Int J Life Cycle Assess
DOI 10.1007/s11367-017-1322-y

Sensitivity-based research prioritization through stochastic characterization modeling

Ben A. Wender[1] · **Valentina Prado**[2] · **Peter Fantke**[3] · **Dwarakanath Ravikumar**[4] · **Thomas P. Seager**[4]

Received: 30 December 2015 / Accepted: 11 April 2017

Abstract
Purpose Product developers using life cycle toxicity characterization models to understand the potential impacts of chemical emissions face serious challenges related to large data demands and high input data uncertainty. This motivates greater focus on model sensitivity toward input parameter variability to guide research efforts in data refinement and design of experiments for existing and emerging chemicals alike. This study presents a sensitivity-based approach for estimating toxicity characterization factors given high input data uncertainty and using the results to prioritize data collection according to parameter influence on characterization factors (CFs). Proof of concept is illustrated with the UNEP-SETAC scientific consensus model USEtox.
Methods Using Monte Carlo analysis, we demonstrate a sensitivity-based approach to prioritize data collection with an illustrative example of aquatic ecotoxicity CFs for the vitamin B derivative niacinamide, which is an antioxidant used in personal care products. We calculate CFs via 10,000 iterations assuming plus-or-minus one order of magnitude variability in fate and exposure-relevant data inputs, while uncertainty in effect factor data is modeled as a central *t* distribution. Spearman's rank correlation indices are used for all variable inputs to identify parameters with the largest influence on CFs.
Results and discussion For emissions to freshwater, the niacinamide CF is near log-normally distributed with a geometric mean of 0.02 and geometric standard deviation of 8.5 PAF m^3 day/kg. Results of Spearman's rank correlation show that degradation rates in air, water, and soil are the most influential parameters in calculating CFs, thus benefiting the most from future data refinement and experimental research. Kow, sediment degradation rate, and vapor pressure were the least influential parameters on CF results. These results may be very different for other, e.g., more lipophilic chemicals, where Kow is known to drive many fate and exposure aspects in multimedia modeling. Furthermore, non-linearity between input parameters and CF results prevents transferring sensitivity conclusions from one chemical to another.
Conclusions A sensitivity-based approach for data refinement and research prioritization can provide guidance to database managers, life cycle assessment practitioners, and experimentalists to concentrate efforts on the few parameters that are most influential on toxicity characterization model results. Researchers can conserve resources and address parameter uncertainty by applying this approach when developing new or refining existing CFs for the inventory items that contribute most to toxicity impacts.

Keywords Characterization factor · Sensitivity analysis · Uncertainty · USEtox

Responsible editor: Stig Irving Olsen

Electronic supplementary material The online version of this article (doi:10.1007/s11367-017-1322-y) contains supplementary material, which is available to authorized users.

✉ Ben A. Wender
bwender@asu.edu

[1] National Academies of Sciences, Engineering, and Medicine, Washington DC, Washington, USA

[2] Institute of Environmental Sciences CML, Leiden University, Einsteinweg 2, 2333, CC Leiden, the Netherlands

[3] Quantitative Sustainability Assessment Division, Department of Management Engineering, Technical University of Denmark, Bygningstorvet 116B, 2800 Kgs. Lyngby, Denmark

[4] School of Sustainable Engineering and the Built Environment, Arizona State University, Tempe, AZ, USA

Published online: 29 April 2017

1 Introduction

Integrated fate-exposure-effect models like USEtox (Rosenbaum et al. 2008), Impact2002 (Pennington et al. 2005), and USES-LCA (van Zelm et al. 2009) are widely used to calculate characterization factors (CFs) for human toxicity and ecotoxicity impacts in life cycle assessment (LCA). CFs allow practitioners and decision makers to quantify potential toxicity-related impacts associated with chemical emissions into the environment quantified in the life cycle inventory (LCI) phase of LCA. Life cycle impact assessment (LCIA) models for characterizing human toxicity and ecotoxicity are relatively complex and require various substance-specific input parameters, and their results are typically characterized by an overall uncertainty of two-to-three orders of magnitude depending on emission compartment, exposure scenario, and data availability (Jolliet and Fantke 2015; Rosenbaum 2015). Thus, these models require continuous improvement, although significant achievements have been made over the last decade. For example, sustained harmonization efforts between divergent toxicity LCIA models resulted in the UNEP-SETAC scientific consensus model USEtox (Rosenbaum et al. 2008; Westh et al. 2015) and the more recent release of USEtox 2.0 (http://usetox.org), which are considered best practice (Hauschild et al. 2013), recommended by the ILCD handbook (EC 2011), and implemented in various LCIA methods such as TRACI (Bare et al. 2012).

The extensive inter-model comparisons and streamlining activities addressed model uncertainty and improved transparency and credibility (Hauschild et al. 2008). However, further development and adoption of current human toxicity and ecotoxicity LCIA models faces challenges related to the large number and diverse properties of potentially emitted substances, limited availability of high-quality data, and sparse treatment of parameter uncertainty or variability (Alfonsín et al. 2014; Gust et al. 2016; Rosenbaum 2015). For example, there is a large discrepancy between the ≈10,000 substances included in the latest Ecoinvent inventory library (Weidema et al. 2013) and the ≈1200 human toxicity and 2500 ecotoxicity CFs available from USEtox 2.0 currently constituting the largest substance coverage in an LCA toxicity characterization model.

