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Discrimination of excess toxicity from narcotic effect: Influence of species sensitivity and bioconcentration on the classification of modes of action

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HIGHLIGHTS

- Some classified compounds share same mode of action to four species, but some are not.
- Species sensitivity can significantly affect the discrimination of excess toxicity.
- Species sensitivity is dependent on toxic mechanism and physiological structure.
- Different cut-offs need to be used in the discrimination of excess toxicity.

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ABSTRACT

The toxicity data of 2624 chemicals to fish, *Daphnia magna*, *Tetrahymena pyriformis* and *Vibrio fischeri* were used to investigate the effects of species sensitivity and bioconcentration on excess toxicity. The results showed that 47 chemical classes were identified as having the same modes of action (MOAs) to all four species, but more than half of the classes were identified as having different MOAs. Difference in chemical MOAs is one of the reasons resulting in the difference in toxic effect to these four species. Other important reasons are the difference in sensitivity and bioconcentration of species. Among the four species, *V. fischeri* has the most compounds identified as reactive MOA. This may be due to some compounds can be easily absorbed into the bacteria, react with the DNA or proteins, disrupt the normal function of the cell and exhibit significantly greater toxicity to the bacteria. On the other hand, the skin and lipid content of aqueous organisms can strongly inhibit the bio-uptake for some reactive compounds, resulting in a less toxic effect than expected. *D. magna* is the most sensitive species and *T. pyriformis* is the least sensitive species of the four species. For a comparison of interspecies toxicity, we need to use the same reference threshold of excess toxicity. However, some reactive compounds may be identified as baseline or less inert compounds for low sensitive species from the threshold developed from high sensitive species. The difference in the discrimination of excess toxicity to different species is not only because of the difference in MOAs for some compounds, but also due to the difference in sensitivity and bioconcentration.

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1. Introduction

The assignment of compounds to a particular mode of action (MOA) is important in the development and utilization of quantitative structure–activity relationships (QSARs) for ecotoxicity (Schwöbel et al., 2011), since it is based not only on the chemical itself but also on the understanding of interaction between the chemical and the living organism. Baseline chemicals (or polar narcotics) are composed of several substituted hydrocarbons, such as alkanes, alcohols, ethers, ketones and benzenes with halogen substituents. Less inert (or polar narcotics) are formed by substituted phenols, anilines, pyridines and aliphatic primary amines. Reactive chemicals include compounds with different types of action, including oxidative phosphorylation uncoupling, Michael addition, bi-molecular nucleophillic substitution (S_N2), aromatic nucleophilic substitution (S_NAr), acylation and Schiff base formation. Excellent

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reviews of reactive compounds have been reported in the literature (Verhaar et al., 1992; Russom et al., 1997; Enoch et al., 2011; Schwöbel et al., 2011).

The discrimination of excess toxicity from narcotic effect plays a crucial role in the study of modes of action of organic compounds (Von der Ohe et al., 2005). For the identification of reactive compounds from excess toxicity, the concept of toxic ratio (TR) was employed to discriminate the excess toxicity from narcotic effect. The excess toxicity values were calculated from predicted baseline toxicity divided by the experimental values (Verhaar et al., 1992). Until now, several TR thresholds have been reported in the literatures in the discrimination of excess toxicity to different species (Von der Ohe et al., 2005; Koleva et al., 2011). The threshold of log TR = 1 was commonly used to discriminate excess toxicity from narcotic effect (Verhaar et al., 1992; Russom et al., 1997; Schramm et al., 2011). However, this threshold was only based on the distribution of toxicity data to fish (guppy). The effect of species sensitivity on the discrimination of excess toxicity from the threshold to different species has not been reported in the literature.

The discrimination of excess toxicity from narcotic effect to two species (*Daphnia magna* and *Tetrahymena pyriformis*) has been investigated in our previous paper (Zhang et al., 2013). The results showed that both experimental uncertainty and bioconcentration could bring about difficulties in the discrimination of the toxic category of chemicals, resulting in different toxic ratios and leading to mis-identification of toxic category and outliers. In this paper, toxicity data of 2624 compounds (949 to fish, 757 to *D. magna*, 990 to *T. pyriformis* and 1239 to *Vibrio fischeri*) compiled from literature and databases were used to study the effects of species sensitivity, as well as bioconcentration and experimental uncertainty, on the discrimination of MOAs to four species. The compounds were classified into different classes or homologues based on the substituted functional groups and MOA of the compounds. The toxic ratios (TR) were calculated for these class-based compounds. The aim of the work was: first, to perform analysis on the species sensitivity from the overlapped compounds and interspecies correlation between the toxicity data of class-based compounds to any two of four species, respectively; second, to develop baseline and less inert models and use them to discriminate the excess toxicity from narcotic effect levels of organic compounds; third, to examine the similarity and difference of toxicity to species with different sensitivity; fourth, to discuss the effect of species sensitivity and bioconcentration on the discrimination of excess toxicity and identification of reactive compounds to the four species.

