Time and interspecies extrapolation

Which percentile of a distribution should be chosen to define an assessment factor?

WORKSHOP ON BAUA-RESEARCH PROJECT F2437

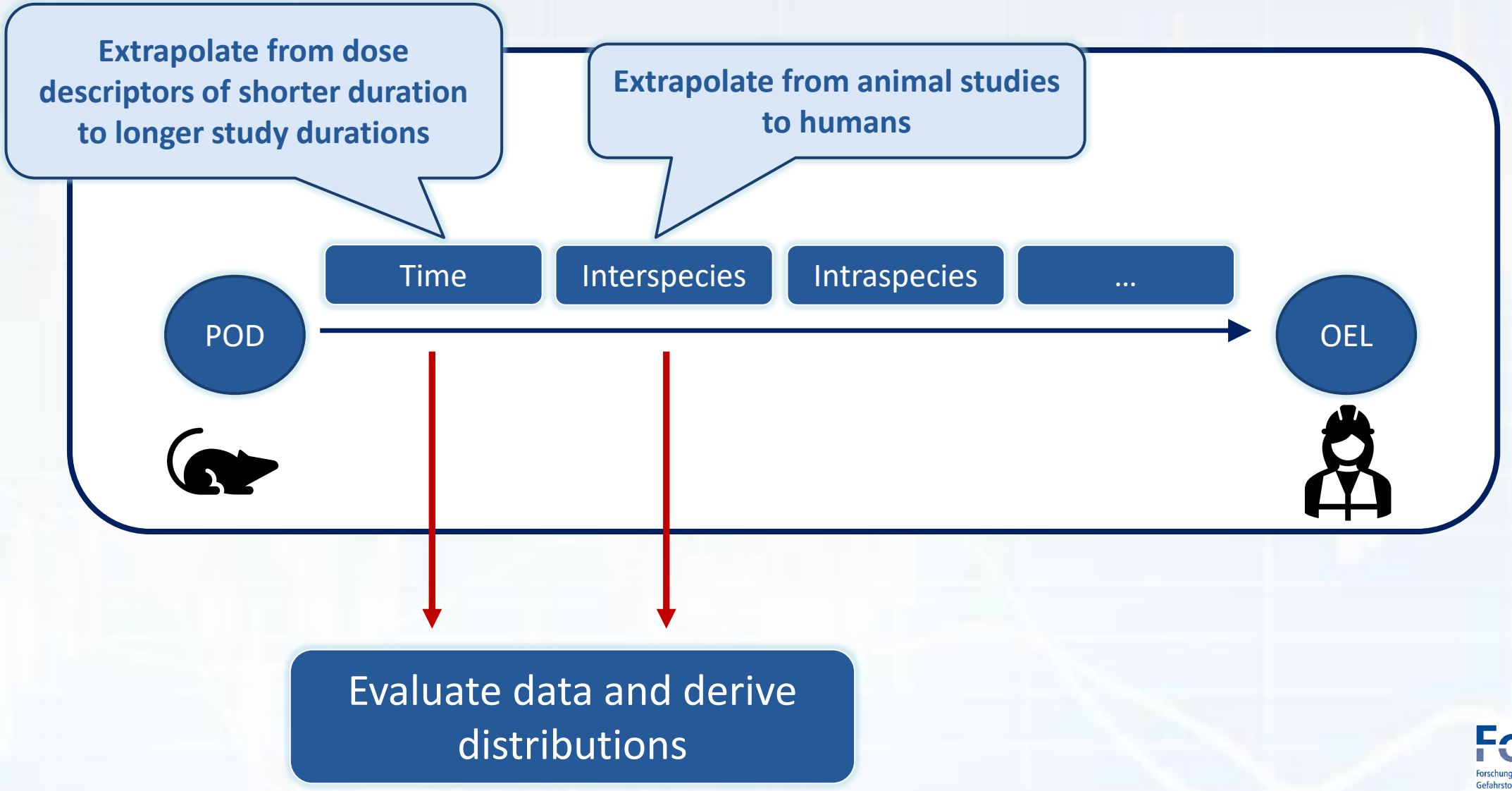
TOPIC 5: Time and interspecies extrapolations

