STRUCTURAL ALERTS TO CLASSIFY INHALATION TOXICITY

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INTRODUCTION

TTC CONCEPT

- **Threshold of Toxicological Concern (TTC): Generic human exposure threshold values for groups of compounds [1]**
- **Below TTC no appreciable risk to human health assumed**
- **Originally developed for oral toxicity**
- **Recently applied to inhalation toxicity [2]**

TTC CLASSES

- **Application of TTC requires classification into TTC classes**
- **Usual approach: Cramer scheme [3]**
- **Cramer scheme not optimal choice for TTC**

NEW APPROACH

- **Derive new TTC values for inhalation toxicity**
- **Replace Cramer classes by new TTC classes**
- **This presentation: Development of structural rules to assign TTC classes**

PROJECT

- **Duration: 2010-2012**
- **Partners:**
  FhG Item, Hannover (principal investigator)
  UFZ, Leipzig

SCOPE

- **Aim: Development of new potency classes for inhalation toxicity**
- **Hypothesis: Local effects of respiratory tract and eyes dominate the very low NOEC values and thus trigger inhalation thresholds**

KEY QUESTIONS

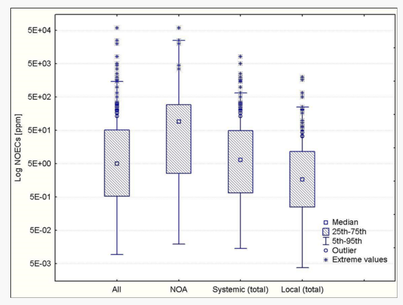
- **Does local toxicity trigger inhalation TTC values?**
- **Potency classes based on toxic modes of action?**
- **Potency classes based on structural alerts for low or high NOEC?**

APPROACH

- **TTC database taken from RepDose [4]**
- **Three datasets based on mode of action (local, systemic, combined)**
- **Combined set: Study NOEC triggered by either local or systemic effect**

DATA SET

- **296 rodent repeated dose inhalation studies derived from the RepDose database [4]**
- **121 studies for local effects**
- **214 studies for systemic effects**
- **67 studies for both local and systemic effects**



Data distribution

CHEMICAL DOMAIN

- ***Atom types:***
  Mainly C, H, O, halogens (197),
  some with N, P, S, Si
- ***Complexity*:**
  Mainly max. 1 functional group (202) partly with multiple occurrence
- ***Polarity*:**
  Many hydrogen bond acceptors (126),
  also nonpolar compounds (71) and hydrogen bond donors (73)

STRUCTURAL RULES FOR GROUPING ACCORDING TO LOCAL OR SYSTEMIC TOXICITY

STRUCTURAL RULES

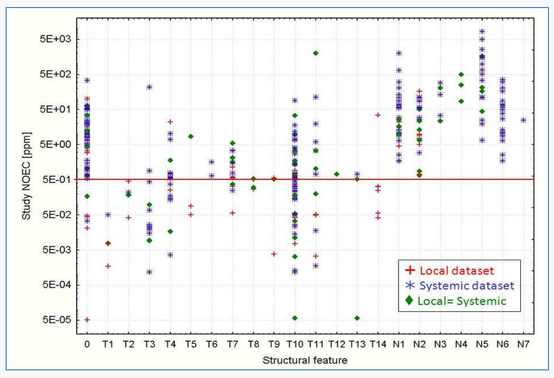
- **Separation into low, medium, high toxicity separately for local and systemic effects**
- **4 Separate rule sets for low/high local/systemic effects**
- **Group medium assigned in absence of rule matches**
- **Significant differences in local and systemic effect rules not observed**

⇨ **Finally two sets: 7 Rules for low and 14 alerts for high toxicity**

- **For automated runs, implemented in ChemProp [5]**

RESULTS

- **High toxic 75 (86%), low toxic 33 (37%) compounds correctly trigger rule, 41 (46%) medium toxic compound correctly do not trigger rule**
- **High or low toxic compounds not triggering correct alerts also do not trigger opposite rule ⇨ grouped for medium toxicity**

