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Introduction

TTC = threshold of toxicological concern: derives thresholds for structural groups of compounds below which a risk for human health is negligible assuming a life-time, daily, oral intake of the substances (1).

Derivation of the TTC values from datasets of repeated-dose studies with inhalation exposure results in low thresholds. Reasons may be route specific differences e.g. high sensitivity of respiratory tract for local effects (2,3).

Step by Step: An integrative grouping concept to derive threshold values

Step I – Local versus systemic

- Compounds grouped according to their NOEC values in inhalation studies (TTC RepDose dataset, 296 compounds).
- Three datasets according to Mode of action (MoA): locally and systemically active compounds and compounds without any effect (NOA=no organ affected, Figure 1).

Figure 1: Boxplot of NOEC values (ppm): NOA (no organ affected), systemic or local effects at LOEC in the TTC RepDose DB (all).

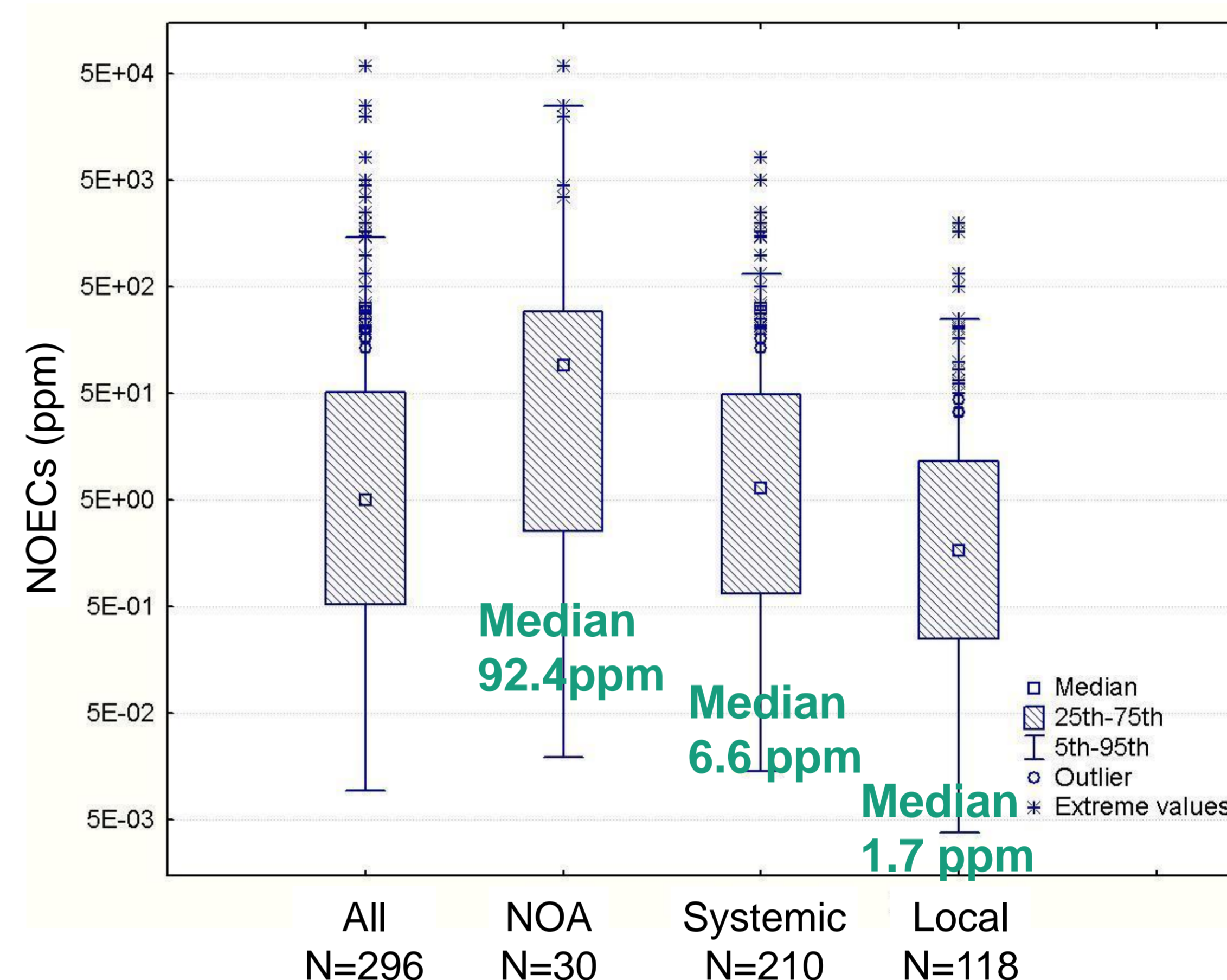
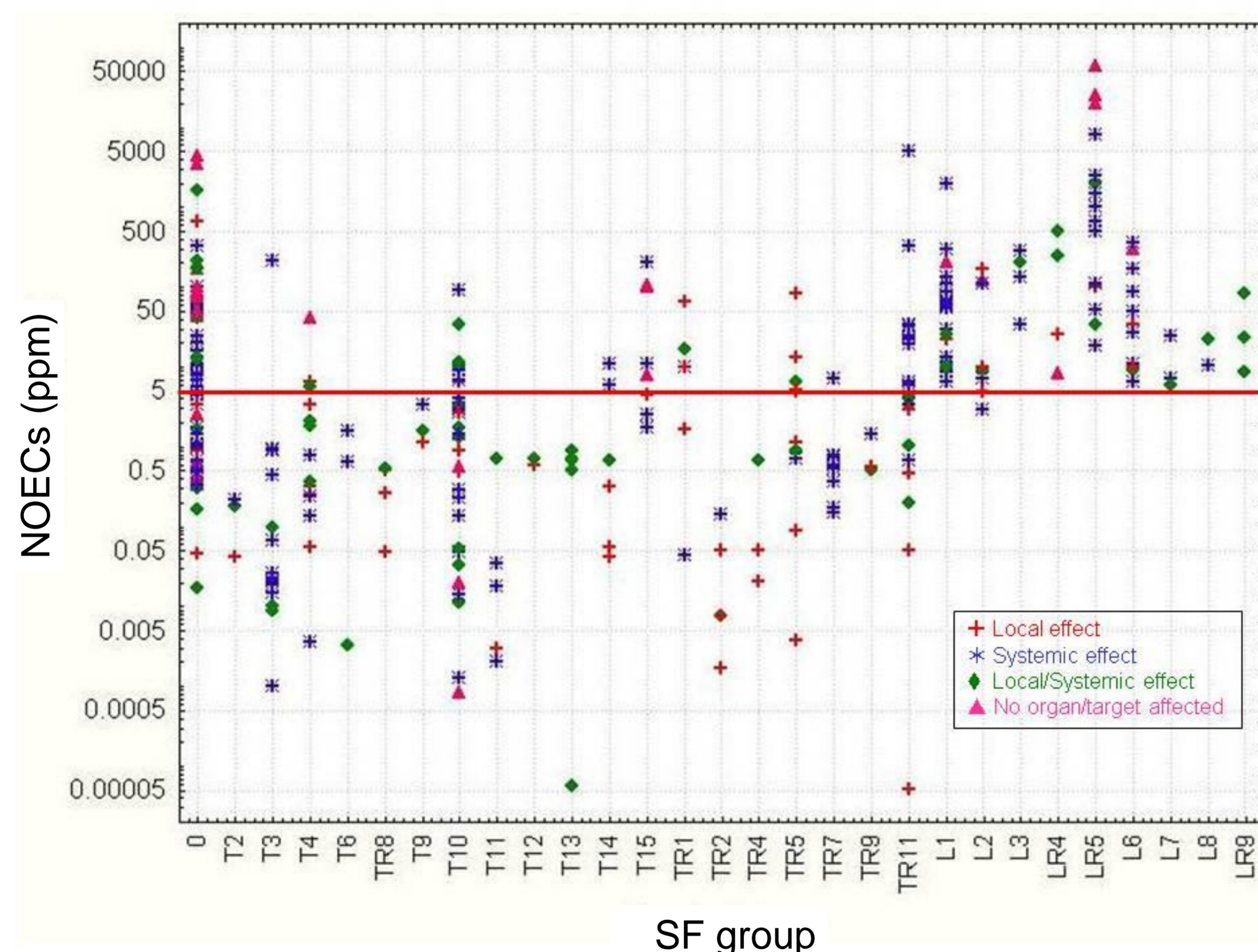


