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Expected Risk as basis for assessment of safe use of chemicals

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Abstract

This paper describes a straightforward modeling procedure to derive 'expected risk' (*ER*) of chemical substances. Starting from proposed use volumes, intended uses, physical and chemical substance properties and toxicity information, the procedure combines multimedia environmental fate modeling with species sensitivity modeling to derive the probability that exposure concentrations exceed critical effect concentrations. The procedure was tested on 1977 so-called mono-constituent organic chemicals that had been registered to be marketed in the EU, after 'possibility to be used safely' had been demonstrated by showing that the possible Risk Quotients (*RQ*) defined as PEC/PNEC ratios (Predicted Exposure Concentration & Predicted No Effect Concentration) were expected to remain below the value of 1, as required by REACH. It appears from this study that (i) *RQ* and *ER* of chemicals can be calculated readily, reliably, transparently and reproducibly, that (ii) both *RQ* and *ER* can be used to assess whether a new chemical may exceed a chosen acceptability level, but that (iii) in addition *ER* can be straightforwardly used to rank chemicals according to expected environmental safety. In conclusion, the paper states that modeling *ER* of chemicals (instead of estimating *RQ* values), could strengthen the scientific basis of environmental risk assessment for use in REACH. The paper further recommends that more robust environmental risk calculation can be done by using acute EC50, instead of chronic NOEC as critical effect concentration.

Keywords Environmental risk of chemicals, Risk modeling, Expected risk, Risk Quotient

Background

Quantitative risk assessment provides a scientific basis for evaluating potentially toxic chemicals. Central in the concept of environmental risk is that it depends on both exposure and toxicity. Chemicals will only express their toxicity when they exceed a concentration at which a defined target becomes affected. Regulatory use of risk assessment often combines absolute and comparative forms of assessment. Risks are assessed to decide whether chosen critical values or environmental quality criteria are exceeded, while at the same time assessments are used to compare chemicals and prioritize them for needs of regulatory measures.

Quantitative risk assessment started in the 1980s with taking simple Risk Quotients (RQ): ratios of exposure concentrations (PEC), relative to no-effect concentrations (NEC). Risk quotients greater than 1 triggered

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action; in the EU, this usually meant that, according to EU guidelines [1] new chemicals could be marketed only when predicted quotients fell below 1. This simple approach was widely adopted in regulatory risk assessment practice.

In the early 1990s, environmental risk assessment scientists started to apply the concept of Species Sensitivity Distributions to work out a mathematical methodology to quantify environmental risk of toxic substances. As explained in detail in various chapters of the so-called SSD book (as referenced in [2], risk can be quantified mathematically by the convolution of the distribution functions of exposure concentrations and species sensitivities. The outcome of this mathematical operation was interpreted by Van Straalen [3] as 'the probability of the undesired occurrence of exposure concentrations exceeding critical effect concentrations', or 'ecological risk', and by Aldenberg et al. [4] as 'expected risk' (ER) (after [5, 6]). The same approach is applied in the EU System for the Evaluation of Chemicals EUSES [7] as a tool to 'demonstrate the possibility to use a chemical safely', which is the scientific rationale of the REACH regulation. There is broad scientific consensus [8] that environmental risk is reflected well by the probability of exceedance of critical effect concentrations.

However, the simple risk quotient approach applied in many national and international regulatory frameworks, including the EU REACH program, ignores the notion that exposure concentrations and critical effect concentrations are not fixed numbers but stochastic variables that follow probability distributions. While the method described by Van Straalen [3] and Aldenberg et al. [4] assesses the probability that PEC exceeds NEC, the simple quotient method merely compares point estimates of PEC and NEC, demanding that PEC does NOT (i.e., never, under no circumstance) exceed NEC.

Recently, the integrative ER method (Van Straalen, Aldenberg and others, as referenced in [2]) has been used in the EU project SOLUTIONS to assess ecological risks of currently used toxic chemicals in Europe (https://www.solutions-project.eu/, [9, 10]). The integrative ER approach used in the SOLUTIONS project has been thoroughly tested by making calculations for nearly 2000 different chemicals that are currently in use in the EU [11]. The SOLUTIONS method, which fully accounts for variability and uncertainty, is known as probabilistic risk assessment [12] and has been introduced and applied both in environmental [12] and human health-oriented risk assessment [13]. This method is deemed suitable as a screening tool under REACH to prioritize the long list of chemicals, assuring that those posing unacceptable risks are adequately risk managed.

In the present study, we have compared expected risks of 1977 registered REACH chemicals with the PEC/PNEC-quotients of the same substances. We have tested the use of ER as a means to demonstrate the possibility of using a chemical safely, as pursued in the EU REACH legislation. We have used the SOLUTIONS model SimpleRisk to calculate ER of 1977 so-called mono-constituent organic substances for which possibilities for 'safe use' had been demonstrated by showing that PEC/PNEC-quotients for all possible uses were expected to remain smaller than one.

Methods

SimpleRisk

SimpleRisk is a tool that follows the REACH guidance [14] to predict PEC and PNEC in a probabilistic way. This Excel-based SimpleRisk spreadsheet system is almost identical to the modeling system that was used in the SOLUTIONS project. It comprises separate spreadsheet models for estimating emission rates from use volumes, for assessing removal during treatment of wastewater, for assessing exposure concentrations from emission rates, and for assessing environmental impact from exposure concentrations and SSD-moments. SimpleRisk has been described in detail by Van de Meent et al. [11]. The spreadsheet model used in this study is given as supplemental material. For convenience, a summarized description is given below.

Emission model

Different chemical groups have different emission patterns. Some chemicals are made to be released to the environment. For instance, plant protection products used in open field applications are released almost entirely to crops and soils. Similarly, chemicals used in 'down-the-drain' household products find their way to the environment via domestic sewage collection and incomplete removal in treatment systems, as mandated in EU legislation [15]. Other chemicals are made for use as constituents of durable products, from which variable amounts are released into the environment. Yet other chemicals are not meant to be used as such at all, but serve as industrial intermediates, or as fuel in vehicles and power plants. Still other chemicals enter the environment due to accidental spillage or accidents. We have developed a general-purpose substance-flow estimation procedure that accounts for these very different uses of chemicals with vastly different release rates. Releases of chemicals from all possible uses in the entire life cycle of chemicals are considered (Fig. 1).