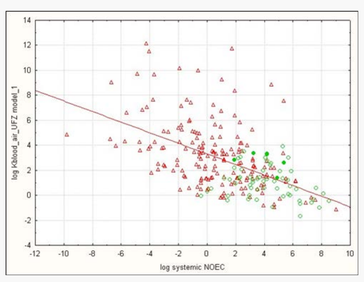


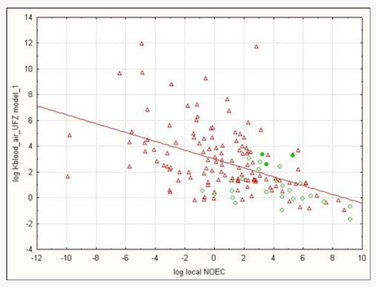
NOEC distribution for the individual rules

EXTENSION WITH PARTITION COEFFICIENTS

- **Inhalation exposure: Ratio absorbed in lung relevant**
- **Approach: Blood/air partition coefficient K_{ba}**
- **Model: UFZ model as available in ChemProp [5]**
- **Note: Available K_{ba} data (and thus model domain) focus on volatile compounds, many compounds of the TTC sets not in domain (marked red in plots below)**

⇨ **At least weak correlation obvious**

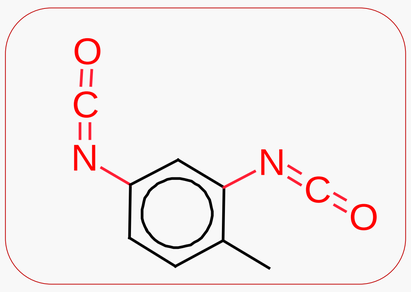




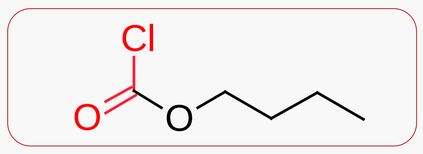
Logarithmic blood/air partition coefficient vs.
log systemic NOEC **log local NOEC**

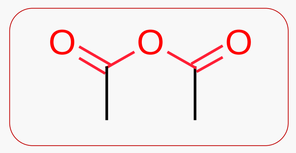
EXAMPLES

HIGH TOXICITY



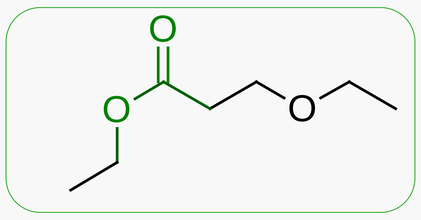
	2,4-Toluenediisocyanate	Dichloromethyl benzene	Dimethyl chlorothiophosphate	Dibutylamine
NOEC	0.05 ppm	0.22 ppm	0.009 ppm	2.1 ppm
ALERT	Isocyanate	Aromatic di /trichlorides	Phosphoric derivatives	*s/t* Aliphatic amines

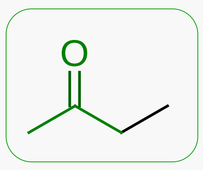


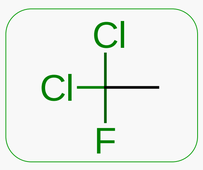


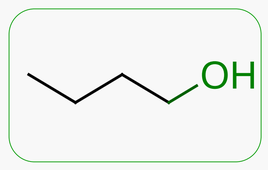
	Butyl chloroformiate	Acetic anhydride
NOEC	0.53 ppm	0.67 ppm
ALERT	Carbonyl- and sulfuric chlorides	Anhydrides

LOW TOXICITY









	Ethyl 3-ethoxypropionate	2-Butanone	1,1-Dichlorofluoroethane	1-Butanol
NOEC	56 ppm	252 ppm	1505 ppm	11 ppm
GROUP	Aliphatic esters	Aliphatic ketones	Particular hydrocarbons	Aliphatic alcohols

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[1] Barlow S 2005. Threshold of toxicological concern (TTC) – a tool for assessing substances of unknown toxicity present at low levels in the diet. In: International Life Science Institute Europe Concise Monograph Series. ILSI Europe a. i. s. b. l., Brussels, 1-32.

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