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## Sensitivity-based research prioritization through stochastic characterization modeling

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4 **Sensitivity analysis for research prioritization through stochastic characterization modeling**  
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4 **Abstract**  
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6 **Purpose** Product developers using life cycle toxicity impact assessment models to understand potential  
7 impacts of material substitutions face serious challenges related to large data demands and high  
8 uncertainty. This motivates greater focus on model sensitivity toward input parameter variability,  
9 particularly in the context of emerging contaminants like engineered nanomaterials (ENMs), to guide  
10 future efforts in data refinement and design of experiments. This study presents a Monte Carlo tool  
11 designed for use with USEtox 1.0 that allows researchers to rapidly prioritize data needs according to  
12 influence on characterization factors (CFs).  
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15 **Methods** Using Monte Carlo analysis we demonstrate a sensitivity-based approach to prioritize  
16 research through a case study comparing aquatic ecotoxicity CFs for the ENM C<sub>60</sub> and the vitamin B  
17 derivative niacinamide, two antioxidants used in personal care products. We calculate CFs via 10,000  
18 iterations assuming plus-or-minus one order of magnitude variance for fate and exposure-relevant  
19 inputs. Spearman Rank Correlation Indices are used for all variable inputs to identify parameters with  
20 the largest influence on CFs, which we prioritize for data refinement and future experimental  
21 investigation. Based on the importance of aggregate multi-species toxicity (average log EC<sub>50</sub>) and  
22 studies suggesting solvent residues may yield erroneous toxicity estimates, we recalculate C<sub>60</sub> CFs  
23 omitting all studies using solvents in sample preparation.  
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28 **Results and discussion** For emissions to freshwater, the C<sub>60</sub> CF is log-normally distributed with a  
29 geometric mean of 280 and geometric standard deviation (GSD) of 2.1 PAF m<sup>3</sup> day/kg compared to 2.6  
30 with a GSD=1.8 PAF m<sup>3</sup> day/kg for niacinamide. C<sub>60</sub> CFs are most sensitive to varied suspended solids  
31 partitioning coefficients (K<sub>pss</sub>) and average log EC<sub>50</sub>, whereas variation of other substance parameters  
32 has comparatively little effect on model results. Insufficient experimental evidence hampers to revise  
33 assumptions for K<sub>pss</sub>, and we suggest prioritizing future experiments that elucidate C<sub>60</sub> interactions with  
34 suspended solids. Recalculating C<sub>60</sub> CFs without toxicity studies that use solvents reduces the geometric  
35 mean by more than a factor of ten. This reinforces the importance of thorough characterization of  
36 released ENMs, in this case regarding the presence of solvent residues.  
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40 **Conclusion** Calculating stochastic CFs allows sensitivity-based prioritization of data needs and future  
41 experiments, which is particularly helpful in the context of emerging contaminants like C<sub>60</sub>. Researchers  
42 can conserve resources and address parameter uncertainty by applying our approach when developing  
43 new or refining existing CFs for the inventory items that contribute most to toxicity impacts. The Monte  
44 Carlo tool can be applied to current toxicity characterization models like USEtox and is freely available at  
45 <https://www.dropbox.com/home/MC%20USETox/Interface/20151222>  
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## Introduction

Coupled 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 quantified in the life cycle inventory (LCI) phase of LCA. Life cycle impact assessment (LCIA) models for characterizing human toxicity and ecotoxicity are complicated, 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 further improvement, although significant achievements have been made over the last decade. For example, sustained harmonization efforts between divergent toxicity LCIA models resulted in the consensus model USEtox (Rosenbaum et al. 2008; Westh et al. 2015) and the recently released 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 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 relevant emitted substances, limited availability of high quality data, and sparse treatment of parameter uncertainty or variability (Alfonsín et al. 2014; Gust et al. 2015; Rosenbaum 2015). For example, there is a large discrepancy between the  $\approx 10,000$  substances included in the latest Ecoinvent inventory library (Weidema 2013) and the  $\approx 1,200$  human toxicity and 2,500 ecotoxicity CFs available from the recent USEtox 2.0 update (<http://usetox.org>). Each individual CF requires approximately ten substance-specific input parameters, thereby challenging the experimental and data curation efforts required for database validation and expansion. As a result, a large share of CFs in USEtox relies on substance data estimated using outputs from quantitative structure activity relationships (QSARs) such as EPI Suite (USEPA 2015b), which are essential for filling data gaps but often lack experimental evidence and therefore are considered of lower quality than measured values (Huijbregts 2010a). Thus, there is a critical need to explore the sensitivity of human toxicity and ecotoxicity LCIA results – and those used in other impact categories – to variability and uncertainty in required substance input data, which may help expedite database expansion, refinement, and development of future research agenda (Cellura et al. 2011; Cucurachi and Heijungs 2014).

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 values (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 define research agenda and conserve resources by focusing attention 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.

The benefits of applying sensitivity-based research prioritization may be greatest in the context of emerging contaminants such as engineered nanomaterials (ENMs). Widespread concern regarding

