Environmental Science & Technology

Article

pubs.acs.org/est

Dietary Toxicity Thresholds and Ecological Risks for Birds and Mammals Based on Species Sensitivity Distributions

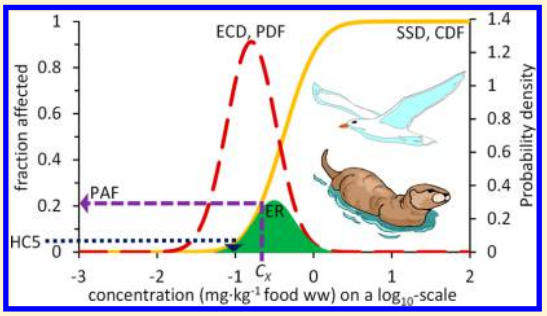
John C. Korsman,*[,†] Aafke M. Schipper,[†,‡] and A. Jan Hendriks[†]

[†]Institute for Water and Wetland Research, Department of Environmental Science, Radboud University, P.O. Box 9010, 6525 AJ Nijmegen, The Netherlands

[‡]PBL Netherlands Environmental Assessment Agency, P.O. Box 303, 3721 MA Bilthoven, The Netherlands

Supporting Information

ABSTRACT: Species sensitivity distributions (SSDs) are commonly used in regulatory procedures and ecological risk assessments. Yet, most toxicity threshold and risk assessment studies are based on invertebrates and fish. In the present study, no observed effect concentrations (NOECs) specific to birds and mammals were used to derive SSDs and corresponding hazardous concentrations for 5% of the species (HC5 values). This was done for 41 individual substances as well as for subsets of substances aggregated based on their toxic Mode of Action (MoA). In addition, potential differences in SSD parameters (mean and standard deviation) were investigated in relation to MoA and end point (growth, reproduction, and survival). The means of neurotoxic and respirotoxic compounds were significantly lower than those of narcotics, whereas no differences were found between end points. The standard deviations of the SSDs were similar across MoA's and end points. Finally, the SSDs obtained were used in a case study by calculating Ecological Risks (ER) and multisubstance Potentially Affected Fractions of species (msPAF) based on 19 chemicals in 10 Northwestern European estuaries and coastal areas. The assessment showed that the risks were all below 2.6×10^{-2}. However, the calculated risks underestimate the actual risks of chemicals in these areas because the potential impacts of substances that were not measured in the field or for which no SSD was available were not included in the risk assessment. The SSDs obtained can be used in regulatory procedures and for assessing the impacts of contaminants on birds and mammals from fish contaminants monitoring programs.



Downloaded via RADBOUD UNIV NIJMEGEN on June 19, 2018 at 12:40:13 (UTC).
See https://pubs.acs.org/sharingguidelines for options on how to legitimately share published articles.

INTRODUCTION

In risk assessment of chemicals, species sensitivity distributions (SSDs) are commonly used for deriving threshold concentrations and assessing ecological risks.[1−4] An SSD is typically characterized by a mean and a standard deviation of $\log_{10}$-transformed toxicity data pertaining to growth, reproduction, and survival or a combination thereof.[4] After estimation of the SSD parameters, a point estimate known as the HC5 (hazardous concentration for 5% of the species) is calculated.[5] The HC5 is the concentration at which less than 5% of the species within an ecosystem is expected to be affected and is often used for deriving environmental quality standards. The SSD parameters are also used for quantification of toxic risks in contaminated ecosystems by calculating the Ecological Risk (ER) or the fraction of species potentially affected by a certain concentration (PAF).[6,7] The ER and PAF are compatible with risk assessments proposed for multiple toxic and nontoxic stress factors.[7−9] For aquatic species (invertebrates and fish), SSDs have been derived for many substances, based on chronic no observed effect concentration (NOEC) data (e.g., Newman et al.[10]). For birds and mammals, however, SSDs are predominantly based on acute median lethal dose (LD50) data.[11,12] Acute LD50-based SSDs might be used for a coarse estimation of the risk a chemical poses to organisms.[4] However, in most cases, it is unlikely that concentration of a chemical in the environment will be high enough to cause acute lethal effects, so NOECs are usually preferred for calculating HC5s, PAFs, and ERs.[4−7,13]

So far, NOEC-based SSDs for birds and mammals have been derived only for cadmium, DDT, dieldrin, lead, lindane, and methylmercury.[14−16] Therefore, deriving NOEC-based SSDs for a larger number of substances is desirable. SSDs can be derived from open literature sources for a few of the 100 000+ chemicals to be assessed.[17] As empirical toxicity studies are severely limited because of practical, financial, and ethical constraints, detecting regularities in available toxicity data and translating these to indicative SSDs is crucial for ecological risk assessment of new and untested substances.[18] Hence, the aims of the present study were to (1) derive SSDs and corresponding HC5s for birds and mammals for a large number of substances from dietary toxicity studies, (2) identify similarities and differences in the means and standard deviations of the SSDs between different MoA's (Modes of Action) and end points (growth, reproduction, survival), and (3) provide an example of how the SSDs obtained

Received: March 13, 2016
Revised: August 29, 2016
Accepted: August 31, 2016
Published: August 31, 2016

© 2016 American Chemical Society

DOI: 10.1021/acs.est.6b01258
Environ. Sci. Technol. 2016, 50, 10644−10652

can be used in risk assessments for birds and mammals by calculating ERs and PAFs for 10 Northwestern European estuaries and coastal areas. Estuarine and coastal environments were selected because they are often contaminated with persistent, bioaccumulative, and toxic substances, including polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons (PAHs), and metals, which may pose an ecological risk to birds and mammals.[19−21]

For identifying similarities and differences in the means and standard deviations of the SSDs (aim 2), we hypothesized that (A) means are higher for narcotics than for substances with a specific MoA, similar to previous findings for SSDs based on LD50s;[17] (B) means for survival are higher than for growth and reproduction, because sublethal end points are generally more sensitive than lethal end points;[22,23] (C) standard deviations (i.e., interspecies variability in sensitivity) are similar for narcotics and substances with specific MoA, similar to previous findings for SSDs based on LD50s;[17] (D) standard deviations are smaller for survival than for growth and reproduction, because survival covers only mortality, while growth and reproduction include more effects variables, such as weight, length, egg production, and number of embryo implantations.[24]

MATERIALS AND METHODS

Toxicity Data Collection and Identification of MoA. Toxicity data on birds and mammals were collected from the ECOTOX database and priority substances.[25,26] We selected only studies on dietary exposure with effects on growth, reproduction, and survival.[4] As chronic effects on bird and mammal populations rarely become manifest in short-term studies (<30 days), we selected only NOECs from long-term studies.[14−16] NOECs expressed as a dose (e.g., mg per kg of body weight per day) were converted to a concentration in food (mg·kg^{-1} food), based on the body weight and daily food intake of the test species as given in the original study.[4] If these data were not provided, the NOECs expressed as a dose were discarded. Toxicity values for metals were corrected based on the relative contribution of the metal (e.g., Cd) to the molecular weight of the compound for which a study was carried out (e.g., $CdCl_2$).[4,14] All collected NOECs were $\log_{10}$-transformed. In case of multiple NOECs for a single substance and a single species on the same end point, the geometric mean was determined prior to the log transformation. Next, we assigned each substance to a MoA using the "Assessment Tools for Evaluation of Risk" (ASTER) and pesticide manuals, following the classification used in Hendriks et al.[17,27] Substances with a narcotic MoA were classified as narcotics. Substances with a neurotoxic MoA and substances known for uncoupling or blocking of the oxidative phosphorylation (compounds with a respirotoxic MoA), a process fundamental to all living organisms, were classified as MoA specific (but not confined) to birds and mammals. Substances known for binding to SH, NH_2, COOH of proteins, and nucleic acids (compounds with a reactive MoA) and compounds with a specific MoA in the plant and fungi kingdom (phytotoxic and fungitoxic compounds) were assigned to a separate group, because the MoA of these substances in birds and mammals is mostly unknown. In the analysis, we focused on 15 MoA's for which most data were available. The collected toxicity data are provided in the Supporting Information (SI, Table S1).

