Time extrapolation factors for risk assessment: are group specific extrapolation factors possible? (eTOX V)

2684/P184

Sylvia E. Escher[1], M. Pastor[2], P. Carrio[2], S. Hoffmann-Dörr[3] ,Thomas Steger-Hartmann[4], I. Mangelsdorf[1]

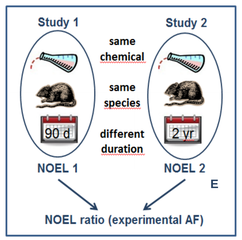
[1]ITEM Fraunhofer, Hanover, Germany; [2]GRIB, IMIM, Universitat Pompeu Fabra, Barcelona, Spain; [3]Henkel AG & Co.KGaA, Düsseldorf, Germany; [4]Investigational Toxicology, Bayer Pharma, Berlin, Germany

ABSTRACT

- In risk assessment time extrapolation factors (EFs) are used when a short time study is available, but chronic exposure needs to be considered.
- Probabilistic analyses are needed to substantiate current EFs by exploring large experimental datasets.
- EFs were derived from paired studies, each representing the ratio of the long term study NOEL divided by the short term study NOEL

Aims: Collect the largest possible dataset to derive robust EFs, evaluate grouping strategies to learn more about potential group specific EFs

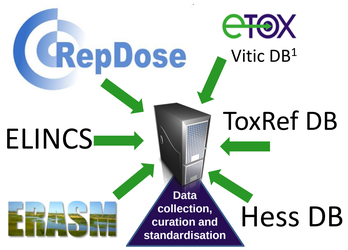
EFs calculated from paired studies



$$EF = \frac{\text{short term study NOEL}}{\text{long term study NOEL}}$$

DATA COLLECTION- IN VIVO STUDIES

- Oral repeated dose toxicity studies in rodents were extracted from literature and high quality databases:
- ToxRef, eTOX-Vitic DB, ELINCS, ECHA, Hess (as available from the OECD toolbox v3.3) FhG RepDose®, and industrial studies from the ERASM consortium.
- Two large dataset obtained:

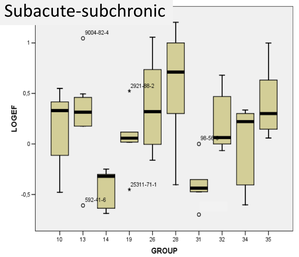


Subacute to subchronic	302 EFs for 172 chemicals
Subchronic to chronic	1059 EFs for 462 chemicals

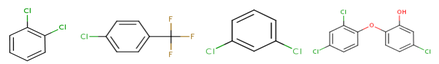
GROUPING ACCORDING TO STRUCTURE

- The compound similarities were estimated using structural fingerprints and Tanimoto distances. Then hierarchical clustering (complete linkage) was applied to obtain groups of structurally similar compounds.

Subacute-subchronic



- Using a distance cutoff of 0.88 and clusters with a minimum of 4 compounds we obtained 10 groups with significantly different mean EF (ANOVA, $p < 0.001$)

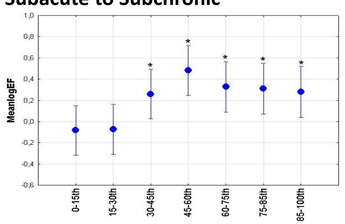


Some structures in the group with the lowest mean logEF (group 31)

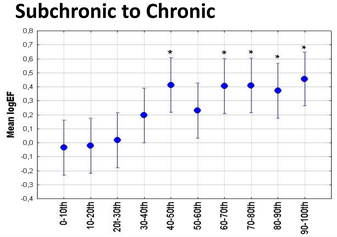
GROUPING ACCORDING TO POTENCY

- In ascending order of toxicity (NOEL of the short tem study) groups of compounds were built, each representing 10 or 15% percent of the entire dataset.
- A consistent trend is observed: EFs increase with decreasing toxicity in short term toxicity study

Subacute to Subchronic



Subchronic to Chronic



RESULT AND DISCUSSION

- Geometric Mean (GM): Most robust value to derive EF based on distribution functions
- Spread of EF distribution increases with increasing data uncertainty
- Data uncertainty arises from differences in study scope (inter- and intra-study type); high differences in dose spacing and dose selection; studies testing only one dose group etc. (data not shown)
- EFs of 1.8 (subchronic-chronic) and 1.6 (subacute-subchronic); confirming our earlier findings with a smaller dataset (Batke et al. 2010[2])
- EFs are lower than those currently proposed in the REACH guidance: 2 (subchronic-chronic) and 3 (subacute-subchronic)

Extrapolation	Dataset	Cut-off (mmol/kgbw/d)	EF		
			N	GM	GSD
Subchronic – Chronic	All		462	1.8	5.0
	Toxic	<0.0016	142	1.0	4.9
	Low toxic	>0.0016	320	2.3	4.7
Subacute - Subchronic	All		172	1.6	4.1
	Toxic	<0.02	50	0.8	3.6
	Low toxic	>0.02	122	2.1	4.0

- Structural grouping results in 10 groups for each dataset with significantly different EFs. Further analyses are foreseen to better define their structural and toxicological boundaries.
- Potency analysis indicated significantly different EFs for low and high toxic compounds: EFs of 1 for toxic and about 2 for groups of less toxic compounds for both extrapolations.
- The conditions under which these group specific EFs may replace the general EF need to be further evaluated.

References

1. Briggs K, Cases M, Heard DJ, Pastor M, Pognan F, Sanz F, Schwab CH, Steger-Hartmann T, Sutter A, Watson DK, Wichard JD. Inroads to Predict In Vivo Toxicology. An Introduction to the eTOX Project. *Int J Mol Sci* 2012; **13**(3): 3820-46
2. Batke, M., S. Escher, et al. (2011). "Evaluation of time extrapolation factors based on the database RepDose." Toxicol Lett **205**(2): 122-129.

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement nº 115002 (eTOX), resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contributions. This project was further financially supported by ERASM (Environmental Risk Assessment and Management).