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4 potential toxicity-related impacts associated with emissions of ENMs galvanized an active research  
5 community and produced volumes of published data that demonstrates high variability between  
6 published parameter estimates (NSTCCT 2014). The suitability of human and ecotoxicity LCIA models for  
7 ENMs is a known issue (Klopffer 2007) and relatively well covered in recent literature (Gilbertson et al.  
8 2015; Miseljic and Olsen 2014b; Salieri et al. 2015). Less emphasized are critical data-related challenges  
9 include:  
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- 12 1) The large number of commercially-relevant ENMs and possible permutations made through  
13 alternative surface coatings leaves comprehensive characterization and collection of sufficient  
14 data for all ENM emissions impracticable (Alvarez et al. 2009; Cohen et al. 2013; Grieger et al.  
15 2010),  
16  
17 2) Material heterogeneity within even narrow classes of ENMs – for example carbon nanotubes  
18 with differing lengths, number of walls, chirality – results in high variability in risk-relevant  
19 parameters reported in the literature (Hendren et al. 2015; Saleh et al. 2015; Seager and Linkov  
20 2008), and  
21  
22 3) Computational approaches to estimating substance properties for ENMs are nascent (Alvarez et  
23 al. 2009; Cohen et al. 2013; Eisenberg 2015) and QSARs designed for conventional chemical  
24 pollutants may be inapplicable. For example, EPI Suite does not apply to the ENM C<sub>60</sub> because  
25 the closed-cage structure is incomparable to other carbonaceous materials.  
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29 Together these challenges limit the applicability of existing human and ecotoxicity LCIA models to ENMs,  
30 and to date there are no CFs for ENMs included in any commercial LCA software package or database.  
31 Nanomaterial LCA review articles identified the lack of ENM-specific CFs as preventing quantification of  
32 toxicity impacts associated with ENM emissions (Gavankar et al. 2012; Hischier and Walser 2012;  
33 Miseljic and Olsen 2014a). In the literature fewer than five studies have developed aquatic ecotoxicity  
34 CFs for ENMs, predominantly through innovative modifications of USEtox including: development of  
35 realistic and worst-case scenarios for the ENM's CF (Eckelman et al. 2012), precautionary assumptions  
36 (Miseljic and Olsen 2014a), qualitative discussion of uncertainty (Rodriguez-Garcia et al. 2014), and  
37 development of simplified colloidal transport models within USEtox (Salieri et al. 2015). Only Eckelman  
38 et al (2012) conducts a thorough Monte Carlo sensitivity analysis on substance properties, but the  
39 emphasis was on comparing the magnitude of cumulative upstream ecotoxicity impacts with those  
40 directly from ENM releases, and therefor did not include the relative influence of variable substance  
41 data on characterization results.  
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46 The present paper introduces a Monte Carlo tool that can be combined with USEtox 1.01 to specify  
47 substance data as variable distributions, as opposed to point value estimates, and presents resulting CFs  
48 as frequency distributions. We apply the tool to compare aquatic ecotoxicity CFs of the ENM C<sub>60</sub> (CAS  
49 99685-96-8) and the vitamin B derivative niacinamide (CAS 98-92-0), both of which are used at low  
50 concentrations in commercial personal care products because of their antioxidant properties (Benn et  
51 al. 2011; Lens 2009; PEN 2013). The comparison represents a hypothetical decision context in which  
52 personal care product developers are considering the emerging material C<sub>60</sub> as an alternative for a  
53 conventional chemical providing the same function. Given high environmental and regulatory  
54 uncertainty regarding ENMs, product developers are unsure of potential toxicity impacts and what  
55 further research is necessary to improve confidence in the material comparison. Differences in  
56 performance, which are often the motivation for adoption of new materials, would be reflected in  
57 functional unit definition and differences in emitted mass are tracked in the life cycle inventory, both of  
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which are beyond the scope of this manuscript. More importantly, the comparison illustrates one component of an *anticipatory* approach to LCA that compares an emerging technology to conventional alternatives in order to guide research and development decisions towards reduced environmental impacts (Wender et al. 2014b), and that might help moving toward fundamentally more sustainable substitutions (Fantke et al. 2015).

## 2.0 Methods

USEtox calculates freshwater ecotoxicity CFs in a **CF** matrix per unit mass of emitted substance, expressed as comparative toxicity units CTUe (PAF m<sup>3</sup> d/kg<sub>emitted</sub>), and interpreted as the product of a fate factor matrix (**FF**, kg<sub>in compartment</sub> per kg<sub>emitted</sub>/d), an exposure factor matrix (**XF**, kg<sub>bioavailable</sub>/kg<sub>in compartment</sub>), and an effect factor matrix (**EF**, PAF m<sup>3</sup>/kg<sub>bioavailable</sub>) (Equation 1). FF, XF, and EF represent the residence time in freshwater, dissolved fraction in freshwater, and aggregated multi-species toxicological response, respectively (Henderson et al. 2011; Huijbregts 2010a):

$$CF = EF \cdot XF \cdot FF \quad \text{Eq. 1}$$

Model structure, assumptions, and landscape data of USEtox 1.01 were not targeted in our Monte Carlo tool and thus model uncertainty is not addressed in this study as the focus is exclusively on prioritization of research into substance data.

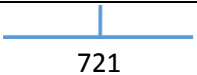
### 2.1 Description of the Monte Carlo Tool

To facilitate Monte Carlo operation, we developed a user-friendly interface where USEtox-required substance data can be described as any combination of uniform, normal, log-normal and triangular distributions, or remain point values as applied in USEtox. These distributions are sampled independently n-specified times, the values were used as input to USEtox, and resulting CFs plotted as frequency distributions along with descriptive statistics. Additionally, the Monte Carlo tool calculates Spearman Rank Correlation Indices for all inputs that are not point values (SI 2.1). Results for each material presented are based on 10,000 Monte Carlo runs, taking approximately one hour to complete (2.0 GHz intel i7). The JAVA-based tool is open source, further modifications welcomed, and a beta version made available for download at <https://www.dropbox.com/home/MC%20USETox/Interface/20151222>.

### 2.2 Fate and Exposure Data and Modeling Assumptions

C<sub>60</sub> partitions strongly to dissolved organic carbon, suspended solids, and natural organic matter (Yang et al. 2015). Thus, we implement values from available literature according to USEtox requirements for metals as shown in Table 1. The large quantity of publications detailing fate-relevant studies for C<sub>60</sub> and its aggregates, combined with inconsistent reporting of nanomaterial and matrix characteristics, prohibits a comprehensive review. To emphasize the method of sensitivity-based research prioritization we have selected only studies which report USEtox-required parameters by name, for example as opposed to studies reporting removal percentages by biomass.