Calculating each individual CF requires approximately ten substance-specific input parameters, some of which are extrapolated from underlying background data. Thus, database validation and expansion requires extensive efforts in data collection and curation, including potentially costly experiments. As a result, many CFs in USEtox (and any other LCIA toxicity model) often rely on substance data estimated using outputs from, e.g., quantitative structure activity relationship (QSAR) models, such as models in the EPISuite program (USEPA 2015b), which are essential for filling data gaps but often lack experimental evidence and therefore are, for many parameters, considered of lower representativeness than measured values (Huijbregts et al. 2010a). There is a critical need to explore the sensitivity of human toxicity and ecotoxicity LCIA results to variability and uncertainty in required substance input data, which may help expedite database expansion, refinement, and prioritization of future data-related research needs (Cellura et al. 2011; Cucurachi and Heijungs 2014). More broadly, using sensitivity analysis within life cycle environmental models to prioritize environmental research and technology development decisions is an example of anticipatory LCA (Ravikumar et al. 2013; Ravikumar et al. 2017; Wender et al. 2014a).

One available method to evaluate LCIA model sensitivity to variability in substance data is to use Monte Carlo analysis to sample from specified distributions (Sonnemann et al. 2003) and calculate CFs as frequency distributions as opposed to point estimates (Lloyd and Ries 2007; van Zelm and Huijbregts 2013). Calculating stochastic CFs enables sensitivity analyses that can help expedite data collection by identifying the substance-specific parameters with the greatest influence on model output variability (Saltelli et al. 2008). This can help conserve resources by focusing future research on experiments with the greatest potential to reduce uncertainty of model results, while substance data with little impact on results may be revealed as a low investigative priority (Fantke et al. 2016).

The present paper introduces a Monte Carlo approach that can be combined with toxicity characterization models to specify substance input data as variable distributions, and presents resulting CFs as frequency distributions. To illustrate this sensitivity-based approach, we apply it to USEtox 1.01 to develop stochastic aquatic ecotoxicity CFs for the vitamin B derivative niacinamide (CAS 98-92-0), currently used at low concentrations in commercial personal care products because of its antioxidant properties (Bissett et al. 2006). This illustration represents a hypothetical case in which personal care product developers are unsure about the potential ecotoxicity impacts and want to improve their confidence. It is critically important to align LCA interpretation methods to support complex environmental decision-making under uncertainty (Prado-Lopez et al. 2015). Results identify parameters with most influence over the resulting CF.

2 Methods

USEtox calculates freshwater ecotoxicity CFs stored in a matrix *CF* where matrix elements are expressed in comparative toxicity units CTUe (PAF m^3 d) per unit mass of emitted substance, and calculated as the product of a matrix *FF* of fate factors ($kg_{in\ compartment}$ per $kg_{emitted}$/d), a matrix *XF* of ecosystem exposure factors ($kg_{bioavailable}/kg_{in\ compartment}$), and a matrix *EF* of ecosystem effect factors (PAF $m^3/kg_{bioavailable}$)

(Eq. 1). Fate factors, eco-exposure factors, and ecotoxicity effect factors represent the chemical residence time in freshwater (for an emission to freshwater), dissolved fraction in freshwater, and aggregated multi-species toxicological response, respectively (Henderson et al. 2011; Huijbregts et al. 2010a).

$$CF = EF\ XF\ FF \quad (1)$$

Model structure, assumptions, and landscape data of USEtox are not targeted in our study as they have been assessed elsewhere, whereas the focus in the present study is exclusively on prioritization of research regarding substance input data.

2.1 Sensitivity-based approach

The sensitivity-based approach builds upon an existing toxicity characterization model, except data inputs are specified as probability distributions as opposed to point estimates. Input data distributions are sampled independently 10,000 times, and the values were used as input to USEtox to calculate fate, eco-exposure, and ecotoxicity effect factors, and resulting CFs plotted as frequency distributions along with descriptive statistics. To evaluate the relative influence of input parameter variability on calculated CFs, we compare Spearman's rank correlation indices for all inputs that are not point estimates.

2.2 Fate and exposure data and modeling assumptions

Data are collected primarily from EPISuite (USEPA 2015b) and supplemented with available literature as summarized in Table 1. Niacinamide is included in USEtox 2.0 (http://usetox.org) with fate- and exposure-relevant parameter values nearly identical to those presented in Table 2 (Electronic Supplementary Material, Section 2.2). We collected parameter estimates from an OECD Screening Information Dataset, which reports experimentally-determined estimates for Kow of 0.42 L/L and water solubility of $6.9–10 \times 10^5$ mg/L (UNEP 2002), which correspond closely with values reported by EPISuite (USEPA 2015b). The National Center for Biotechnology Information database reports Henry's Constant (Kh) as 2.9×10^{-7} Pa m^3/mol and a vapor pressure of 0.05 Pa (PubChem 2015b). We combine EPISuite outputs and the USEtox organics manual (Huijbregts et al. 2010b) to model CFs assuming uniform distributions for all degradation rate constants and bioaccumulation factors (BAF) in fish following the baseline scenario of plus-or-minus one order of magnitude from these point estimates as one possible way of varying input parameters. A uniform distribution was applied to all parameters (except the molecular weight which is a known quantity) to illustrate the sensitivity-based approach given little formal uncertainty information and to reduce efforts in data collection.

