Route to Route Extrapolation Factors
for Regulatory Risk Assessment – a Probabilistic Approach

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Introduction

In human risk assessment any relevant exposure route (oral, inhalation and dermal) has to be addressed. Usually only oral studies are conducted while inhalation and dermal studies are not available. Avoiding additional testing according to the 3R principles (Reduction, Refinement and Replacement of animal testing), route-to-route (R2R) extrapolation factors (EF) can be applied to derive the route-specific no-adverse-effect-level (NOAEL). One prerequisite for this approach is the use of scientifically sound extrapolation factors, which are based on a high quality and broad data basis.

Description of the Dataset and the Analyses

- RepDose database (~ 2800 studies on ~ 850 chemicals, see table for study details).
- Study pairs from different routes were formed based on the conditions: same chemical, same species, same duration.
- As a probabilistic approach, distribution functions for the EFs oral to inhalation and oral to dermal were evaluated.
- Distinction between local and systemic effects:
  - oral studies: all effects were considered, because the same LOAELs were derived for local & systemic effects
  - inhalation studies: all effects were considered but local and systemic effects were separately analysed (respiratory tract vs other organs)

    → resulted in different types of EFs: any EF, local EF and systemic EF, e.g.

$$any\ EF = \frac{\text{oral study NOAEL}}{\text{inhalation study NOAEL}} \qquad systemic\ EF = \frac{\text{oral study NOAEL}}{\text{inhalation systemic NOAEL}} \qquad local\ EF = \frac{\text{oral study NOAEL}}{\text{inhalation local NOAEL}}$$

  - dermal studies: only systemic effects are considered $systemic\ EF = \frac{\text{oral study NOAEL}}{\text{dermal systemic NOAEL}}$
  - corresponding LOAELs were taken if no NOAEL pair was available
- Consistency of the dataset was checked by analyzing the effects of differences in study design on the EF.

Study Numbers in RepDose

Route	Duration	Species		Total / Duration	Total / Route
		Rat	Mouse		
Oral	Short	107	60	169	1911
	Subacute	459	33	499	
	Subchronic	483	102	589	
	Chronic	360	260	654	
Inhalation	Short	116	24	140	769
	Subacute	140	15	155	
	Subchronic	228	71	301	
	Chronic	104	69	173	
Dermal	Short	15	9	24	112
	Subacute	28	2	30	
	Subchronic	26	11	37	
	Chronic	8	13	21	

Extrapolation Factors from Oral to Inhalation

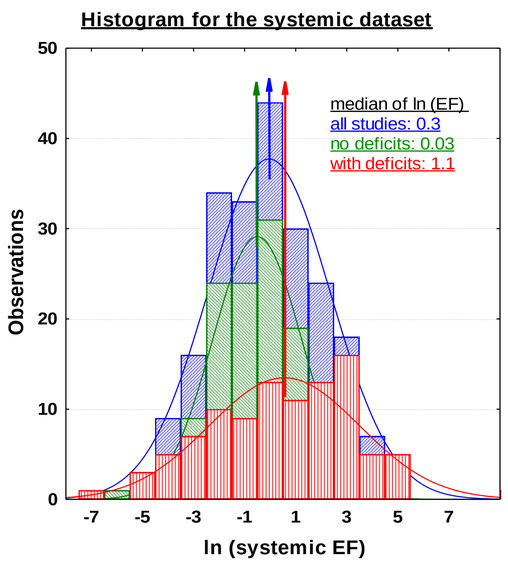
Description of the Inhalation Studies in the Dataset

Type of effects observed	n	Comments
Local effects only	17	no systemic effects
Local effects trigger LOAEL	37	with systemic effects at higher doses
Local & systemic effects @ LOAEL	67	study LOAEL = systemic LOAEL = local LOAEL
Systemic effects trigger LOAEL	21	with local effects at higher doses
Systemic effects only	100	no local effects
no target organ (nto)	4	No effects observed
Total	246	➔226 systemic & 142 local EFs (study pairs)

Influence of Study Design on all EF Types (any, systemic, local)

- Within all EF types ~50% of the study pairs have deficits (high dose spacing, no dose overlapping, no target organ , 1-dose-studies).
- Significant difference between studies with and without deficits, t-test performed with logarithmic EFs, p-value ≤ 0.0009.
- For studies without deficits an EF of ~1 was derived for local & for systemic EFs.

