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Investigation on baseline toxicity to rats based on aliphatic compounds and comparison with toxicity to fish: Effect of exposure routes on toxicity

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ABSTRACT

The aim of this paper was to investigate baseline toxicity to rats and effect of exposure routes on toxicity in rats and fish. In this paper, 1588 industrial chemicals were selected to investigate baseline toxicity to rats. The results showed that rat toxicity varies around a constant for classified compounds or homologues. The toxic contributions of substituted functional groups have been calculated and alkanes were used as baseline toxicity. The toxic contributions, equal to toxic ratios (TR), show that small changes in chemical structure can result in different toxic effect in rat toxicity. However, this situation has not been observed in fish toxicity because the threshold of excess toxicity (e.g. log TR = 1) was too high to distinguish differences in toxicity. Very close critical body residues (CBRs) calculated from percentage of absorption and bioconcentration factors indicate that most of aliphatic chemicals may share the same modes of toxic action between rat and fish species. The high estimation error of bioconcentration factor calculated from computer programs for some compounds suggests that classification of excess toxicity should be based on the CBRs, rather than the TR because the TR is closely related to the exposure routes.

1. Introduction

Estimation of rodent acute toxicity (LD_{50}) is an important task in drug design and toxicological risk assessment of chemicals. Rats and mice are the main species used in these studies. Acute toxicity is considered as the adverse effects occurring within a given time, following a single exposure to a substance (OECD Guideline, 2008). There were a number of QSAR (quantitative structure–activity relationship) models available in the literature for predicting the acute toxicity of chemicals to rats (Tsakovska et al., 2008; Koleva et al., 2011). Some of these predictive methods have been derived from limited data sets of structurally similar chemicals such as alcohols or anilines (Devillers and Devillers, 2009). Recent reviews of existing QSAR methods showed that only a few successful QSAR models were capable of predicting LD_{50} values for structurally diverse chemicals (Tsakovska et al., 2008; Sazonovas et al., 2010). Among such works were the models reported by Enslein et al. (1989), Zhu et al. (2009) and Lagunin et al. (2011). LD_{50} after gavage dosing depends on so many variable biological mechanisms that reliable predictions are difficult (Sazonovas et al., 2010). Most of published QSARs are local models, i.e. restricted to single classes of chemicals, such as alcohols, phenols and anilines (Tsakovska et al., 2008).

The chemicals that are not reactive and do not interact with specific receptors form the so-called baseline (or non-polar narcotics) in aquatic toxicity. In principle, the baseline narcosis is the minimum toxicity that compounds exhibit. The narcosis model for baseline toxicity in aquatic toxicology was based on the earlier works (Ferguson, 1939; Könemann, 1981; Verhaar et al., 1992), who proposed that narcosis was caused when the thermodynamic activity of chemicals reaches a threshold and normal physiological processes were disrupted. It has been traditionally assumed that accumulation of compounds in lipoid membranes of nerve cells plays a key role in narcosis-related toxicity (Wolf et al., 2004). Chemicals acting by a narcosis mechanism achieve their effect once a critical concentration or critical volume has been reached within some biophase sites of action within the organism (Ferguson, 1939). The critical concentration, or called "critical body residues" (CBRs), were found to be equal for all non-reactive chemicals, when expressed on a molar basis (mol/kg) (McCarty et al., 1991; McCarty and Mackay, 1993). The baseline organic compounds cause mortality within a very narrow range of whole-body

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tissue concentrations (2–8 mmol/g wet weight or about 50 mmol/g lipid) in small aquatic organisms (Meador et al., 2011).

Aliphatic and aromatic hydrocarbons, chlorinated substituted compounds, alcohols, ethers, ketones, aliphatic secondary and tertiary amines were classed as baseline or non-polar narcotics compounds (Verhaar et al., 1992). Hydrophobicity was commonly found to correlate well with acute toxicity to aquatic organisms for these compounds. In contrast to the aquatic toxicity, the situation in mammalian toxicity is rather different and even small changes in chemical structure can result in different modes of toxic action (Jäckel and Klein, 1991). The study by Lipnick (1991) utilized a baseline QSAR approach, deriving a simple bi-linear log P correlation on LD_{50} for chemically simple compounds, in order to identify new toxicological effects for more complex compounds that were identified as outliers in the baseline correlation analysis. However, unsaturated alcohols do not fit the model used for aliphatic alcohols due to different modes of toxic action. Baseline toxicity in mammalian toxicology could be expected for alcohols, acids, ketones, and one-ring aromatics. The aliphatic amines and aldehydes obviously exceed such baseline-toxicity (Jäckel and Klein, 1991; Wolf et al., 2004; Veith et al., 2009).

