Update of time extrapolation factors for risk assessment – the benefit of combined databases and probabilistic analyses.

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Introduction

- In regulatory risk assessment, extrapolation factors (EFs) are used to extrapolate from experimental conditions (animal studies) to human exposure.
- Time extrapolation: a short time study is available, but safety assessment for chronic exposure conditions is required.
- The NO(A)EL (no observed (adverse) effect level) of the long term study is then estimated by applying the corresponding EF.

Dataset description

EFs were calculated from paired studies with oral exposure for the same chemical/species/route but different study durations:

$$EF = \frac{\text{short term study NO(A)EL}}{\text{long term study NO(A)EL}}$$

Data were extracted from literature and different databases* e.g. ToxRef, Vitic (from the IMI eTOX project), ELINCS, Hess and RepDose.

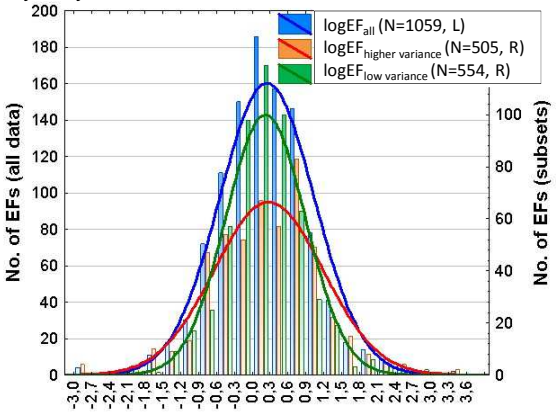
- Subacute to subchronic: 302 EFs for 172 chemicals
- Subchronic to chronic : 1059 EFs for 462 chemicals

I. Data uncertainty and variability

The impact of limitations in study design and comparability of study pairs on EF distribution functions was analysed

- High differences in dose spacing (N= 281 EFs)
- Dose selection: tested concentrations do not overlap (N= 46 EFs)
- Only one concentration tested in one or both studies (N=29 EFs)
- No effects observed in one or both studies (N= 30 EFs)
- Study quality not specified or EFs result from the combination of a low and high quality study (N= 237 EFs)

Figure 1



- Spread increases with increasing data uncertainty and variability
- GM is not significantly different

II. Group specific EFs possible?

Group definition:

- One characteristic structural feature (CSF)
- One CSF and a shared metabolism (CSF + Met)
- One CSF and a similar mode of action (CSF + MoA)
- A CSF and a shared use (CSF + Use) – a selection is shown

Table 1	ID	Name		EF				
			N	GM	GSD	-95% CI	+95% CI	p
	1	All_subchr.-chronic	462	1.8	5.0	1.52	2.04	ref
CSF + MoA	1.1	Carbamates	33	1.6	9.3	0.72	3.51	0.71
CSF + MoA	1.2	OPs	33	1.3	3.7	0.84	2.12	0.30
CSF + Use	1.3	Surfactants	10	0.7	3.4	0.30	1.70	0.07
	2	All_aliphatics	132	1.8	5.2	1.38	2.42	ref
CSF	2.1	Haloalkanes	16	1.8	2.2	1.15	2.67	0.91
CSF	2.2	Phospho	8	2.8	7.3	0.53	14.76	0.45
CSF + Met	2.4	Alcohol/ether	15	2.1	3.2	1.07	3.94	0.77
CSF + Met	2.5	Ester/carboxylic acids	9	1.3	2.7	0.59	2.78	0.51
	3	All_aromatics	318	1.7	4.8	1.41	1.99	ref
CSF	3.2	Phenol	18	1.7	6.5	0.68	4.37	0.43
CSF + MoA	3.4	Aniline	15	1.5	2.1	1.00	2.26	0.78
CSF + MoA	3.5	Nitrobenzene	11	0.9	3.9	0.37	2.30	0.20
CSF + Use	3.7	P#-azole	16	0.6	6.8	0.23	1.78	<0.05
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III. EF according to toxicolog. potency?

- In ascending order of toxicity groups of compounds were built, each representing 10 or 15% percent of the entire dataset.
- EFs per group were analysed
- A consistent trend was observed for both datasets: EFs increase with decreasing toxicity in short term toxicity study

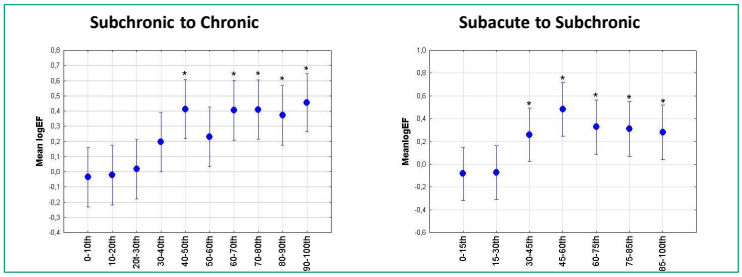

Table 2: Time EFs subchronic-chronic and subacute-subchronic

Extrapolation	Dataset	Cut-off (mmol/kgbw/d)	EF				
			N	GM	GSD	-95% CI	+95% CI
Subchronic – Chronic	All		462	1.8	5.0	1.5	2.0
	Toxic	<0.0016	142	1.0	4.9	0.7	1.3
	Low toxic	>0.0016	320	2.3	4.7	1.9	2.7
Subacute - Subchronic	All		172	1.6	4.1	1.3	2.0
	Toxic	<0.02	50	0.8	3.6	0.6	1.2
	Low toxic	>0.02	122	2.1	4.0	1.7	2.8

IV. Results and conclusion - which EF to use?

- EF based on large datasets
- GM most robust value to derive EF based on distribution functions. High and low percentiles are influenced by data variability and uncertainty (Figure 1)
- Group specific EF could not be derived (Table 1), because of small datasets, high spread, low statistical power
- Remarkably - potency analysis indicated sign. different EFs for low and high toxic compounds (Table 2), same trend observed for inhalation route (systemic effects, data not shown).
- Our analysis resulted in EFs of 1.8 for subchronic -chronic and 1.6 for subacute-subchronic extrapolation, confirming our earlier findings with a smaller dataset (Batke et al. 2010#). These EF are lower than the EFs currently proposed in the REACH guidance of 2 and 3, respectively.

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Batke, M., S. Escher, et al. (2011). "Evaluation of time extrapolation factors based on the database RepDose." Toxicol Lett **205**(2): 122-129.