SSD Calculations. *Substance-specific SSDs and HC5 values.* A substance-specific SSD and corresponding HC5 were estimated for substances with NOECs from at least four different species ($n_s \geq 4$) for at least one of the end points' growth, reproduction, or survival (Figure 1).[11] In addition, substance-specific SSDs and HC5 values were estimated based

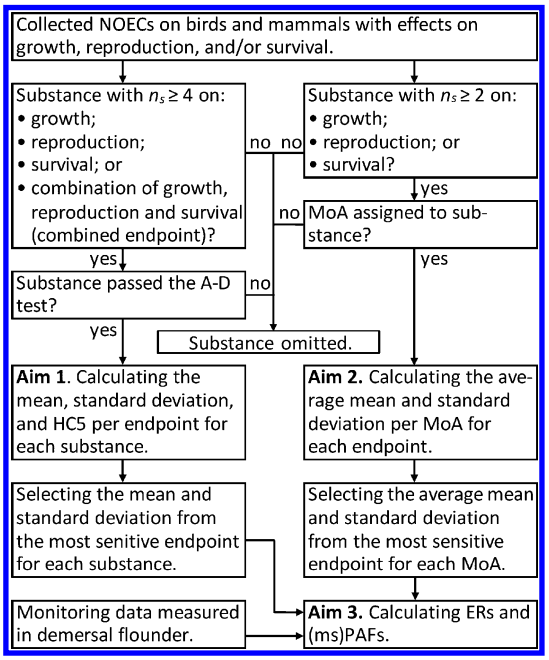


Figure 1. Flowchart visualizing the steps for calculating substance-specific SSDs and HC5s, MoA-specific SSDs, ecological risks (ERs), and multisubstance Potentially Affected Fractions (msPAFs). n_s represents the number of different species tested.

on a combination of the three end points, provided that the number of species tested was sufficient ($n_s \geq 4$). If for a single species a NOEC was available on more than one end point, we selected the NOEC from the most sensitive end point of that particular species for the combined SSD and HC5, following the guidelines of the European Chemicals Bureau.[4,14] The minimum number of NOECs from four different species ($n_s \geq 4$) is lower than recommended in the guidelines of the European Chemicals Bureau ($n_s \geq 10$) and U.S. Environmental Protection Agency ($n_s \geq 8$) for deriving environmental quality standards that protect the whole community (i.e., bacteria to mammals). However, as we include only two taxonomic groups (birds and mammals), we considered a minimum of four species to be sufficient, given that the variation in sensitivity to toxic stressors within a limited number of taxonomic groups is generally lower than over a whole community.[11,28] Moreover, a threshold of at least three to four species is commonly used to derive SSDs for species from a limited number of taxonomic groups.[14−16,28,29] Using a more stringent criterion than the minimum number of four species would lead to a considerably lower number of substances included in this study. For example, using a criterion of at least 10 species would retain only 5 out of the 41 substances. A normal distribution curve was fitted to the collected $\log_{10}$-transformed NOECs. The fit of the model was evaluated using the Anderson−Darling (A-D) test.[6] For substances that passed the A-D criterion of $p > 0.05$, a HC5 was estimated according to

$$\log(\mathrm{HC5}) = \hat{\mu} - k_s \cdot \hat{\sigma} \quad (1)$$

with $\hat{\mu}$ and $\hat{\sigma}$ as the sample mean ($\bar{x}$) and sample standard deviation (s) of the set of $\log_{10}$-transformed NOECs, respectively, and parameter k_s representing a factor to account for the number of species tested, ranging from $k_s = 1.83$ ($n_s = 4$)

DOI: 10.1021/acs.est.6b01258
Environ. Sci. Technol. 2016, 50, 10644−10652

to k_s = 1.64 (n_s > 500).[30] The k_s values as a function of n_s are provided in the SI (Table S2). Compounds that did not pass the A-D test were omitted.

MoA-Specific SSDs. Next to our aim to derive SSDs and corresponding HC5s for specific substances, we also aimed to identify similarities and differences in SSD parameters between different MoA's and end points. To that end, we followed Hendriks et al.[17] and selected substances with NOECs from at least two different species ($n_s \geq 2$; Figure 1). Substances with $n_s \geq 2$ on either growth, reproduction, or survival were aggregated per end point and MoA. Following Hendriks et al.,[17] the average mean and the average standard deviation per MoA for each end point were calculated, each with their standard deviation and 95% confidence interval. Substances to which no MoA was assigned were omitted. As response may be related to the fraction of molecules occupying receptors, we converted the NOECs from weight basis to molar weight.[17] Molecular weights were obtained from the EPISUITE database.[31] The differences in means and standard deviations between MoA's (hypotheses A and C) and end points (hypotheses B and D) were tested for significance ($p < 0.05$) by analysis of variance (ANOVA) using SPSS 17. The differences between narcotics and specific MoA's were tested with the means and standard deviations grouped by growth, reproduction, survival, and a combination thereof. The differences between end points were tested with the means and standard deviations grouped as narcotics, specific MoA's, and the 15 major MoA's combined. Prior to the ANOVA, Levene's tests were conducted to evaluate equality of variances among groups. The Levene's test indicated that the assumption of homogeneity of variance was not violated.

Field Data Acquisition and Treatment. Monitoring data of contaminant concentrations in biota measured in Northwestern European countries were retrieved from the Transitional, Coastal, and Marine (TCM) database.[32] We selected the demersal flounder *Platichthys flesus* as an example prey species because this species is a well-known food source for birds and mammals and one of the most sampled species in Northwestern European marine waters.[32,33] Samples marked as unreliable in the TCM database were omitted. Concentrations in *P. flesus* have been measured in various organs, particularly in liver and muscle. Concentrations on lipid basis were converted to wet weight (ww) basis based on the organ-specific lipid content. If reported, we took the lipid fractions of the corresponding sample. If the lipid fraction was not reported, we used an averaged lipid fraction of 10.0% and 5.6% for liver and muscle, respectively, calculated from all *P. flesus* samples in the whole TCM database. Because predators typically consume the whole fish, we converted the organ-specific concentrations to whole body residues. For organic substances, we assumed that the chemical concentration was uniformly distributed across *P. flesus'* body fat. Methylmercury and metals, however, are known to accumulate at varying concentrations in different organs of fish.[34,35] Residues of methylmercury and metals were commonly measured in *P. flesus'* muscle and liver, respectively.[32] For methylmercury, we used a muscle−whole body ratio (ww) of 1.5, calculated as a geometric mean value based on values of 1.2, 1.4, and 1.9 reported for herring (*Clupea harengus*), perch (*Perca fluviatilis*), and bald notothen (*Pagothenia borchgrevinki*), respectively.[34,36] For cadmium, we used a liver-whole body ratio (ww) of 9.3, calculated as a geometric mean value based on values of 6.3, 9.1, and 14.2 reported for perch, herring, and bald notothen, respectively.[34,36] Liver−whole body ratios (ww) based on bald notothen and catfish (*Clarias gariepinus*) ranged from 3.8 to 24.5 for copper, 1.9 to 122.4 for lead, and 2.5 to 68.0 for zinc, corresponding with a geometric mean liver−whole body ratio of 9.7 for copper, 15.4 for lead, and 13.1 for zinc.[36,37] For the other metals, a liver-whole body ratio (ww) of 10 was used.[35] Mercury compounds in *P. flesus* have been reported as mercury in the TCM database. Mercury compounds in muscle of high trophic level fish species like *P. flesus* consisted of 80% to 100% methylmercury and up to 20% inorganic mercury.[38] Therefore, mercury concentrations in *P. flesus'* muscle were converted to methylmercury and inorganic mercury assuming that 80% of the mercury consisted of methylmercury and 20% of inorganic mercury.[38]

Geographic coordinates or names for each sampling location were retrieved from the TCM database. Sampling locations were pooled when the sampling location name or coordinates pertained to the same estuary or coastal area. To exclude historical residue levels, we selected samples taken in the year 2000 or later. With this boundary, we retained a number of at least two samples per location, which is required to calculate ER. On the basis of the data available, we selected 10 locations in four European countries for the risk assessment (see the flowchart in the SI, Figure S2). For the 10 locations, a total number of 8671 samples were obtained from the TCM database. Of these, the measured concentrations of 977 samples were below the detection limit. Measured concentrations below the detection limit were set to half the detection limit. We analyzed the influence of alternative methods for handling nondetects on the measured concentrations by setting the nondetects at the same value as the corresponding detection limit and by omitting the nondetects. The collected monitoring data are available in the SI (Table S9).