The emission model is based on the Environmental Release Category (ERC) approach currently used for Chemical Safety Assessment in REACH [14], which

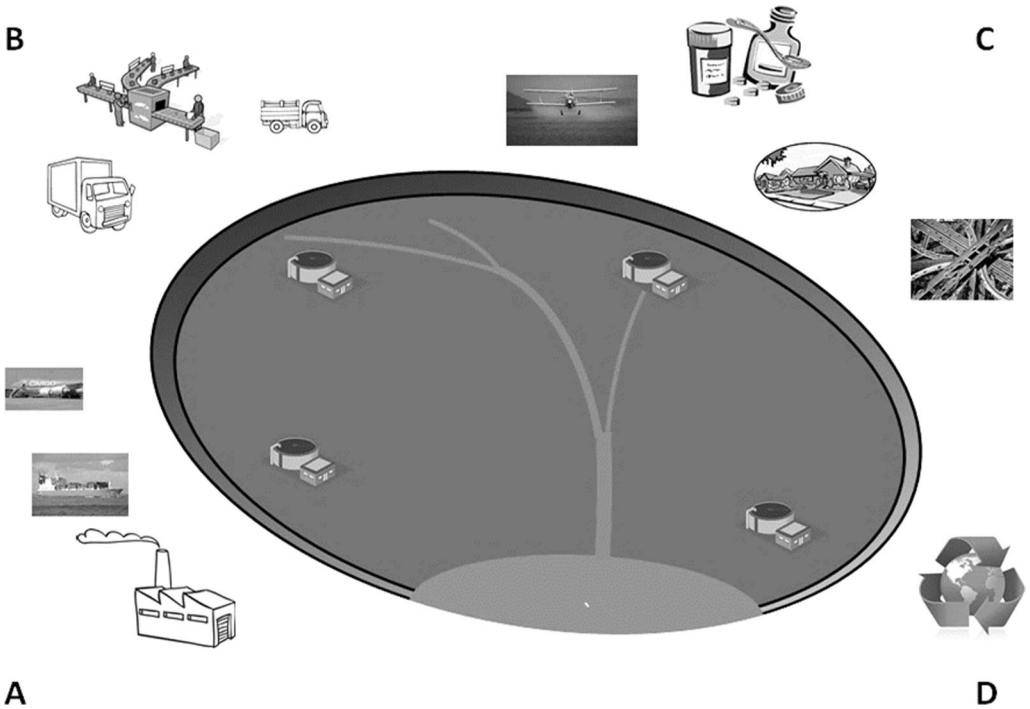

Fig. 1 In SimpleRisk releases of chemical substances are estimated for all chemicals based on different emission processes during the chemicals' life cycle stages: manufacturing and transport (**A**), formulation and distribution (**B**), service life (**C**) and recycling/waste stage (**D**). Release to the environment can take place mediated by (household or industrial) wastewater treatment

was further developed into the generic emission model by using the so-called spERC (Specific Environmental Release Category) tables, published by industry [16].

Total emission into the environment is modeled as the product of use volume, release fraction and fraction not retained in the process of waste treatment:

$$E_{i,j,k} = \sum_{i,j,k} \left(UseVol_i \cdot ActCat_{i,j} \right) \cdot RF_{j,k} \cdot Fstp_{i,k}, \quad (1)$$

where $E_{i,j,k}$ denotes the EU-wide emission rate [kg.s^{-1}] of substance i from use j into environmental medium k, $\left(UseVol_i \cdot ActCat_{i,j} \right)$ represents the volume of substance i, used in activity category j [kg.s^{-1}], $RF_{j,k}$ is the (dimensionless) fraction [–] of this use that is released into medium k and $Fstp_{i,k}$ [–] denotes the fraction of substance released to medium k upon sewage treatment, as predicted by the STP model SimpleTreat, recommended in the REACH Guidance [14]. The applicability of Eq. 1 to estimate release rates for the purpose of chemical safety assessment of chemicals under REACH was tested for all chemical substances known to be used in Europe per April 2015 ([11]. The 169 specific Environmental Release Categories [16], claimed to be 'best possible estimates' were categorized into the 12 composite main uses listed in Table 1.

Exposure model

Expected exposure concentrations of chemicals in a 'typical EU-water body' were calculated from estimated emission rates using the multimedia mass balance model SimpleRisk (Fig. 2). SimpleRisk is a simplified (spatially and temporally invariable) version of the model used in the EU project SOLUTIONS. SimpleRisk combines the above emission estimation model with the environmental fate simulation models SimpleBox vs 4 [17] and SimpleTreat vs 4 [18, 19]. The SimpleRisk model has been used and was validated in the EU project SOLUTIONS [11], to test the usefulness and plausibility of the outcomes of the emission model for use in chemical safety assessments. SimpleRisk simulates emissions of chemicals at so-called 'local' and 'regional' spatial scales, and calculates expected steady-state concentrations of chemicals in a 'generic receiving environment' (air, water, soil).

Exposure concentrations are uncertain, due to spatial variability and uncertainty in true values of model parameters. Different chemicals have different exposure distributions (i.e., different means and variances). Taking variability and uncertainty into account results in distributions of exposure concentrations, characterized by medians and variances, rather than point estimates. For the purpose of this study, we assumed equal variances of exposure concentrations for all chemicals. An estimated

Table 1 Estimated release fractions in the various uses and life cycle stages, based on published and unpublished reports

Activity category		Release (%)	To air (%)	To water (%)	To soil (%)
Stage I	Use1: MANUFACTURING	0.4	0.2	95	5
Stage I	Use2: DISTRIBUTION & FORMULATION	0.5	60	39	1
Stage I	Use3: INDUSTRIAL PROCESSING	0.5	59	35	6
Stage II	Use4: USE in AGRICULTURE	100	15	1	84
Stage II	Use5: USE in MEDICINE	12	0.0	100	0
Stage II	Use6: WIDE-DISPERSIVE USE in 'down-the-drain	100	0.0	100	0
Stage II	Use7: Other WIDE-DISPERSIVE USES	100	73	11	16
Stage II	Use8: WIDE-DISPERSIVE 'low-release' USES	5	73	11	16
Stage II	Use9: USE as FUEL	0.04	96	4	0
Stage II	Use10: Other stage-II USES	0.5	26	22	9
Stage III	Use11: TREATMENT, RECYCLING	5	33	33	33
Stage III	Use12: SOLID WASTE DISPOSAL	10	0.0	0.0	100
Use-weighted averages, based on selected SpERCs		25	63	31	6

SpERC Specific Environmental Release Category; from Van de Meent et al. [11]

value ($\sigma_{\mathrm{CONC}}=0.3$) was used, based on the outcomes of previously conducted Monte Carlo simulations of exposure model uncertainty [20], and of validation studies carried out in the EU project SOLUTIONS [11, 21]. The assumption of homogenous variance can easily be relaxed in specific cases, as the mathematical derivation of the risk equation does not critically depend on it.

Impact model

SimpleRisk adopts the derivation procedure described by Van Straalen [3] and Aldenberg et al. [4], to quantify 'expected risk' *ER* as the probability that concentrations in the environment (which are known to vary in space and time), are greater than critical effect concentrations (which vary across species). In this study, we have calculated *ER* from distributions of modeled concentrations in 'typical EU water' ([11] and distributions of laboratory-measured chronic NOECs. Additionally, we have calculated *ER* of the same chemicals, based on acute EC50, as derived by [21]. We closely followed Van Straalen [3], by taking integrals of the products of probability density functions of modeled concentrations in surface water and the cumulative distribution functions of no-effect concentrations (Fig. 3).

Because distributions of chemical concentrations are commonly skewed, we consider the $\log_{10}$ of the concentration. In addition, we followed the recommendation by Aldenberg et al. [4] to toxicologically standardize cumulative SSDs according to

$$z=\frac{\log c-\mu_N^c}{\sigma_N^c}, \tag{2}$$

where μ_N^c is the mean of $\log_{10}$ of *NEC* and σ_N^c the $\log_{10}$ of standard deviation of critical effect concentrations. This facilitates evaluation of many chemicals in a multiple exposure scenario. Assuming a normal distribution and applying the z-transform to each of them, gives all SSDs mean zero and unity variance, so effectively merges them into one distribution. After transformation, expected risk *ER* is calculated from:

$$ER(z)=\delta=\int_{-\infty}^{\infty}p(z)N(z)dz, \tag{3}$$

as shown in Fig. 3. Distributions of exposure concentrations p and no-effect concentrations N can now be visualized by plotting them on the new (dimensionless) z-transformed concentration axis.