**Table 1 Fate and exposure relevant data and modeled variance for C<sub>60</sub>**

Parameter	Description	Units	Midpoint value(s)	Baseline variance	Reference
MW	Molecular weight	g/mol	721		Chemical formula

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Kow	Octanol-water partitioning coefficient	L/L	$4.6 \times 10^6$		Jafvert & Kulkarni, 2008
Koc	Organic carbon partitioning coefficient	L/kg	$1.2 \times 10^7$ $5 \times 10^3$		Chen & Jafvert, 2009 Avanasi et al, 2014
Kh	Henry's law constant	Pa $m^3/mol$	$1 \times 10^{-20}$		USEtox manual
Pvap	Vapor pressure	Pa	$6 \times 10^{-4}$ $1 \times 10^{-20}$		SES Research, 2010 USEtox manual
Sol	Solubility in water	mg/L	$2-8 \times 10^{-6}$ $<100 nC_{60}$		Jafvert & Kulkarni, 2008 Fortner et al, 2005
Kdoc Kpss Kpsl Kpsd	Partitioning coefficient between: dissolved organic carbon; Suspended solids; Soil particles; Sediment particles	L/kg	$3.2 \times 10^4$		USEtox regression: $K_{doc}=0.08 \cdot K_{ow}$ Assume $K_{doc} = K_{pss} = K_{psl} = K_{psd}$
kdeg, air	Degradation rate in air	1/s	$1 \times 10^{-20}$ $2 \times 10^{-5}$		USEtox manual, Tiwari et al, 2014
kdeg, water	Degradation rate in water		$4.5 \times 10^{-8}$		Avanasi et al, 2014 USEtox manual
kdeg, soil	Degradation rate in soil		$2.25 \times 10^{-8}$		
kdeg, sed	Degradation rate in sediment		$5 \times 10^{-9}$		
BAF fish	Bioaccumulation factor in fish	L/kg	$3.2 \times 10^4$ $5.12 \times 10^5$		Li et al, 2010 Jafvert & Kulkarni, 2008

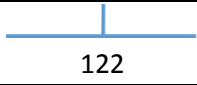
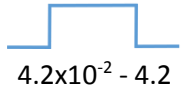
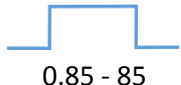
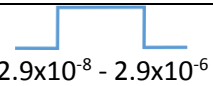
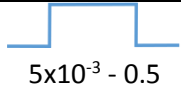
A growing weight of evidence suggests that  $C_{60}$  released to water partitions to natural organic matter, biological membranes, and settles to sediment rapidly (PubChem 2015a; Pycke et al. 2012; USEPA 2010). Nonetheless some fate-relevant parameters published data show high variability, for example Chen and Jafvert (2009) reported the first estimate of an organic carbon-water partitioning coefficient (Koc) of  $\approx 1.2 \times 10^7$  mL/g, whereas five years later Avanasi et al. (2014) report Koc values as low as  $5 \times 10^3$  mL/g based on soil type. We model Koc as a uniform distribution across this range.  $C_{60}$  solubility ranges from virtually insoluble ( $<10^{-9}$  mg/L) as isolated particles to nearly 100 mg/L as water-

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4 stable aggregates (Avanasi et al. 2014), which we model as uniform between  $5 \times 10^{-6}$  and 100 mg/L.  
5 Similarly, atmospheric degradation rates ( $k_{deg, air}$ ) of  $2 \times 10^{-5}$  1/s by environmentally-relevant ozone  
6 concentrations was shown in Tiwari et al. (2014), although other carbon nanomaterials have been  
7 modeled as resistant to degradation (e.g.,  $1 \times 10^{-20}$  1/s) (Rodriguez-Garcia et al. 2014). Thus we model  
8  $k_{deg, air}$  as uniform between these two values. In part the variability in fate and exposure relevant  
9 substance data for  $C_{60}$  is related to the large number of publications on the ENM, as compared to the  
10 less-studies niacinamide. Thus, future efforts can incorporate the number of studies into estimates of  
11 parameter uncertainty or variability as has recently been demonstrated for pesticide dissipation half  
12 lives in plants (Fantke et al. 2014) and related CFs for human exposure to pesticide residues in crops  
13 (Fantke and Jolliet 2015).  
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18 Fate and exposure relevant parameters for which only point values are reported in literature or  
19 available from QSAR programs were assumed to have an arbitrary baseline scenario of uniform variable  
20 distributions of plus-or-minus one order of magnitude from the midpoint value. The USEtox 1.01  
21 manual describes a simple regression to estimate the dissolved organic carbon partitioning coefficient  
22 ( $K_{doc}$ ) as  $0.08 \times K_{ow}$ , giving the midpoint value of  $3.2 \times 10^4$  L/kg. In the absence of experimental data,  
23 we assume  $K_{doc}$  is equal to the suspended solids partitioning ( $K_{pss}$ ), sediment particle partitioning  
24 ( $K_{psd}$ ), and soil particle partitioning ( $K_{psl}$ ) coefficients (Eckelman et al. 2012). Based on the classification  
25 of  $C_{60}$  as recalcitrant (Avanasi et al. 2014; Kümmerer et al. 2011) and the USEtox manual (Huijbregts  
26 2010b), we model the aquatic degradation rate ( $k_{deg, water}$ ) as  $4.5 \times 10^{-8}$  1/s, and the soil and sediment  
27 degradation rates as 1/2 and 1/9 of  $k_{deg, water}$  respectively. Bioaccumulation factors for fish (BAF fish)  
28 have been reported as  $\approx 3 \times 10^4$  L/kg (Li et al. 2010) and  $5 \times 10^5$  L/kg (Jafvert and Kulkarni 2008), which is  
29 less than the assumed baseline variability, thus we model BAF fish as uniform between  $5 \times 10^4$  and  $5 \times$   
30  $10^6$  L/kg.  
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35 The conventional antioxidant niacinamide that  $C_{60}$  may replace is the subject of relatively fewer  
36 studies, which is why we rely primarily on EPISuite (USEPA 2015b) and supplement with available  
37 literature as summarized in Table 2.  
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**Table 2 Fate and exposure relevant data and modeled variance for niacinamide**