Risk Assessment. *Ecological Risk.* The ER (dimensionless) expresses the probability that a species in the field is exposed to a concentration exceeding its NOEC.[6] The ER is calculated as

$$\mathrm{ER} = \int_{-\infty}^{\infty} \mathrm{PDF}_{\mathrm{ECD}} \cdot \mathrm{CDF}_{\mathrm{SSD}}\, \mathrm{d}x \qquad (2)$$

with PDF as the normal probability density function of the exposure concentration distribution (ECD) of substance x and the CDF as the cumulative distribution function of the sensitivities of the species to increasing x, as quantified by the SSD. The overlap between the $\mathrm{PDF}_{\mathrm{ECD}}$ and $\mathrm{CDF}_{\mathrm{SSD}}$ curves is proportional to the degree of ER expected (Figure 2). For each substance, the ER was calculated with the MS Excel function

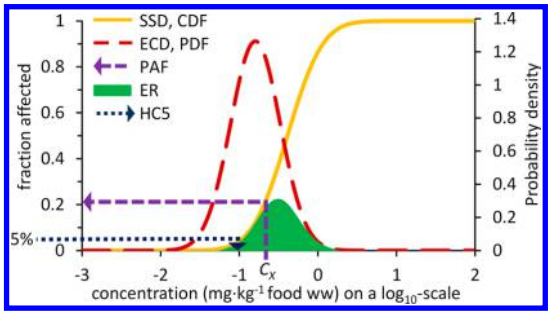


Figure 2. Graphical representation of ecological risk (ER), defined as the overlap between the cumulative probability distribution (CDF) of species sensitivities (i.e., the SSD) and the probability density function (PDF) of the exposure concentration distribution (ECD) of substance x in the field. The arrows indicate the inference of the hazardous concentration for 5% of the species (HC5) and the potentially affected fraction (PAF) of species at a given exposure concentration C_x.

DOI: 10.1021/acs.est.6b01258
Environ. Sci. Technol. 2016, 50, 10644−10652

Table 1. Substance-Specific Mean $\hat{\mu}$, Standard Deviation $\hat{\sigma}$, and Corresponding HC5 (with Corresponding 95% Confidence Intervals) of $\log_{10}$-Transformed NOECs (mg·kg^{-1} Wet Weight in Food) for Substances Tested on at Least Four Different Species ($n_s \geq 4$) on the End Points Growth, Reproduction, Survival, and a Combination Thereof (Combined)[a]

		growth			reproduction			survival			combined			
substance	CAS	$\hat{\mu}$	$\hat{\sigma}$	n_s	$\hat{\mu}$	$\hat{\sigma}$	n_s	$\hat{\mu}$	$\hat{\sigma}$	n_s	$\hat{\mu}$	$\hat{\sigma}$	n_s	HC5
4,4′-DDE	72559										1.8	0.55	4	0.81 (−1.03, 1.41)
4,4′-DDT	50293	2.2	0.47	4	1.5	0.55	5	2.2	0.67	7	1.8	0.80	9	0.41 (−0.64, 0.99)
amitraz	33089611	1.3	0.35	5							1.3	0.35	5	0.67 (−0.19, 1.01)
atrazine	1912249										2.1	0.24	4	1.71 (0.91, 1.97)
benfluralin	1861401										2.5	0.43	4	1.75 (0.32, 2.22)
boric acid	10043353	3.1	0.63	5							3.0	0.75	5	1.64 (−0.18, 2.37)
bromacil	314409										3.2	0.39	4	2.50 (1.21, 2.92)
cadmium	7440439	1.3	0.61	8							1.1	0.62	10	0.01 (−0.74, 0.43)
carbaryl	63252	2.9	0.67	5	3.0	0.62	6	2.9	0.63	4	2.9	0.53	7	2.00 (1.11, 2.44)
carbofuran	1563662	2.2	0.29	4										
chlorotetracycline	57625	1.6	0.75	4							1.6	0.75	4	0.22 (−2.25, 1.03)
chlorpyrifos	2921882	1.3	0.69	4	1.9	0.32	4				1.3	0.60	6	0.30 (−0.87, 0.83)
copper	7440508	1.9	0.57	12	2.4	0.70	6				1.8	0.55	12	0.85 (0.28, 1.19)
cymperator	52315078										1.5	0.21	4	1.14 (0.44, 1.37)
cyromazine	66215278										2.3	0.44	4	1.45 (−0.01, 1.92)
deltamethrin	52918635										1.6	1.30	4	−0.80 (−5.11, 0.62)
diazinon	333415				1.0	0.33	4				1.0	0.33	5	0.37 (−0.43, 0.69)
dichlorvos	62737	1.3	0.44	4	1.2	0.51	4				1.4	0.75	6	0.08 (−1.40, 0.74)
dicofol	115322	1.6	0.52	5	1.6	0.75	4				1.5	0.70	6	0.30 (−1.06, 0.91)
dieldrin	60571				0.6	0.40	7	0.7	0.47	7	0.6	0.45	10	−0.21 (−0.76, 0.10)
difethialone	104653341							−0.5	0.44	4	−0.5	0.44	4	−1.30 (−2.76, −0.82)
diflubenzuron	35367385				2.4	0.13	5				2.4	0.11	5	2.2 (1.93, 2.30)
dimethoate	60515										1.2	0.60	4	0.10 (−1.87, 0.75)
endosulfan	115297										1.1	0.44	5	0.35 (−0.71, 0.78)
endrin	72208										0.7	0.71	4	−0.65 (−3.01, 0.13)
fenitrothion	122145										1.7	0.40	4	0.97 (−0.35, 1.40)
fenvalerate	51630581	2.3	0.74	4							1.9	1.12	5	−0.05 (−2.75, 1.02)
ferrous sulfate	7720787	2.4	0.33	4							2.4	0.33	4	1.85 (0.76, 2.20)
fipronil	120068373										1.8	0.85	4	0.28 (−2.55, 1.20)
hexachlorobenzene	118741										1.5	0.55	4	0.49 (−1.32, 1.08)
lead	7439921	2.9	0.76	6							2.8	0.74	8	1.53 (0.43, 2.09)
lindane	58899										1.6	0.56	4	0.54 (−1.30, 1.14)
mercaptodimethur	2032657										1.6	0.94	4	−0.10 (−3.22, 0.92)
mercury	7439976							0.7	0.59	4	0.6	0.42	5	−0.10 (−1.11, 0.31)
methylmercury	22967926										0.3	0.35	10	−0.29 (−0.72, −0.05)
methylparathion	298000										1.1	0.90	5	−0.49 (−2.68, 0.38)
propoxur	114261										1.3	0.76	4	−0.08 (−2.60, 0.75)
quintozine	82688	2.9	0.48	6	3.4	0.46	4				2.8	0.59	6	1.80 (0.64, 2.31)
sodium fluoride	7681494	1.9	0.74	5							1.8	0.74	5	0.45 (−1.35, 1.16)
trifluralin	1582098	2.6	0.70	5										
zinc	7440666	2.4	0.69	8	2.8	0.84	6	2.8	0.97	5	2.4	0.71	9	1.23 (0.29, 1.74)

[a]Substances are ordered alphabetically by common chemical name. The HC5's for growth, reproduction, and survival are provided in the SI (Table S3).