When both *p(z)* and *N(z)* are normal distributions, the expected risk integral of Eq. 3 can be solved analytically [4]:

$$ER=\Phi\left(\frac{\mu_p^c-\mu_N^c}{\sqrt{\sigma_p^{c2}+\sigma_N^{c\,2}}}\right)=\Phi\left(\frac{\mu_p^z}{\sqrt{\sigma_p^{z2}+1}}\right), \tag{4}$$

where Φ is the cumulative standard normal distribution function, μ_p^z is the mean of z-transformed exposure concentrations and σ_p^z is the standard deviation of z-transformed no-effect concentrations.

Case study

The SimpleRisk spreadsheet modeling procedure for deriving expected risk was applied to the 1977 mono-constituent organic chemicals that had been registered under the REACH legislation for marketing in the EU until April 2015, as described in an earlier paper [11]. EU tonnages, proposed uses, physical and chemical substance properties were taken from this study. For 1977

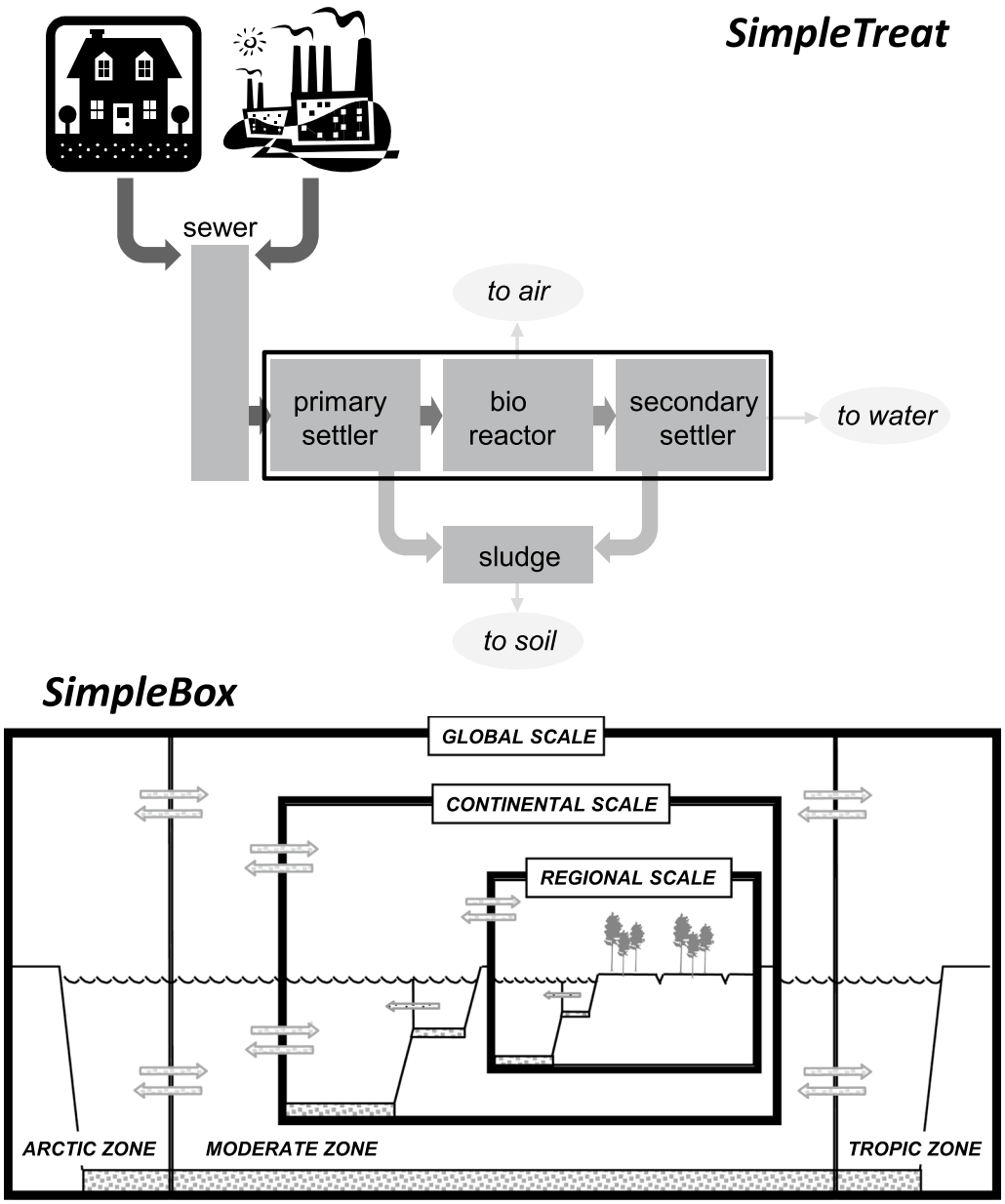

Fig. 2 Principle of exposure modeling in SimpleRisk. The multimedia mass balance model SimpleBox [17], combined with the sewage treatment plant simulation model SimpleTreat [18, 19], is used to estimate expected exposure concentrations of chemical substances, describing, explaining and predicting how and why different chemicals behave differently in the environment, depending on their physical and chemical substance properties

of these, first and second moments (i.e., across-species averages and variances of acute EC50 and chronic NOEC were obtained from an earlier study by Posthuma et al. [21]. It should be noted that for 1428 out of the 1977 chemicals (72%), averages and standard deviations of NOECs and/or EC50s in Posthuma and De Zwart's database [21] were derived from three different test species only, which is barely sufficient to generate reliable SSD moments in isolation.

In addition to calculating expected risks, we used the same modeled exposure concentrations and the same toxicity data to derive the environmental risk quotients as required by REACH in order to assess whether the 'safe use' is possible:

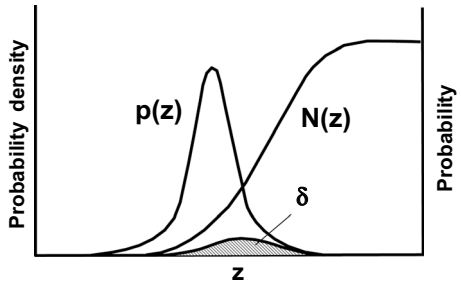

Fig. 3 The expected risk of a chemical, denoted δ, is defined as the probability that *PEC* is greater than *NEC*, where both *PEC* and *NEC* are random variables: $\delta = \text{Prob}(PEC > NEC)$. Figure from Van Straalen [27]

$$RQ(c) = \frac{PEC}{PNEC} = \mu_p^c - HC5_N^c = \mu_p^c - \left(\mu_N^c - 1.64\sigma_N^c\right). \quad (5)$$

Note that in this study we used the 5th percentile of the NOEC distribution, *HC5*, to estimate *PNEC*. Note that, as prescribed by REACH, only the mean of possible *PEC*s is used, disregarding possible variation and uncertainty.

