Ecotoxicology and Environmental Safety 97 (2013) 10–16

Contents lists available at ScienceDirect

Ecotoxicology and Environmental Safety

journal homepage: www.elsevier.com/locate/ecoenv

Sensitivity of species to chemicals: Dose–response characteristics for various test types (LC_{50}, LR_{50} and LD_{50}) and modes of action

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ARTICLE INFO

Article history:
Received 2 March 2013
Received in revised form
11 June 2013
Accepted 22 June 2013
Available online 9 August 2013

Keywords:
LC_{50}
LD_{50}
Species sensitivity distribution
Narcosis

ABSTRACT

While variable sensitivity of model species to common toxicants has been addressed in previous studies, a systematic analysis of inter-species variability for different test types, modes of action and species is as of yet lacking. Hence, the aim of the present study was to identify similarities and differences in contaminant levels affecting cold-blooded and warm-blooded species administered via different routes. To that end, data on lethal water concentrations LC_{50}, tissue residues LR_{50} and oral doses LD_{50} were collected from databases, each representing the largest of its kind. LC_{50} data were multiplied by a bioconcentration factor (BCF) to convert them to internal concentrations that allow for comparison among species. For each endpoint data set, we calculated the mean and standard deviation of species' lethal level per compound. Next, the means and standard deviations were averaged by mode of action.

Both the means and standard deviations calculated depended on the number of species tested, which is at odds with quality standard setting procedures. Means calculated from (BCF) LC_{50}, LR_{50} and LD_{50} were largely similar, suggesting that different administration routes roughly yield similar internal levels. Levels for compounds interfering biochemically with elementary life processes were about one order of magnitude below that of narcotics disturbing membranes, and neurotoxic pesticides and dioxins induced death in even lower amounts. Standard deviations for LD_{50} data were similar across modes of action, while variability of LC_{50} values was lower for narcotics than for substances with a specific mode of action. The study indicates several directions to go for efficient use of available data in risk assessment and reduction of species testing.

1. Introduction

Traditionally, effects of chemicals have been related to exposure by describing the fraction of individuals or species affected as a sigmoid function of contaminant levels (Bliss, 1935; Kooijman, 1987). These distribution functions, known as Species Sensitivity Distributions (SSDs), are increasingly used in environmental research and management to indicate potential biodiversity loss due to both toxic and non-toxic stressors (Awkerman et al., 2008; Posthuma et al., 2002; Raimondo et al., 2007; Smit et al., 2008). Describing sensitivity in a standard way provides fundamental insight in the way tolerance to stressors is distributed in the plant and animal kingdom, e.g., when comparing generic and specific modes of action. Furthermore, SSDs are applied in various types of assessment. In Life Cycle Analysis (LCA), SSDs have been adopted as assessment methods for various environmental pressures (Huijbregts et al., 2011). In Risk Assessment (RA) of chemicals, SSDs are used to derive the relative and cumulative risks of individual compounds. Nowadays, environmental quality standards are often based on SSDs as well (e.g., Aldenberg and Jaworska, 2000; EU, 2000; Stephan et al., 1985; Van Straalen and Denneman, 1989). In addition, SSDs are increasingly used in Environment Impact Assessment (EIA) to describe and explain abundances observed in the field observations (Fedorenkova et al., 2012).

Despite frequent use, meta-analyses describing, explaining and predicting patterns in SSDs are scarce (cf. De Zwart, 2002, Harbers et al., 2006). As a result, means and standard deviations characterizing these log-normal distributions have been obtained empirically on a case by case basis, covering a few chemicals tested on a few species at a time. This approach however, is no longer tenable. Each second, one new chemical is added to the more than 65,000,000 already registered (http://www.cas.org/). In the EU and the USA, 100,000$^+$ compounds are awaiting assessment (EU, 2006; USA, 1976). In addition to these chemical challenges, evaluation of biological effects is equally complex. Worldwide, 8000,000$^+$ species, of which 10,000$^+$ are endangered,

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http://dx.doi.org/10.1016/j.ecoenv.2013.06.020

need protection (Baillie et al., 2004). As empirical studies are severely limited because of practical, financial and ethical constraints, detecting regularities in available data is crucial. With the immense task ahead, all information available in related disciplines should be used. While integration of ecological and human risk assessment is often advocated, few studies have actually addressed similarities comparing, e.g., aquatic (LC_{50}) and oral (LD_{50}) toxicity. Explorative investigations have demonstrated correlations between lethal levels for bacteria, fish and rat, suggesting common principles at least for some of modes of action (Delistraty, 2000; Kaiser et al., 1994). In addition, variability between species has been attributed partly to differences in toxicokinetics, suggesting that internal lethal residues (LR_{50}) are less variable than external (LC_{50}) effect concentrations (Hendriks et al., 2005; McCarty and Mackay, 1993).

While differences between modes of action have been addressed in previous studies covering some specific substances, tests and species (De Zwart, 2002, Harbers et al., 2006), a full comparison including the influence of modes of action, test type and species groups is as yet lacking. Hence, the aim of our study was to identify similarities and differences in sensitivities of species to chemicals grouped into several modes of action. To that end, data on three types of toxicity tests were collected from databases: water concentrations LC_{50} [$\mu g\ L^{-1}$] and tissue residues LR_{50} [$\mu g\ kg^{-1}$] lethal to plants and cold-blooded animals as well as oral doses lethal to warm-blooded species LD_{50} [$\mu g\ kg^{-1}$]. First, data on different species were merged per chemical, yielding means μ and standard deviations σ reflecting their sensitivity. Next, the means μ and standard deviations σ of individual substances were averaged by mode of action (MoA). We hypothesized that:

I. Average lethal levels (μ) of estimated internal concentrations for a chemical and MoA ($BCF \cdot LC_{50}$), residues (LR_{50}) and oral doses (LD_{50}) are similar, representing inherent toxicity levels that are consistent between test types.
II. Average lethal levels (μ) for generic MoAs are larger than for specific MoAs across cold-blooded as well as warm-blooded species.
III. Variability of lethal levels (σ) for water exposed cold-blooded species is larger than for orally dosed warm-blooded species reflecting differences in exposure routes and species composition.
IV. Variability of lethal levels (σ) for specific MoAs is larger than for generic MoAs.