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

Eva Kaiser - FoBiG, Forschungs- und Beratungsinstitut Gefahrstoffe GmbH, www.fobig.de

FoBiG
Forschungs- und Beratungsinstitut Gefahrstoffe GmbH

Time and Interspecies extrapolation



Data basis for both evaluations

NTP studies (National Toxicology Program in the US)

- Studies can be completely accessed via NTP homepage
- Selection criteria:
  - Studies with inhalation or oral exposure
  - Draft study reports excluded
  - At least two studies with different exposure duration available (2 weeks, 13 weeks, 2 years)
- Studies on **256** substances in the dataset for the evaluation

Study type	Body weight	Local effects in the respiratory tract (only for inhalation studies)	Systemic effects
2 weeks	X		
13 weeks	X	X	X
2 years	X	X	X

- For each evaluated endpoint, a NOAEL and a LOAEL were identified

Data basis for both evaluations

REACH data (IUCLID registration data on repeated dose toxicity)

- Data provided confidentially by ECHA
- Selection criteria:
  - Studies with inhalation or oral exposure and a reliability of 1 or 2
  - Additional selection criteria established (e.g. studies without appropriate guideline excluded) → data cleaned
- At the beginning: 150 000 study records

→ In the end 8500 dose descriptors for oral studies and 1800 for inhalation studies

What was done with the data?

- NOAELs or LOAELs from two studies were compared
- Calculation of ratios for time and species comparisons

Example 1: Studies in rats
90-day study: NOAEC = 100 mg/m³
2-year study: NOAEC = 20 mg/m³

Ratio: 100/20 = 5

- NTP data:
  - Calculation of ratios for any pairs of
    - 2 study types of different lengths (but with same species)
    - 2 study types of different species (but with same length)

Example 2: 90-day studies
Rat study: NOAEL = 100 mg/kg bw/d
Mouse study: NOAEL = 150 mg/kg bw/d