Results

Results of the case study are given in the supplemental information (Additional file 1: Table S1), and summarized in Figs. 4–6.

Histograms of the EU-wide annual use volumes and emission rates of the 1977 mono-constituent organic REACH chemicals are shown in Fig. 4. Expected emission rates in the EU range from less than 1 ton per year to over 100 million tons per year. SimpleRisk-modeled expected exposure concentrations in the aquatic EU environment (Fig. 5) range from picograms per liter to milligrams per liter. Note that outputs of first-order steady-state environmental fate models (expected exposure concentrations) are directly proportional to the inputs (emission rates). The proportionality constant between exposure emission rate and concentration varies from chemical to chemical, in reflection of differences in environmental behavior of the substances studied—in Life Cycle Impact Assessment (LCIA), such proportionality constants are called 'environmental fate factor' [22]. The environmental fate factors of the 1977 mono-constituent organic REACH substances in this study did not vary widely, which explains why ranges in emission rates and exposure concentrations do not differ much: expected exposure concentrations depend more on the amount of chemical used than on the properties of the chemical.

SimpleRisk-modeled Risk Quotients, RQ_{NOEC} and Expected Risks, ER_{NOEC} and ER_{EC50} are shown, in histogram format, in Fig. 6. *ER*s of individual chemicals are generally very low: for nearly 90% of the tested 1977 REACH chemicals, both EC50-based and NOEC-based

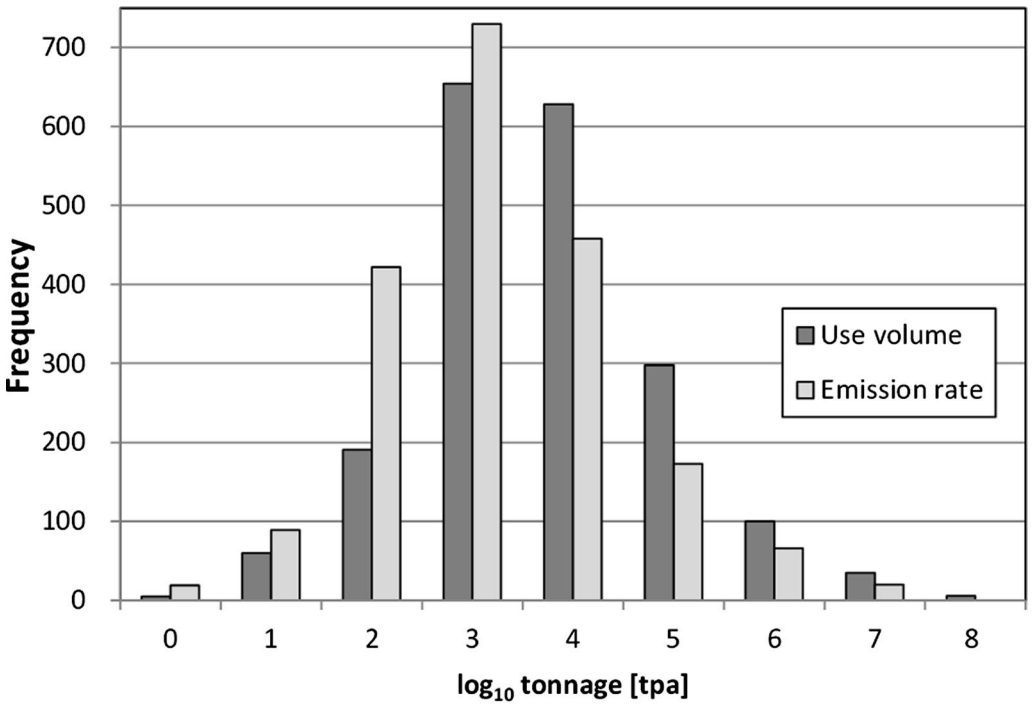

Fig. 4 Registered market volumes and model-estimated emission rates (in tons per year) of 1977 mono-constituent organic REACH chemicals

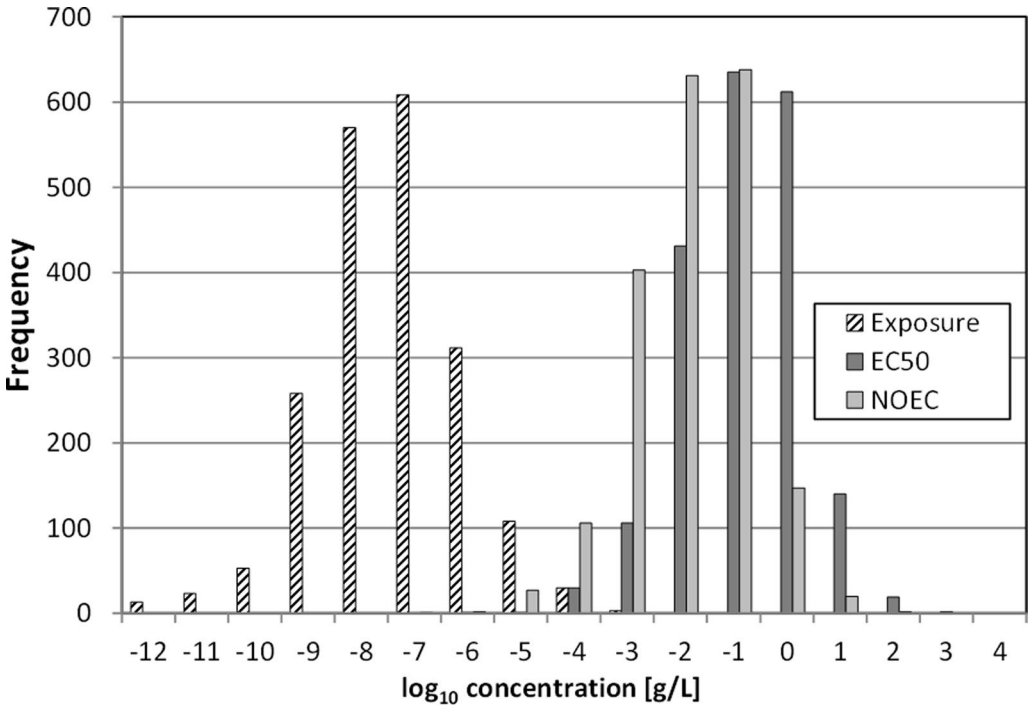

Fig. 5 Histograms of SimpleRisk-modeled median expected exposure concentrations in 'typical EU fresh water' and of median critical effect concentrations (average aquatic log-EC50-acute and log-NOEC-chronic (data from [21])) of the 1977 REACH-registered mono-constituent organic chemical substances in a 'typical EU-water body'

*ER*s can be considered 'negligible': the probability of encountering undesired events in which species are exposed to concentrations that exceed their critical effect concentration are insignificant. A few of the tested chemicals had NOEC-based Risk Quotients that exceeded the value of one, or NOEC-based Expected Risks that exceeded the value of 0.05 (5%), which equals -1.301 on the $\log_{10}ER$ scale. This *ER* value is considered maximally acceptable under REACH.

Figure 7 compares the expected risks and risk quotients that were calculated for 1977 organic REACH chemicals. It can be seen that good correlations as fitted with quadratic regression curves are found for substances with near equal interspecies variations of sensitivity (σ_{NOEC} in Fig. 7A, σ_{EC50} in Fig. 7B). For substances with unequal σ_{NOEC} or σ_{EC50}, *ER* and *RQ* appear unrelated in the sense that substances with equal risks *ER* may have very different risk quotients *RQ*, and substances with equal *RQ* may have very different *ER*.

