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Comparison of toxicity of class-based organic chemicals to algae and fish based on discrimination of excess toxicity from baseline level

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ABSTRACT

Toxicity data to fish and algae were used to investigate excess toxicity between species. Results show that chemicals exhibiting excess toxicity to fish also show excess toxicity to algae for most of the compounds. This indicates that they share the same mode of action between species. Similar relationships between log K_{OW} and toxicities to fish and algae for baseline and less inert compounds suggest that they have similar critical body residues in the two species. Differences in excess toxicity for some compounds suggest that there is a difference of physiological structure and metabolism between fish and algae. Some reactive compounds (e.g. polyamines) exhibit greater toxic effects for algae than those for fish because of relatively low bio-uptake potential of these hydrophilic compounds in fish as compared with that in algae. Esters exhibiting greater toxicity in fish than that in algae indicate that metabolism can affect the discrimination of excess toxicity from baseline level. Algae growth inhibition is a very good surrogate for fish lethality. This is not only because overall toxicity sensitivity to algae is greater than that to fish, but also the excess toxicity calculated from algal toxicity can better reflect reactivity of compounds with target molecules than fish toxicity.

1. Introduction

Fish and algae belong to different trophic levels. Algae are primary producers and fish are consumers in the aquatic food cycles. Environmental hazard and risk assessment of chemicals require aquatic toxicity data from different trophic levels. In the fish toxicity test, the lethal concentration (LC_{50}) is determined through measuring 50% lethality after exposure for 48, 72, or 96 h. In the algal toxicity test, the effective concentration (EC_{50}) is obtained through measuring 50% growth inhibition after exposure for 48, 72, or 96 h (OECD, 1992, 2011). Comparison of toxicity to different species is very important in ecotoxicology. It not only allows the prediction of toxicity to one species from another species, it is also very helpful in the interpretation of mechanisms.

Comparison of acute toxicity data (fish, Daphnia and algae) from the New Chemicals Database of the European Chemicals Bureau showed that the algal growth inhibition test was the most sensitive for 694 diverse compounds (Weyers et al., 2000). Algae revealed considerably higher sensitivity to organic toxicants (e.g. benzenes, aldehydes, and alkanes) compared with fish, Daphnia and other organisms (Tsai and Chen, 2007). On the other hand, analysis on the toxicity data for 3848 chemicals showed that fish had a less sensitive trophic level than algae, whereas Daphnia had the highest sensitivity (Henegar et al., 2011). However, this analysis showed that algae displayed a higher sensitivity towards chemicals containing acid fragments whereas fish presented a higher sensitivity towards chemicals containing aromatic ether fragments. It has been observed that Daphnia are more sensitive than algae and fish for anilines and their chlorinated derivatives (Dom et al., 2010). It is clear that species sensitivity in toxicity is associated with characteristics of chemical structures.

Interspecies correlation is a very useful tool for predicting toxicity and sensitivity comparison among species. Investigation on the toxicity to three organisms showed that the correlation of fish with Daphnia toxicity values was better than that with algae and correlation between the three toxicity tests was better than between log K_{OW} and any toxicity test (Weyers et al., 2000; Tebby et al., 2011). The same situation has been observed in research on other ecotoxicity databases (Lessigiarska et al., 2004). The difference in correlation to different organisms may be due to difference in bio-uptake and mode of toxic action (MOA) (Zhang et al., 2010). The algal toxicity data does not well correlate either with fish or Daphnia toxicity data on a diverse range of compounds, but when

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excluding the classes acting specific MOA toward one organism (insecticides and several classes of herbicides), good relationships were found (Tremolada et al., 2004). Satisfactory correlation relationships between toxicity data from algae and other aquatic organisms were found (R^2 = 0.66–0.82) for 90 organic chemicals with various MOA (Tsai and Chen, 2007). The compounds acting with the same MOA towards two different species have a higher probability of showing good interspecies correlation. Structurally comparable chemicals with a non-specific MOA (e.g. narcotics and less inert compounds) normally show relatively small interspecies toxicity differences, the lower the specificity of MOA of the compounds, the stronger are the relationships. Although the species sensitivity and interspecies correlation are very useful in the comparison of difference in toxicity among species, no systemic investigation has been carried on the species sensitivity for the compounds with a diverse range of structures. More importantly, it is very difficult to reveal if the studied chemicals share the same or different MOAs from the species sensitivity and interspecies correlation.

The excess toxicity expressed as the toxic ratio (TR) is calculated by dividing predicted baseline toxicity by the experimental values. The toxicity for less inert (polar narcotic) chemicals is between 5 and 10 times higher than that predicted by baseline toxicity model, whereas the toxicity for reactive chemicals, as well as for specifically acting chemicals is between 10 and 10^4 times higher than that predicted by baseline toxicity equation (Verhaar et al., 1992). The threshold of TR = 10 was commonly used to discriminate excess toxicity from narcotic effect (Russom et al., 1997; Schramm et al., 2011). The advantage of using the concept of excess toxicity is that not only we can compare if chemicals have same or different species sensitivity, but also reveal if chemicals share the same or different MOAs among species. In this paper, toxicity data of fish for 949 compounds and algae (*Pseudokirchneriella subcapitata*, also known as *Selenastrum capricornutum* and *Raphidocelis subcapitata*) for 468 compounds compiled from literature and database were used to study the excess toxicity of fish and algal 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 interspecies correlation analysis between the toxicity data of class-based compounds to fish and algae, and investigate the sensitivity of species; Second, to discriminate the excess toxicity from narcotic levels for classified compounds; Third, to compare the excess toxicity to different classes of compounds and discuss their MOAs; Fourth, to investigate the factors that can affect the classification of MOAs.