NORMSDIST $((\hat{\mu}_1 - \hat{\mu}_2)/\sqrt{(\hat{\sigma}_1^2 + \hat{\sigma}_2^2)})$, where $\hat{\mu}_2$ and $\hat{\sigma}_2$ represent the mean and standard deviation of the $\log_{10}$-transformed NOECs for each individual substance, respectively.[6] Factors $\hat{\mu}_1$ and $\hat{\sigma}_1$ represent the parameters of the PDF_{ECD} function of each individual substance. The total ecological risk due to multiple substances was calculated by response addition of the single-substance ERs as

$$\text{total ER} = 1 - \prod_{x=1}^{n_x} (1 - \text{ER}_x) \quad (3)$$

with n_x as the number of substances and ER_x as the ecological risk for each substance individually.[9]

Potentially affected fraction. The PAF (dimensionless) represents the fraction of species potentially affected above their NOECs at a given measured environmental concentration (Figure 2). For each substance, the PAF was calculated by the MS Excel function NORMDIST ($\log(C_x)$, $\hat{\mu}_2$, $\hat{\sigma}_2$, 1) with C_x as the geometric mean exposure concentration and parameters $\hat{\mu}_2$ and $\hat{\sigma}_2$ representing the mean and standard deviation of the $\log_{10}$-transformed NOECs for each individual substance, respectively.[7,39]

Multisubstance Potentially Affected Fraction of Species. The combined (concentration-added) effect of a group of substances with the same MoA ($msPAF_{MoA}$; dimensionless) was calculated by the MS Excel function NORMSDIST (log-

DOI: 10.1021/acs.est.6b01258
Environ. Sci. Technol. 2016, 50, 10644−10652

Table 2. Mean and Standard Deviation of $\log_{10}$-Transformed NOECs ($mol \cdot kg^{-1}$) with Effects on Growth, Reproduction, and Survival Averaged over n_x Compounds per Mode of Action (MoA), with Corresponding 95% Confidence Intervals[a]

	growth[b]				reproduction[c]				survival[d]			
MoA	mean	standard deviation	n_x	n_s	mean	standard deviation	n_x	n_s	mean	standard deviation	n_x	n_s
narcotics												
narcotic A	−2.9 (−3.7, −2.1)	0.31 (0.09, 0.52)	6	2.2	−3.4 (−3.9, −3.0)	0.37 (0.13, 0.61)	9	2.1	−2.9 (−3.7, −2.2)	0.43 (0, 0.86)	3	2.0
narcotic B	−2.7 (−3.0, −2.5)	0.29 (0.06, 0.51)	3	3.3	−2.1	0.46	1	4.0	−2.6 (−3.0, −2.2)	0.57 (0, 1.27)	2	2.5
narcotic C					−3.6 (−4.2, −3.0)	0.19 (0, 0.57)	2	2.0				
MoA's specific to birds and mammals												
neurotoxic A	−3.8 (−4.1, −3.4)	0.57 (0.39, 0.75)	9	2.8	−3.7 (−3.9, −3.4)	0.46 (0.24, 0.68)	16	2.6	−3.4 (−3.8, −3.0)	0.40 (0.21, 0.60)	7	2.9
neurotoxic B	−4.8 (−5.2, −4.4)	0.61 (0.01, 1.21)	3	2.3	−4.7 (−5.1, −4.2)	0.34 (0.11, 0.57)	4	3.5	−4.2 (−5.0, −3.3)	0.42 (0.17, 0.67)	3	3.7
neurotoxic C	−3.9 (−4.2, −3.5)	0.47 (0.32, 0.62)	19	2.6	−3.9 (−4.2, −3.6)	0.48 (0.32, 0.64)	23	2.7	−3.7 (−4.1, −3.4)	0.44 (0.20, 0.69)	10	2.4
respirotoxic A	−3.4 (−4.6, −2.1)	0.44 (0, 1.03)	2	2.5	−3.7 (−5.7, −1.8)	0.26 (0, 0.75)	2	2.0	−3.8 (−5.0, −2.5)	0.25 (0, 0.60)	4	2.0
respirotoxic B	−2.8	0.08	1	2.0					−3.1	0.88	1	2.0
other specific MoA's												
phytotoxic A	−3.2 (−3.6, −2.8)	0.61 (0.16, 1.05)	6	2.3	−3.1 (−3.4, −2.8)	0.29 (0.13, 0.44)	13	2.2	−2.7 (−3.8, −1.7)	0.33 (0, 0.66)	3	2.0
phytotoxic B	−1.8 (−3.2, −0.5)	0.69 (0.18, 1.20)	3	2.3								
phytotoxic C					−2.3 (−2.8, −1.7)	0.12 (0, 0.23)	7	2.0				
fungitoxic A					−3.7 (−4.0, −3.3)	0.59 (0.16, 1.02)	3	2.3	−3.3 (−3.7, −3.0)	0.99 (0.54, 1.43)	2	2.5
fungitoxic B					−3.3 (−3.8, −2.8)	0.24 (0.08, 0.39)	8	2.1	−4.1	0.49	1	2.0
reactive (org.)	−3.0	0.72	1	2.0	−3.4 (−4.6, −2.2)	0.19 (0, 0.57)	2	2.0	−3.4 (−4.0, −2.8)	0.25 (0, 0.57)	3	2.3
reactive (metal)	−3.6 (−4.5, −2.8)	0.47 (0.28, 0.66)	9	5.1	−3.5 (−4.5, −2.4)	0.62 (0.36, 0.88)	6	3.7	−3.7 (−4.8, −2.6)	0.44 (0.14, 0.74)	5	4.4
15 MoA's	−3.5 (−3.8, −3.3)	0.49 (0.40, 0.57)	62	2.9	−3.5 (−3.7, −3.3)	0.38 (0.31, 0.45)	96	2.5	−3.5 (−3.7, −3.0)	0.44 (0.34, 0.54)	44	2.7
all MoA's[e]			99				202				67	

[a] n_s represents the average number of tested species. [b] Of all NOECs with effects on growth, 27% were tested on Norway rat (*Rattus norvegicus*), 15% on mallard duck (*Anas platyrhynchos*), 14% on northern bobwhite quail (*Colinus virginianus*), 14% on house mouse (*Mus musculus*), 10% on domestic chicken (*Gallus domesticus*), and 20% on other species. [c] Of all NOECs with effects on reproduction, 35% were tested on mallard duck, 33% on northern bobwhite quail, 9% on Norway rat, 6% on domestic chicken, 5% on house mouse, and 12% on other species. [d] Of all NOECs with effects on survival, 22% were tested on northern bobwhite quail, 20% on mallard duck, 16% on Norway rat, 11% on house mouse, 9% on domestic chicken, and 22% on other species. [e] Sum for all chemicals, including other MoA.

(TU_{MoA}), 0, average(σ_{MoA})), with TU_{MoA} and σ_{MoA} as the effective toxicity (in dimensionless toxic units) and the average standard deviation of the group of substances with the same MoA, respectively.[7] TU_{MoA} values were calculated as

$$TU_{MoA} = \sum_{x \in MoA} \frac{C_x}{10^{\mu_{1,x}}} \quad (4)$$

Assuming complete independence of the different MoA's, the combined (response-added) effect of all substances present in a mixture (i.e., the multisubstance PAF or msPAF) was calculated as[7]

$$msPAF = 1 - \prod_{MoA} (1 - msPAF_{MoA}) \quad (5)$$

If available, substance-specific SSD parameters were used for calculating ER and PAF (Table 1). If a substance-specific SSD was not available, the means and standard deviations from the MoA-specific SSDs were converted to weight basis and used instead (Table 2). If for a substance an SSD was available on more than one end point, we selected the SSD from the most sensitive end point of that particular substance (Figure 1).