It also appears from Fig. 7 that, near $RQ=1$, all substances with equal *RQ*, regardless of their interspecies differences in sensitivities σ_{tox}, do have the same *ER*, namely $ER=0.05$ (5%). This can be understood bearing in mind that $RQ_{NOEC}=1$ means that PEC = HC5, i.e., 5% of the species have NOEC smaller than PEC. It is also true that all substances with $RQ>1$ have $ER>0.05$, and all substances with $RQ<1$ have $ER<0.05$. It can be seen from Fig. 7 that this is not true at smaller risk quotients and expected risks. Substances that have *RQ* much smaller than 1, have *RQ* that seem unrelated to *ER*. Substances with equal *RQ* may have *ER* that differ by many orders of magnitude, depending on differences in interspecies differences in sensitivities σ_{tox}.

Note that many REACH chemicals in this study (340 out of 1977) have interspecies sensitivity variations of $\sigma_{tox}=0.70\pm0.05$), and that many of these share the non-polar narcotics mode of action, for which $\sigma_{tox}=0.70$ is the median observed value reported by De Zwart [23]. The chemicals with $\sigma_{tox}\approx 0.7$ are represented in Fig. 7A and B by black dots, and nicely fall onto the same *ER*-*RQ* curves in Fig. 7A and B.

Discussion

Central in the concept of science-based quantitative environmental risk assessment is that ecotoxicological risk depends on both exposure and toxicity. There are different ways to objectively compare exposure with toxicity. In this study, we have considered the two most widely used ways: the simple risk quotient (*RQ*) approach and the more sophisticated expected (*ER*) risk method. The simple *RQ* approach to risk assessment of chemicals has been adopted in the EU chemicals legislation (REACH)

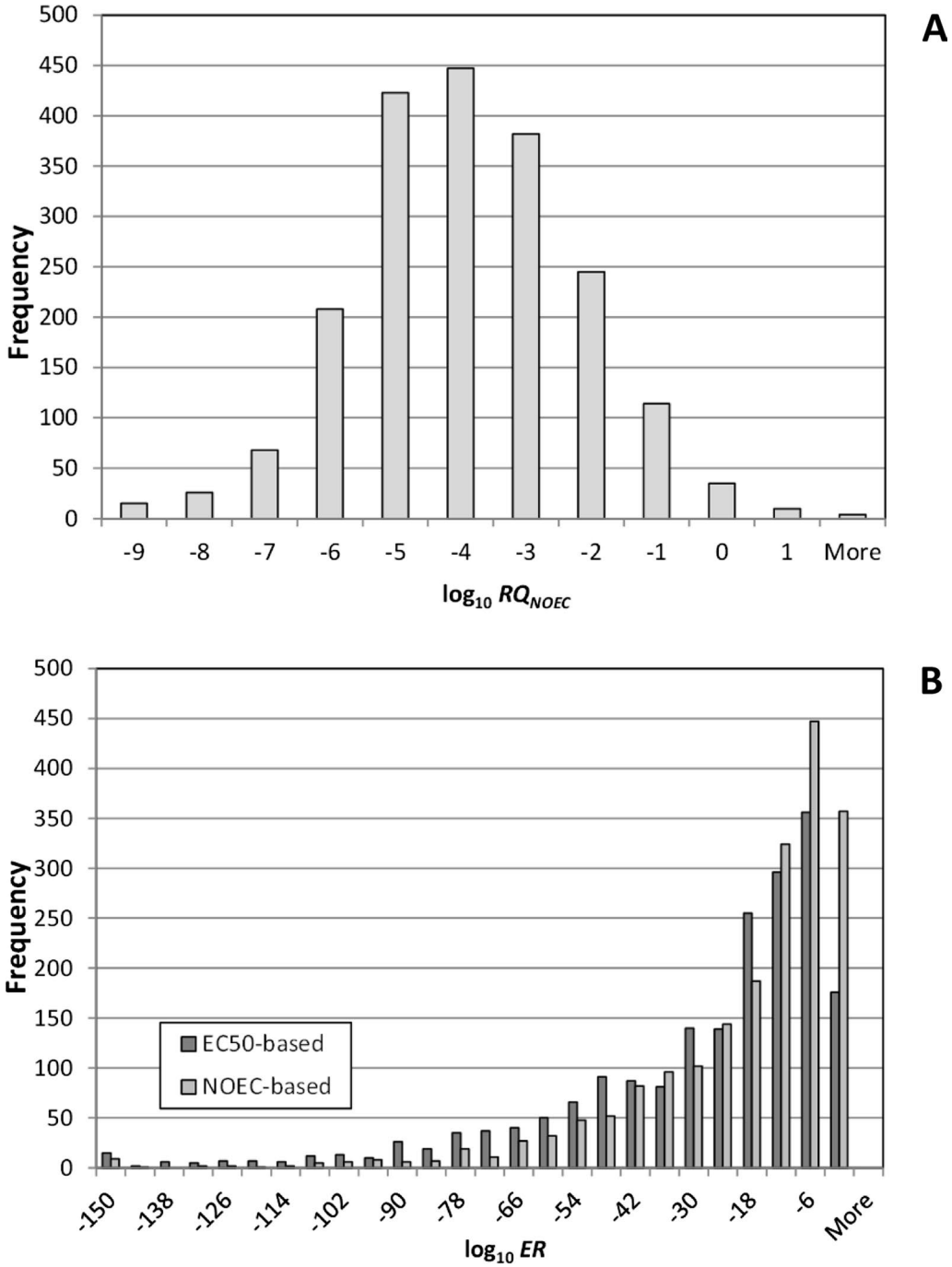

Fig. 6 Risk Quotients, calculated as PEC/HC5 (Panel A), and expected risks of organic chemicals used in Europe (Panel B), calculated from the overlap of distributions in Fig. 5

and various other regulatory platforms. The integrative *ER* method (Eqs. 3 and 4) has mainly found application as a means to compare and prioritize chemicals: the greater *ER*, the greater the priority for taking risk reduction measures. This approach has been successfully taken in many scientific studies (Posthuma et al. [2] and references herein), most recently in the EU project SOLUTIONS (https://www.solutions-project.eu/, [9, 10]).