2. Materials and methods

2.1. Biological data

2.1.1. 50% lethal concentration (LC_{50}) to fish

The toxicity data expressed by LC_{50} (M), the concentration required to kill 50% of fish within 96 h for 949 compounds, were taken from several references and a database. The LC_{50} values to guppy (*Poecilia reticulata*) and rainbow trout (*Oncorhynchus mykiss*) were taken from Raevsky et al. (2008) and Raevsky et al. (2009). The LC_{50} values to fathead minnow (*Pimephales promelas*) were taken from Russom et al. (1997), Yuan et al. (2007), Papa et al. (2005), Eroglu et al. (2007), and Raevsky et al. (2008) and Raevsky et al. (2009) respectively. These LC_{50} values to fathead minnow were averaged and are presented in Table S1 of Supplementary material. The LC_{50} values to medaka (*Oryzias latipes*) were taken from CHRIP (Chemical Risk Information Platform, http://www.safe.nite.go.jp/english/db.html). The interspecies correlation shows that the toxicities are well correlated to each other with high correlation coefficients between four fish species. Therefore, a single combined toxicity data set for fish was constructed in this paper. The $\log 1/LC_{50}$ to the four fish species collected from different sources, together with names, SMILES and CAS numbers for all the compounds, are in Table S1 of Supplementary material.

2.1.2. 50% effective concentration (EC_{50}) to Daphnia magna

The toxicity data to *D. magna* for 757 compounds were collected from the Japan database CHRIP and references (Pedersen and Petersen, 1996; Genoni, 1997; Seymour et al., 1997; Jin et al., 1998; Peng and Roberts, 2000; Abe et al., 2001; Kamaya et al., 2005; Papa et al., 2005; von der Ohe et al., 2005; Frank et al., 2010). The toxicity values were reported either as LC_{50} (50% lethal concentration in 48-h) or EC_{50} (50% effective concentration in 48-h). Some studies used mortality (LC_{50}) and immobilization (EC_{50}) as identical endpoints in the context of *D. magna* toxicity (Genoni, 1997; von der Ohe et al., 2005). The $\log 1/EC_{50}$ (including $\log 1/LC_{50}$) collected from different sources, together with names, SMILES and CAS numbers for all the compounds, are in Table S2 of Supplementary material.

2.1.3. 50% growth inhibition concentration (IGC_{50}) to Tetrahymena pyriformis

The toxicity data of the concentrations producing a 50% growth inhibition on *T. pyriformis* in 40-h that is expressed as $\log 1/IGC_{50}$ for 990 compounds were compiled from different references (Schultz, 1997 and Schultz et al., 2005; Cronin and Schultz, 1998; Cronin et al., 2002; Katritzky et al., 2003; Dimitrov et al., 2004; González et al., 2004; Roy et al., 2005; Castillo-Garit et al., 2008). 48-h growth inhibition of the ciliates *T. pyriformis* determined for 18 organic narcotics, 13 epoxides, and two thiiranes by Schramm et al. (2011) was also compiled in this paper. No significant difference was observed between 40-h and 48-h assay for the overlapped compounds and some of these compounds even have exactly same toxicity values in the two endpoints. The $\log 1/IGC_{50}$ collected from different sources, together with names, SMILES and CAS numbers, can be found in Table S3 of Supplementary material.

2.1.4. 50% bioluminescence inhibition concentration (IBC_{50}) to Vibrio fischeri

The concentration values causing a 50% inhibition of bioluminescence after 15 or 30 min exposure to *V. fischeri* (expressed as IBC_{50}) for 1239 compounds were taken mainly from several references (Kaiser and Palabrica, 1991; Cronin et al., 1998 and Cronin et al., 2000; Zhao et al., 1998; Terasaki et al., 2009; Dearden et al., 2000; Aruoja et al., 2011; Jones et al., 2011; Qin et al., 2010; Shi et al., 2012; Villa et al., 2012). No significant difference was observed in the two toxicity endpoints. Preference was given to 15 min over 30 min where available (Zhao et al., 1998). The $\log 1/IBC_{50}$ collected from different sources, together with names, SMILES and CAS numbers, can be found in Table S4 of Supplementary material.

2.1.5. Toxicity to four species

For the development of QSAR models, the toxicity reported either in mM or mg l^{-1} was transformed in logarithmic unit in M for the four species. The total number reported in this paper is for 2624 compounds. The averaged toxicity values were used for the overlapped compounds in each species. Charged and organometallic compounds were not used in the analysis from the data sets. The 2624 compounds were classified into different classes/homologues based on the structure and the substituted functional groups. The toxicity values to the four species, together with names, SMILES and CAS numbers, can be found in Table S5 of Supplementary material.

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