Type of EF	Study design	n	GM	Median	10th	90th	p-value for ln EF
Any EF	All studies	246	2.2	1.9	0.1	48.0	
	With deficits	111	4.4	3.7	0.1	159.7	0.00006
	No deficits	135	1.2	1.3	0.1	11.9	
Systemic EF	All studies	226	1.5	1.3	0.1	33.7	
	With deficits	99	2.8	3.0	0.1	82.6	0.0009
	No deficits	127	1.0	1.0	0.1	9.1	
Local EF	All studies	142	3.3	2.8	0.1	119.9	
	With deficits	78	7.4	5.2	0.1	909.1	0.0002
	No deficits	64	1.2	1.3	0.1	12.3	



Conclusion

- Our analysis justifies an EF of 1 for the route to route extrapolation from oral to inhalation, both for systemic and local effects.
- R2R extrapolation is generally applicable also if local effects are expected in inhalation studies.
- No influence of level of toxicity on any, local and systemic EF (data not shown).

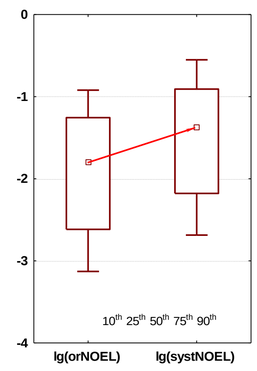
Extrapolation Factors from Oral to Dermal

Description of the Dermal Studies in the Dataset

Type of effects observed	n	Comments
Local effects only	4	no systemic effects
Local effects trigger LOAEL	10	with systemic effects at higher doses
Local & systemic effects @ LOAEL	13	study LOAEL = systemic LOAEL = local LOAEL
Systemic effects trigger LOAEL	4	with local effects at higher doses
Systemic effects only	19	no local effects
no target organ	2	No effects observed
Total	52	➔ 48 systemic EFs (study pairs)

Influence of Study Design on Systemic EF

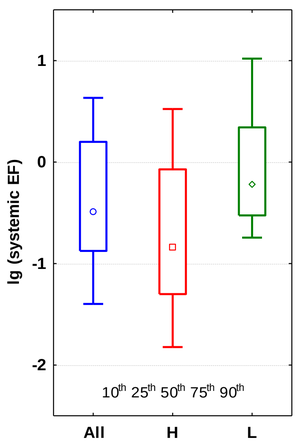
- 12/48 study pairs identified with deficits
- No significant difference between studies with and without deficits, t-test performed with logarithmic EFs.
- Systemic EF of 0.4 was derived, significantly different from 1 based on the 95 % confidence interval, distributions of the corresponding NOAELs, see Box-Plot).



Influence of Toxicity (Tox) on Systemic EF

- The dataset was divided in low (L) and high (H) toxic compounds based on the cut off of 0.01 mmol/kg bw = median of standardized oral NOAELs.
- Significant difference for H and L dataset: t-test performed with logarithmic systemic EF p-value = 0.03.
- Two different EFs were derived for low and high toxic compounds, 0.9 and 0.1, respectively.

Tox	n	GM	Median	10th	90th	p-value for lg EF
All	30	0.4	0.4	0.04	4.4	
H	14	0.1	0.1	0.02	3.3	0.03
L	14	0.9	0.8	0.2	10.5	



Conclusion

- Our analysis resulted in an EF of 0.4 for the route to route extrapolation from oral to dermal for systemic effects.
- Preliminary analysis indicates that EF depends on level of toxicity.

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