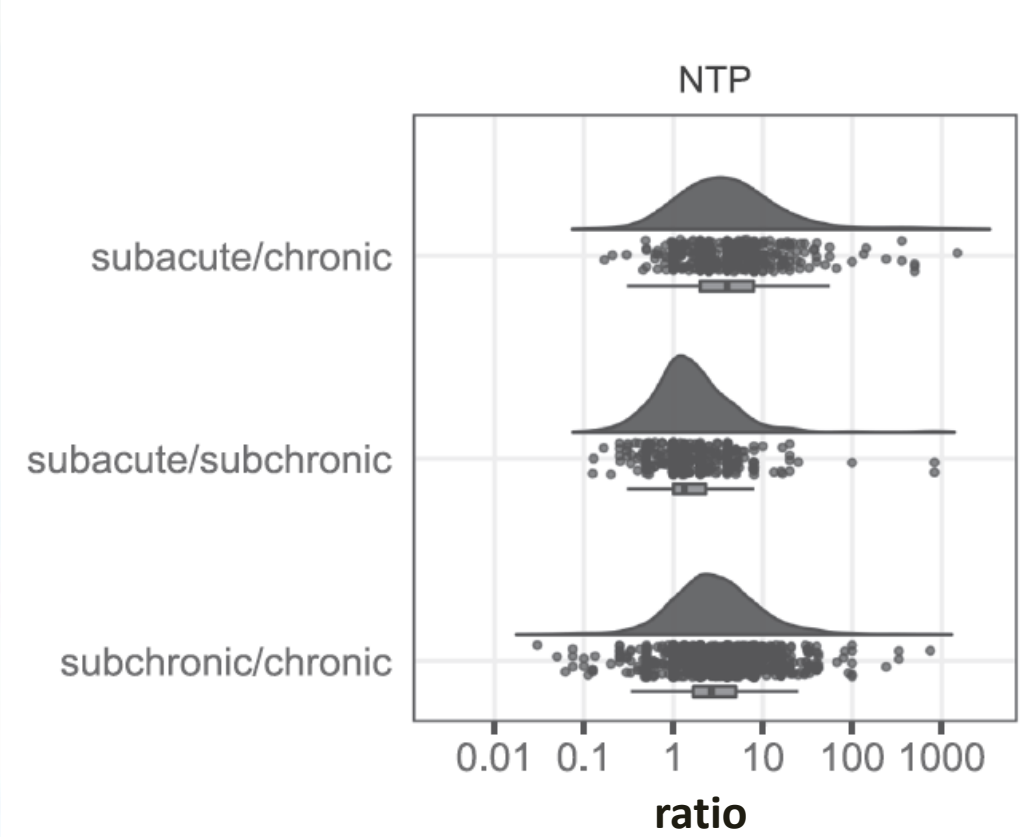
Ratio: 100/150 = 0.67

- REACH data: number of ratios relatively low (compared to NTP data)

→ Not further reported here

Time extrapolation - Results

- Empirical distributions



Dilger et al., 2022; J. Appl. Tox; DOI: 10.1002/jat.4305

Study pair	Exposure route	GM (95% CI)	75th perc. (95% CI)	n
sa/c	Oral	4.40 (3.85–5.06)	8.00 (6.27–8.33)	305
sa/c	Inhalation	3.25 (2.58–4.17)	6.83 (4.67–8.00)	91

- Stratification by
  - Exposure route (inhalation/oral)
  - Species
  - Sex
  - Endpoint
  - Target organ
  - Structural properties of the test substance