Parameter	Description	Units	Midpoint value(s)	Baseline variance	Reference
MW	Molecular weight	g/mol	122		Chemical formula
Kow	Octanol-water partitioning coefficient	L/L	0.42		OECD SIDS
Koc	Organic carbon partitioning coefficient	L/kg	8.5		EPISuite, Kocwin
Kh	Henry's law constant	Pa m <sup>3</sup> /mol	$2.9 \times 10^{-7}$ $6.45 \times 10^{-6}$		PubChem database USEtox Guidance
Pvap	Vapor pressure	Pa	0.026 0.05		EPISuite, MPBPVP PubChem database



Solubility	Solubility in water	mg/L	5e5 6.9-10 x 10 <sup>5</sup>	5x10 <sup>4</sup> - 5x10 <sup>6</sup>	EPISuite, exper. OECD SIDS
kdeg, air	Degradation rate in air	1/s	1.8 x 10 <sup>-6</sup>	1.8x10 <sup>-7</sup> - 1.8x10 <sup>-5</sup>	EPISuite, AOPWin USEtox manual
kdeg, water	Degradation rate in water		2.1 x 10 <sup>-7</sup>	2.1x10 <sup>-8</sup> - 2.1x10 <sup>-6</sup>	EPISuite, Biowin USEtox manual
kdeg, soil	Degradation rate in soil		1 x 10 <sup>-7</sup>	1x10 <sup>-8</sup> - 1x10 <sup>-6</sup>	
kdeg, sed	Degradation rate in sediment		2.3 x 10 <sup>-8</sup>	2.3x10 <sup>-9</sup> - 2.3x10 <sup>-7</sup>	
BAF fish	Bioaccumulation factor in fish	L/kg	0.9	0.09 to 9.0	EPISuite, BCFBAF

Niacinamide was not included in USEtox 1.01, but was covered in the recently released USEtox 2.0 (<http://usetox.org>) with fate and exposure-relevant parameter values nearly identical to those presented in Table 2 (SI, 2.2.2). We collected parameter estimates from an OECD Screening Information Dataset, which reports experimentally-determined estimates for Kow of 0.42 and solubility of 6.9-10 x 10<sup>5</sup> mg/L (UNEP 2002), which correspond closely with values reported in EPISuite (USEPA 2015b). The National Center for Biotechnology Information database reports Henry's Constant (Kh) as 2.9 x 10<sup>-7</sup> Pa m<sup>3</sup>/mol and a vapor pressure of 0.05 Pa (PubChem 2015b). We combine EPISuite outputs and the USEtox organics manual (Huijbregts 2010c) to model uniform distributions for all degradation rates and BAF fish following the baseline scenario of plus-or-minus one order of magnitude from these midpoint values.

### 2.3 Effect Factor Data and Modeling Assumptions

We calculate EF for both materials 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 2010a). Toxicity data for C<sub>60</sub> and niacinamide – typically reported as the concentration at which 50 percent of the exposed organisms over background exhibit the studied effect (EC<sub>50</sub>), inhibited growth (IC<sub>50</sub>), or lethality (LC<sub>50</sub>) – was taken from available literature and is summarized in Table 3 and Table 4, respectively.

**Table 3 Data from individual ecotoxicity studies of C<sub>60</sub>**

Reference	Species (n=10)	Test type and endpoint	Reported value(s)	Stabilization method	Chronic equiv. EC <sub>50</sub> value
<i>Producers</i>					
Tao et al, 2015	<i>S. obliquus</i>	72h Chronic IC <sub>50</sub>	1.94 mg/L	THF then membrane filtered	1.9 mg/L
Gelca et al, 2012	<i>S. capricornutum</i>	5d Chronic IC <sub>50</sub> dark	0.04 mg/L	Stirred then filtered, average of size ranges taken	0.04 mg/L
		5d Chronic IC <sub>50</sub> light	0.02 mg/L		0.02 mg/L

