Sound oral to inhalation extrapolation factors (EFs) for human health risk assessment

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Introduction

- Route to Route extrapolation (R2R) is required if no in vivo data on the appropriate route are available
- R2R needs to be performed in a case by case approach for the individual substance
- Criteria for R2R are: only systemic toxicity; critical toxic effect is not a local effect; no significant differences in metabolism in both routes; first pass effect is minimal; the substance is soluble in body fluids; account for differences in absorption (ECHA default factor of 2)

Is a general oral to inhalation extrapolation factor of 2 justified?

Method - Tiered Approach

- Probabilistic approach
- Distinction of systemic and local toxicity (Figure 1)
- Amount and quality of data in the database RepDose allows an tiered approach (Table 1).
  1.) same chemical + species
  2.) same chemical + species + study duration
- All factors of all studies (study level)/ one factor for each chemical (chemical level) are analysed

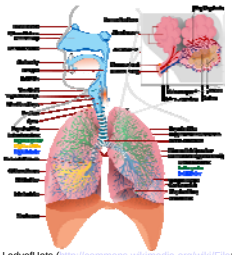
Figure 1: Local and systemic target organs for inhalation exposure

Local targets/organs

eye, respiratory tract (nose, larynx, pharynx, trachea, bronchi, lung)

Systemic targets/organs

liver, kidney, spleen, thymus, testes ...



LadyofHats (http://commons.wikimedia.org/wiki/File:Respiratory_system_complete_en.svg)

Table 1: Content of the RepDose database

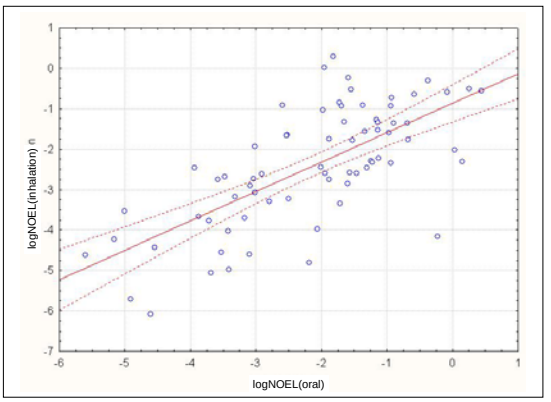
Study Type		Number of	
		Chemicals	Studies
All		661	2217
Route	Oral	543	1527
	Inhalation	284	690
Duration	Subacute	244	325
	Subchronic	366	665
	Chronic	272	513

Results – systemic toxicity

Table 2: Median, GM and percentiles of the oral to inhalation EFs. Small datasets are indicated in grey.

Same ...	Type		EF oral/inhalation N	GM	GSD	5th	Median	90th	95th
Chemical + Species	Study level		245	1.7	2.9	0.03	1.5	43	85
	Chemical level		69	1.4	3.1	0.02	1.1	43	142
Chemical + Species + Duration	Study level	All	87	1.7	3.0	0.03	1.4	44	70
		Subacute	25	0.8	3.1	0.03	0.6	37	43
		Subchronic	48	2.3	2.7	0.09	2.6	44	53
		Chronic	14	2.3	3.4	0.01	1.1	85	167
	Chemical level	All	53	1.2	3.1	0.01	1.1	37	53
		Subacute	17	1.2	3.6	0.01	1.3	43	62
		Subchronic	25	2.0	2.8	0.09	2.4	49	53
		Chronic	11	0.4	2.9	0.01	0.3	5	33

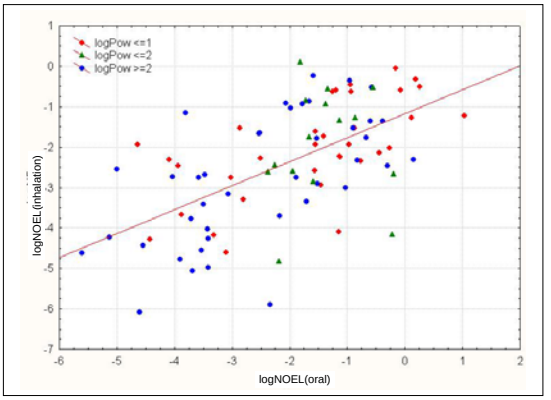
Figure 2: Linear regression analysis



Results/Conclusion

- A general R2R EF based on the Geometric Mean (GM) or Median ranges between 1.1 and 2.6 for systemic toxicity or non-irritating substances (Table 2).
- 90 percent of all chemicals will be predicted in a conservative manner using a general EF of about 40 (37 to 49).
- The regression of log(NOELinhal) versus log(NOEL oral) shows a linear correlation
- The initial linear regression already predicts the NOELvalue of an inhalation study for 48% of all substances in the RepDose dataset (Figure 2, R^2=0.48, p <0.01)
- Subgroups of chemicals will be over- or underpredicted by an general route to route EF.
- Figure 3 depicts subgroups using logPow as descriptor

Figure 3: Illustration of subgrouping using logPow as descriptor



Perspectives

- Multiple regression analysis to increase the predictivity of inhalation NOELs
- Analysis of outliers
- Specific R2R - extrapolation factors for subgroups like
  non-reactive substances e.g. solvents ...
- Several descriptors will be used for multiple regression analyses and subgroup identification
  structural descriptors
  descriptors of reactivity like EHOMO, ELUMO
  physicochemical descriptors e.g. vapour pressure

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