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The discrimination of excess toxicity from baseline effect: Effect of bioconcentration

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HIGHLIGHTS

- Linear logBCF-logK_{OW} relationship is basis for discrimination of excess toxicity.
- Excess toxicity should be based on toxic ratio of internal effect concentrations.
- CBR – logK_{OW} Relationships are parallel for baseline and less inert chemicals.
- Bioconcentration can significantly affect the discrimination of excess toxicity.

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ABSTRACT

Toxic ratio TR is a valuable tool in the discrimination of excess toxicity from baseline effect. Although some authors realized that internal effect concentration or critical body residual (CBR) calculated from bioconcentration factor (BCF) should be used in the TR, the effect of BCF on the discrimination of excess toxicity from baseline effect has not been investigated. In this paper, 951 acute toxicity data to fish (LC_{50}) and 1088 BCFs were used to investigate the relationship between TR and BCF. The results showed that some compounds identified as reactive compounds exhibit excess toxicity, but some do not. BCF is closely related to TR and can significantly affect the TR value. The real excess toxicity which is used to identify reactive chemicals from baseline should be based on the toxic ratio of internal effect concentrations, rather than on the ratio of external effect concentrations, TR. The use of LC_{50} alone to determine TR can result in errors in TR because toxicokinetics (as estimated by the BCF) are ignored. The foundation in the discrimination of excess toxicity from baseline effect is based on the linear relationship between log BCF and hydrophobicity expressed as log K_{OW}. However, log BCF is not linearly related with log K_{OW} for all the compounds. The BCFs with log K_{OW} >7 or <0 are either overestimated or underestimated by the linear baseline BCF model. Parallel lines are observed from calculated log CBR values for baseline and less inert compounds. The log BCF values overestimated or underestimated by log K_{OW} from the baseline BCF model can result in mis-prediction and mis-classification among baseline, less inert and reactive compounds.

1. Introduction

There is an increasing interest in predicting the toxicological effects of chemicals from their structure and physical properties (Schultz et al., 2003; Netzeva et al., 2008). The assignment of compounds to a particular mode of action is important in the development and utilization of quantitative structure–activity relationships (QSARs) for ecotoxicity (Enoch et al., 2008). This requires knowledge of mode of action and the translation of the chemistry responsible for the toxicological effect into usable models (Schwöbel et al., 2011). Major modes of action include non-polar narcosis, polar narcosis, oxidative phosphorylation uncoupling, respiratory inhibition, inhibition of the electron transport chain, acetylcholinesterase (AChE) inhibition, or neurotoxicity. A series of structural rules which aimed to classify compounds according to mechanisms or modes of action have been reported in the literature (Hermens, 1990; Russom et al., 1997; von der Ohe et al., 2005; Enoch et al., 2011).

The chemicals that are not reactive and do not interact with specific receptors form the so-called baseline (or non-polar narcotics). These organic compounds, such as hydrocarbons and halogen substituted hydrocarbons, produce their toxicity by partitioning into biological membranes and causing a nonspecific disturbance of the integrity and function of the cell. Less inert chemicals (or polar narcotics) are not reactive but slightly more toxic than baseline predicted from hydrophobicity. These compounds are usually characterized as possessing hydrogen bond donor acidity, e.g. phenols and anilines. There are strong

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arguments in favor and against the separation of the two mechanisms of action (Dearden et al., 2000). Significantly different regression equations found for non-polar and polar chemicals indicate difference in mechanism (Verhaar et al., 1992). However, other workers have proposed that there is no difference and that the apparent distinction arises through unequal distribution of the compounds between target and non-target lipids, and not by different mechanisms (Vaes et al., 1998; Escher and Hermens, 2002; Escher et al., 2011). The difference between non-polar and polar narcosis is suggested to be due to the inappropriate choice of log K_{OW}, which underestimates the partitioning of polar narcotic compounds between phospholipid cell membranes and water (Roberts and Costello, 2003).