In this study, we have applied the SimpleRisk/EUSES modeling concept to calculate integrative expected risks *ER* and simple risk quotients *RQ* of 1977 potentially toxic chemicals that had been registered for marketing

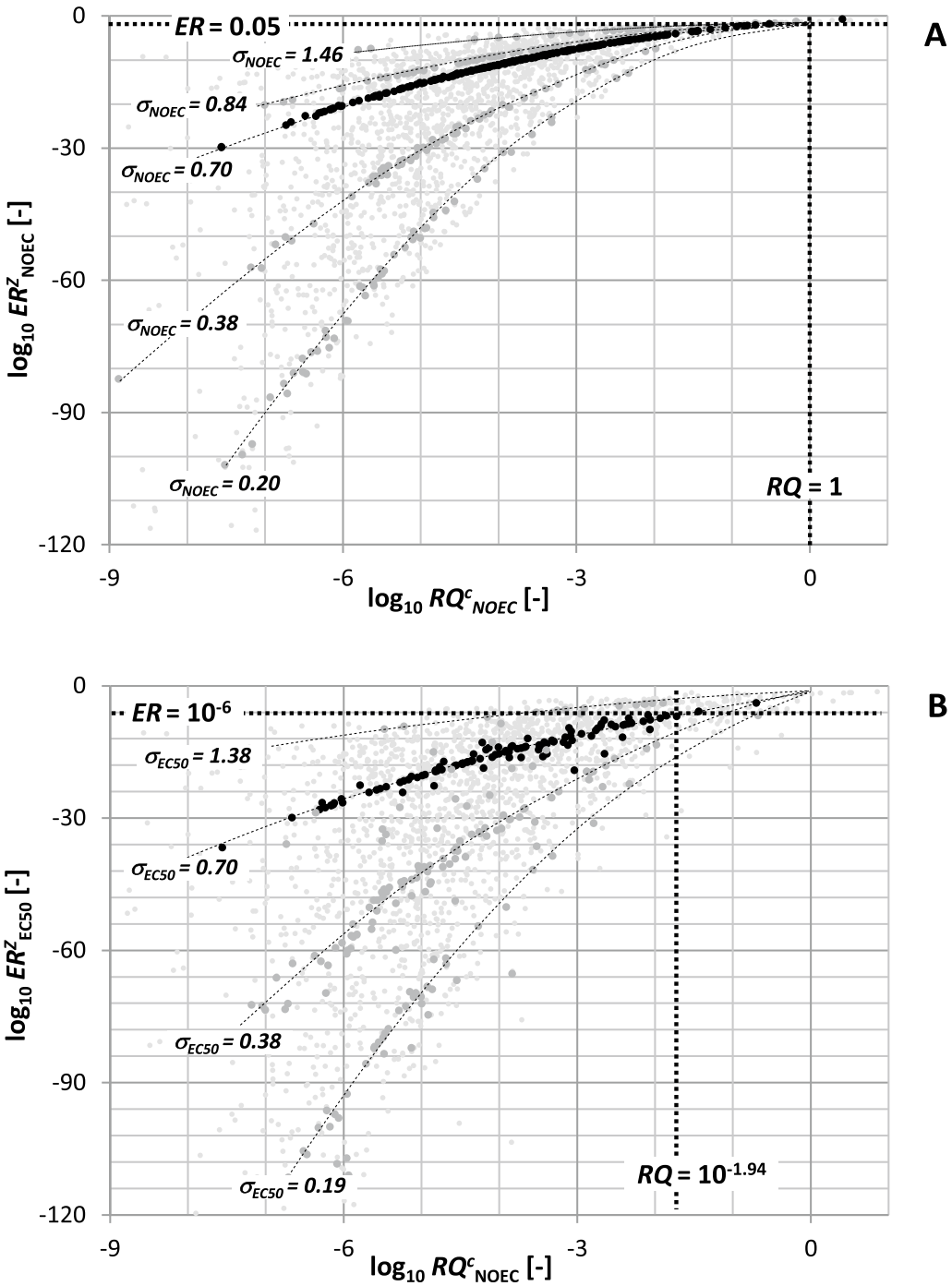

Fig. 7 Comparison of Risk Quotients and Expected Risks (**A**: RQ_{NOEC} vs. ER_{NOEC}; **B**: RQ_{NOEC} vs. ER_{EC50}) of 1977 organic chemicals used in the EU. Each dot indicates one chemical. Curved lines represent quadratic regressions through substances of equal interspecies variance (σ_{NOEC}, σ_{EC50}) as published by Posthuma et al. [21]

under the EU REACH regulation before 2015. We use the results of this study to test whether (i) relevant quantitative indicators of environmental risks of chemicals can be obtained by modeling, and to decide which indicators can offer scientific support to regulatory decision-making.

Suitability of SimpleRisk to model environmental risks of chemicals

It appears from this study that both *RQ* and *ER* can be readily modeled for all chemical substances offered for registration. The SimpleRisk spreadsheet used in this

study models the environment according to the substances evaluation concept, which was introduced in the late 1970s [24], in response to the concerns raised by early environmentalists, who observed undesired biological consequences of the growing use of toxic organic chemicals [25]. Environmental fate modelers reasoned that those necessary regulatory measures would be served best and most fairly by modeling the possible consequences of releases of different chemical substances into the same hypothetical standard environment, which they named 'Unit World'. SimpleRisk adopts this concept, and the steady-state mass balance modeling system ('Fugacity Modeling') [26], that comes with it. SimpleRisk calculates expected concentrations and expected risks from use volumes, physical–chemical substance properties and toxicities, assuming releases into an assumed hypothetical environment—instead of Mackay's Unit World, SimpleRisk uses a so-called 'typical' EU-environment. Earlier studies in the SOLUTIONS project have shown how the SimpleRisk/EUSES modeling concept can be applied to all chemicals used in Europe, producing all outputs necessary for making regulatory decisions about acceptable uses of chemicals in a transparent way.

Suitability of ER and RQ to measure environmental risks of chemicals

The simple *RQ* calculation and the integrative *ER* method are mathematically related, but distinctly different. The approaches are related in the sense that both are mathematical functions of (partly) the same variables, namely the means and variances of the distributions of exposure concentrations and critical effect concentrations. The approaches are distinctly different, too, because the functions *ER* (Eq. 4) and *RQ* (Eq. 5) are certainly not the same. When applied to the same large set of chemicals, outcomes were different (this study, Fig. 7), which should not come as a surprise.

When applied to different chemicals, *ER* and *RQ*, although based on the same exposure- and critical effects data, appear unrelated. This can be concluded from Fig. 7, where it is shown that two different chemicals can have equal *ER*, while at the same time they have greatly different *RQ*. The apparent, perhaps counter-intuitive, nonconformity of *ER* and *RQ* can be understood from the mathematical differences in derivation between the two approaches. The integrative *ER* calculation (Eqs. 2–4) measures the extent of ecotoxicological risk probabilistically by assessing the overlap between exposure concentrations and critical effect concentrations, to yield the probability that one exceeds the other. The simple *RQ* method merely serves to test whether the mean of possible *PEC*s exceeds the 5th percentile of possible *NEC*s (Eq. 5). However, *RQ* does not yield information about the magnitudes of risks expected for different chemicals, while *ER*, being designed to serve this purpose, does. As a consequence, *ER* of different chemicals (with unequal interspecies differences in sensitivities) can be compared directly, regardless of the possible interspecies differences in sensitivities (σ_{tox}). *RQ* of different chemicals can be compared only for chemicals with equal σ_{tox} (Fig. 7); only *ER*s and *RQ*s of chemicals with equal σ_{tox} plot on distinguished curves, whereas calculation results of chemicals with unequal σ_{tox} scatter widely. While *ER* can (and must) be interpreted as an exceedance probability [27] and can, in that quality, serve as a quantitative measure of ecotoxicological risk, this is not true for *RQ*. This study demonstrates that, certainly, the two methods express different aspects of environmental risk of chemicals, and can, therefore, not be used interchangeably. Consequences for regulatory application of risk-based comparison of chemicals are serious. Both *RQ* and *ER* are perfectly suitable to support binary (yes/no) decisions with respect to acceptability of chemical risks, while only *ER* is suitable to quantify and compare environmental risks of different chemicals!