2.3 Effect factor data and modeling assumptions

We calculate freshwater ecotoxicity effect factors (EF) for niacinamide using variable toxicology data from acute and chronic toxicity tests on producers (algae), primary consumers (invertebrates), and secondary consumers (fish) (Hauschild and Huijbregts 2015; Huijbregts et al. 2010a). Toxicity data used in the present paper are reported as the concentration at which 50% of the exposed organisms over background exhibit the studied effect (EC_{50}), inhibited growth (IC_{50}), or lethality (LC_{50}) (Müller et al. 2017), and were taken from available literature as summarized in Table 2. These studies correspond with values reported in the REACH database, with the exception of reported acute toxicity to the common guppy fish (*Poecilia reticulata*) which we report as >1000 mg/L and the REACH database reports at 4 g/L (REACH 2017).

We divide the acute toxicity data points reported in Table 2 by a generic acute-to-chronic conversion factor of 2 to extrapolate the chronic equivalent EC_{50}, which in itself is a rough and uncertain extrapolation due to general lack of chronic data that is worthy of further research. It is noteworthy that for niacinamide, only acute toxicity data were available, in part, because chronic tests may be considerably more expensive, which points to a broader research need to fill data gap related to chronic toxicity impacts. The dataset contains a misclassified acute EC_{50} value of 0.34 mg/L reported in the ECOTox and RIVM ETox databases (RIVM 2015; USEPA 2015a), which references to a study that considers nicotine and 6-aminonicotinamide (Dawson and Wilke 1991) instead of niacinamide, which has been brought to the attention of the respective database managers. Unfortunately, this is the only value implemented in the recently released USEtox 2.0, which results in a niacinamide ecotoxicity CF for emission to freshwater on the order of 10^5 PAF m^3 d/kg—surprisingly large for a vitamin B derivative widely considered to be innocuous at relevant commercial and environmental concentrations (CIREP 2005). Thus, we exclude this value in calculating EFs for niacinamide, although the influence of the data point on aggregate multi-species hazardous concentration (avLog EC_{50}) estimation and standard error on the mean (SEM) calculation is significant (Electronic Supplementary Material, Section 2.3.1).

To calculate hazardous concentrations avLog EC_{50} from the individual studies reported in Table 2, we take the log of the geometric mean across all reported EC_{50} values per species and then calculate the average of these values across all species (Huijbregts et al. 2010a; Müller et al. 2017) (Electronic Supplementary Material, Section 2.3.2). This represents the concentration at which half of the exposed aquatic species are affected above their median EC_{50} values, and is $10^{3.2}$ = 1850 mg/L for niacinamide with a standard error on

Table 1 Fate and exposure-relevant data for USEtox 1.0 and modeled variance

Parameter	Description	Units	Point value(s)	Baseline variance	Reference
MW	Molecular weight	g/mol	122	122	Chemical formula
Kow	Octanol-water partitioning coefficient	L/L	0.42	4.2×10^{-2} – 4.2	OECD SIDS
Koc	Soil organic carbon-water partitioning coefficient	L/kg	8.5	0.85 – 85	EPISuite, Kocwin
Kh	Henry's law constant	Pa m^3/mol	2.9×10^{-7} 6.45×10^{-6}	2.9×10^{-8} – 2.9×10^{-6}	PubChem database USEtox Guidance
Pvap	Vapor pressure	Pa	0.026 0.05	5×10^{-3} – 0.5	EPISuite, MPBPVP PubChem database
Solubility	Solubility in water	mg/L	5e5 $6.9–10 \times 10^5$	5×10^4 – 5×10^6	EPISuite, exper. OECD SIDS
kdeg, air	Degradation rate constant in air	L/s	1.8×10^{-6}	1.8×10^{-7} – 1.8×10^{-5}	EPISuite, AOPWin USEtox manual
kdeg, water	Degradation rate constant in water		2.1×10^{-7}	2.1×10^{-8} – 2.1×10^{-6}	EPISuite, Biowin USEtox manual
kdeg, soil	Degradation rate constant in soil		1×10^{-7}	1×10^{-8} – 1×10^{-6}	
kdeg, sed	Degradation rate constant in sediment		2.3×10^{-8}	2.3×10^{-9} – 2.3×10^{-7}	
BAF fish	Bioaccumulation factor in fish	L/kg	0.9	0.09 – 9.0	EPISuite, BCFBAF

the mean (SEM) of 0.04 for niacinamide (Electronic Supplementary Material, Section 2.3.2). Uncertainty in the average toxicity ($\overline{\text{avLog}}$) follows a Student's t distribution (Golsteijn et al. 2012; Van Zelm et al. 2007) centered around avLog EC_{50} and scaled by the SEM, shown in Eq. 2:

$$\overline{\text{avLog}} = \text{avLog}\, EC_{50} + SEM^{*}t \quad (2)$$

where t represents a two-tailed t distribution with n-1 degrees of freedom from n different species with reported toxicity data (Electronic Supplementary Material, Section 2.3.2).

3 Results and discussion

Freshwater aquatic ecotoxicity CFs for niacinamide emitted directly into air, water, and soil compartments (Fig. 1) show two or more orders of magnitude variability resulting from the assumed plus-or-minus one order of magnitude variation of input data in the baseline scenario. These results are generated through the full sampling of distributions specified in Table 1 as well as $\overline{\text{avLog}}$, and thus represent freshwater aquatic ecotoxicity CFs resulting from simultaneous changes in all variable substance input data.

