

Development of a database to derive inhalation TTC values for airborne compounds

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Introduction

Thresholds of Toxicological Concern (TTC) are generic human exposure threshold values for groups of compounds below which a risk for human health is negligible.

Developed for oral exposure, oral TTC values have been determined for three structural classes – low, moderate and high toxicity (Cramer class 1 to 3). This classification and oral TTC values cannot be directly extrapolated for inhalable compounds and inhalation risk assessment.

AIM: Define appropriate threshold values for airborne materials below which inhalation exposure is of low to negligible risk to human health

Objectives

- Obj. 1: Identify possible toxicity data sources and constructing the combined inhalation TTC database (WP1)
- Obj. 2: Define criteria for local and systemic effects to compile a database with NOAEC and LOAEC values (WP1)
- Obj. 3: Develop the appropriate chemical discrimination approach based on toxicity potency (machine learning) (WP2)
- Obj. 4: Define the 5th percentile thresholds (WP2)
- Obj. 5: Build the prediction tool (WP2)
- Obj. 6: Publication and dissemination of project output (WP3)

Data model



- Oriented to Fraunhofer database: RepDose®
- Terminology mapped to OECD Harmonized Templates
- Database includes: basic study details with inhalation type and exposure form, detailed effect data

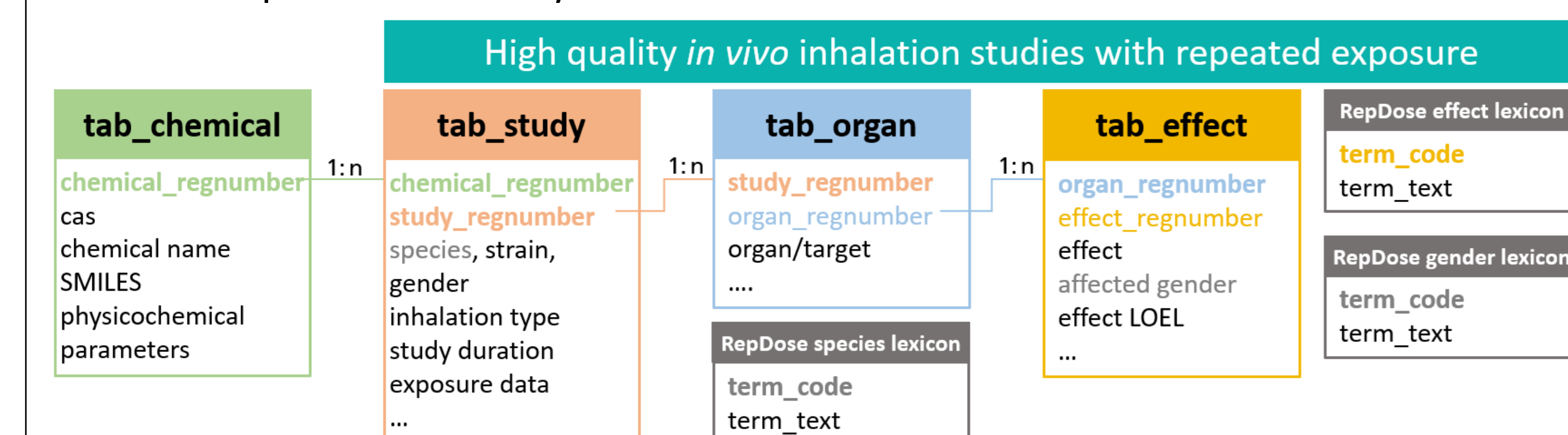


Figure 1: Data model, adapted from RepDose®

Database construction

- High-quality repeated-dose inhalation exposure studies

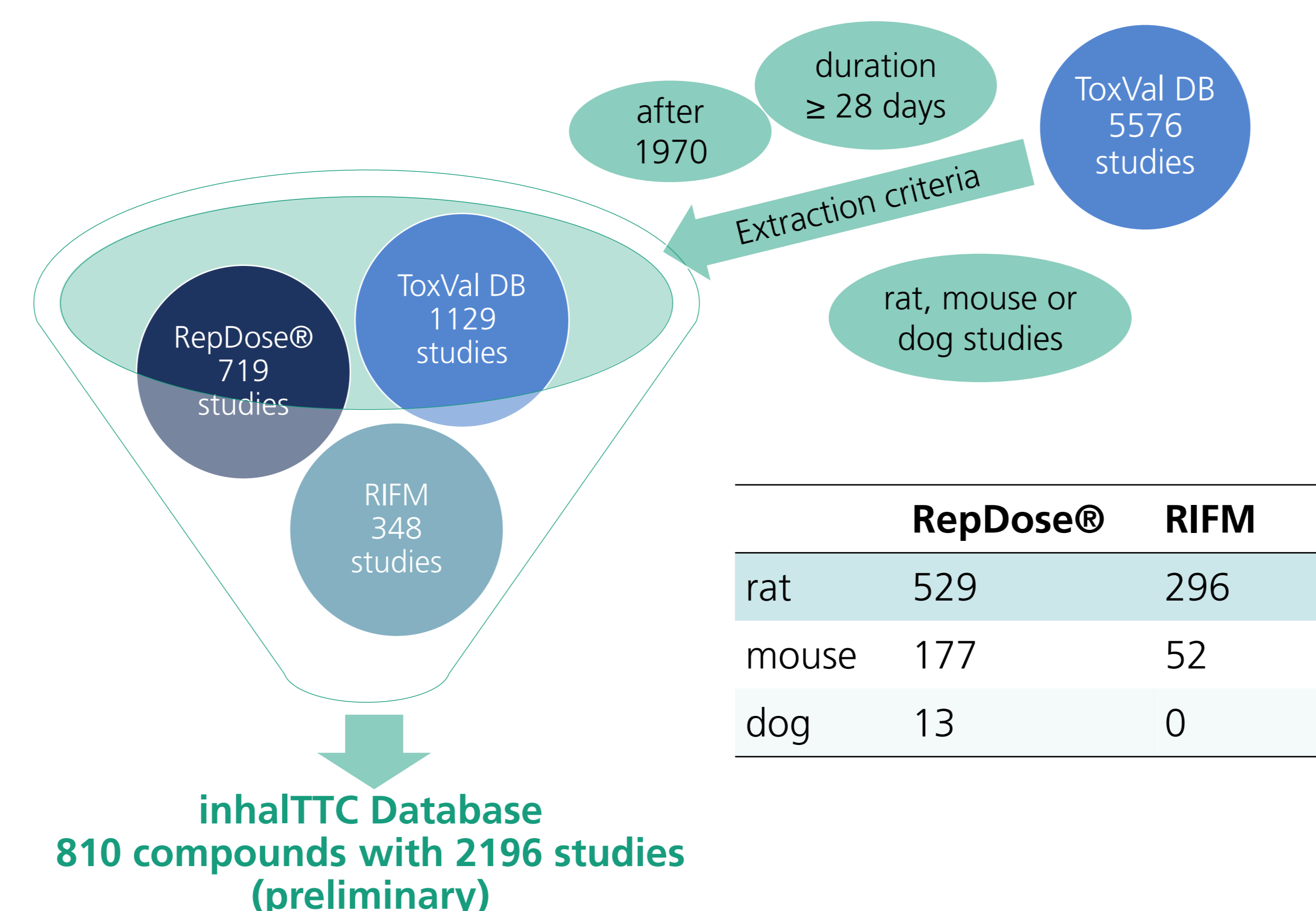


Figure 2: Data sources for the inhalTTC Database, ToxVal DB studies are added to the existing databases RIFM and RepDose®

Status of data entry (since June 2021)



Figure 3: Distribution of the studies entered so far stratified to examined animals and study duration^a

Deriving LOAEC/NOAEC values

- Study effect profiles reviewed to distinguish local and systemic lowest observed adverse effect concentrations (LOAEC)