Suitability of ER and RQ to measure risks of mixtures

The outcome of *ER* calculation (Eqs. 2–4) is a probability. *ER* is a dimensionless number that expresses the probability that exposure concentrations exceed critical effect concentrations. Thanks to this, *ER* is additive in the sense that, in the case of combined exposure to different chemicals (mixtures), the overall *ER* of the mixture can be found by addition of the *ER*s of the components of the mixture. The outcome of the *RQ* calculation (Eq. 5) is also a dimensionless number, but not a probability. Addition of the *RQ*s of the mixture components would only result in a meaningful overall mixture *RQ*, when the components of the mixture have the same interspecies variation of toxic sensitivities σ_{tox}. In toxicological practice, this limits the use of *RQ* for risk assessment purposes to consideration of single chemicals, or to mixtures of chemicals with similar species sensitivities. The suitability to quantitatively assess risks of combined exposure to mixtures of chemicals with different toxicological modes of action is a useful added value of *ER* over *RQ*.

Suitability of ER and RQ to address uncertainty

Being the quotient of two uncertain and/or variable figures, *RQ* is an intrinsically uncertain variable. Uncertainties and variabilities in exposure concentrations and critical effect concentrations propagate into *RQ* in a known, predictable way. As a result, *RQ*s are usually very uncertain. The outcome of the *ER* calculation, is an exceedance probability. Unlike *RQ*, *ER* is not uncertain. The magnitude of *ER* follows from the magnitudes of the

variances in exposure concentrations and critical effect concentrations. Unlike in *RQ*, greater variances result in greater *ER*, not in more uncertain *ER*. This suitability to include the consequences of uncertain input to risk quantification is another important added value of *ER* over *RQ*.

Suitability of ER and RQ for risk-based regulatory decision-making

When regulatory risk assessment of chemicals is needed to support yes/no decisions about acceptability of potentially riskful applications of chemicals, both the simple *RQ* method and the integrated *ER* can be used. When it is necessary to determine the magnitude of risk to be taken, the only available option is to use a method that is capable of comparing risks of different chemicals. We have shown in this study that such comparative risk assessments can be made by means of *ER*, but CANNOT, and should not, be made using *RQ*, i.e., not by means of *RQ* calculated from Eq. 5, using untransformed data.

We have tested whether *RQ* could be turned useful for this purpose by calculating it from z-transformed concentration data, as done for *ER* (Eq. 2). It can be seen from Fig. 8, that this is possible. The differences in *RQ* for chemicals with equal *ER* (as in Fig. 7) disappeared after application of z-scaling: chemicals with near equal ER^z also have near equal RQ^z. Data points for different chemicals, which were scattered when RQ^c was calculated from unstandardized data (light gray dots in Fig. 8) collapse onto a much narrower band (dark gray black dots in Fig. 8) after recalculation from z-scaled concentrations. Remaining scatter disappeared completely when uncertainty in *PEC* (which is accounted for in ER^z, but not in RQ^z) was assumed zero.

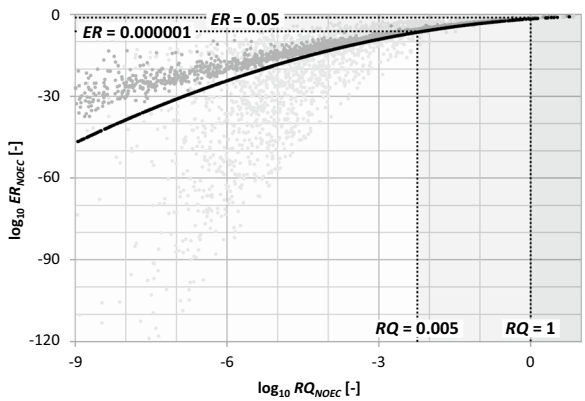

Fig. 8 Expected risk *ER* versus risk quotients *RQ* of 1977 mono-constituent organic REACH chemicals. Light gray symbols: *RQ* calculated as in REACH (from untransformed concentration data); dark gray symbols: *RQ* calculated alternatively (from z-transformed concentration data), with σ_{PEC} of all chemicals set to 0.3; black symbols: *RQ* calculated alternatively (from z-transformed concentration data), with all σ_{PEC} set to 0

When both *ER* and *RQ* are calculated from z-scaled concentrations, both *ER* and *RQ* can be used in risk-based regulatory decision-making. In the EU, where maximum acceptable risk of chemicals, and maximum acceptable exposure concentrations are chosen to be characterized by the $PEC = PNEC$ standard, chemicals with risk quotients greater than 1 (or expected risks greater than 0.05 (5%)—in this study, this applied to less than 1% of the 1977 substances considered—are "unacceptable" according to criteria, and cannot be allowed on the market. Chemicals with expected risk based on acute EC50 values below 10^{-6} (or risk quotients below 0.005)—in this study, this applied to 82% of the 1977 REACH substances considered—can be considered "safe for use" and can be registered for marketing. For the remaining 17% of the tested chemicals, this screening-level assessment does not suffice for risk-based decisions about the possibility to use a chemical safely.

Recommendations

Clearly, *RQ* could be turned useful for the purpose of quantitative environmental risk assessment of chemicals by calculating it from z-transformed concentration data, as this is done for *ER*. To do so, the long-used PEC/PNEC risk quotient calculation would need to be abandoned, replacing it by a similar quotient, built from completely new z-transformed concentrations. We feel that making such changes would meet great resistance, and would take great effort and much time. We feel that international regulatory bodies are more likely to be convinced of the need to introduce the additional, but long-known variable *ER* in environmental risk assessment. From a scientific perspective, it would suffice to stop misinterpretation of PEC/PNEC ratios by stopping to call them Risk Quotients. Rather than that, the European Commission should limit use of *RQ* to state that PEC/PNEC quotients greater than one mean that "use is not sufficiently safe to allow registration under REACH".

On the basis of the results of this study, we recommend using *ER* in addition to *RQ*. Use of screening-level *RQ* (as currently practiced in the EU) should be limited to making decisions about exceedance of maximum acceptability levels. Support for regulatory decisions about priorities for risk reduction or authorization requires more extensive knowledge of environmental risks of chemicals. In a recent opinion article, Van Straalen et al. [28] have summarized the scientific and practical reason for this recommendation.

Moreover, the calculation of ER with acute EC50 data should be preferred due to the following reasons:

- The statistical derivation of EC50 is far more robust than the test design dependent derivation of NOEC.
- As compared to the availability of chronic NOEC data, many more acute EC50 data are available for many more substances and many more species, making the statistical derivation of SSD curves much more reliable.
- It has been demonstrated that *ER* based on acute EC50 data more closely reflects the impact on biodiversity and ecological status that can be observed in field exposed communities of species [29–31]. This is very useful when mixture toxicity needs to be addressed.

Supplementary Information

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Additional file 1. Supplemental data.