Table 2 Data from individual acute ecotoxicity studies

Reference	Species $n = 3$	Test type and endpoint	Reported value(s) (mg/L)	Chronic eqiv. EC_{50} value (mg/L)	
Producers					
OECD SIDS, 2002		*S. subspicatus*	72 h acute EC_{50}	>1000	500
		Algae—generic	QSAR, 96 h Acute EC_{50}	8934	4500
Primary consumers					
OECD SIDS, 2002		*D. magna*	24 h acute EC_{50}	>1000	500
		Daphnid—generic	48 h acute EC_{50}, QSAR	16,456	8000
Secondary consumers					
OECD SIDS, 2002		*P. reticulata*	96 h acute LC_{50}	>1000	500
		Fish—generic	96 h acute LC_{50}, QSAR	18,189	9000
ECOTox database, 2015[a]		*X. laevis*	96 h acute EC_{50}, embryonic	0.34	0.17

[a] Misclassified data point contained in ECOTox database

Results in Fig. 1e are obtained from USEtox 1.01, where niacinamide (nicotinamide USEtox) is treated as neutral as opposed to a weak dissociating base. Table 3 compares the results from Fig. 1 to those reported by USEtox 2.0, which includes dissociation of the weak base niacinamide. The geometric mean of the CF distributions from Fig. 1 (rows 6) are consistently smaller in magnitude than the point estimate CFs obtained using parameter values from USEtox 2.0 (rows 1 and 2), whereas the arithmetic mean is within one order of magnitude for each emission scenario. Inclusion of the misclassified ecotoxicity data point from the RIVM and EPA databases discussed in Section 2.3 above results in CF estimates two or three orders of magnitude larger (rows 1 and 3) than calculations for which this data point is omitted (rows 2 and 4), regardless of which USEtox model version or emission compartment is considered. Comparison of rows 2 and 4 shows that inclusion of dissociation has relatively small influence on the CFs calculated for niacinamide, and that using USEtox version 1.01 is justifiable for illustrating our approach for this chemical.

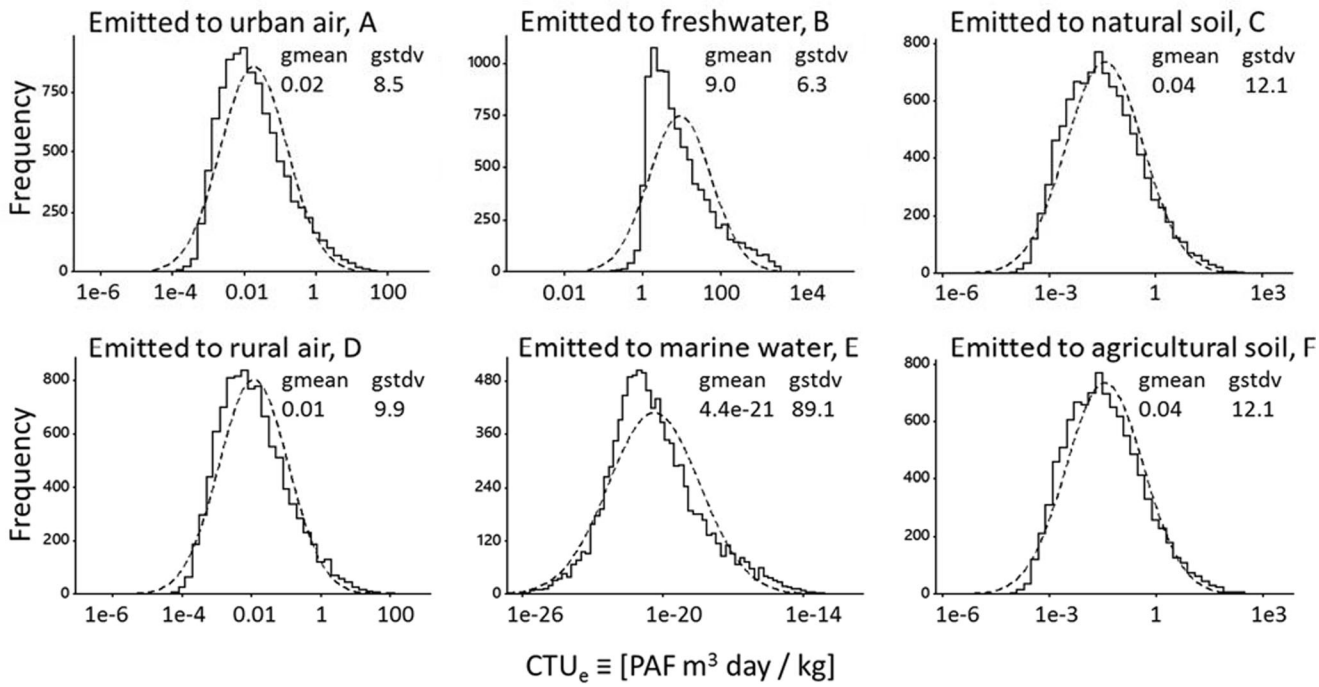

Fig. 1 Stochastic freshwater aquatic ecotoxicity CFs for the antioxidant niacinamide emitted to urban air (**a**), continental freshwater (**b**), natural soil (**c**), rural air (**d**), marine water (**e**), and agricultural soil compartments (**f**). *Solid lines* are frequency distributions from 10,000 Monte Carlo runs and *dashed lines* are normal distributions fit to the log-transformed data