Industrial chemicals, such as alcohols, ethers, amines and other aliphatic compounds, usually do not involve highly specific interactions with receptors (Lipnick, 1999). QSAR models of these industrial chemicals as baseline toxicity for aquatic effects are well developed. However, no systematic efforts have been made to develop QSAR models for narcosis as baseline toxicity in mammals for these industrial chemicals (Veith et al., 2009). It is obvious that toxic effects of a chemical are dependent on the exposure routes. As previously reported, variation in acute toxicity between rats and fish (rainbow trout) was reduced when exposure routes were matched (Delistraty et al., 1998; Delistraty, 2000). The comparison of acute toxicity within and between species over various exposure routes can provide insight into mechanisms of toxic action. In this paper, 1588 well-characterized industrial chemicals, such as alkanes, alkenes, alcohols, ethers, aldehydes, ketones, esters, acids and their derivatives, were selected to investigate the baseline toxicity in mammalian toxicology. The aim of this work is: (1) to explore the relationship between rat acute toxicity and hydrophobicity/substructures for aliphatic compounds; on this basis, (2) to investigate the mammalian baseline toxicity and effect of exposure routes on toxicity; (3) to discuss the factors that influence classification of baseline compounds to rats and fish. The ultimate goal of the paper is to explore if baseline compounds defined in acute fish toxicity can also be defined as baseline compounds in acute rat toxicity.

2. Materials and methods

2.1. Rat acute toxicity data (LD_{50})

LD_{50} values used in this paper were compiled from Zhu et al. (2009). Upon request, a collection of 7385 compounds featured in this publication was kindly provided by the authors in its full format, including all the structures and experimental LD_{50} values. The values of LD_{50} for each compound were expressed as log $1/LD_{50}$ in mol/kg (mol per kg of rat body weight) according to standard QSAR practices. After aromatic compounds, sulfides, phosphides, and heterocyclic compounds were removed, the remaining acute toxicity data included 1588 aliphatic compounds. These compounds covering well-characterized aliphatic molecular structures were then classified into different series based on chemical functional groups. The name of each functional group and the number of compounds in each class are summarized in Table 1. Details of the classification, together with CAS number can be found in Tables S1 and S2 of Supplementary material.

Table 1
Toxic contributions of functional groups.

No.	Functional groups	Number of compounds	Toxic contributions
1	Alkane		1.670
2	Alkene/alkyne	507	0.233
3	Alcohol	348	−0.108
4	Ether	313	−0.080
5	Aldehyde	67	0.007
6	Ketone	116	0.042
7	Formate	9	−0.112
8	Ester	337	−0.118
9	Acid	109	−0.015
10	Ring	216	0.101
11	Epoxy-	33	−0.051
12	Carbonate	10	0.433
13	Amine	281	0.404
14	Carbamate	20	0.357
15	Amide	74	0.102
16	Urea	34	0.206
17	Carbamoyl-oxime	7	1.790
18	Acyl chloride	11	0.213
19	Carbonochloridate	5	0.708
20	Nitro-	26	0.527
21	Nitroso-	63	0.464
22	Isocyanato-	14	0.269
23	Nitrate	14	0.890
24	Nitrile	115	0.482
25	Oxime	6	0.275
26	Hydrazine	5	1.080
27	Guanidine	7	0.240
28	N=N/C=N	10	0.475
29	Fluoro-	55	0.900
30	Chloro-	252	0.617
31	Bromo-	58	0.901
32	Iodo-	9	1.220
33	Silane	84	−0.151
34	Total compounds	1588	AE = 0 AAE = 0.44 RMSE = 0.57

Note: The toxic contribution of alkanes is obtained from intercept of the regression. The number of compounds illuminates how many compounds contain the functional group. Because compounds contain more than two functional groups, the sum of the compounds in classes 1–33 is more than the number of total compounds 1588.

2.2. Fish 50% lethal concentration (LC_{50})

The acute toxicity data expressed by LC_{50}, the concentration required to kill 50% of fish within 96 h, were taken from Raevsky et al. (2008, 2009). They presented two datasets containing the acute toxicity of chemicals to guppy (*Poecilia reticulata*), fathead minnow (*Pimephales promelas*) and rainbow trout (*Oncorhynchus mykiss*), respectively. They confirmed the well-known good correlations of toxicity between the three fish species (Katritzky et al., 2001) and mentioned that the quality of the experimental data was not perfect for fathead minnow and rainbow trout. This is primarily because data were obtained in different laboratories with different errors of measurements. Therefore, the 96 h-LC_{50} values in fish for 97 aliphatic compounds used in this paper were based on the toxicity data to guppy. A few data on fathead minnow and rainbow trout were used where data to guppy were missing. Aromatic compounds were excluded from this paper. These data can be found in Table S3 of Supplementary material.

2.3. Fish bioconcentration factor (BCF) and rat intestinal absorption (%Abs.)

The internal concentrations were calculated from BCF and %Abs for fish and rats, respectively. The log BCF values were estimated from a log BCF–log K_{OW} relationship (Eq. (1)). This equation is used to estimate the log BCF values for compounds (excluding