Baun et al, 2008*	<i>P. subcapitata</i>	48h Chronic IC <sub>30</sub>	90 mg/L	Stirring	90 mg/L
Blaise et al, 2008*	<i>P. subcapitata</i>	72h Chronic IC <sub>25</sub>	100 mg/L	Mixing	100 mg/L
Seki et al, 2008**	<i>P. subcapitata</i>	72h Chronic IC <sub>50</sub>	14.8 mg/L extrapolated	Grinding with sugar and oil	15 mg/L
<b>Primary Consumers</b>					
Seki et al, 2008	<i>D. magna</i>	48h Acute EC <sub>50</sub> immobilization	>2.25 mg/L (LOEC)	Grinding with sugar and oil	5 mg/L
Blaise et al, 2008	<i>T. platyurus</i>	24h Acute LC <sub>50</sub>	>10 mg/L	Mixing	5 mg/L
	<i>H. attenuata</i>	96h Acute EC <sub>50</sub> morphological	>10 mg/L		5 mg/L
Lovern & Klaper, 2006	<i>D. magna</i>	48h Acute LC <sub>50</sub>	7.9 mg/L	Sonication	3.9 mg/L
			0.46 mg/L	THF, filtered then evaporated	0.2 mg/L
Zhu et al, 2009	<i>D. magna</i>	48h Acute LC <sub>50</sub>	10.5 mg/L	Shaken	5.3 mg/L
		48h Immobility EC <sub>50</sub>	9.34 mg/L		4.6 mg/L
Ji et al, 2014	<i>D. magna</i>	96h Acute LC <sub>50</sub> dark	1.85 mg/L (NOEC)	Mixing then filtered through .2 micron	17 mg/L
		96h Acute LC <sub>50</sub> light	0.46 mg/L (NOEC)		4.1 mg/L
	96h Acute LC <sub>50</sub> dark	4.1 mg/L			
	96h Acute LC <sub>50</sub> light	4.1 mg/L			
<i>M. macrocopa</i>					
Tao et al, 2009	<i>D. magna</i>	48h Acute LC <sub>50</sub> neonatal	0.44 mg/L	THF then evaporated	0.2 mg/L
Zhu et al, 2006	<i>D. magna</i>	48h Acute LC <sub>50</sub>	0.8 mg/L	THF then evaporated	0.4 mg/L
Oberdorster et al, 2006	<i>D. magna</i>	96h Acute LC <sub>50</sub>	>35 mg/L (LOEC)	Stirring	78 mg/L
		21d Chronic Molting delay, number of offspring	2.5 mg/L (LOEC)		5.6 mg/L
Baun et al, 2008	<i>D. magna</i>	48h Chronic Mobility	<50 mg/L (NOEC)	Stirring	450 mg/L
<b>Secondary consumers</b>					
Seki et al, 2008	<i>O. latipes</i>	96h Acute LC <sub>50</sub>	>2.15 (NOEC)	Grinding with sugar and oil	19 mg/L
Oberdorster et al, 2006	<i>O. latipes</i>	96h Acute LC <sub>50</sub>	0.5 mg/L (NOEC)	Stirring	4.5 mg/L
	<i>P. promelas</i>		1 mg/L (NOEC)		9 mg/L
Usenco et al, 2007	<i>D. rerio</i>	96h Acute LC <sub>50</sub> embryonic	0.2 mg/L	C <sub>60</sub> or C <sub>70</sub> sonicated in DMSO	0.1 mg/L
			4 mg/L	C <sub>60</sub> (OH) <sub>24</sub>	2 mg/L
Usenco et al, 2008	<i>D. rerio</i>	5d Acute LC <sub>50</sub> dark	0.3 mg/L	C <sub>60</sub> sonicated in DMSO	0.15 mg/L
		5d Acute LC <sub>50</sub> light	0.2 mg/L		0.1 mg/L

		5d Chronic EC <sub>50</sub> Fin malformation	0.15 mg/L		0.15 mg/L
Zhu et al, 2007	<i>D. rerio</i>	96h Chronic EC <sub>50</sub> developmental	1.5 mg/L	C <sub>60</sub> in THF then evaporated	1.5 mg/L
			50 mg/L (NOEC)	C <sub>60</sub> (OH) <sub>24</sub>	450 mg/L

\*Although USEtox manual specifies EC<sub>50</sub> values, we retain data from studies reporting 25 and 30 percent effected concentrations as additional uncertainty is included in EF modeling.

\*\*Seki et al (2008) do not reach 50 percent inhibitory concentrations but report an extrapolated EC<sub>50</sub> value based on lower effect-level concentrations.

This curated data set demonstrates high variability between reported values, with at least two orders of magnitude difference in every trophic level and five orders of magnitude difference across all species. In spite of ongoing improvements to toxicity testing for ENMs (Petersen et al. 2015) there is general consensus that C<sub>60</sub> presents relatively low hazard to aquatic species (Andrievsky et al. 2005). As noted in Table 3, many of the studies compare fullerene toxicity between:

- 1) Alternative sample preparation methods (Lovern and Klaper 2006; Seki 2008; Usenko et al. 2007; Zhu et al. 2006; Zhu et al. 2007) to elucidate the extent to which solvents or other contaminants may cause erroneously high toxicity estimates (Henry et al. 2011; Kovochich et al. 2009), and
- 2) Testing conditions exposed to light or kept in darkness (Gelca et al. 2012; Ji et al. 2014; Usenko et al. 2008) to understand the importance of photoexcitation and degradation in driving toxicity (Kolosnjaj et al. 2007).

A noteworthy source of uncertainty is converting acute, no observed effect concentration (NOEC), and lowest observed effect concentration (LOEC) endpoints reported in the majority of studies into equivalent chronic EC<sub>50</sub> values by dividing by an acute to chronic ratio of 2 (Huijbregts 2010a), 1/9, and 4/9 respectively, following studies for non-cancer endpoints (Eckelman et al. 2012; Huijbregts et al. 2005). We apply these factors consistently across both materials, and do not test the sensitivity of CFs to these assumptions.

The conventional alternative niacinamide again is the subject of relatively fewer studies than the emerging material C<sub>60</sub>. Reported toxicity data for niacinamide are consistently greater than C<sub>60</sub> by at least two orders of magnitude, and all exceed 1 g/L as shown in Table 4.

**Table 4 Data from individual ecotoxicity studies of niacinamide**

Reference	Species n=3	Test type and endpoint	Reported value(s)	Chronic equiv. EC <sub>50</sub> value
<i>Producers</i>				
OECD SIDS, 2002	<i>S. subspicatus</i>	72h Acute EC <sub>50</sub>	>1000 mg/L	500 mg/L
	Algae - generic	QSAR, 96h Accute EC <sub>50</sub>	8,934 mg/L	4,500 mg/L
<i>Primary consumers</i>				
	<i>D. magna</i>	24h Acute EC <sub>50</sub>	>1000 mg/L	500 mg/L

OECD SIDS, 2002	Daphnid - generic	48h Acute EC <sub>50</sub> , QSAR	16,456 mg/L	8,000 mg/L
<i>Secondary consumers</i>				
OECD SIDS, 2002	<i>P. reticulata</i>	96h Acute LC <sub>50</sub>	>1000 mg/L	500 mg/L
	Fish - generic	96h Acute LC <sub>50</sub> , QSAR	18,189 mg/L	9,000 mg/L
ECOTOx database*	<i>X. laevis</i>	96h Acute EC <sub>50</sub> , embryonic	0.34 mg/L	0.17 mg/L

\*Misclassified data point contained in ECOTOx database.