Table 3 Comparison of our results to USEtox 1.01 and 2.0 CFs

Model description	Freshwater ecotoxicity CF [PAF m^3 d/kg] for emission to:					
	Urban air	Rural air	Freshwater	Marine water	Natural soil	Agricultural soil
USEtox 2.0	1.98E + 04	1.90E + 04	1.15E + 05	8.72E-03	2.72E + 04	2.74E + 04
USETox 2.0 w/ correct data	3.2	3.1	19.3	1.4E-6	4.5	4.5
USEtox 1.0 w/ erroneous data point	3.4E + 04	3.4E + 04	1.2E + 05	8.9E-03	4.8E + 04	4.8E + 04
USEtox 1.0 w/ correct data	3.6	3.6	12	9.5E-07	5.2	5.2
Arithmetic mean from stochastic CF	0.29	0.25	3.0	1.4e-7	0.46	0.46
Geometric mean from stochastic CF	0.02	0.01	9.0	4e-21	0.04	0.04

3.1 Identifying the most influential substance input parameters

To estimate the relative influence of varied input parameters used to calculate niacinamide freshwater ecotoxicity CFs, we take the absolute value of the Spearman's rank correlation index for emissions to all six considered compartments (Fig. 2). Spearman rank correlation assumes independence of observations within each parameter and makes no assumptions about the distribution type (Gauthier 2001). However, many of the substance parameters in USEtox are themselves calculated as a function of other substance input parameters

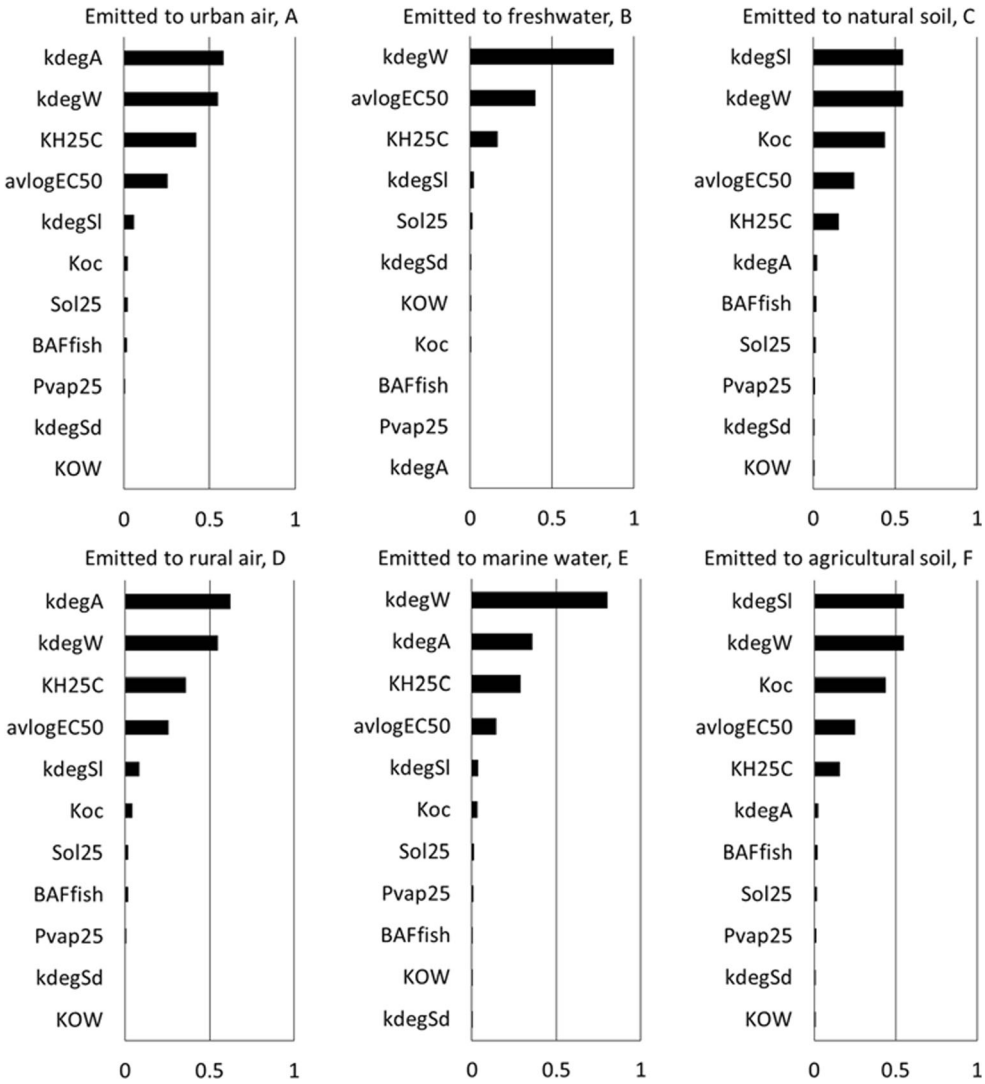

Fig. 2 The Spearman rank correlation indices with the greatest magnitude out of all variable inputs for six niacinamide freshwater aquatic ecotoxicity CFs as shown in Fig. 1. *Greater magnitude* indicates that the input parameter has a greater influence on CF variability for that emission compartment