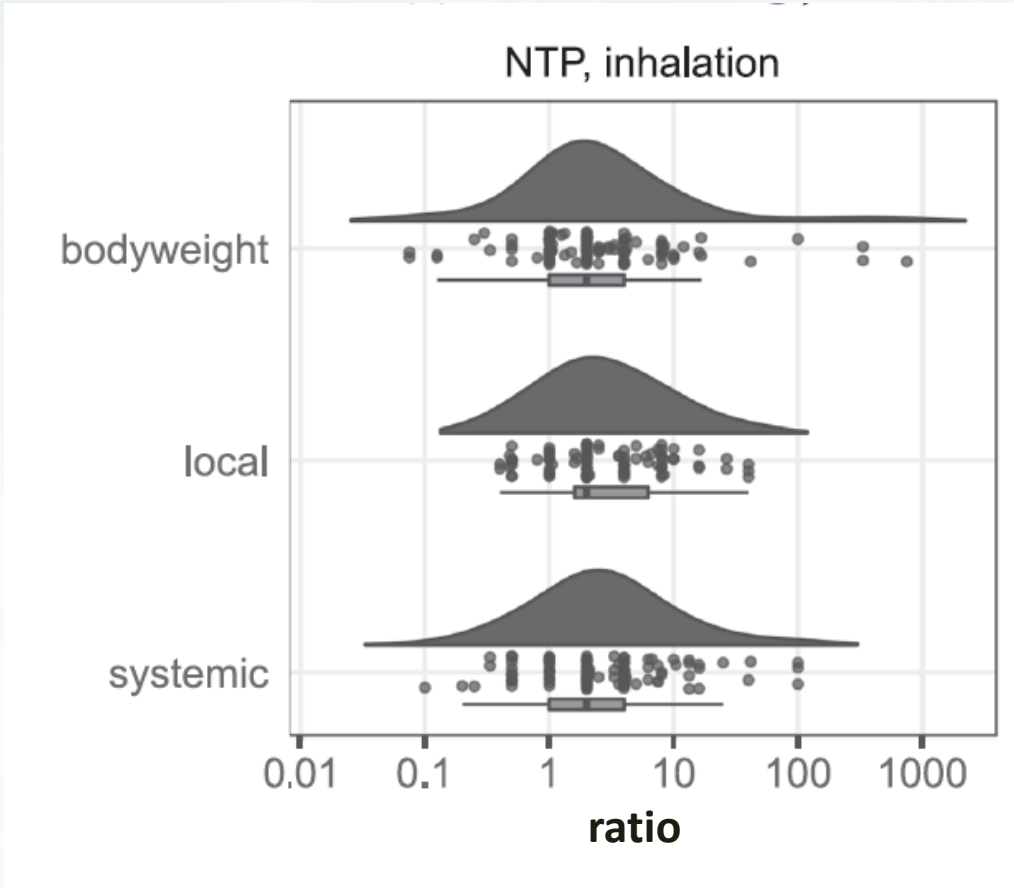
revealed only minor differences

FoBiG
Forschungs- und Beratungsinstitut Gefahrstoffe GmbH

Stratification by toxicity endpoints and route

- Only investigated for subchronic/chronic comparison, inhalation exposure

endpoint	GM (95% CI)	75th perc. (95% CI)	n
local	2.73 (2.20-3.43)	6.25 (4.00-8.00)	101
systemic	2.70 (2.17–3.48)	4.01 (4.00-7.50)	107
bodyweight	2.40 (1.83-3.14)	4.00 (3.00-7.98)	115



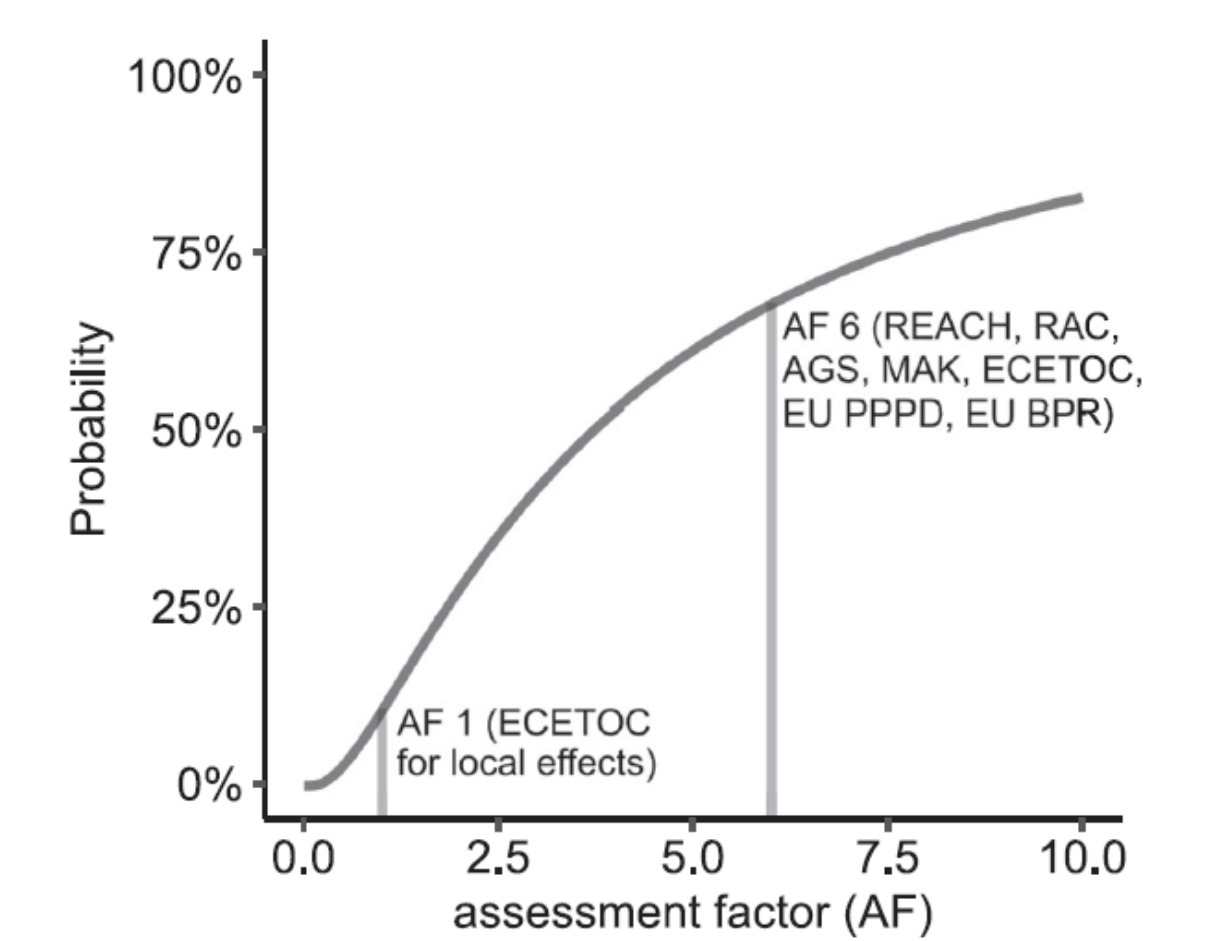
→ **No significant differences observed between local and systemic effects**

