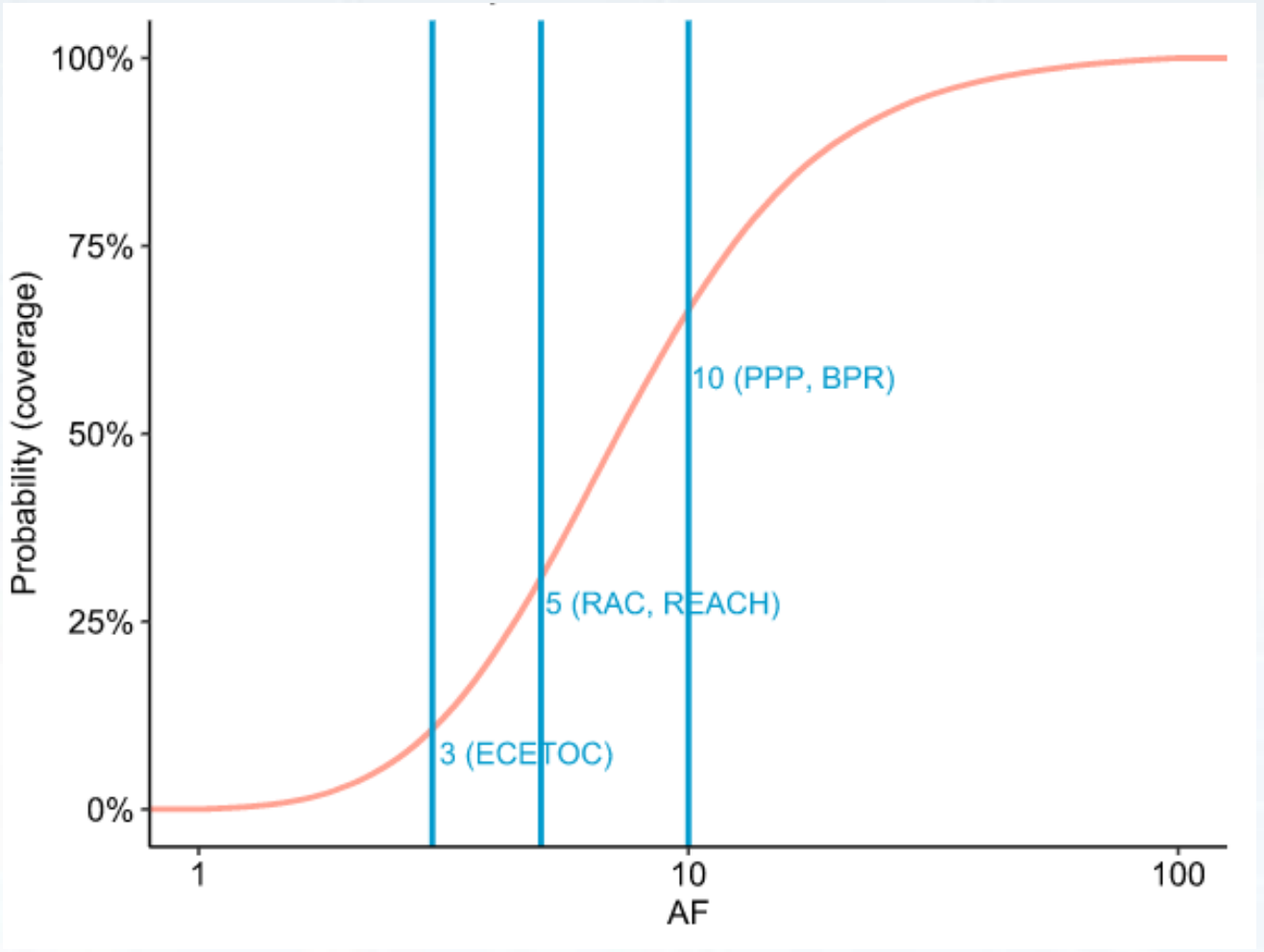
Combined TK and TD intraspecies variability distribution



Probability for covering 95% of the population

FoBiG
Forschungs- und Beratungsinstitut Gefahrstoffe GmbH

Combined TK and TD intraspecies variablity distributions



Probability for covering 99% of the population

Conclusions

- We established a new database for toxicokinetic variability, including inhalation data for industrial chemicals
- The distribution for toxicodynamic variability is based on *in vitro* data by Abdo et al. 2015
- Consideration of inter-individual variability requires to define the percentile of the population (workers) to be covered
- We derived distributions for the levels 95% and 99% as examples (for both TK and TD and combined)
- In order to derive deterministic assessment factors a decision on the pursued probability is required
- Both our TK and TD results describe a somewhat lower variability compared to Hattis et al., as used by WHO (2014)
- Most existing assessment factors fail to provide protection with a high probability