RESULTS

Substance-Specific SSDs. Substance-specific SSDs and HC5s for birds and mammals could be obtained for 41 substances from $\log_{10}$-transformed NOECs ($mg \cdot kg^{-1}$ wet weight in food) on the end point growth, reproduction, survival, or a combination thereof (Table 1; SI Figure S1). The mean ranged from −0.5 to 3.4, pertaining to difethialone (survival) and quintozine (reproduction), respectively. The standard deviation ranged from 0.11 to 1.30, pertaining to diflubenzuron (combined) and deltamethrin (combined). No SSDs were calculated for carbofuran (combined), dichlorophenoxyacetic acid (combined), methylmercury (survival and growth), and trifluralin (combined), because the NOEC distributions of these substances significantly deviated from a normal distribution ($p < 0.05$).

DOI: 10.1021/acs.est.6b01258
Environ. Sci. Technol. 2016, 50, 10644−10652

MoA-Specific SSDs. *Numbers.* NOECs on at least two different species ($n_s \geq 2$) were obtained for 271 individual compounds in total. The mean and standard deviation of $\log_{10}$-transformed NOECs with effects on growth were calculated for 99 substances. Of these, 62 substances belonged to one of the 15 major MoA's distinguished. Analogously, means and standard deviations were calculated from NOECs with effects on reproduction and survival for 96 and 44 substances, respectively (Table 2). Of all NOECs with effects on growth and survival, about 50% were tested on birds and 50% on mammals. For reproduction, however, 80% of the NOECs were tested on birds and 20% on mammals. All SSD parameters in Table 2 were obtained from NOECs of at least one bird and one mammal. Exceptions were found for narcotic C (reproduction) and respirotoxic B (growth and survival) which were entirely based on birds and mammals, respectively.

Means. The means of the $\log_{10}$-transformed NOECs averaged by MoA ranged from −4.8 (neurotoxic B, growth) to −1.8 (phytotoxic B, growth). For narcotics, means were in the range of −3.6 to −2.1. The means for substances with a specific MoA (neurotoxic and respirotoxic compounds) were in the range of −4.8 to −2.8. For all end points, the means of substances for specific MoA's for birds and mammals were significantly lower than those for narcotics (growth $p < 0.001$; reproduction $p < 0.05$; survival $p < 0.05$; growth, reproduction, and survival combined $p < 0.001$), confirming hypothesis A (SI, Table S4). For all MoA groups, the means for survival were similar to those for growth or reproduction ($p > 0.05$ for each of the three MoA groups; SI, Table S5). Thus, hypothesis B was not confirmed. The means of DDT (reproduction), diazinon (reproduction), dichlorvos (reproduction), dicofol (reproduction), and methylmercury (growth and survival) were lower than the lower limit of the 95% confidence interval of the corresponding MoA and end point. The means of carbaryl (growth, reproduction, survival), carbofuran (growth), chlorpyrifos (reproduction), copper (reproduction), fenvalerate (growth), lead (growth), and zinc (growth, reproduction, survival) were higher than the upper limit of the 95% confidence interval of the corresponding MoA and end point.

Standard Deviations. The standard deviations of the $\log_{10}$-transformed NOECs averaged by MoA ranged from 0.08 to 0.99, pertaining to respirotoxic B (growth) and fungitoxic A (survival). The standard deviations for narcotics and specific MoA's ranged from 0.19 to 0.57 and 0.08 to 0.88, respectively. For all end points, the standard deviations for narcotics were not significantly higher or lower than those for MoA's specific to birds and mammals ($p > 0.05$ for all end points), confirming hypothesis C. For all MoA groups, the standard deviations for survival were not significantly smaller than those for growth or reproduction ($p > 0.05$ for all MoA groups). Thus, hypothesis D was not confirmed. The standard deviations of carbofuran (growth), chlorpyrifos (reproduction), ferrous sulfate (growth), and methylmercury (growth) were lower than the lower limit of the 95% confidence interval of the corresponding MoA and end point. The standard deviations of carbaryl (growth), dicofol (reproduction), chlorpyrifos (growth), DDT (survival), lead (growth), and zinc (growth, survival) were higher than the upper limit of the 95% confidence interval of the corresponding MoA and end point.

Risk Assessment. Total ecological risk (total ER) and multisubstance PAF (msPAF), combining the risks of all stressors, were calculated for 10 Northwestern European estuaries and coastal areas based on 19 individual substances (Table 3). Substance-specific SSDs were used for 10 substances, whereas calculations for the other nine were based on the MoA-specific SSDs (SI, Table S10). The total ER ranged from 2.7×10^{-3} (Esperance Bugt) to 2.5×10^{-2} (Sørfjord). The highest ER of an individual substance was 1.3×10^{-2} (methylmercury in Sørfjord). The ERs for zinc, copper, methylmercury, and cadmium ranged from 1.7×10^{-3} to 7.2×10^{-3}, 8.8×10^{-4} to 1.0×10^{-2}, 5.5×10^{-7} to 1.3×10^{-2}, and 3.0×10^{-7} to 5.5×10^{-3}, respectively. The ERs of the other substances were all below 1.0×10^{-3}. The maximum difference between total ER and msPAF was 8.3×10^{-3} (Forth estuary; Table 3). The maximum difference between ER and PAF for an individual substance was 1.3×10^{-2} (methylmercury in Sørfjord). ERs and PAFs did not change with the approach used to handle samples with nondetects (SI, Table S11−S12).

Table 3. Total Ecological Risk (total ER) and Multisubstance Potentially Affected Fractions of Species (msPAF) for Birds and Mammals in 10 Northwestern European Estuaries and Coastal Areas[a]

location	total ER	msPAF	*n*
Clyde estuary	8.3×10^{-3}	2.9×10^{-3}	2.1×10^{2}
Ems-Dollard	6.1×10^{-3}	3.3×10^{-3}	1.5×10^{3}
Esperance Bugt	2.7×10^{-3}	6.0×10^{-4}	1.1×10^{3}
Forth estuary	1.7×10^{-2}	8.8×10^{-3}	1.3×10^{2}
Hardangerfjord	4.8×10^{-3}	1.6×10^{-3}	6.9×10^{2}
Køge Bugt	8.4×10^{-3}	4.3×10^{-3}	6.1×10^{2}
OMØ	8.3×10^{-3}	1.7×10^{-3}	1.6×10^{3}
Sandefjord	5.1×10^{-3}	2.1×10^{-3}	7.8×10^{2}
Sørfjord	2.5×10^{-2}	2.2×10^{-2}	6.3×10^{2}
Scheldt estuary	6.6×10^{-3}	3.3×10^{-3}	1.4×10^{4}

[a] *n* represents the number of measured samples. The ER and PAF of the individual substances are provided in the SI (Table S10).