Consistent with our treatment of C<sub>60</sub> ecotoxicity studies, we divide the acute toxicity data points reported in Table 4 by an acute to chronic conversion factor of 2 to estimate the chronic equivalent EC<sub>50</sub>. The dataset contains a misclassified acute EC<sub>50</sub> value of 0.34 mg/L reported in the ECOTOx and RIVM ETox databases (RIVM 2015; USEPA 2015a), which references a study that considers nicotine and 6-aminonicotinamide (Dawson and Wilke 1991) not nicotinamide, and 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<sup>5</sup> PAF m<sup>3</sup> 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 toxic concentration (aveLog EC<sub>50</sub>) estimation and standard error on the mean (SEM) calculation is significant (SI 2.3.1).

To calculate aveLog EC<sub>50</sub> from the individual studies reported in Tables 3 and 4, we take the log of the geometric mean of each trophic class, and then calculate the arithmetic mean of these values (Huijbregts 2010a) (SI 2.3.2). This represents the concentration at which half of aquatic species are exposed above their median EC<sub>50</sub> values, and is 0.43 and 3.2 log mg/L for C<sub>60</sub> and niacinamide respectively. We calculate the SEM from the log EC<sub>50</sub> data, which is 0.12 for C<sub>60</sub> and 0.04 for niacinamide (SI 2.3.2). Uncertainty in the average toxicity (*ave Log*) follows a Student's t distribution (Golsteijn et al. 2012; Van Zelm et al. 2007) centered around aveLog EC<sub>50</sub> and scaled by the SEM, shown in Eq. 2:

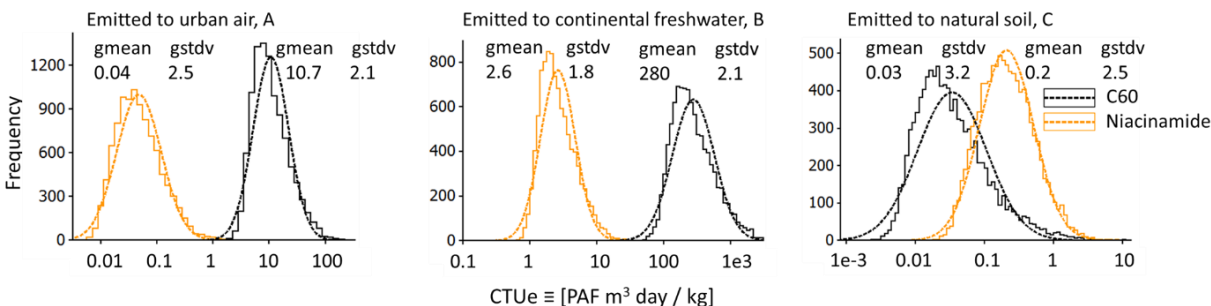
$$\overline{ave\ Log} = ave\ Log\ EC_{50} + SEM * t \quad \text{Eq. 2}$$

Where t represents a two-tailed t-distribution with n-1 degrees of freedom from n different species with experimental toxicity data (SI 2.3.2).

### 3 Results and Discussion

Freshwater aquatic ecotoxicity CFs for C<sub>60</sub> and niacinamide emitted directly to urban air, continental freshwater, and natural soil (Figure 1 A-C) show approximately two orders of magnitude variability resulting from the assumed plus-or-minus one order of magnitude in the baseline scenario. These results are generated through the full sampling of distributions specified in Tables 1 and 2 as well as *ave Log* for each material, and thus represent the global sensitivity of freshwater aquatic ecotoxicity CFs to simultaneous changes in all substance properties. Emissions to rural air and agricultural soil show

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4 similar variability and order of preference, and niacinamide emissions to marine water are more than 15  
5 orders of magnitude greater than  $C_{60}$  due to its resistance to removal via sedimentation (SI 3.1).  
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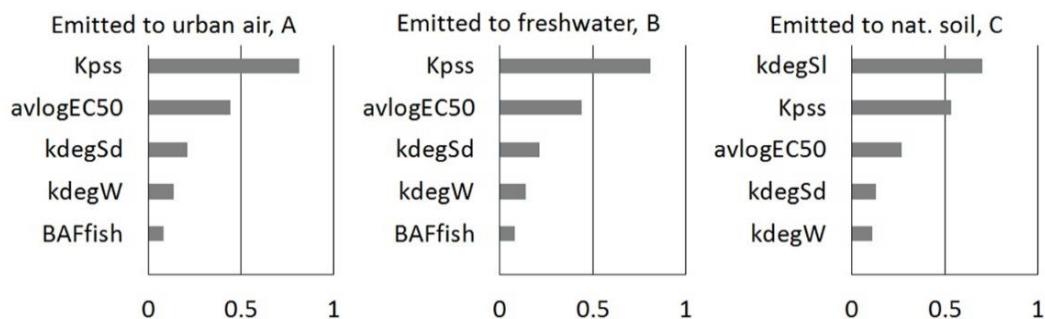