- Transparent set of criteria are under development to set the LOAEC. Exclusions to date are:

Organ	Effect	Rational	Decision
Kidney	Alpha2u nephropathy	Typical age-related effect in male rats; not human relevant	Not human relevant
Spleen	Hemosiderosis	Typically seen in aged rats; not considered to be adverse if seen in isolation e.g. without hematological findings or disturbed hematopoiesis in bone.	Not adverse
Body weight	Weight change	Weight change < 10%	Not adverse
Organ weight	Weight change	In relation to bw. change; brain and testes do not decrease with decreasing bw. - here we consider abs. wt. changes as finding. For liver and other proliferating organs rel. wt. changes are indicative.	Case by case
Clinical chemistry	Enzyme change	Without additional effects such as histopathology or wt. changes, the effect is considered potentially adaptive	Potentially adaptive
Lymph node		Local lymph node data is an indicator of local effects but only if sufficient details are available; otherwise considered a systemic effect	Systemic vs. local
Body weight	Body weight gain	With food consumption alone as only systemic effects	Not adverse
FOB		All effects considered to be systemic	Systemic
Eye/nose	Encrustation/exudate	Without matching effect in histopathology	Not adverse

FOB = functional observational battery

Outlook

- Clustering substances according to toxic potency using machine learning
- Potential parameters to include: structure, physicochemical properties, fraction unbound, inhalation type, MMAD

Figure 4: Possible methods for machine learning approach (source: datasciencedojo.com/blog/machine-learning-101/)

Acknowledgment

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Disclaimer: This poster does not reflect US EPA policy.

References

- RepDose® Database accessible from <https://repdose.item.fraunhofer.de/>
- Toxicity Values Database (ToxVal DB) accessible from <https://comptox.epa.gov/>
- ^aAnimal figures are from Servier Medical Art by Servier, licensed under a Creative Commons Attribution 3.0 unported license