Identifying sources of variability in toxicological effects across a wide range of chemicals, modes of action, test types and species improves our ability to use existing data more effectively in risk assessment. If hypothesis I is confirmed, differences caused by kinetics, including biotransformation, are minor and the MoA is likely to be similar for cold-blooded and warm-blooded species. For practical purposes, integration of different types of tests (LC_{50} vs LD_{50}) would become feasible, reducing costs and number of model species to be tested or alternatively producing better environmental forecasts from the same information. While similarities among specific modes of action (hypothesis II) appear likely, this has not been confirmed across as many chemicals and species as are covered in the present study. More fundamentally, we may wonder how tolerance to dissimilar MoAs has evolved to be so different.

Variability in toxicological sensitivity across species, as expressed by the standard deviation of the normal distribution, is also important when assessing risk to a diverse group of species. In fact, variability in response has been identified as the most sensitive parameter for linking emissions to impact (Harbers et al., 2006). Identifying groups of organisms in which uncertainty in sensitivity is greater (hypothesis III) also facilitates effective use of existing toxicological data. In particular, we test the hypothesis that standard deviation varies across different MoAs (hypothesis IV). The practical implication might be that one may use the standard deviation derived in the present study as a default value for a chemical with the same MoA that has not been test to a sufficient number of species. Variability in SSDs can be dependent on the amount of species tested (De Zwart, 2002). Identifying sources of variability across MoAs, test types and species groups might help to guide use of existing data as well as appropriate ways to address uncertainty in species' sensitivity.

In general, a meta-analysis like this provides several benefits to risk assessment, depending on the situation. If a compound has been tested on few species, the average and standard deviation obtained for that compound may be underpinned by a comparison to the typical values reported in the present study for the same MoA (De Wolf et al., 2004; Breitholz et al., 2006; Henning-De Jong et al., 2009). Large discrepancies in sensitivity may indicate unusual test conditions, unexpected modes of action, or biased species selection. If an untested chemical is suspected to act according to a certain MoA, a first prediction of its toxicity to different species can be taken from the meta-analysis. If a statistical characteristic such as the standard deviation turns out to be independent of the MoA, its value may be used even if the MoA of the untested chemical is unknown. Despite the range of benefits expected, it should be stressed that the present paper is intended to demonstrate promising directions for extrapolation rather than ready to use solutions for management.

2. Methods

2.1. Data collection

We collected data from three databases, each representing the largest in its kind. Data collection and treatment have been described in detail in earlier papers and will therefore be briefly described here (Awkerman et al., 2008; De Zwart, 2002; Hendriks et al., 2005).

The acute median effect concentration for plants and the median effect concentrations, including lethality and immobility for cold-blooded animals, together denoted as LC_{50}, were taken from the AQUIRE and the eToxBase databases compiled by the U.S. Environmental Protection Agency (USEPA) and the Dutch National Institute for Public Health and the Environment (RIVM), respectively (De Zwart, 2002). Values were included in the analysis if exposure had lasted for less than 1 to 7 days, depending on the species. In addition, response was taken into account if mortality or immobility of half of the individuals had been observed. Modes of actions were assigned to the compounds using the "Assessment Tools for Evaluation of Risk" (ASTER) and pesticide manuals, following the classification used in Hendriks et al., 2005.

The lethal residues LR_{50} for cold-blooded species were collected from reviews, original papers and the Environmental Residue-Effects Database (ERED) maintained by the U.S. Army Corps of Engineers and the U.S. Environmental Protection Agency (Hendriks et al., 2005). Experiments carried out for determining internal effect residue levels were much rarer and far less standardized than LC_{50} and LD_{50} tests. Hence, we included all residues reporting some reduction of growth (plants) and survival (animals). Most data apply to whole body residues, but a few organ levels were included as well. As the response fraction classes of >0 percent, 50 percent and 100 percent covered about 1/4, 1/2 and 1/4 of the data, respectively, the overall averages are probably still close to the median lethal residue LR_{50}.

The acute median lethal doses, LD_{50}, for warm-blooded species were obtained from the ICE database (http://www.epa.gov/ceampubl/fchain/webice). Data represent single oral applications followed by a 14-day observation period. To cover most of the chemicals often monitored in surveys, we collected additional LD_{50} and LC_{50} values on 2,3,7,8-TCDD and LD_{50} values on cadmium and mercury (Aquire, 2011; Geyer et al., 1993; Romijn et al., 1991).

2.2. Data treatment

LC_{50}, LR_{50} and LD_{50} datasets were treated separately, but in the same way:

1. Reported values were converted to the same unit. If more than one median lethal level was available for a compound and a species, we used their geometric average in the analysis.
2. We aggregated the data of different species per compound by calculating the mean μ and standard deviation σ of the log-transformed values. The accuracy of the means μ and standard deviations σ increased with the number of species