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18 **Fig 1 Stochastic aquatic ecotoxicity CFs for  $C_{60}$  (black) and niacinamide (orange) antioxidants emitted**  
19 **to urban air (A), freshwater (B), and natural soil (C) compartments. Solid lines are frequency**  
20 **distributions from 10,000 Monte Carlo runs and dashed lines are normal distributions fit to the log-**  
21 **transformed data (i.e., CFs are log normal distributions).**  
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23 For emissions to air and freshwater, niacinamide is characterized by a lower toxicity potential per unit  
24 mass than  $C_{60}$ , as opposed to emissions to soil in which case  $C_{60}$  has a lower average CF due to its strong  
25 partitioning to soil over water. For emission to freshwater, stochastic CFs for  $C_{60}$  and niacinamide are  
26 log normally distributed with a geometric mean of 280 and 2.6 and geometric standard deviation of 2.1  
27 and 1.8, respectively. All of these differences are significant (Welch's t-test  $p < 0.001$ ), with the closest  
28 scenario (i.e., emission to soil) yielding a Welch's t-test statistic  $< 0.05$  (SI 3.2) (Fagerland and Sandvik  
29 2009). Although model uncertainty is relatively well studied and beyond the scope of this study, these  
30 differences are significant with respect to model uncertainty, and variability in CFs in the baseline  
31 scenario is smaller in magnitude than estimated model uncertainty (Rosenbaum et al. 2008) (SI 3.3).  
32 Given baseline scenario assumptions, the hypothetical product developers can conclude that  $C_{60}$  has  
33 greater potential for ecotoxicity impacts per unit mass than niacinamide,  
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### 38 3.1 Identifying the Most Influential Substance Parameters

39 To estimate the relative influence of varied input parameters used to calculate  $C_{60}$  CFs we take the  
40 absolute value of the Spearman Rank Correlation Index for emissions to urban air, continental  
41 freshwater, and natural soil (Figure 2A-C). Spearman rank correlation assumes independence of  
42 observations within each parameter and makes no assumptions about the distribution type (Gauthier  
43 2001). Many of the substance parameters in USEtox are themselves calculated as function of other  
44 substance input parameters using simple regressions, for example estimating Kdoc based on Kow, and  
45 are thereby not independent. We do not account for the interdependence of parameters as the focus is  
46 on identifying only the few most influential substance properties, although Fantke et al. (2012)  
47 demonstrate how to truly decouple parameter uncertainty (e.g., in Kdoc) from regression-related  
48 uncertainty.  
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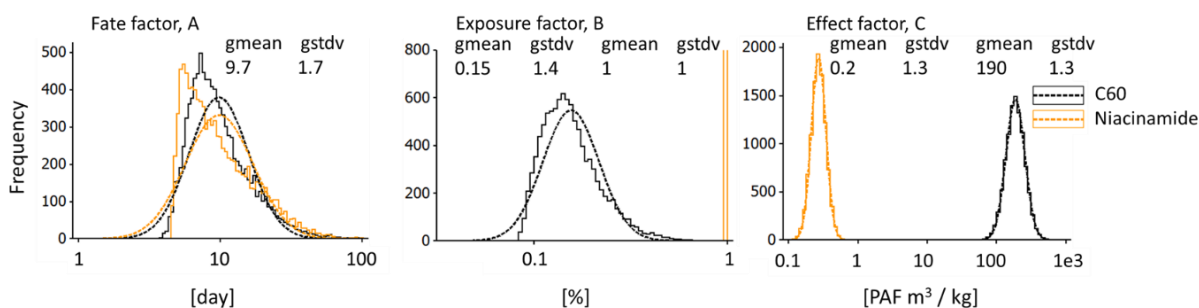


**Fig 2 The five Spearman rank correlation indices with the greatest magnitude out of all variable inputs for three C<sub>60</sub> aquatic ecotoxicity CFs. Greater magnitude indicates which input parameters have the greatest influence on CF variability for each emission compartment.**

Figure 2 calls attention to the importance of variability in the suspended solids partitioning coefficient (Kpss), *ave Log* aggregate ecotoxicity, and to a lesser extent sediment, aquatic, and soil degradation rates (kdegSd, kdegW, kdegSI) as driving variance in C<sub>60</sub> CF results. Uncertainty in *ave Log* is derived solely from statistical variation in underlying ecotoxicity studies as opposed to considering the slope of the effect factor or working point on the potentially affected fraction curve (Hauschild 2007). Despite the large variability modeled for C<sub>60</sub> solubility, this parameter has negligible effect on CFs (SI 3.4). The importance of removal through aggregation and sedimentation is consistent with recent reports for other ENMs (Dale et al. 2015). Thus we prioritize C<sub>60</sub> Kpss and *ave Log* for further data refinement and future experimental research, while the remainder of material parameters have relatively little influence on CFs (SI 3.5). In the case of niacinamide, uncertainty in degradation rates in air, water, and soil have the greatest influence for all emission scenarios, followed by Henry's constant, the organic-carbon partitioning coefficient, and *ave Log* (SI 3.6).

### 3.2 Decomposing CFs into Fate, Exposure, and Effect Components

The two antioxidant compounds display significant differences in terms of their freshwater residence time (fate factor FF), dissolved fraction (exposure factor XF), and aggregate multi-species toxicity (effect factor EF) as shown in Figure 3A-C, and the product of these three yields the CF following equation 1.



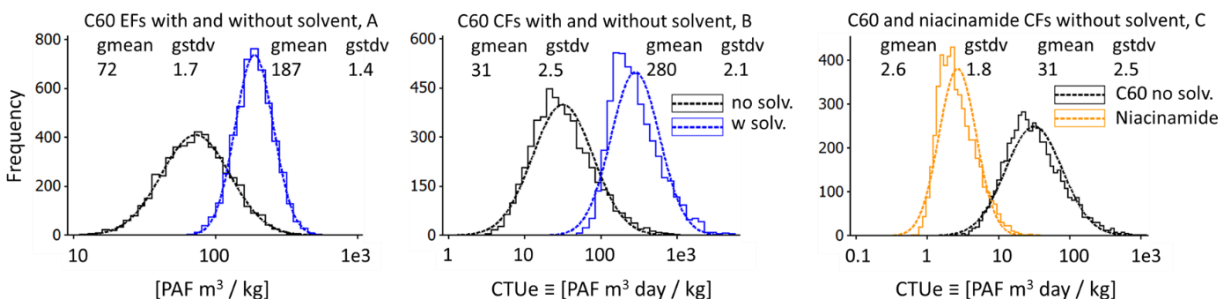
**Fig 3 Component fate (A), exposure (B), and effect factors (C) for niacinamide (orange) and C<sub>60</sub> (black) identify significant differences between the two antioxidants, specifically the high exposure and low toxicity of niacinamide compared to C<sub>60</sub>. Solid lines are frequency distributions of 10,000 Monte Carlo runs and dashed lines are normal distributions fit to the log-transformed data.**