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Author contributions
The study described in this manuscript was carried out collectively by members of the Association of Retired Environmental Scientists ARES. DvdM, DdZ and JS co-authored SimpleBox, SimpleTreat and SimpleRisk4REACH, acquired substance data, carried out calculations and prepared the first draft of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. A copy of the SimpleRisk model—Excel workbook SimpleRisk4Reach 20220313.xlsm—with which all calculations in this study were done, is freely available to any interested party. A data file containing all data used in this study—Additional file 1: Table S1.pdf—is also available. Naturally, the strictly confidential use volumes, which could be used in this study thanks to ECHA and the Netherlands Competent Authority, are NOT included in this data file.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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References

1. Van Leeuwen CJ, Vermeire TG (2007) Risk assessment of chemicals. An introduction, 2nd edn. Springer, Dordrecht, the Netherlands
2. Posthuma L, Suter GW II, Traas TP (2002) Species sensitivity distributions in ecotoxicology. CRC-Press, Boca Raton, FL, USA
3. Van Straalen NM (2002) Theory of ecological risk assessment based on species sensitivity distributions. In: Posthuma L, Suter GW II, Traas TP (eds) Species sensitivity distributions in ecotoxicology. Lewis Publishers, Boca Raton, FL, USA, pp 37–48
4. Aldenberg T, Jaworska JS, Traas TP (2002) Normal species sensitivity distributions in probabilistic ecological risk assessment. In: Posthuma L, Suter GW II, Traas TP (eds) Species sensitivity distributions in ecotoxicology. Lewis Publishers, Boca Raton, FL, USA, pp 49–102
5. Cardwell RD, Brancato MS, Toll J, Deforest D, Tear L (1999) Aquatic ecological risks posed by tributyltin in united states surface waters: Pre-1989 to 1996 data. Environ Toxicol Chem 18(3):567–577
6. Verdonck FAM, Aldenberg T, Jaworska J, Vanrolleghem PA (2003) Limitations of current risk characterization methods in probabilistic environmental risk assessment. Environ Toxicol Chem 22(9):2209–2213
7. EC. 2004. European Union System for the Evaluation of Substances 2.0 (EUSES 2.0). Prepared for the European Chemicals Bureau by the National Institute of Public Health and the Environment (RIVM), Bilthoven, the Netherlands. RIVM report no. 601900005
8. Solomon KR (1996) Overview of recent developments in ecotoxicological risk assessment. Risk Anal 16:627–633
9. Brack W, Altenburger R, Schüürmann G, Krauss M, López Herráez D, Van Gils J, Slobodnik J, Munthe J, Gawlik BM, Van Wezel A et al (2015) The solutions project: challenges and responses for present and future emerging pollutants in land and water resources management. Sci Total Environ 503–504:22–31
10. Brack W, Hollender J, De Alda ML, Müller C, Schulze T, Schymanski E, Slobodnik J, Krauss M (2019) High-resolution mass spectrometry to complement monitoring and track emerging chemicals and pollution trends in European water resources. Environ Sci Eur 31(1):62
11. Van de Meent D, De Zwart D, Posthuma L (2020) Screening-level estimates of environmental release rates, predicted exposures, and toxic pressures of currently used chemicals. Environ Toxicol Chem 39(9):1839–1851
12. Jager T, Vermeire TG, Rikken MGJ, Van der Poel P (2001) Opportunities for a probabilistic risk assessment of chemicals in the European Union. Chemosphere 43:257–264
13. Bogen KT, Cullen AC, Frey HC, Price PS (2009) Probabilistic exposure analysis for chemical risk characterization. Toxicol Sci 109:4–17
14. ECHA. 2016. Guidance on information requirements and chemical safety assessment, chapter r.16: environmental exposure assessment. Version 3.0. European chemicals agency, report echa-16-g-03-en, helsinki. February 2016.
15. EEC. 1991. Council directive 91/271 concerning urban waste water treatment. Oj-1991-l135 p40 91–271-eec, brussels Official journal of the European Communities, Brussels, Belgium. L 135(34):40–52.
16. CEFIC (2012) Specific environmental release categories (spercs). Chemical safety assessments, supply chain communication and downstream user

compliance. Cefic internal document of the sperc core team. Cefic, brussels, october 2012
17. Hollander A, Schoorl M, Van de Meent D (2016) Simplebox 4.0: improving the model while keeping it simple. Chemosphere 148:99–107
18. Lautz LS, Struijs J, Nolte TM, Breure AM, Van der Grinten E, Van de Meent D, Van Zelm R (2017) Evaluation of simpletreat 4.0: simulations of pharmaceutical removal in wastewater treatment plant facilities. Chemosphere 168:870–876
19. Struijs J, Van de Meent D, Schowanek D, Buchholz H, Patoux R, Wolf T, Austin T, Tolls J, Van Leeuwen K, Galay-Burgos M (2016) Adapting simpletreat for simulating behaviour of chemical substances during industrial sewage treatment. Chemosphere 159:619–627
20. Zijp MC, Posthuma L, Van de Meent D (2014) Definition and applications of a versatile chemical pollution footprint methodology. Environ Sci Technol 48(18):10588–10597
21. Posthuma L, Van Gils J, Zijp MC, Van de Meent D, de Zwart D (2019) Species sensitivity distributions for use in environmental protection, assessment, and management of aquatic ecosystems for 12 386 chemicals. Environ Toxicol Chem 38(4):905–917
22. Henderson A, Hauschild M, Van de Meent D, Huijbregts MJ, Larsen H, Margni M, McKone T, Payet J, Rosenbaum R, Jolliet O (2011) Usetox fate and ecotoxicity factors for comparative assessment of toxic emissions in life cycle analysis: sensitivity to key chemical properties. Int J Life Cycle Assess 16(8):701–709
23. De Zwart D (2002) Observed regularities in species sensitivity distributions. In: Posthuma L, Suter GW, Traas TP (eds) Species sensitivity distributions in ecotoxicology. Lewis, Boca Raton, pp 133–154
24. Baughman GL, Lassiter RR (1978) Prediction of environmental pollutant concentration. In: Cairns J, Dickson KL, Maki AW (eds) Estimating the hazard of chemical substances to aquatic life. ASTM International, West Conshohocken, PA, pp 35–54
25. Carson R (1962) Silent spring. Houghton Mifflin Co, Boston
26. Mackay D (1991) Multimedia environmental models: the fugacity approach. Lewis Publishers, Chelsea, MI
27. Van Straalen NM. 1990. New methodologies for estimating the ecological risk of chemicals in the environment. Rotterdam.
28. Van Straalen NM, Den Haan KH, Hermens JLM, Van Leeuwen CJ, Van de Meent D, Parsons JR, De Voogt WP, De Zwart D (2022) Risk assessment acknowledging variability in both exposure and effect. Environ Sci Technol 56(20):14223–14224
29. De Zwart D, Posthuma L, Dyer S, Hawkins C (2005) Mixture toxicity and habitat alterations attributed to effects on species composition of fish in ohio rivers. AGU Spring Meet Abstr 1:02
30. Posthuma L, Dyer SD, De Zwart D, Kapo K, Holmes CM, Burton GA Jr (2016) Eco-epidemiology of aquatic ecosystems: Separating chemicals from multiple stressors. Sci Total Environ 573:1303–1319
31. Posthuma L, Zijp MC, De Zwart D, Van de Meent D, Globevnik L, Koprivsek M, Focks A, Van Gils J, Birk S (2020) Chemical pollution imposes limitations to the ecological status of European surface waters. Sci Rep 10(1):14825

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