DISCUSSION

Substance-Specific SSDs and HC5s. SSDs were calculated, and corresponding HC5s were derived from long-term NOECs for 41 substances. Other studies calculated HC5s for six substances based on a combination of long-term NOECs, short-term NOECs, and LOECs, where short-term NOECs and LOECs were converted to long-term NOECs by dividing them by assessment factors of 10 and 2, respectively.[15,16] The $\log_{10}$-transformed HC5s reported in these studies were 0.21 to 0.73 lower than those reported in the present study (equivalent to a factor of 2 to 5 toxicity increase; SI Table S6). An analysis of the NOECs used by these authors revealed that for each substance, except dieldrin, the lowest NOEC was derived from a short-term NOEC or a LOEC. The lowest NOEC has been identified as the most sensitive parameter for calculating a HC5, indicating that the short-term NOECs and LOECs were responsible for the lower HC5s reported in the other studies.[6] Indeed, omitting the lowest NOEC for cadmium from the $\log_{10}$-transformed NOECs in Luttik et al.[15] showed that the HC5 increased from −0.46 to 0.21. We decided to use only long-term NOECs to avoid potential bias related to the usage of arbitrary assessment factors. Including short-term NOECs and LOECs from the ECOTOX database will increase the number of substances for which a HC5 can be derived to over 100. Yet, care must be taken when the lowest NOEC is derived from a short-term NOEC or a LOEC. Additional toxicity data for birds and mammals might be acquired from literature by selecting nondemographic end

DOI: 10.1021/acs.est.6b01258
Environ. Sci. Technol. 2016, 50, 10644−10652

points, such as inhibition of enzyme activities, up-regulation of the expression of stress proteins, changes in RNA or DNA incidences, and incidences of mutagenicity or carcinogenicity.[40] In addition, supplementary toxicity data might be generated by using, for example, quantitative structure−activity relationships between chemicals, or interspecies correlation estimation models.[27,41]

MoA-Specific SSDs. *Means.* The means of substances for specific MoA's for birds and mammals were significantly lower than those for narcotics (Table 2). Similar results were found for short-term LD50s for birds and mammals.[17] Substances with a specific MoA interfere directly with specific receptors in processes in an organism, such as uncoupling or blocking of the oxidative phosphorylation and inhibition of regulatory components (nerves), whereas narcotics do not react with specific receptors in an organism, thus explaining why narcotics are relatively less toxic.[17] Herbicides and fungicides may kill target organisms with a specific MoA. Yet, these compounds may affect birds and mammals via other, less toxic mechanisms. Indeed, our means and the means of LD50s indicated that herbi- and fungicides affected birds and mammals at levels similar to those of narcotics.[17]

As we found information on MoA's in birds and mammals for only 46 substances, we used the MoA's from ASTER based on acute response by aquatic species.[17,27] Yet, for the 46 substances, the MoA in birds and mammals was highly similar to those in fish and invertebrates (SI, Table S7).[42−46] A comparison of MoA-specific SSD parameters derived specifically for birds and mammals (SI, Table S8) with those for fish and invertebrates (Table 2) further showed that the average means of the $\log_{10}$-transformed NOECs were similar, except that the mean of substances with a sodium channel modulation MoA (survival) and inhibition of Cl transport MoA (all end points) in birds and mammals were 0.7 to 0.9 higher than the average means of corresponding MoA (neurotoxic A and B compounds) in aquatic species.[27] These differences might be explained by the low number of individual compounds (n_x = 1 to 3) that were available for calculating MoA-specific SSDs specifically for birds and mammals. Despite the suggested similarity in MoA for the limited number of substances investigated, it should be noted that a particular substance classified as having a specific MoA in fish and invertebrates might have a narcotic MoA in birds and mammals. This may imply that the means of specific MoA's overestimate the toxicity of that particular substance for birds and mammals. In addition, while the MoA's from ASTER were based on acute response from high acute exposure concentrations, the MoA of a particular substance might be different at a low chronic exposure concentration.

Irrespective of end point, the average mean for substances over the 15 major MoA's was −3.5, based on an average number of species ranging from 2.5 (reproduction) to 2.9 (growth; Table 2). On the basis of the same average number of species and the same 15 MoA's, Hendriks et al.[17] calculated a $\log_{10}$-transformed mean of −3.1 on short-term LD50s on birds and mammals, indicating a factor of 3 toxicity difference between LD50s and NOECs. In comparison, Mineau et al.[47] found a factor of 1 to 87 and 4 to 16 difference between short-term median lethal concentrations (LC50s) and lowest observed effect concentrations (LOECs) of pesticides on mallard duck and quail, respectively.

On the basis of LD50s on birds and mammals, Hendriks et al.[17] found that testing about 60−100 species rather than two to three species decreased the mean by 1 order of magnitude, indicating that species commonly selected for toxicity testing do not represent a random sample. As the means of the different MoA's were predominantly based on only two to five different species (Table 2), the means of the MoA-specific SSDs may underestimate the overall sensitivity to chemicals.

For most MoA's, the means for survival were higher than for growth and reproduction, but the differences were not statistically significant. No other studies compared the toxicity between end points for birds or mammals, but a few studies reported on differences in aquatic species. Jin et al.[40] calculated SSDs for nonylphenol on aquatic species and found that the mean of acute data on survival was a factor of 4 to 36 higher than the means of chronic data on growth and reproduction. In addition, NOECs on fish species for survival were nearly always higher than for reproduction and growth.[22,23]

Standard Deviations. The standard deviations for narcotics and specific MoA were similar, indicating similar interspecific variation in sensitivity to different compounds (Table 2). This corresponds with results based on short-term LD50s for birds and mammals.[17] The average standard deviations for substances belonging to one of the 15 major MoA's were about 0.4 to 0.5, which were based on an average number of species ranging from 2.5 (reproduction) to 2.9 (growth). On the basis of the same average number of species and the same 15 MoA's, Hendriks et al.[17] calculated a standard deviation of 0.3 on short-term LD50s on birds and mammals. The higher standard deviations for chronic dietary NOECs might reflect a less standardized test setup compared to acute oral LD50s studies. For example, exposure periods of chronic exposure are more variable than single oral doses, and oral administration by a feeding tube might represent a more standardized way of testing animals than exposure via food.[17] On the basis of LD50s on birds and mammals, Hendriks et al.[17] found that testing about 60−100 species rather than two to three species increased the standard deviation by a factor of 2. As the standard deviations of the different MoA's were predominantly based on only two to five different species (Table 2), the standard deviations of the MoA-specific SSDs probably underestimate interspecies variability in sensitivity.

Few studies compared the variability in sensitivity among birds or mammals between different end points. One notable exception is Luttik et al.[24] who reported a standard deviation of 0.37 for both short-term LD50s on survival and long-term NOECs on reproduction for pesticides. A study that assessed the effect of nonylphenol on aquatic species found that the standard deviation of acute data on survival (0.6) was similar to the standard deviations of chronic data on growth and reproduction (both 0.7).[40]

Our tentative comparison of MoA-specific SSD parameters derived specifically for birds and mammals (SI, Table S8) with those for fish and invertebrates (Table 2) showed that the average standard deviations of the $\log_{10}$-transformed NOECs were similar, except that the standard deviations of substances with a sodium channel modulation MoA (survival) and inhibition of Cl transport MoA (growth and survival) in birds and mammals were a factor of 2 lower than the average standard deviation of corresponding MoA (neurotoxic A and B compounds) in aquatic species.[27] In contrast, the average standard deviation of substances with an inhibition of Cl transport MoA (reproduction) in birds and mammals was a factor of 2 higher than the average standard deviation of corresponding MoA (neurotoxic B compounds) in aquatic species.[27] These differences might be explained by the low

DOI: 10.1021/acs.est.6b01258
Environ. Sci. Technol. 2016, 50, 10644−10652

number of individual compounds (n_x = 1 to 3) that were available for calculating MoA-specific SSDs specifically for birds and mammals.

