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Probabilistic assessment of risks of diethylhexyl phthalate (DEHP) in surface waters of China on reproduction of fish☆

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ABSTRACT

Diethylhexyl phthalate (DEHP) is considered to be an endocrine disruptor, which unlike other chemicals that have either non-specific (e.g., narcotics) or more generalized reactive modes of action, affect the Hypothalamic-pituitary-gonadal (HPG) axis and tend to have specific interactions with particular molecular targets within biochemical pathways. Responding to this challenge, a novel method for deriving predicted no-effect concentration (PNEC) and probabilistic ecological risk assessment (PERAs) for DEHP based on long-term exposure to potentially sensitive species with appropriate apical endpoints was development for protection of Chinese surface waters. PNECs based on potencies to cause lesions in reproductive tissues of fishes, which ranged from 0.04 to 0.20 μg DEHP L^{-1}, were significantly less than those derived based on other endpoints or other taxa, such as invertebrates. An assessment of risks posed by DEHP to aquatic organisms in surface waters of China showed that 88.17% and 78.85% of surface waters in China were predicted to pose risks to reproductive fitness of fishes with thresholds of protection for aquatic organisms based on 5% (HC_5) and 10% (HC_{10}), respectively. Assessment of risks of effects based on effects mediated by the HPG-axis should consider effects on chronic, non-lethal endpoints for specific taxa, especially for reproductive fitness of fishes.

1. Introduction

Diethylhexyl phthalate (DEHP) is one of the most important phthalic acid esters (PAEs). Most of the 1.3 million tons of PAEs produced and consumed in China every year were DEHP and di-n-butyl phthalate (DnBP) (CPCIA, 2009). Because of its versatility, robustness and relatively low cost, DEHP is widely used as an additive to make plastic more flexible and in personal care and medicinal products. However, phthalates are not irreversibly bound to the matrix, so they are easily released once encountered water or organic solvents, and then diffuse into various compartments of the environment. For example, concentrations of DEHP as great as 110 mg L^{-1} have been found in river sediments (Horn et al., 2004). DEHP has been widely detected in Chinese rivers and lakes, including sources of drinking water (He et al., 2013; Li et al., 2015; Shi et al., 2012a, 2012b; Zhang et al., 2015a,b), and therefore concern about DEHP by regulators and the public has been increasingly. DEHP can remain in aquatic ecosystems for relatively long periods of time, and pose risks to aquatic organisms. DEHP causes three primary initiating events in animals (Mathieu-Denoncourt et al., 2015). First, as an endocrine disruptor, DEHP can mimic endogenous estrogen (E2) that can be displaced from carrier proteins and DEHP can bind to the estrogen receptor (ER) where it acts as a weak agonist to activate the ER (Mankidy et al., 2013; Xi et al., 2012). Second, DEHP can affect development of aquatic organisms by disrupting functions of thyroid hormone (TH) and growth hormone (GH), which can increase time to hatching and metamorphosis, histological changes in testes or ovaries (Liu

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et al., 2009). Last, DEHP can alter expression of peroxisome proliferator-activated receptors (PPARs) in mammals, increasing fatty acid oxidation and reducing the animal's ability to cope with the high level of reactive oxygen species (ROS), increasing the occurrences of malformation (Mathieu-Denoncourt et al., 2015). Due to potential for toxicity of DEHP to aquatic organisms, assessing risk of DEHP is crucial to protection of aquatic organisms in surface waters of China.

