Evaluation of risk assessment factors for interspecies and time-extrapolation

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Introduction

- Standard Assessment factors have been suggested e.g. by ECHA to extrapolate from animal to human data as well as from non-chronic to chronic exposure
- Publications on extrapolation factors using probilistic approaches are often based on small datasets (1,2) indicating that there is a need for further justification
- The aim of the project is to assess time and interspecies extrapolation factors based on a solid databasis using the Fraunhofer database RepDose (www.fraunhofer-repdose.de) (Table 1)
- Special focus of the project is the applicability of the derived extrapolation factors to surfactants

Table 1: Content of the RepDose database

Study Type		Number of	
		Chemicals	Studies
All		661	2217
Species	Rat	644	1590
	Mouse	335	627
Route	Oral	543	1527
	Inhalation	284	690
Duration	Subacute	244	325
	Subchronic	366	665
	Chronic	272	513

Time extrapolation

Tiered approach

same chemical + species + oral route in mmol/kg bw/d
same chemical + species + inhalation exposure (local/systemic toxicity)

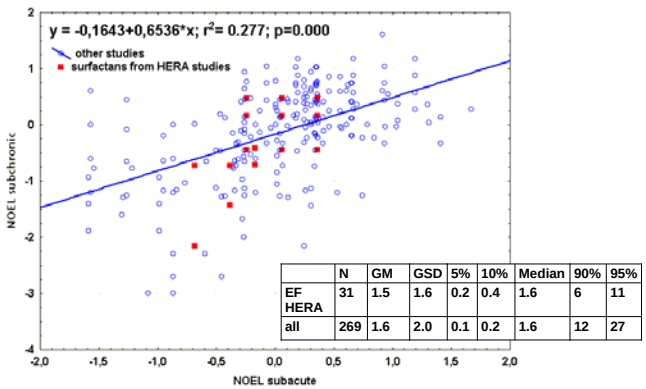
Table 1: Time extrapolation for oral exposure– with the database RepDose

Route	Same chemical + species		EF study duration						
			N	GM	GSD	5th	Median	90th	95th
Oral (mmol/kg b/d)	Study level	Subacute-subchronic	74	2.7	2.0	0.3	1.9	28	53
		Subchronic-chronic	234	1.5	1.8	0.2	1.8	8	12
		Subacute-chronic	49	2.9	2.0	0.1	2.8	25	33
	Chemical level	Subacute-subchronic	49	2.7	2.1	0.3	2.0	28	53
		Subchronic-chronic	109	1.2	1.8	0.2	1.3	5	10
		Subacute-chronic	33	4.2	2.0	0.6	3.0	24	33

Table 2: Time extrapolation for inhalation (local and systemic toxicity). Small datasets are indicated in grey.

Route	Same chemical + species (study level)		EF study duration						
			N	GM	GSD	5th	Median	90th	95th
Inhalation (ppm)	Systemic	Subacute-subchronic	70	1.2	2.1	0.05	1.0	10	16
		Subchronic-chronic	287	1.9	2.0	0.1	2.0	14	16
		Subacute-chronic	29	1.5	1.8	0.2	1.3	7	13
	Local	Subacute-subchronic	16	1.9	1.8	0.2	1.5	13	19
		Subchronic-chronic	61	2.7	1.9	0.5	2.0	19	39
		Subacute-chronic	15	3.4	2.0	0.3	3.4	30	54

Figure 1: Scatterplot of NOEL values for subacute to subchronic extrapolation for oral exposure. Surfactants are indicated in red.



	N	GM	GSD	5%	10%	Median	90%	95%
EF HERA	31	1.5	1.6	0.2	0.4	1.6	6	11
all	269	1.6	2.0	0.1	0.2	1.6	12	27

Results time extrapolation

- Time extrapolation factors differ for oral and inhalation exposure.
- Oral exposure: time extrapolation factors are: 2/1.3/3. They are smaller than those proposed by ECHA (3/2/6).
- Inhalation exposure: local and systemic toxicity have to be distinguished.
- Factors for systemic inhalation toxicity are 1/2/1.3.
- The time extrapolation factors fits well to extrapolate surfactants.

Interspecies extrapolation

Tiered approach

same chemical + duration + oral exposure
same chemical + duration + inhalation exposure

Table 3: Interspecies extrapolation – with the database RepDose

Route	Same chemical, duration		EF interspecies (mouse/rat)						
			N	GM	GSD	5th	Median	90th	95th
Oral (mmol/kg bw/d)	Study level	Subacute	11	1.6	2.9	0.1	1.0	99	192
		Subchronic	148	2.3	1.8	0.3	2.1	14	25
		Chronic	144	2.6	1.9	0.5	2.0	16	27
	Chemical level	Subacute	7	1.2	2.8	0.1	1.0	99	99
		Subchronic	103	2.3	1.8	0.3	2.1	13	25
		Chronic	116	2.6	1.8	0.5	2.0	15	23
Inhalation (ppm)	Study level	Subacute	7	1.3	2.6	0.1	1.0	152	152
		Subchronic	58	0.9	1.8	0.1	1.0	8	8
		Chronic	51	1.2	1.6	0.2	1.0	5	7
	Chemical level	Subacute	6	2.0	1.9	0.4	1.0	152	152
		Subchronic	43	1.2	2.0	0.1	1.0	8	8
		Chronic	37	1.3	1.6	0.2	1.0	5	9

Results – interspecies

Oral

- according to allometric scaling the interspecies factor mouse/rat would be (bw rat/bw mouse)$^{0.25}$ = 1.75
- a mouse/rat extrapolation factor of up to 2.6 is derived, which is slightly higher than the factor just derived by allometric scaling, based on standard assumptions for body weight.

Inhalation

- a factor of 1 would be expected from allometric considerations
- a mouse/rat extrapolation factor of 0.9-1.3 is derived, which confirms allometry

Overall, an additional factor of 2.5, which is proposed to be used for "further interspecies differences" is not confirmed in this approach.

Perspectives

The analysis for time extrapolation factors will be continued, next steps are:

- Analysis of outliers

- Subgrouping of chemicals, and derivation of specific extrapolation factors for e.g.
  - accumulating substances
  - irritating substances

- The combination of extrapolation factors will be evaluated.

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References

1-Vermeire, T. et al (2001), TNO report V3489
2-Schneider, K. et al (2002), Bericht zum UFOPLAN Projekt 20165202, Freiburg