Risk Assessment. The risk assessment showed that the total ERs and msPAFs ranged from 2.7×10^{-3} to 2.5×10^{-2} and from 6.0×10^{-4} to 2.2×10^{-2}, respectively, with zinc, copper, methylmercury, and cadmium contributing most. There are several reasons why the calculated risks underestimate the actual risks of chemicals in these estuaries. First, substances measured in *P. flesus* for which no SSD was available were not included in the risk assessment, namely dioxin-like PCBs, noncoplanar PCBs, polybrominated diphenyl ethers, and arsenic. Next, recent field studies have shown high or increasing concentrations of a range of substances of concern in estuarine and marine environments, including tributyltin, toxaphene, nonyl- and octylphenol, phthalate esters, perfluorochemicals, and pharmaceuticals.[20] These substances were not measured in *P. flesus*. Finally, no assessment or conversion factors were applied to the NOECs. Yet, it has been suggested that toxicity data derived from birds and mammals exposed to food in the laboratory should be corrected before being applied to predators in the field, by applying an assessment factor of 5 for the differences in food intake rate, caloric content of food, metabolic rate, and food and pollutant assimilation efficiency.[4,48] We assessed the influence of a laboratory-field assessment factor on the ERs and PAFs by dividing the NOECs with a factor of 5.[48] This resulted in total ERs and msPAFs ranging from 6.0×10^{-2} to 3.5×10^{-1} and from 4.9×10^{-2} to 3.4×10^{-1}, respectively (SI, Table S13). However, whether a laboratory-field assessment factor should be used on bird and mammal toxicity data is still under debate.[4]

As *P. flesus* is a demersal fish that lives in and near sediments, its internal chemical concentrations might be higher compared to concentrations in pelagic fish species.[49] As most birds and mammals feed also on pelagic fish and invertebrates, the ER and PAF values based on merely *P. flesus* might overestimate the actual risk.[33] The risk assessment can be improved by including pelagic fish and invertebrates in the field data set, such as the frequently measured herring (*Clupea harengus*) and the common mussel (*Mytilus edulis*).[32]

The MoA-specific SSDs (Table 2) were used for substances without a substance-specific SSD. As we found information on MoA's in birds and mammals for only 46 substances, we used the MoA's from ASTER based on acute response by aquatic species.[17,27] Yet, based on 46 substances, we estimated the MoA-specific SSDs based on the MoA in birds and mammals (SI, Table S8) and used these MoA-specific SSDs for estimating the total ERs and msPAFs. The total ERs and msPAFs based on MoA-SSDs specific to birds and mammals were similar to those based on the MoA in aquatic species (SI, Table S14).

Implications. In the present study, we derived SSDs and corresponding HC5s for birds and mammals for 41 substances (Table 1). If no toxicity data are available for a chemical, the mean and the standard deviation values reported per MoA may serve as a first indication of the SSD characteristics to be expected (Table 2). The SSDs in the present study can be used in regulatory procedures and for assessing the impacts of contaminants on birds and mammals from fish contaminants monitoring programs. The risk assessment could be further improved by including pelagic fish and invertebrates as a food source for birds and mammals.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.6b01258.

Further information on the toxicity data (Table S1−S8; Figure S1), the field data (Table S9; Figure S2), and the risk assessment (Table S10−14) (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*Phone: 0031-62-152-8190. Fax: 0031-24-355-3450. E-mail: johnkorsman@hotmail.com.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the anonymous reviewers for their comments and suggestions, which have improved the quality of this manuscript.

■ REFERENCES

(1) *Guidelines for Deriving Numerical National Water Quality Criteria for the Protection of Aquatic Organisms and Their Uses*; PB 85-227049; U.S. EPA: Duluth, MN, 1985. www.epa.gov/sites/production/files/2016-02/documents/guidelines-water-quality-criteria.pdf.

(2) Report of the OECD Workshop on the Extrapolation of Laboratory Aquatic Toxicity Data to the Real Environment. *Environment Monographs No. 59*; OECD: Paris, France, 1992. www.oecd.org/chemicalsafety/testing/34528236.pdf.

(3) Posthuma, L.; Suter, G. W.; Traas, T. P. *Species Sensitivity Distributions in Ecotoxicology*; Lewis Publishers: Boca Raton, FL, 2002.

(4) *Technical guidance document on risk assessment − Part II*; ECB (European Chemicals Bureau), Institute for Health and Consumer Protection, European Commission: Ispra, Italy, 2003. https://echa.europa.eu/documents/10162/16960216/tgdpart2_2ed_en.pdf.

(5) Van Straalen, N. M.; Denneman, C. A. J. Ecotoxicological evaluation of soil quality criteria. *Ecotoxicol. Environ. Saf.* **1989**, *18*, 241−251.

(6) Aldenberg, T.; Jaworska, J. S.; Traas, T. P. Normal species sensitivity distributions and probabilistic ecological risk assessment. In *Species Sensitivity Distributions in Ecotoxicology*; Posthuma, L., Suter, G. W., Traas, T. P., Eds.; Lewis Publishers: Boca Raton, FL, 2002; pp 49−102.

(7) Traas, T.; Van de Meent, D.; Posthuma, L.; Hamers, T.; Kater, B. J.; De Zwart, D.; Aldenberg, T. The potentially affected fraction as a measure of ecological risk. In *Species Sensitivity Distributions in Ecotoxicology*; Posthuma, L., Suter, G. W., Traas, T. P., Eds.; Lewis Publishers: Boca Raton, FL, 2002; pp 315−344.

(8) Azevedo, L. B.; De Schryver, A. M.; Hendriks, A. J.; Huijbregts, M. A. J. Calcifying species sensitivity distributions for ocean acidification. *Environ. Sci. Technol.* **2015**, *49*, 1495−1500.

(9) Van Straalen, N. M. Theory of ecological risk assessment based on species sensitivity distributions. In *Species Sensitivity Distributions in Ecotoxicology*; Posthuma, L., Suter, G. W., Traas, T. P., Eds.; Lewis Publishers: Boca Raton, FL, 2002; pp 37−48.

(10) Newman, M. C.; Ownby, D. R.; Mezin, L. C. A.; Powell, D. C.; Christensen, T. R. L.; Lerberg, S. B.; Anderson, B. A. Applying species-sensitivity distributions in ecological risk assessment: Assumptions of distribution type and sufficient numbers of species. *Environ. Toxicol. Chem.* **2000**, *19*, 508−515.