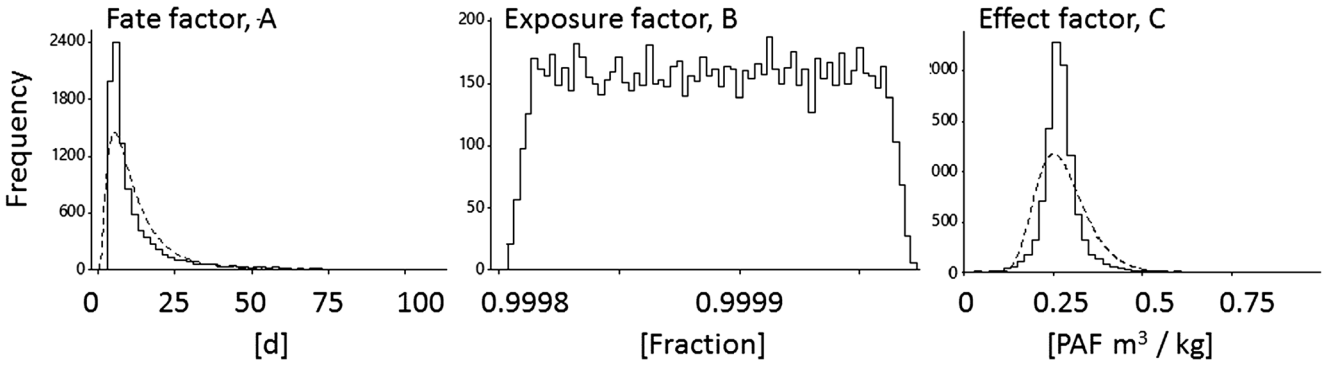

Fig. 3 Component fate (**a**), exposure (**b**), and effect factors (**c**) for niacinamide. *Solid lines* are frequency distributions of 10,000 Monte Carlo runs and *dashed lines* are log normal and normal distributions fit to the FF and EF data, respectively

using simple regressions, for example, calculating degradation rate constants for soil and sediment with linear extrapolation factors, and are therefore not independent. We do not account for the interdependence of input parameters, as the focus here is on identifying only the few most influential substance properties, although, e.g., Fantke et al. (2012) demonstrate how it is possible to decouple parameter uncertainty (e.g., in Koc) from regression-related uncertainty for correlated parameters (e.g., estimating Koc from Kow).

Spearman's rank correlation results show that degradation rate constants in the receiving compartment are the most influential parameters in calculating CFs, with aquatic degradation rate constants always first or second in all emission scenarios (Fig. 2). In addition to degradation rate constants, Henry's constant is influential for air and water emissions, whereas soil organic carbon-water partitioning coefficient is more influential for emissions to soil. The toxicity indicator avLog is within the top five most influential parameters for all emission scenarios, but is generally less influential than the aforementioned fate-relevant parameters. The remaining parameters have little influence on CF variability for the studied chemical, thus narrowing the assumed variability will have little impact. Uncertainty in degradation rate constants were evaluated as a range of plus-or-minus one order of magnitude based on EPISuite point estimates (Table 2). Given the importance of degradation rate constants in estimating the potential freshwater ecotoxicity, further research into degradation mechanisms are high priorities for reducing uncertainty in niacinamide freshwater aquatic ecotoxicity CFs. Because CFs are not linear with respect to input parameters such as Kow, these results should not be interpreted across chemicals, as many will likely be most sensitive to changes in this parameter (Fantke and Jolliet 2016).

3.2 Decomposing CFs into fate, exposure, and effect components

Decomposition of niacinamide CFs into the component fate factor (FF) for emission to freshwater, the dissolved fraction (exposure factor XF), and aggregate multi-species toxicity (effect factor EF) (Fig. 3a–c) shows that XF is essentially one, whereas FF and EF show approximately two orders of magnitude variability from the assumed plus-or-minus one order of magnitude variability assumed around input parameters.

Figure 3 shows that the average residence time for niacinamide in freshwater is approximately 14 days, with the dominant removal pathway being degradation. XF is effectively a point value of 1, which represents 100% of emitted niacinamide as dissolved and bioavailable in freshwater. EF has an average value of 0.27 compared to 2900 PAF m^3/kg that is obtained when using reported freshwater ecotoxicity data from the Etoxbase database as applied in USEtox 2.0, with the large difference due to the omission of one misclassified data point in Etoxbase. The lower value is intuitive for the vitamin B derivative and on the same order of magnitude as chemicals such as urea and isopropyl alcohol.

Overall, it is important to note that sensitivity of characterization factors toward the different input parameters used in USEtox or other models will differ largely between chemicals. For example, it has been shown that fate and bioaccumulation factors are very sensitive to Kow, particularly for very lipophilic chemicals, where Kow is known to drive many fate and exposure processes (MacLeod et al. 2002; Fantke et al. 2016). Furthermore, any non-linear relationship between input and output parameters will not allow for transferring sensitivity conclusions from one chemical to another as soon as chemicals have different physicochemical property values. Nonetheless, for each chemical individually, our sensitivity analysis is able to identify further research and data priorities to improve toxicity characterization modeling.

