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Investigation on modes of toxic action to rats based on aliphatic and aromatic compounds and comparison with fish toxicity based on exposure routes

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HIGHLIGHTS

- The toxic contributions of functional groups have been calculated.
- Reference threshold of excess toxicity has been developed in rat toxicity.
- Different MOAs were observed in rat and fish toxicity.
- Some compounds are classified as less inert compounds for rats, but not for fish.
- Different toxic effects on rat and fish are due to the difference in exposure routes.

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ABSTRACT

The modes of toxic action (MOAs) play an important role in the assessment of the ecotoxicity of organic pollutants. However, few studies have been reported on the MOAs in rat toxicity. In this paper, the toxic contributions of functional groups in 1255 aromatic compounds were calculated from regression and were then compared with the toxic contributions in aliphatic compounds. The results show that some functional groups have same toxic contributions both in aromatic and aliphatic compounds, but some have not. To investigate the MOAs in rat toxicity, the distribution of toxic ratio (TR) was examined for well-known baseline and less inert compounds and thresholds of log TR = 0.3 and 0.5 were used to classify baseline, less inert and reactive compounds. The results showed that some compounds identified as baseline compounds in fish toxicity were also classified as baseline compounds in rat toxicity. Except for phenols and anilines which were identified as less inert compounds in fish toxicity, aromatic compounds with functional groups such as ether, nitrile, nitrophenol, isocyanatoe and chloro were identified as less inert chemicals in rat toxicity. Reactive compounds identified in fish toxicity exhibit greater toxicity to rats. These compounds can undergo nucleophilic substitution, acylation and Schiff base formation with biological macromolecules. The critical body residues (CBRs) calculated from absorption and bioconcentration show that log 1/CBRs in rat toxicity are not equal to that in fish for some compounds. It suggests that the exposure route can affect the identification of MOAs between these two species for these compounds.

1. Introduction

Mammalian acute toxicity is an important biological endpoint for drug design and toxicological risk assessment of chemicals. They can be obtained by a single administration of a chemical within 24 h period and expressed as median lethal dose (LD_{50}) of the chemical. The preferred animal for experimental testing is the rat although other rodent species may be used (Moore et al., 2013; Lu et al., 2014). However, experimental testing of compounds on rodent acute toxicity is costly and criticized for ethical reasons. The alternative approach using quantitative structure–activity relationships (QSAR) has been suggested as a means of identifying the presence or absence of hazardous properties of the substances (Tsakovska et al., 2008; Lagunin et al., 2011). QSAR methods on mammalian toxicology have been proposed for predicting LD_{50},

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but most of these were derived from limited data sets of structurally similar chemicals such as alcohols or anilines (Devillers and Devillers, 2009; Sazonovas et al., 2010). For example, the data on the rat oral LD_{50} values for saturated monohydric alcohols were well-fitted by a bilinear model. Polyamines require a fragment-descriptor reflecting the poly functionality and anilines were best predicted by a combination of electronic, steric and hydrophobic parameters (Jäckel and Klein, 1991; Koleva et al., 2011).

The efforts already made to develop QSAR models for mammalian toxicity demonstrate the usefulness of the approach not only for predictive purposes but also for a better understanding of the multiple mechanisms involved in the toxicity, such as non-polar narcosis, polar narcosis and reactive mechanisms (Tsakovska et al., 2008). Baseline toxicity is associated with chemicals acting by narcosis mechanism which is the reversible suppression of physiological function brought about by hydrophobic binding of chemicals to cell membranes and proteins. Because these weak interactions impact countless membranes and proteins non-specifically, normal physiological functions decline and lethality is approached for a broad array of chemical structures (Veith et al., 2009; Aruoja et al., 2014). It has been estimated that about 70% of monomeric industrial organic compounds exert their toxicity to aquatic organisms via the narcosis mechanism (Bradbury and Lipnick, 1990). The toxic mechanism of polar narcosis is not clear. The interaction of polar compounds with biological macromolecules may be through physical interaction rather than chemical reaction. It is well-known that the reactive mechanism includes the formation of covalent bonds between electron-poor (electrophilic) substrate and a biological electron-rich (nucleophilic) target molecule, especially biological macromolecules such as nucleic acids and proteins (Lipnick, 1999; Schwöbel et al., 2011). Such as Schiff base formation, bi-molecular nucleophilic substitution (S_N2), acylation and aromatic nucleophilic substitution (S_NAr), these are the most important direct acting covalent binding mechanisms (Aptula and Roberts, 2006; Aptula et al., 2006; Schultz et al., 2006; Roberts et al., 2007).