2. Materials and methods

2.1. Toxicity data to green algae and fish

Algal toxicity data of growth rate expressed as EC_{50} (mol/L), the 50% growth inhibition concentration within 72 or 96 h, were derived from our compiled data set (Fu et al., 2015). This data set contains 2323 log $1/EC_{50}$ values for 1081 chemicals to 26 green algal species, but only 468 log $1/EC_{50}$ values to *P. subcapitata* were extracted in this paper. Evaluation on algal toxicity data showed that algal toxicity is species-dependent and significantly different toxicity sensitivity has been observed for some algal species. Therefore, only one algal species, *P. subcapitata*, was used in the analysis. This species has commonly been used in the algal toxicity test and has the most toxicity data in the data set. Because no great difference was observed in toxicity between 72 and 96 h, the toxicity data to *P. subcapitata* were taken either from 72 h, 96 h exposure period or their averaged values.

The toxicity data expressed by LC_{50} (mol/L), the concentration required to kill 50% of fish within 96 h for 949 compounds, were taken from several references and have been published in our previous paper (Li et al., 2015). The fish species includes guppy (*Poecilia reticulata*), rainbow trout (*Oncorhynchus mykiss*), fathead minnow (*Pimephales promelas*) and medaka (*Oryzias latipes*). The interspecies correlation shows that the log $1/LC_{50}$ values are well correlated to each other with high correlation coefficients between four fish species. Same situation has been observed by other authors (Raevsky et al., 2008, 2009). Therefore, a single combined toxicity data set for fish was constructed and used in this paper.

The total number of compounds reported in this paper is 1074 compounds. The charged compounds were excluded in this paper. The compounds were classified into different classes based on their functional groups. The names, SMILES and CAS numbers of all the compounds can be found in Table S1 of Supplementary material.

2.2. Excess toxicity

In order to evaluate and discriminate the excess toxicity, TR values were calculated from the difference of the predicted baseline or minimum toxicity and the experimentally determined value (Verhaar et al., 1992; Von der Ohe et al., 2005; Neuwoehner et al., 2010; Schramm et al., 2011).

$$\mathrm{TR} = \mathrm{LC}_{50\,\mathrm{pred}}\,(\mathrm{baseline})/\mathrm{LC}_{50\ \mathrm{exp}} \quad (1)$$

$$\log\,\mathrm{TR} = \log\,1/\mathrm{LC}_{50\ \mathrm{exp}} - \log\,1/\mathrm{LC}_{50\,\mathrm{pred}}\,(\mathrm{baseline}) = \mathrm{Residual} \quad (2)$$

A threshold of TR = 10 (or log TR = 1) was used to discriminate excess-toxic compounds from narcotic level. A TR-value close to 1 and less than 10 indicates baseline or less inert toxicity. A TR-value significantly greater than 10 (or log TR > 1) indicates excess toxicity due to the existence of a reactive or more specific MOA. The toxicity value used in Eq. (1) is the lethal concentration expressed in LC_{50}. It can be converted into logarithmic form log $1/LC_{50}$ (see Eq. (2)).

2.3. Molecular descriptors and statistical analysis

Logarithms of octanol/water partition coefficients (log K_{OW}) were obtained from the KOWWIN programme in the EPISuite version 4.0 (http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm). Where possible measured log K_{OW} values were used in preference to calculated values. The relationship between the log K_{OW} and log $1/EC_{50}$ or log $1/LC_{50}$ was performed using a least-squares linear regression with the Minitab software (version 14). For each regression, the following descriptive information is provided: number of observations used in the analysis (N), coefficient of determination (R^2), standard error of the estimate (S) and Fisher's criterion (F). The species sensitivity in toxicity was evaluated from the Pearson correlation coefficient (R), average residual (AR) and absolute average residual (AAR) between the species toxicity endpoints (AR = $\sum(\log 1/EC_{50} - \log 1/LC_{50})/N$, AAR = $\sum|\log 1/EC_{50} - \log 1/LC_{50}|/N$).

3. Results

3.1. Interspecies correlation between toxicities of fish and algae

Fig. 1 presents a plot of experimental log $1/LC_{50}$ and log $1/EC_{50}$ values for fish versus algal species for 343 overlapping chemicals. The Pearson correlation coefficient (R) for the 343 chemicals is 0.81 and coefficient of determination is 0.66. The interspecies regression equation is:

$$\log\,1/\mathrm{LC}_{50} = 0.732\,\log\,1/\mathrm{EC}_{50} + 1.04$$
$$N = 343 \quad R^2 = 0.66 \quad S = 0.64 \quad F = 667 \quad (3)$$