Assessment factors in human health risk assessment and their associated level of safety

Sylvia E. Escher*, Simone Hoffmann-Doerr, Monika Batke*, Inge Mangelsdorf***

*** Fraunhofer Institute for Toxicology and Experimental Medicine - ITEM, Hannover, Germany**
****BASF Personal Care and Nutrition GmbH, Duesseldorf, Germany**

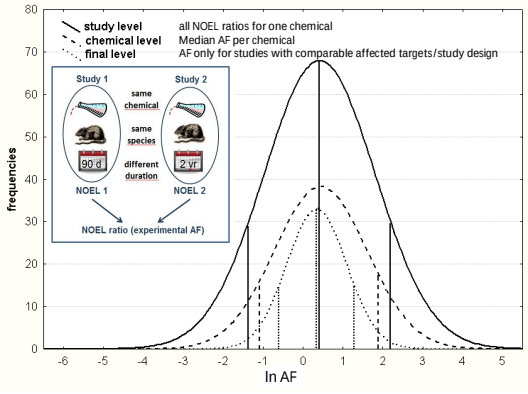
Poster #1965

Probabilistic analyses of extrapolation functions with the RepDose DB.

Human health risk assessment of chemicals requires solid information on adverse effects after long-term exposure. Because of ethical considerations, human data or even long-term studies with animals are in general scarce. Consequently, reliable assessment factors (AF) are often used in risk assessment to overcome e.g. differences between short-term animal studies and the human situation. In human health risk assessment, usually more than one extrapolation step is required, e.g. the use of factors for interspecies-, intraspecies and time extrapolation. According to *Vermeire*, the multiplication of several conservative assessment factors – representing worst case assumptions – increases the level of conservatism in the risk assessment. By means of probabilistic distributions for the derivation of an overall assessment factor, the overestimation of risk could be reduced (Vermeire et al. 2001). Furthermore, a discussion about the overall degree of data variability and uncertainty and the confidence of the obtained overall assessment factor cannot be addressed within deterministic safety assessment.

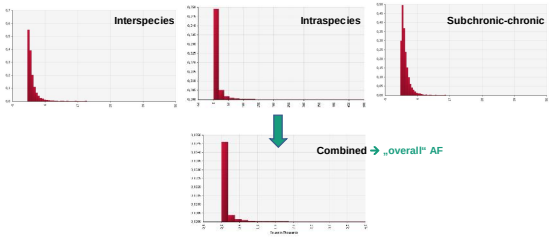
Our analyses aimed therefore at the derivation of assessment factors based on the evaluation of distribution functions when applied solely or in combination. The toxicological database (DB) RepDose, which contains about 2500 repeated dose toxicity studies on 700 chemicals, served as the basis for the derivation of robust probabilistic assessment factors such as time (Batke et al. 2011, Figure 1) and interspecies extrapolation (Escher et al. 2013). RepDose is available online: www.fraunhofer-repdose.de (Bitsch et al. 2006).

Figure 1: Variability in the comparison of subchronic and chronic data



- **AF account for differences in toxicity after subchronic and chronic exposure**
- **Spread of distribution decreases if not toxicity-related data variability is excluded e.g. from the study to final level.**
- **The relative position of the distribution, represented by its geometric mean (GM) remains stable.**
- **The „final level" includes only studies with comparable affected targets, dose spacing and dose selection. However, the distribution functions are based on NOEL ratios. NOELs are non-continuous data points and dose selection is an inherent source of data variability.**

Figure 2: Monte Carlo simulation to combine extrapolation functions



- **Monte Carlo analysis used to characterize the variability and uncertainty of the combination of several input distributions (program @risk, Palisade Corporation).**
- **Extrapolation steps are:**
  - **Interspecies x Intraspecies**
  - **Interspecies x Intraspecies x Time**
- **The quality and reliability of the input distributions determines the reliability of their combination/output distribution. For our analyses, we combined those distributions which do as far as possible represent solely toxicological differences and are based on a reliable database (Table 1).**
- **All applied input functions are described to have a log normal characteristic.**