DOI: 10.1021/acs.est.6b01258
Environ. Sci. Technol. 2016, 50, 10644−10652

(11) Luttik, R.; Aldenberg, T. Extrapolation factors for small samples of pesticide toxicity data: Special focus on LD50 values for birds and mammals. *Environ. Toxicol. Chem.* **1997**, *16*, 1785−1788.
(12) Mineau, P.; Baril, A.; Collins, B. T.; Duffe, J.; Joerman, G.; Luttik, R. Pesticide acute toxicity reference values for birds. *Rev. Environ. Contam. T.* **2001**, *170*, 13−74.
(13) Iwasaki, Y.; Kotani, K.; Kashiwada, S.; Masunaga, S. Does the choice of NOEC or EC10 affect the hazardous concentration for 5% of the species? *Environ. Sci. Technol.* **2015**, *49*, 9326−9330.
(14) Romijn, C.; Luttik, R.; Van den meent, D.; Slooff, W.; Canton, J. H. Presentation of a general algorithm to include effect assessment on secondary poisoning in the derivation of environmental quality criteria. Part 1. Aquatic food-chains. *Ecotoxicol. Environ. Saf.* **1993**, *26*, 61−85.
(15) Luttik, R.; Romijn, C. A. F. M.; Canton, J. H. Presentation of a general algorithm to include secondary poisoning in effect assessment. *Sci. Total Environ.* **1993**, *134*, 1491−1500.
(16) Spurgeon, D. J.; Hopkin, S. P. Risk assessment of the threat of secondary poisoning by metals to predators of earthworms in the vicinity of a primary smelting works. *Sci. Total Environ.* **1996**, *187*, 167−183.
(17) Hendriks, A. J.; Awkerman, J. A.; De Zwart, D.; Huijbregts, M. A. J. Sensitivity of species to chemicals: Dose−response characteristics for various test types (LC_{50}, LR_{50} and LD_{50}) and modes of action. *Ecotoxicol. Environ. Saf.* **2013**, *97*, 10−16.
(18) Hendriks, A. J. How to deal with 100,000^{+} substances, sites, and species: Overarching principles in environmental risk assessment. *Environ. Sci. Technol.* **2013**, *47*, 3546−3547.
(19) Lotze, H. K.; Lenihan, H. S.; Bourque, B. J.; Bradbury, R. H.; Cooke, R. G.; Kay, M. C.; Kidwell, S. M.; Kirby, M. X.; Peterson, C. H.; Jackson, J. B. C. Depletion, degradation, and recovery potential of estuaries and coastal seas. *Science* **2006**, *312*, 1806−1809.
(20) Hylland, K.; Vethaak, A. D. Impact of contaminants on pelagic ecosystems. In *Ecological Impacts of Toxic Chemicals*; Sánchez-Bayo, F., van den Brink, P. J., Mann, R. M., Eds.; Bentham Science Publishers: Oak Park, IL, 2011; pp 212−224.
(21) Smith, J. T.; Walker, L. A.; Shore, R. F.; Durell, S. E. A.; Howe, P. D.; Taylor, M. Do estuaries pose a toxic contamination risk for wading birds? *Ecotoxicology* **2009**, *18*, 906−917.
(22) Suter, G. W.; Rosen, A. E.; Linder, E.; Parkhurst, D. F. Endpoints for responses of fish to chronic toxic exposures. *Environ. Toxicol. Chem.* **1987**, *6*, 793−809.
(23) Mayer, F. L.; Mayer, K. S.; Ellersieck, M. R. Relation of survival to other endpoints in chronic toxicity tests with fish. *Environ. Toxicol. Chem.* **1986**, *5*, 737−748.
(24) Luttik, R.; Mineau, P.; Roelofs, W. A review of interspecies toxicity extrapolation in birds and mammals and a proposal for long-term toxicity data. *Ecotoxicology* **2005**, *14*, 817−832.
(25) U.S. EPA. The ECOTOXicology knowledgebase (ECOTOX). http://cfpub.epa.gov/ecotox/.
(26) EC European Commission Data sheets. https://circabc.europa.eu/webdav/CircaBC/env/wfd/Library/working_groups/priority_substances/advisory_substances/eqs_fraunhofer_report/eqs_sheets_annex.
(27) Hendriks, A. J.; Traas, T. P.; Huijbregts, M. A. J. Critical body residues linked to octanol−water partitioning, organism composition and LC50-QSARs: Meta-analysis and model. *Environ. Sci. Technol.* **2005**, *39*, 3226−3236.
(28) Carsten Von der Ohe, P.; Liess, M. Relative sensitivity distribution of aquatic invertebrates to organic and metal compounds. *Environ. Toxicol. Chem.* **2004**, *23*, 150−156.
(29) Fedorenkova, A.; Vonk, J. A.; Breure, A. M.; Hendriks, A. J.; Leuven, R. Tolerance of native and non-native fish species to chemical stress: A case study for the River Rhine. *Aquat. Invasions* **2013**, *8*, 231−241.
(30) Aldenberg, T.; Jaworska, J. S. Uncertainty of the hazardous concentration and fraction affected for normal species sensitivity distributions. *Ecotoxicol. Environ. Saf.* **2000**, *46*, 1−18.
(31) U.S. EPA Estimation Programs Interface (EPI) Suite Database. www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface.
(32) EEA Transitional, coastal and marine (TCM) waterbase (v.12) from the European Environment Agency (EEA). www.eea.europa.eu/data-and-maps/data/waterbase-transitional-coastal-and-marine-waters.
(33) Heath, M. R. Ecosystem limits to food web fluxes and fisheries yields in the North Sea simulated with an end-to-end food web model. *Prog. Oceanogr.* **2012**, *102*, 42−66.
(34) Boalt, E.; Miller, A.; Dahlgren, H. Distribution of cadmium, mercury, and lead in different body parts of Baltic herring (*Clupea harengus*) and perch (*Perca fluviatilis*): Implications for environmental status assessments. *Mar. Pollut. Bull.* **2014**, *78*, 130−136.
(35) Hendriks, A. J.; Heikens, A. The power of size. 2. Rate constants and equilibrium ratios for accumulation of inorganic substances related to species weight. *Environ. Toxicol. Chem.* **2001**, *20*, 1421−1437.
(36) Honda, K.; Sahrul, M.; Hidaka, H.; Tatsukawa, R. Organ and tissue distribution of heavy metals, and their growth-related changes in antarctic fish, *Pagothenia borchgrevinki*. *Agric. Biol. Chem.* **1983**, *47*, 2521−2532.
(37) Gbem, T. T.; Balogun, J. K.; Lawal, F. A.; Annune, P. A. Trace metal accumulation in *Clarias gariepinus* (Teugels) exposed to sublethal levels of tannery effluent. *Sci. Total Environ.* **2001**, *271*, 1−9.
(38) Fowler, B. A.; Alexander, J.; Oskarsson, A. Toxic metals in food. In *Handbook on the Toxicology of Metals*, Fourth ed.; Nordberg, G. F., Fowler, B. A., Nordberg, M., Eds.; Academic Press: San Diego, CA, 2015; pp 123−140.
(39) De Zwart, D. Ecological effects of pesticide use in The Netherlands: Modeled and observed effects in the field ditch. *Integr. Environ. Assess. Manage.* **2005**, *1*, 123−134.
(40) Jin, X.; Wang, Y.; Jin, W.; Rao, K.; Giesy, J. P.; Hollert, H.; Richardson, K. L.; Wang, Z. Ecological risk of nonylphenol in China surface waters based on reproductive fitness. *Environ. Sci. Technol.* **2014**, *48*, 1256−1262.
(41) Awkerman, J. A.; Raimondo, S.; Barron, M. G. Development of species sensitivity distributions for wildlife using interspecies toxicity correlation models. *Environ. Sci. Technol.* **2008**, *42*, 3447−3452.
(42) O'Neil, M. J. *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals*; Merck: Whitehouse Station, NJ, 2001.
(43) Brunton, L. L.; Chabner, B. A.; Knollmann, B. C., Eds. *Goodman and Gilman's the Pharmacological Basis of Therapeutics*. McGraw-Hill: New York, 2011.
(44) Lewis, K. A.; Green, A.; Tzilivakis, J.; Warner, D. The Veterinary Substance Database (VSDB) developed by the Agriculture and Environment Research Unit (AERU). http://sitem.herts.ac.uk/aeru/vsdb.
(45) Luckey, T. D.; Venugopal, B. Introduction to heavy metal toxicity in mammals. In *Physiologic and Chemical Basis for Metal Toxicity*; Springer: Boston, MA, 1977; pp 1−37.
(46) Schafer, E. W. Bird control chemicals — Nature, modes of action, and toxicity. In *CRC Handbook of Pest Management in Agriculture*; Pimentel, D., Ed.; CRC Press: Boca Raton, FL, 1991; pp 599−610.
(47) Mineau, P.; Boersma, D. C.; Collins, B. An analysis of avian reproduction studies submitted for pesticide registration. *Ecotoxicol. Environ. Saf.* **1994**, *29*, 304−329.
(48) Traas, T. P.; Luttik, R.; Jongbloed, R. H. A probabilistic model for deriving soil quality criteria based on secondary poisoning of top predators: I. Model description and uncertainty analysis. *Ecotoxicol. Environ. Saf.* **1996**, *34*, 264−278.
(49) Yi, Y.; Wang, Z.; Zhang, K.; Yu, G.; Duan, X. Sediment pollution and its effect on fish through food chain in the Yangtze River. *Int. J. Sed. Res.* **2008**, *23*, 338−347.

DOI: 10.1021/acs.est.6b01258
Environ. Sci. Technol. 2016, 50, 10644−10652