4 Conclusions

LCIA method developers can apply this sensitivity-based approach in combination with existing LCIA toxicity characterization models to expedite expansion and review of toxicity databases by identifying the most influential substance input data for distinct chemical classes, and then focusing their

efforts on reducing parameter uncertainty on these estimates by finding or providing experimental data or otherwise improved estimates. Analogous to the case of niacinamide discussed within this manuscript , it is likely that only few model input parameters are significant for each chemical, and analyzing uncertainty estimates for these parameters may allow future quantification of parameter uncertainty for all chemicals currently included and foreseen for inclusion in LCIA models (similar to what has been done for global estimates of model uncertainty). Furthermore, we encourage LCA practitioners to apply this same approach to the life cycle inventory items that contribute most to ecotoxicity impacts to increase confidence in interpretation of LCIA results.

The approach outlined in the present paper has potential for broader application to different LCIA models and other impact categories that use simplified fate and effect modeling based on variable substance properties. Uncertainty surrounding calculation of potential environmental impacts represents an opportunity to reevaluate LCIA estimates for commercially available, well-studied chemicals. In the context of emerging contaminants, calculating CFs stochastically allows identification of which input parameters are most influential to characterization results, and use this information to help prioritize experimental research. Our results suggest that focusing experimental resources on improving data for degradation in air, water, and soil has the greatest potential to reduce uncertainty of current niacinamide CF estimates. In this capacity, stochastic evaluation of impact assessment models to identify the most influential parameter uncertainties and inform future research constitutes an example of *anticipatory* LCA (Wender et al. 2014b; Ravikumar et al. 2016).

Acknowledgements The authors have benefitted from personal communications with Igor Linkov, Paul Westerhoff, Mark A. Huijbregts, and Lise Laurin, as well as java programming performed by Mukund Manikarnike and Vignesh Soundararajan, both in the School of Computing, Informatics, and Decision Systems Engineering at ASU. This work was funded in part by the U.S. Environmental Protection Agency's (EPA) Science to Achieve Results program through grant #FP1144616 and assistance agreement #RD83558001-0, the U.S. Army Engineer Research and Development Center (ERDC) through cooperative agreement W912HZ-14-P-0130, the National Science Foundation (NSF) through grant #1140190 and #0937591, and the Marie Curie project Quan-Tox (GA No. 631910) funded by the European Commission under the Seventh Framework Programme. This work has not been formally reviewed by the EPA, NSF, or ERDC and the views expressed in this document are solely those of the authors and do not necessarily reflect those of the EPA, NSF, or ERDC.

References

Alfonsín C, Hospido A, Omil F, Moreira MT, Feijoo G (2014) PPCPs in wastewater—update and calculation of characterization factors for their inclusion in LCA studies. J Clean Prod 83:245–255

Bare J, Young D, QAM S, Hopton M, Chief SAB (2012) Tool for the reduction and assessment of chemical and other environmental impacts (TRACI) version 2.1 user manual. EPA/600/R-12/554 2012

Bissett DL, Oblong JE, Berge CA (2006) Niacinamide: a B vitamin that improves aging facial skin appearance. Derm Surg 31:860–866

Cellura M, Longo S, Mistretta M (2011) Sensitivity analysis to quantify uncertainty in life cycle assessment: the case study of an Italian tile. Renew Sust En Rev 15:4697–4705

CIREP (Cosmetic Ingredient Review Expert Panel) (2005) Final report of the safety assessment of niacinamide and niacin. Int J Tox 24:1–31

Cucurachi S, Heijungs R (2014) Characterisation factors for life cycle impact assessment of sound emissions. Sci Tot Env 468–469:280–291

Dawson DA, Wilke TS (1991) Evaluation of the frog embryo teratogenesis assay: Xenopus (FETAX) as a model system for mixture toxicity hazard assessment. Environ Toxicol Chem 10:941–948

EC (European Commission) (2011) International reference life cycle data system (ILCD) handbook—recomendations for life cycle impact assessment in the European context, First edn. Office of the European Union, Luxemburg

ECOTox database (2015) User Guide: ECOTOX Database System. Version 4.0 http:/ www.epa.gov/ecotox

Fantke P, Jolliet O (2016) Life cycle human health impacts of 875 pesticides. Int J Life Cycle Assess 21:722–733

Fantke P, Wieland P, Juraske R, Shaddick G, Itoiz ES, Friedrich R, Jolliet O (2012) Parameterization models for pesticide exposure via crop consumption. Env Sci Techol 46:12864–12872

Fantke P, Arnot JA, Doucette WJ (2016) Improving plant bioaccumulation science through consistent reporting of experimental data. J Env Man 181:374–384

Gauthier TD (2001) Detecting trends using Spearman's rank correlation coefficient. Env Forens 2:359–362

Golsteijn L, Hendriks HWM, van Zelm R, Ragas AMJ, Huijbregts MAJ (2012) Do interspecies correlation estimations increase the reliability of toxicity estimates for wildlife? Ecotox Env Safe 80:238–243

Gust KA, Collier ZA, Mayo M, Stanley JK, Gong P, Chappell M (2016) Limitations of toxicity characterization in life cycle assessment—can adverse outcome pathways provide a new foundation? Integ Env Assess Manage 12:580–590

Hauschild MZ, Huijbregts MA (2015) Life cycle impact assessment. LCA Compendium–The Complete World of Life Cycle Assessment. Springer. doi:10.1007/978-94-017-9744-3

Hauschild MZ et al (2008) Building a model based on scientific consensus for life cycle impact assessment of chemicals: the search for harmony and parsimony. Environ Sci Technol 42:7032–7037