Table 1: Characterization of input distributions

Input Function	Log normal characteristics	Description of analysis and sources of data variability
Interspecies (Escher et al. 2013)	Empirical; Allometry factor x distribution for remaining interspecies differences GM 1, GSD 2.5 ; 160 data points	Distribution based on NOEL ratios from the RepDose DB. Comparable studies from rodents were taken, where one chemical was tested in studies with same study duration, same route of application (e.g. gavage-gavage, food-food, inhalation-inhalation). Further sources of data variability e. g. caused by differences in scope of examination, dose selection and dose spacing are not excluded.
Intraspecies (Schneider et al. 2005)	Empirical; GM 3.8, GSD 4.34, shift +1; 89 substances	Distribution for human data (Hattis et al., 1999). Toxicodynamic and toxicokinetic (partly) aspects are considered. Children are under-represented in the dataset. Ratio between the mean susceptibility and the susceptible person (5th percentile) are calculated to derive the resulting distribution. This depicts the susceptibility of 95% of the population.
Time Subacute-subchronic (Batke et al. 2011)	Empirical; GM 1.3, GSD 2.2; 38 data points	Distributions are based on pairs of NOELs from the RepDose DB. Comparable studies from rodents were taken, where one chemical has been tested in one species with same route of application (e.g. gavage-gavage, food-food). Furthermore, several sources of data variabiliaty not related to toxicity are excluded such as differences in the scope of examination and the study design.
Time Subchronic-chronic (Batke et al. 2011)	Empirical; GM 1.5, GSD 2.2; 77 data points	
Time Subacute-chronic (Batke et al. 2011)	Simulated; GM 1.9, GSD 3.3	The comparison of subacute to chronic studies is of limited reliability because of major differences in the scope of examination. Monte Carlo simulation was used to conclude on a subacute to chronic distribution by combining the subacute to subchronic and subchronic to chronic functions (Batke et al. 2011).

Table 2: Combined extrapolations – resulting distributions

Percentile	Interspecies (rat-human) x Intraspecies	Interspecies (rat-human) x Intraspecies x Time		
		Subchronic-chronic	Subacute-subchronic	Subacute-chronic
5 th	1.98	2.19	1.74	1.81
10 th	3.38	3.81	3.15	3.58
....				
50 th	22.7	30.5	28.6	40.0
60 th	33.0	46.5	44.5	64.7
65 th	40.1	57.9	56.3	82.7
70 th	49.3	73.0	71.7	107.8
75 th	61.4	93.8	93.4	143
80 th	79.0	124	125	195
85 th	105	171	177	282
90 th	151	258	273	449
95 th	257	468	516	892

- **All resulting output functions are described to have a log normal characteristic.**
- **A certain percentile of the resulting distribution might be used for risk assessment. However, the combined distributions still inherit non toxicity-related data variability. This results in a relatively high spread of the distribution and thus very high and very low values for the 1th to 10th and 90th to 99th percentiles.**

Probabilistic risk assessment: fit for application?

- **Probabilistic risk assessment aims to use all available data instead of factors corresponding e.g. to a certain percentile of an empiric distribution.**
- **Data quality and data accuracy of the input distributions are the major impact factors**
- **The spread of the input distributions determines the spread of their combination and thus the high and low percentiles. The GM of the combined distribution remains stable, being the product of the GM of all input distributions.**
- **The spread of the distributions represents:**
  - **susceptibility differences in toxicity**
  - **data variability not related to chemical specific toxicity differences, but due to non-optimal comparisons, e.g. differences in study design, use of NOEL ratios etc.**
- **The input distributions are not completely independent. Some aspects are considered twice e.g. susceptibility differences caused by aging or gender aspects. Aging differences contribute to the extrapolation of time (subchronic-chronic), interspecies (if chronic studies (in both genders) are evaluated) and intraspecies differences.**
- **In further studies, the physico-chemical and toxicological nature of the substances at both extremes of the distribution functions will be analyzed. Another focus for future analyses will be the impact of different routes of exposure (oral, inhalation, dermal).**

References

Batke M, Escher S, Hoffmann-Doerr S, Melber C, Messinger H, Mangelsdorf I (2011) Evaluation of time extrapolation factors based on the database RepDose. Toxicol. Lett. 28:205(2)
Bitsch A, Jacobi S, Melber C, Wahnschaffe U, Simetska N, Mangelsdorf I (2006) REPDOSE: A database on repeated dose toxicity studies of commercial chemicals – a multifunctional tool. Regulatory Toxicology and Pharmacology 46, 202-210
Escher SE, Batke M, Hoffmann-Doerr S, Messinger H, Mangelsdorf I (2013) Interspecies extrapolation based on the RepDose database—A probabilistic approach Toxicology Letters, in press, http://dx.doi.org/10.1016/j.toxlet.2013.01.027.
Hattis D, Banati P, Goble R (1999) Distributions of individual susceptibility among humans for toxic effects. Ann. Ny Acad. Sci 895, 286-316.
Schneider et al. (2005) Uncertainty analysis in workplace effect assessment. Research project No. 1012. ISBN 3-86509-121-6. In the publication series of the Federal institute for occupational safety and health
Vermeire T, Pieters M, Rennen M, Bos P. (2001) Probabilistic assessment factors for human health risk assessment. – A practical guide. TNO Nutrition and Food Research Institute, Zeist, The Netherlands, TNO report V3489

Acknowledgement

The work presented on this poster was funded by ERASM (Environmental Risk Assessment and Management, http://www.erasm.org/)