Table 1: Resulting SF groups – a selection

SF	Description	N	NOEC [ppm]		
			Median	5th	95th
0	Not classified	59	11.11	0.17	1665.64
T2	Aromatic di- and trichlorides	3	0.18	0.042	0.22
T3	(Thio)phosphoric esters	14	0.02	0.001	218.33
T4	Aliphatic sec and tert amines, cyclic amines	15	0.37	0.004	41.16
T6	Nitriles	3	0.65	0.003	1.60
T _R 8	Acylhalogenides	4	0.30	0.049	0.53
T9	Lactams	3	1.61	1.150	3.39
L2	Aliphatic ester,	8	9.48	2.915	166.67
L3	Aliphatic ketones	4	169.00	33.333	282.25
L _R 4	Monoaldehydes	5	250.00	8.41	500.00
L _R 5	Fluorine alkanes, germinal alkenes, vic. fluorines	23	666.49	18.333	25028
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Figure 2: NOECs in the 28 SF groups of the TTC RepDose DB



Conclusion and Perspectives

- Two clearly distinct threshold values were derived: 0.047 ppm/d for low toxic and 2.3×10^{-5} ppm/d for toxic compounds (Table 2)
- Thresholds are more explicit for low toxic and toxic compounds compared to those derived by Munro (5) for oral exposure (Table 2)
- Only few MoA specific SF-groups; one concept for all routes possible?
- 21% of the compounds not yet classified
- Some SF-groups with small number of compounds – validation with complementary datasets needed

Step II – Toxicological and structural boundaries

- Groups with shared structural features (SF groups) were identified by using the method ACF (atom centered fragment⁴) and refined by assessing:
 - Structural homogeneity
 - Differences in absorption: Correlation of NOEC values to the blood/air partition coefficient
 - Mechanism/Metabolism: Evaluation of published data on metabolism and mechanisms
 - Toxicological profile: Analysis of toxicological potency and frequency of affected targets and related effects in the entire group and structural alerts for genotoxicity
- 28 SF groups identified, 9 L-groups and 19 T-groups (Table 1; Figure 2)
- Few SF groups specific for systemic or local activity

Table 2: Inhalation thresholds: O not classified, L=low toxic, T=toxic. TTC values derived by Munro et al. (5) are shown.

Group	N	5th [ppm]	Median [ppm]	95th [ppm]	TTC [ppm/d]	TTC [µg/p/d]*	Munro TTC [µg/p/d]
0	59	0.17	11.11	1665.6	1.2×10^{-3}	103.2	
L	85	6.54	66.7	19938	4.7×10^{-2}	3979.3	1800
T	165	0.003	0.70	66.5	2.3×10^{-5}	2.7	90

*The TTC value in µg/person/d calculated with the median molecular weight of the group (0 T, R, L or all)

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