Reactive chemicals and specifically acting chemicals exhibit significantly higher toxicity (lower LC_{50} or EC_{50} values) than predicted from hydrophobicity alone. Such chemicals may form irreversible covalent bonds with amino acid protein residues or act at specific receptors in a non-covalent manner (Verhaar et al., 1992; Enoch et al., 2011). For the identification of reactive compounds, the concept of toxic ratio TR (or called the excess toxicity, Te) was employed to discriminate the excess toxicity from baseline narcotic effect. The excess toxicity values were calculated by dividing predicted baseline toxicity by the experimental values. The threshold of TR = 10 was commonly used to discriminate excess toxicity from baseline effect. If no consideration is given to the experimental uncertainty, excess toxicity indicates that toxicity enhancement is driven by reactive or specific toxicity. But not all the reactive compounds exhibit excess toxicity (Zhang et al., 2013). The modes of action of specifically acting compounds are complex and involve many steps, including uptake, distribution to target and non-target sites, metabolism, and excretion (Escher and Hermens, 2002). The assessment of TR is based on external effect concentrations in water (e.g. EC_{50}), rather than on the target site concentrations in an organism. EC_{50} heavily depends on the biological, physical and chemical proprieties of a chemical and its environment. When data from measurable concentrations in the environment or test systems were extrapolated to an actual toxic effect, the factors of biological species, test time, exposure condition, bioavailability and speciation play important roles (Escher et al., 2011).

On the other hand, target site concentration is an ideal indicator to reflect the intrinsic toxicity of a chemical. Ferguson (1939) proposed that narcosis is caused when the thermodynamic activity of chemicals reaches a threshold and normal physiological processes are disrupted. Chemicals acting by a lethal narcosis mechanism achieve their effect once a critical concentration or critical volume has been reached within some biophase site of action in the organism. However, the concentration in the target site is difficult to obtain directly. As a surrogate, total concentrations in an organism that elicit a critical effect, termed critical body residues (CBR) or internal effect concentrations (IEC), have been used (McCarty and Mackay, 1993). The rationale behind the use of IEC was the observation that the QSARs of bioconcentration factors (BCF) and of lethality (LC_{50}) for baseline toxicants in aquatic organisms were inversely related to each other, resulting in a more or less constant internal effect concentration (Escher and Hermens, 2002; Landrum et al., 2004). The baseline organic compounds cause mortality within a very narrow range of whole-body tissue concentrations (2–8 mmol/g wet weight or about 50 mmol/g lipid) in small aquatic organisms (van Wezel et al., 1995; Meador et al., 2011).

Although some authors realized that the internal effect concentration should be used as an indicator for the acute intrinsic toxicity of chemicals and CBR can be estimated from BCF, CBR = BCF × LC_{50} (Maeder et al., 2004), studies on the relationship between TR and BCF have not been carried out and the effect of bioconcentration on the discrimination of excess toxicity from baseline effect has not been reported in the literature. The use of LC_{50} alone to determine TR can result in errors in TR because toxicokinetics (as estimated by the BCF) are ignored. In this paper, 951 toxicity data and 1088 BCF values to fish were compiled from the literature and databases. The compounds were classified into different classes or homologues based on the substituted functional groups and modes of action of the compounds. The toxic ratios were calculated for these class-based compounds. The aims of this work are: First, to perform interspecies correlation analysis between the toxicity data of class-based compounds to four fish species; Second, to develop a linear baseline toxicity model for non-polar compounds and discriminate the excess toxicity from baseline narcotic effect of organic compounds; Third, to investigate the toxic difference between non-polar and polar narcosis based on the CBRs calculated from non-polar and polar log BCF-log K_{OW} models, respectively; Fourth, to discuss the effect of bioconcentration on the discrimination of excess toxicity based on the relationships between bioconcentration and hydrophobicity.

2. Materials and methods

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

The acute toxicity data expressed as LC_{50} (mmol/L), the concentration required to kill 50% of fish within 96 h, 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, 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, 2009), respectively. These LC_{50} values to Fathead minnow were averaged and are presented in Table S1 of the 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). After removal of quaternary amines and organometallic compounds, the total number of compounds compiled in this paper is 951. All the toxicity data were converted into logarithmic form log $1/LC_{50}$ (in unit of mmol/L) for all the calculations and analysis in the present paper. The data set covers a wide range of log $1/LC_{50}$ (from −2.90 to 6.38, in unit of mmol/L) and log K_{OW} values (from −6.06 to 9.37) with diverse molecular structures. The compounds were classified into different classes/homologues based on structures and the substituted functional groups. The details of the classification, together with log $1/LC_{50}$ to the four fish species collected from different sources, names, SMILES, and CAS number for each compound, can be found in Table S1 of the Supplementary material.

2.2. Excess toxicity

In order to evaluate and discriminate the excess toxicity, TR values are usually 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).

$$TR = LC_{50\ pred}(\text{baseline})/LC_{50\,exp} \quad (1)$$

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

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