Dilger et al., 2022; J. Appl. Tox; DOI: 10.1002/jat.4305

FoBiG Forschungs- und Beratungsinstitut Gefahrstoffe GmbH

Comparison of distribution with currently used default values

- **Subacute/chronic extrapolation**



- Cumulative distribution function
- Vertical lines represent currently used assessment factors
- AF of 6 corresponds to a coverage of **67.7%** according to the derived uncertainty distributions
- AF of 1 corresponds to **10.6%**

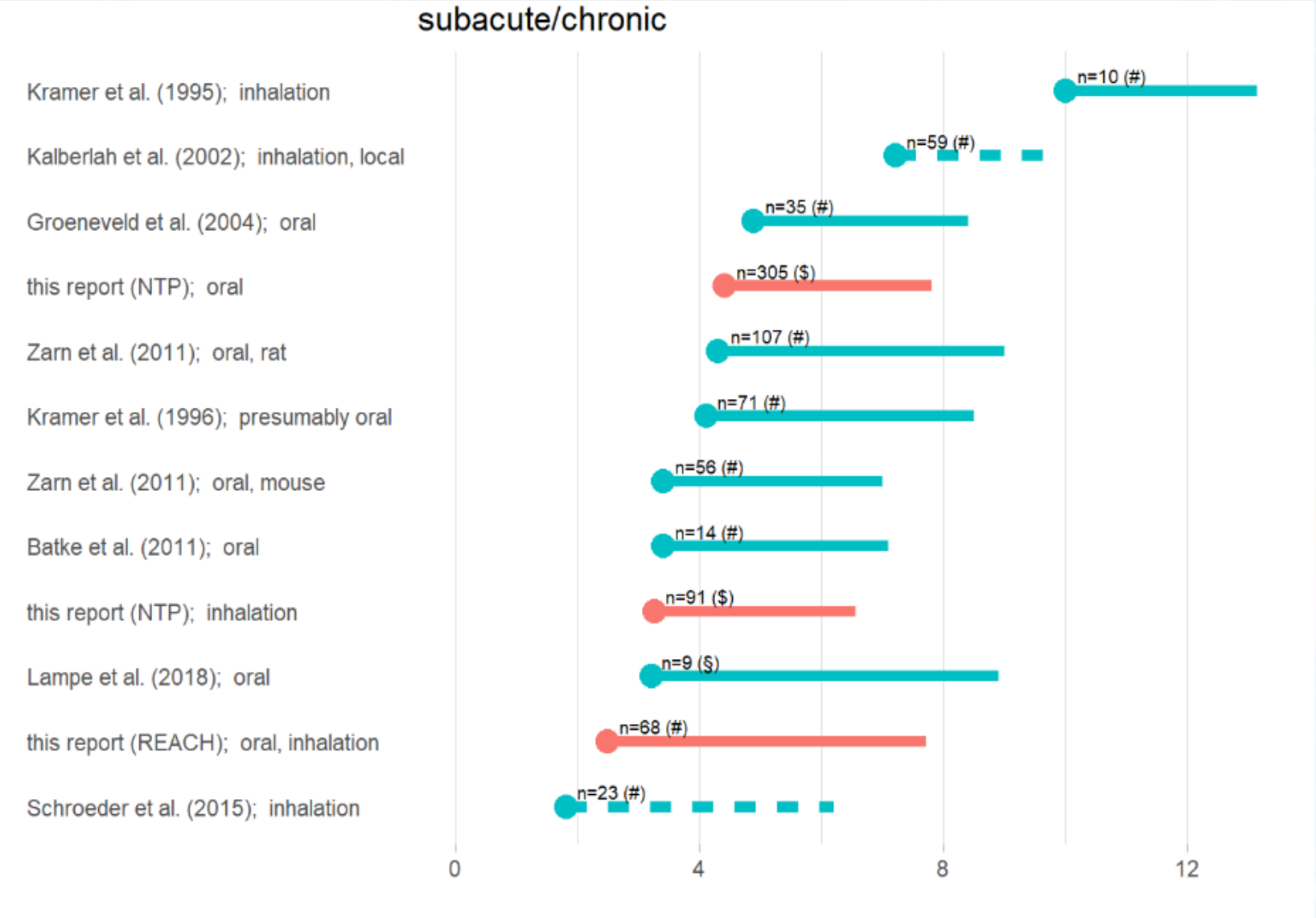
Dilger et al., 2022; J. Appl. Tox; DOI: 10.1002/jat.4305