Despite data on effects of DEHP available for fish, *Daphnia* and algae, no predicted no-effect concentration (PNEC) had been derived for DEHP and its risks to aquatic organisms was thus still unclear, especially in surface waters of China. An important step in assessment of risks of chemicals is determination of PNEC or the maximum concentration at which structure and function of ecosystems are protected. Risks of DEHP to aquatic organisms have been conducted by use of deterministic methods, such as the Hazard Quotient (HQ) (Hu et al., 2012; Luo et al., 2011; Zhang et al., 2015a). However, these assessments have primarily focused on acute lethality of aquatic organisms and derived a toxicity threshold based on assessment factors to correct for uncertainties. DEHP, unlike other chemicals that have either non-specific (narcotics) or more generalized reactive modes of action, is a Hypothalamic-pituitary-gonadal (HPG)-active compound that tends to have more specific interactions with particular molecular targets (Jana et al., 2014). While steroid hormones including estrogen and androgens are core components of the HPG-axis, this system also includes a larger group of tissues and biochemical pathways, which in vertebrates, govern sexual development, maturation, and reproduction (Magdouli et al., 2013). There are a number of consequences arising from this specificity. One important consequence of specificity of xenobiotics, is how criteria are derived when chemicals exceed minimal acute toxicity (Zhang et al., 2015b), but mostly cause longer-term, sub-lethal effects (Ye et al., 2014). In comparison to assessment of risks due to lethality, for those chemicals causing adverse effects on reproduction due to modulation of endocrine function, to be protective of ecosystem structure and function, lesser PNECs, based on sub-lethal effects of reproduction are appropriate (Jin et al., 2014). Second, specificity of molecular targets can also affect specific taxa that are especially sensitive to the chemical MOA of concern. While some biological pathways, such as energy metabolism, tend to be conserved among taxa, others can be quite specific to certain phylogenetic groups. Although control of reproduction through the HPG axis is conserved among classes of vertebrates, taxonomic groups such as invertebrates have different endocrine systems that function differently from those of vertebrates (Caldwell et al., 2008, 2012). As a result, it is likely that data on chronic toxicity for fishes would be the most appropriate for deriving the PNEC for DEHP. Also, it would be unlikely that toxicological data for invertebrate species would drive criteria for these chemicals. Third, assessment factors (AFs) are recognized as a conservative approach for dealing with uncertainty in assessing risks posed by chemicals (Chapman et al., 1998). However, current uses of AFs are based on policy rather than on empirical results, and thus result in values that are protective, but not predictive of effects. These methods are also limited because AFs are somewhat arbitrary and uncertainty of the PNEC is generally not quantified (Chapman et al., 1998). Last, although it is simple, the HQ approach is only appropriate for conservative screening-level risk assessment and for the early stages or tiers of risk assessment. Because risk represents a likelihood or probability of occurrence, it cannot be established from point estimates such as the HQ (Mebane, 2010).

Responding to this challenge, a new method for deriving PNECs and probabilistic ecological risk assessment (PERAs) for DEHP was developed based on long-term exposure to potentially sensitive species with appropriate endpoints. This assessment applied a multi-parametric approach including fitness traits such as survival, growth/development, reproduction, biochemical and molecular biology known to be relevant for health of ecosystems and taxa of aquatic organisms. Probabilistic assessments are considered an improvement on the HQ approach and, thus, recommended for higher tiers of ecological risk assessments (ERA) (Solomon et al., 1996, 2000). Because PERAs can better describe the likelihood of exceeding thresholds for effects and describe risks of adverse effects, this approach has been adopted by a number of researchers (Giesy et al., 1999; Jin et al., 2012a, 2014; Qiao et al., 2007; Zeng et al., 2013). As a higher-tier assessment for a more accurate estimation of ecological risk, the Joint Probability Curve (JPC) was used to describe the likelihood of exceeding the effect thresholds based on different endpoints and the risk of adverse effects for Chinese surface waters.

2. Materials and methods

2.1. Collection of data and generation of SSD

Data for toxic potencies of DEHP were collected from existing toxicity databases (e.g. ECOTOX Database, http://cfpub.epa.gov/ecotox/), published in the literature, and government documents following principles of accuracy, relevance and reliability (Caldwell et al., 2008; Klimisch et al., 1997). For acute toxicity data, selected measurement endpoints were median lethal concentration (LC50) or median effect concentration (EC50) based on immobility for animals and biomass or growth for plants. For chronic toxicity data, no observed effect concentrations (NOECs) were calculated based on values available in the literature. When a NOEC was not available, maximum acceptable toxicant concentration (MATC) or lowest observed effect concentration (LOEC) or ECx values were used. Toxicity data for effects of DEHP on aquatic organisms were divided into four categories of measurement endpoints as follows: survival, growth/development, reproduction and other nontraditional endpoints, e.g. biochemistry and molecular biology (Jin et al., 2014). Effects on fecundity, rate of fertilization, hatchability, expression of vitellogenin in blood plasma (VTG), gonad somatic index, gonadal histology and multiple generation effect to aquatic organisms were classified as effects on reproduction. When the range of values for a taxon was 10-fold or more, or toxicity data of a taxon exhibited greater variability than that for other species, it was eliminated as a outlier (Feng et al., 2015). In the case of multiple values for the same end point and species, the geometric mean was calculated. Toxicity data used for the Species Sensitivity Distributions (SSDs) are reported in the Supporting Information (Table S2).

The SSDs approach is based on the assumption that the toxicity data obtained is a sub-sample of a much larger dataset, and single-species data for many species are fit to a distribution such as the log-normal or log-logistic. In this study, a log-normal distribution model was fitted to different endpoint data points for DEHP, and the fit of the model was evaluated using the Anderson-Darling test. HC_5 (hazardous concentration for 5% species affected) values with 50% confidence were then derived by the ETX 2.0, RIVM software packages. The final PNECs were calculated as the derived HC_5 divided by a factor 1–5, which was a qualitatively chosen factor depending on the amount of supporting evidence, such as non-native species data, multispecies data present, and field data etc (Jin et al., 2014).

2.2. Concentrations of DEHP in surface waters of China

To assess the overall status of DEHP research in aquatic environments of China, data on exposure to DEHP, expressed as