Although QSAR models and MOAs of industrial chemicals for aquatic toxic effects are well developed and investigated, no systematic efforts have been made to develop QSAR models for rat toxicity for industrial chemicals and their MOAs are not clear. In our previous study (He et al., 2014), log $1/LD_{50}$ values of 1588 industrial aliphatic compounds were examined to investigate the baseline toxicity to rats. The result showed that rat toxicity varies around a constant for each specific class of compounds, and chemical classes of alkanes, alcohols, ethers, acetones, esters and acids can be classified as baseline compounds. In the present paper, 1255 well-characterized industrial aromatic chemicals, such as benzenes with the functional groups of halogen, alkanes, alkenes, alcohols, ethers, aldehydes, ketones, esters, acids, amine, nitro, nitroso, isocyanato, nitrate, nitrile and their derivatives were selected to investigate the baseline (non-polar narcotic), less inert (polar narcotic) and reactive compounds in mammalian toxicology. The aims of this work are: (1) to explore the relationship between log $1/LD_{50}$ and substructures for aromatic compounds and compare with log $1/LD_{50}$ of aliphatic compounds; (2) to investigate modes of action (baseline, less inert and reactive compounds) based on the toxic ratios; and (3) to compare the modes of action in rat toxicity with fish toxicity and discuss the effect of exposure routes on toxicity.

2. Materials and methods

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

Experimental LD_{50} values for 7385 compounds were taken from literature with the full format and all the structures (Zhu et al., 2009). After sulfides, phosphides, and heterocyclic compounds were removed, the remaining data included 1588 aliphatic and 1255 aromatic compounds. These well-characterized aliphatic and aromatic molecular structures were classified into different series based on chemical functional groups. The names of functional groups 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.

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

The concentration required to kill 50% of fish within 96 h, were taken from Raevsky et al. (2008, 2009). They confirmed the well-known good correlations of toxicity between the three fish species 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 128 aromatic compounds and 100 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. These data can be found in Table S3 of the Supplementary Material.

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

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 with log K_{OW} in the range from 1 to 7 in the Epi Suite (version 4.0) software (http://www.epa.gov/opptintr/exposure /pubs/episuite.htm).

$$\log\ \mathrm{BCF} = 0.6598\ \log\ K_{OW} - 0.333 \tag{1}$$

$$\%\mathrm{Abs.} = 100 \times [1 - \mathrm{Exp}(-10^{0.747-0.340A-0.155B})] \tag{2}$$

The percentages of rat intestinal absorption (%Abs.) of aromatic compounds were calculated by Eq. (2). Here, A is the overall solute hydrogen bond acidity and B is the overall hydrogen bond basicity. This method was based on the rat intestinal absorption dosed orally by gavage for 105 compounds (Zhao et al., 2003). The predictive ability of the method is good for compounds with high absorption (e.g. %Abs. > 90%).

2.4. Calculation of toxic contributions

The toxic contributions of substituted functional groups were calculated from the multiple linear regression analysis with the Minitab software (version 14). The average error (AE = $\sum$(Obs – Pred)/n), the average absolute error (AAE = $\sum$|Obs – Pred|/n) and the root-mean squared error (RMSE = ($\sum$(Obs – Pred)^2/n)$^{1/2}$) were calculated for all the classified compounds.

3. Results

3.1. Relationship between log $1/LD_{50}$ and structures

Regression analysis has been carried between log $1/LD_{50}$ and molecular descriptors calculated in this paper (e.g. the octanol/water partition coefficient (K_{OW}), the pKa values for acids and bases, the fractions of unionized (F_0), positive (F_+), negative (F_-) and zwitterionic ($F_\pm$) forms at a given pH = 7.4, and the Abraham solvation descriptors (A, B, E, S, V)) for 1255 aromatic compounds. The result showed that the relationship was very poor. The