FoBiG
Forschungs- und Beratungsinstitut Gefahrstoffe GmbH

Comparison of distribution with currently used default values

- **Subchronic/chronic extrapolation**
  - Standard assessment factor of 2 (systemic and local effects) corresponds to a coverage of **36.3%**
  - ECETOC assessment factor of 1 corresponds to a coverage of **14.6%**

Comparison with published data

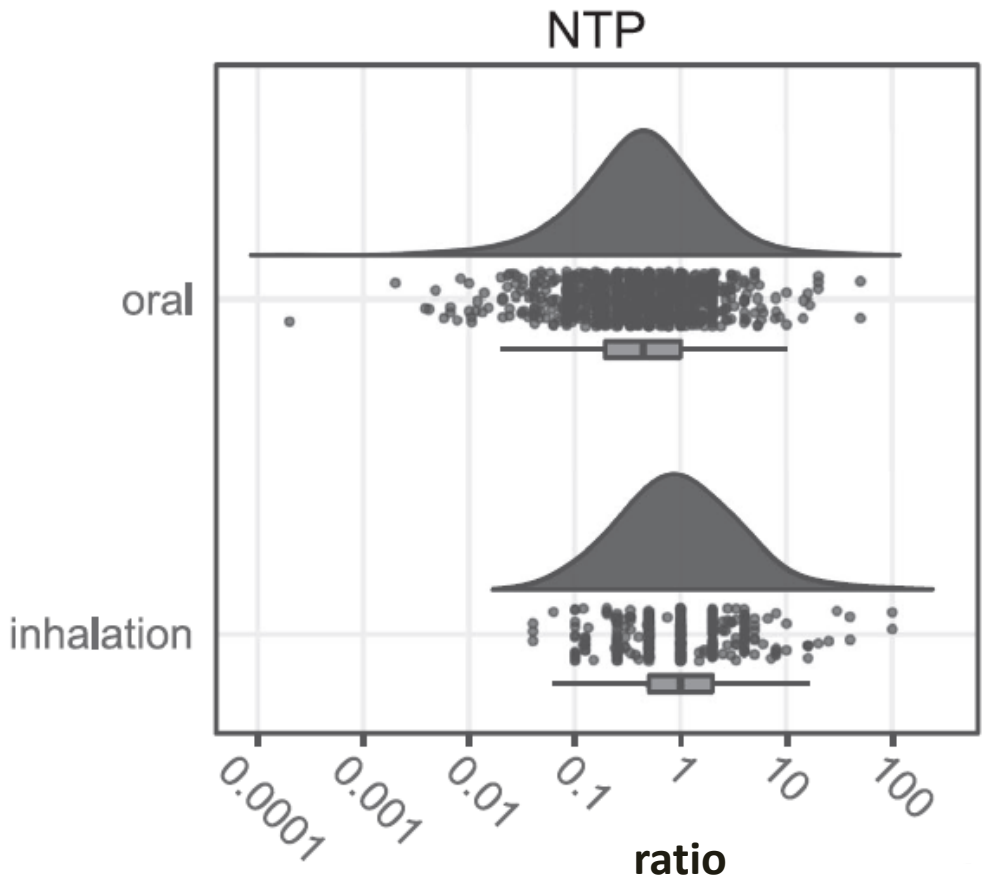


FoBiG
Forschungs- und Beratungsinstitut Gefahrstoffe GmbH

Comparison with published data

Interspecies extrapolation - Results

- Empirical distributions



Study pair	Exposure route	GM (95% CI)	75th perc.	n
Rat/mouse	oral	0.40 (0.37-0.44)	1.00	927
Rat/mouse	inhalation	0.96 (0.84-1.10)	2.00	333

- NOAELs corrected (according to Bokkers and Slob 2007) in the absence of BMDs.
- Stratification by exposure route (inhalation/oral) revealed significant differences