Hauschild M et al (2013) Identifying best existing practice for characterization modeling in life cycle impact assessment. Int J Life Cycle Assess 18:683–697

Henderson A et al (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 16:701–709

Huijbregts MA, Hauschild M Jolliet O, Margni M, McKone T, Rosenbaum RK, van de Meent D (2010a) USEtox User Manual Available at: http://www.usetox.org/sites/default/files/support-tutorials/user_manual_usetox.pdf

Huijbregts MM, van de Meent D, Jollier O, Rosenbaum RK, McKone T, Hauschild M (2010b) USEtox chemcial-specific database: Organics Available at: http://www.usetox.org/sites/default/files/support-tutorials/database_organics.pdf

Jolliet O, Fantke P (2015) Human toxicity, In: Life cycle impact assessment. Springer, pp 75–96

Lloyd SM, Ries R (2007) Characterizing, Propagating, and Analyzing Uncertainty in Life-Cycle Assessment: A Survey of Quantitative Approaches. J Ind Econ 11:161–179. doi:10.1162/jiec.2007.1136

MacLeod M, Fraser AJ, Mackay D (2002) Evaluating and expressing the propagation of uncertainty in chemical fate and bioaccumulation models. Environ Toxicol Chem 21:700–709

Müller N, de Zwart D, Hauschild M, Kijko G, Fantke P (2017) Exploring REACH as potential data source for characterizing ecotoxicity in life cycle assessment. Environ Toxicol Chem 36:492–500

Pennington DW, Margni M, Ammann C, Jolliet O (2005) Multimedia fate and human intake modeling: spatial versus nonspatial insights for chemical emissions in western Europe. Environ Sci Technol 39: 1119–1128

Prado-Lopez V, Wender BA, Seager TP et al (2015) Tradeoff evaluation improves comparative life cycle assessment: a photovoltaic case study. J Ind Ecol 20(4):1–9

PubChem (2015) Compound summary for nicotinamide. National Center for Biotechnology Information. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/936.

Ravikumar D, Wender B, Seager TP, Fraser MP (2013) Towards anticipatory life cycle assessment of photovoltaics. 39th IEEE Photovolt Spec Conf (PVSC). doi:10.1109/PVSC.2013.6744956

Ravikumar D, Sinha P, Seager TP, Fraser MP (2016) An anticipatory approach to quantify energetics of recycling CdTe photovoltaic systems. Prog Photovoltaics 24(5):735–746

Ravikumar D, Wender B, Seager TP, Fraser MP, Tao M (2017) A climate rationale for research and development on photovoltaics manufacture. Appl Eng 189:245–256

REACH (2017) Registered dossier for nicotinamide (EC# 202–713-4; CAS# 98–92-0). Accessed February 2017, available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/14571/6/2/8

RIVM (2015) e-ToxBase National Institute for Public Health and the Environment. http://www.ru.nl/environmentalscience/research/themes-0/risk-assessment/e-toxbase/

Rosenbaum RK (2015) Ecotoxicity. In: Life cycle impact assessment. Springer, pp 139–162

Rosenbaum R et al (2008) USEtox—the UNEP-SETAC toxicity model: recommended characterisation factors for human toxicity and freshwater ecotoxicity in life cycle impact assessment. Int J Life Cycle Assess 13:532–546

Saltelli A et al (2008) Global sensitivity analysis: the primer. John Wiley & Sons

Sonnemann GW, Schuhmacher M, Castells F (2003) Uncertainty assessment by a Monte Carlo simulation in a life cycle inventory of electricity produced by a waste incinerator. J Clean Prod 11:279–292

UNEP (United Nations Environment Program) (2002) OECD SIDS Initial Assessment Report - nicotinamide Available at: http://www.inchem.org/documents/sids/sids/98920.pdf

USEPA (2015) Estimation programs Interface suite™ for Microsoft® Windows, v 4.11. United State Enivronmental Protection Agency, Washington, DC

Van Zelm R, Huijbregts MA, Harbers JV, Wintersen A, Struijs J, Posthuma L, Van de Meent D (2007) Uncertainty in msPAF-based ecotoxicological effect factors for freshwater ecosystems in life cycle impact assessment. Integ Environ Assess Manag 3:e6–e37

Weidema BP, Bauer Ch, Hischier R, Mutel Ch, Nemecek T, Reinhard J, Vadenbo CO, Wernet G (2013) The ecoinvent database: overview and methodology, Data quality guideline for the ecoinvent database version 3

Wender BA et al (2014a) Illustrating anticipatory life cycle assessment for emerging photovoltaic technologies. Environ Sci Technol 48: 10531–10538

Wender BA et al (2014b) Anticipatory life-cycle assessment for responsible research and innovation. J Resp Innov 1:200–207

Westh T, Hauschild M, Birkved M, Jørgensen M, Rosenbaum R, Fantke P (2015) The USEtox story: a survey of model developer visions and user requirements. Int J Life Cycle Assess 20:299–310

van Zelm R, Huijbregts MAJ (2013) Quantifying the trade-off between parameter and model structure uncertainty in life cycle impact assessment. Environ Sci Technol 47:9274–9280

van Zelm R, Huijbregts MJ, van de Meent D (2009) USES-LCA 2.0—a global nested multi-media fate, exposure, and effects model. Int J Life Cycle Assess 14:282–284