  - In agreement with allometric principles ratios <1 were expected (oral)
- Other experimental factors had no (relevant) effects (sex, study duration, endpoint, target organ, structural properties of the test substance)

Dilger et al., 2022; J. Appl. Tox; DOI: 10.1002/jat.4305

Interspecies extrapolation - Results

- „Expected values“ according to metabolic rate scaling (allometric exponent of 0.75)

Study pair	Exposure route	GM (95% CI)	Expected value	75th perc.	n
Rat/mouse	oral	0.40 (0.37-0.44)	**0.59**	1.00	927
Rat/mouse	inhalation	0.96 (0.84-1.10)	**1.00**	2.00	333
Rat/human	oral		**4.1**		

→ Applicability of allometric scaling principles confirmed

- Application of appropriate scaling factors is expected to result in distributions with a GM of 1

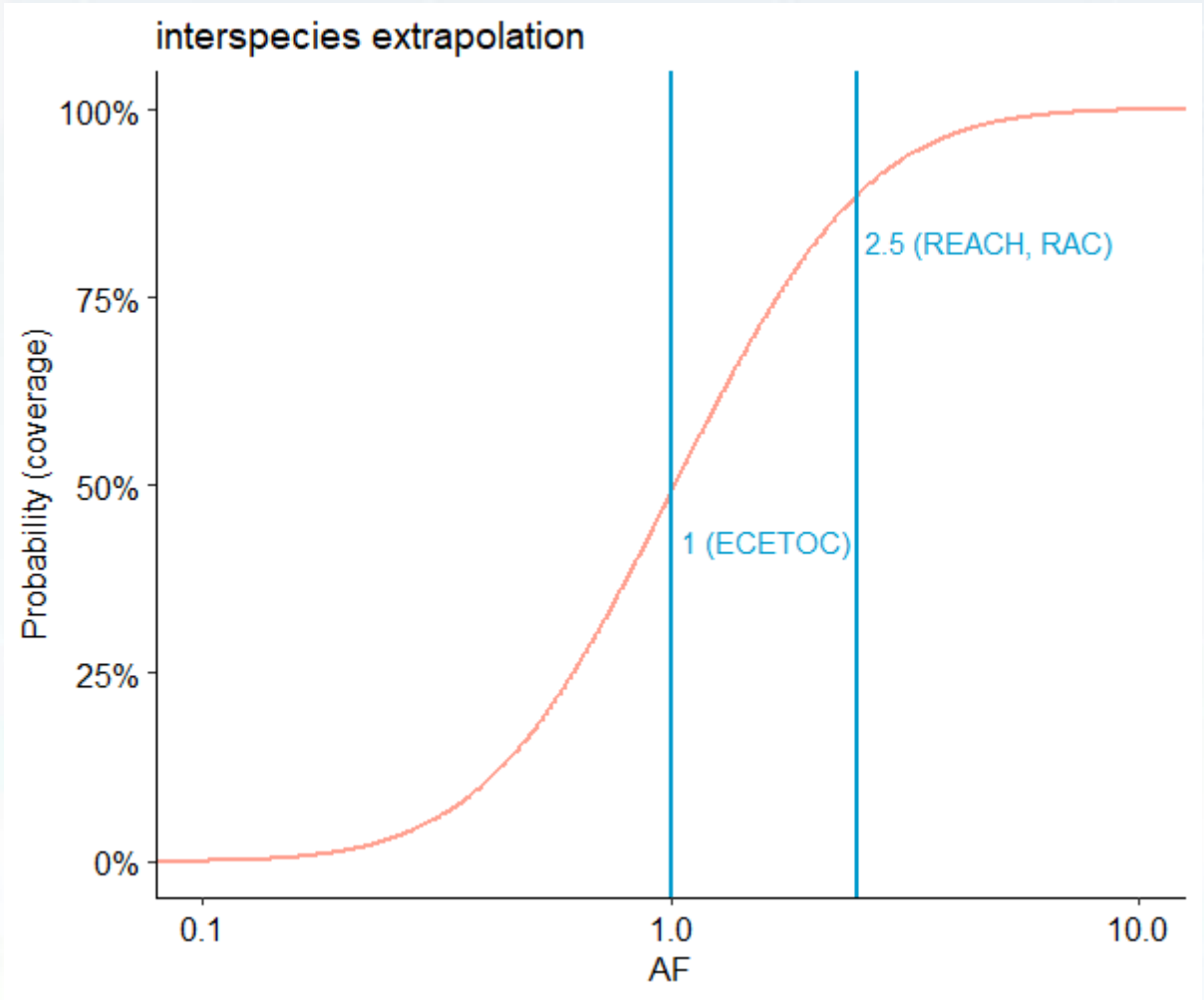
FoBiG
Forschungs- und Beratungsinstitut Gefahrstoffe GmbH

Interspecies extrapolation – Remaining interspecies variability

- Additional variability
  - Substance-to-substance variability due to toxicokinetic differences
  - Uncertainty associated with the values used for calculating the ratios (NOAEL instead of BMD values)

- We propose that the allometric scaling factors are considered as a correction factor when doses are expressed as amount per kg bw
- The remaining differences in toxicokinetics and -dynamics should be accounted for by a separate distribution (GM =1).

Comparison of distribution with currently used default values



- Cumulative distribution function
- Vertical lines represent certain assessment factors
- AF of 2.5 corresponds to a coverage of **88.4%** according to the derived uncertainty distributions
- AF of 1 corresponds to **48.6%**

FoBiG
Forschungs- und Beratungsinstitut Gefahrstoffe GmbH

Comparison with published data

- **Schneider et al., 2004**
  - provide a strong support for application of an allometric scaling exponent that corresponds to caloric demand.
- **Pierce et al, 2008**
  - Reanalyzed data from Schneider et al. → obtained very similar results
- **Bokkers and Slob, 2007 (NTP data)**
  - compared the ratios of NOAELs and BMDs of effects in mice with those of the same effects in rats.
- **Escher et al. 2013 (Rep dose database)**
  - Results are in agreement with caloric demand scaling

Conclusion

- **Time extrapolation**
  - New database with studies from 256 substances
  - Emphasis on comparability of endpoints
  - Largely in agreement with previous evaluations (slightly higher values for subchronic to chronic)
  - Extrapolation factor **subacute/chronic** of 6 used by several organisations results in a probability of **68%**
  - Coverage is less (only **36%**) for the assessment factor of 2 used often for **subchronic/chronic** extrapolation

Conclusion

- **Interspecies extrapolation**
  - Allometric scaling confirmed
  - The interspecies extrapolation factor of 2.5 (for systemic effects applied in combination with allometric scaling to cover remaining uncertainty) provides for a (high) probability of 88%.
  - The interspecies factor of 10 applied in the PPP and BPR framework (without allometric scaling) is achieving the same level of coverage in case of rat studies; for smaller species the probability would be lower, for larger species higher.