FF for each material is equivalent, with partitioning and sedimentation the dominant removal route for C<sub>60</sub> and biodegradation dominant for niacinamide. XF for niacinamide is effectively 1 – representing 100 percent of the emission being bioavailable – whereas the C<sub>60</sub> XF has a geometric mean of 0.1 (corresponding 10 percent dissolved and bioavailable) because of strong partitioning to suspended solids, dissolved organic carbon, and biomass. The greatest difference between the two antioxidants is in EF, where C<sub>60</sub> exceeds niacinamide by three orders of magnitude (geometric mean 190 vs 0.2), which is not surprising given the low ecotoxicity values reported for niacinamide in Table 4.

### 3.3 Refining Estimates of Variability for C<sub>60</sub> Substance Data

Figure 2 indicates that, for the majority of input parameters in Tables 1 & 2, the assumed variability of plus-or-minus one order of magnitude has little influence on C<sub>60</sub> aquatic ecotoxicity CFs. In the case of direct emission to freshwater, the suspended solids partitioning coefficient (K<sub>pss</sub>) and average toxicity (aveLog EC<sub>50</sub>) are prioritized for data refinement and promising candidates for further experimental investigation. The assumed K<sub>pss</sub> with uniform variability between 3 x 10<sup>3</sup> and 3 x 10<sup>5</sup> L/kg is based on the USEtox 1.01 regression for estimating K<sub>doc</sub> from K<sub>ow</sub>, which does not warrant reduction from our high-uncertainty baseline scenario even though experimental values for K<sub>ow</sub> are available. C<sub>60</sub> is expected to exhibit strong partitioning to suspended solids based on reported K<sub>oc</sub> values (PubChem 2015a), although there are reports of variable removal between 10 and 90 percent by high concentrations of heterogeneous biomass (which likely has a higher organic content than suspended solids) between alternative C<sub>60</sub> preparation methods (Kiser et al. 2010). Thus, further reduction of variability in K<sub>pss</sub> requires identification of dominant preparation methods and experimental investigation of C<sub>60</sub> partitioning to suspended solids with realistic compositions and concentrations.

Uncertainty in aveLog EC<sub>50</sub> for C<sub>60</sub> is similarly influential to CFs, and for conventional emissions influenced by combination of acute and chronic toxicity data through fixed conversion factors as well as unequal distribution of studies between different species (Pennington 2003). In the context of the emerging contaminant C<sub>60</sub>, uncertainty in aveLog EC<sub>50</sub> is further complicated by differences between alternative preparation methods, particularly regarding the presence of solvent residues and their potential contribution to erroneously high toxicity estimates (Henry et al. 2011). C<sub>60</sub> used in cosmetics is commonly stabilized in castor oil or polymer coatings such as polyvinylpyrrolidone (Benn et al. 2011; Lens 2009), and likely will not be prepared using solvents. To explore the sensitivity of C<sub>60</sub> EFs and CFs to preparation method, we exclude all studies in Table 3 that used solvents to stabilize C<sub>60</sub> and calculate a revised EF with a geometric mean of 72 and revised CF of 31, as opposed to 187 and 280 in the baseline scenario including all preparation methods, (Figure 4A&B).



**Fig 4 Removal of all ecotoxicity studies relying on solvents (black without, blue with) reduces the C<sub>60</sub> effect factor (A) and characterization factor (B) by more than one order of magnitude. With no**

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4 **solvents the toxicity potential of C<sub>60</sub> is closer to niacinamide (orange) but still significantly different for**  
5 **emissions to freshwater (C).**  
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8 The revised CF for C<sub>60</sub> emissions to freshwater still exceeds niacinamide by an order of magnitude  
9 (4C) and is significantly different (Welch's t test  $p < 0.001$ ). This suggests that, if solvent residues are not  
10 present in C<sub>60</sub> emissions, the aquatic ecotoxicity potential is marginally greater than niacinamide for  
11 direct emission to freshwater. For emissions to rural and continental air, the geometric mean of the C<sub>60</sub>  
12 CF is at least two orders of magnitude greater than niacinamide, whereas for emissions to natural soil,  
13 agricultural, and marine water niacinamide significantly exceeds C<sub>60</sub> (SI 3.7). Thus, the order of  
14 preference for the materials depends on the emission compartment. Furthermore, there is a critical  
15 need to: 1) characterize the form of C<sub>60</sub> released regarding the presence of solvent residues, and 2) to  
16 design new experiments to elucidate suspended solids partitioning behavior.  
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#### 19 **4.0 Conclusion**

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21 LCIA method developers can apply the Monte Carlo tool to expedite expansion and review of  
22 toxicity databases by identifying the most influential substance data for distinct chemical classes, and  
23 then focusing their efforts on reducing parameter uncertainty on these estimates by finding or providing  
24 experimental references. Analogous to the case shown above, it is likely that only a few model input  
25 parameters are significant for each chemical class, and analyzing uncertainty estimates for these  
26 parameters may allow future quantification of parameter uncertainty for all chemicals currently  
27 included and foreseen for inclusion in LCIA models (similar to what has been done for global estimates  
28 of model uncertainty). Furthermore, we encourage LCA practitioners to apply the Monte Carlo tool to  
29 the life cycle inventory items that contribute most to ecotoxicity impacts to increase confidence in  
30 interpretation of LCIA results.  
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34 In the context of emerging contaminants, calculating CFs stochastically allows identification of which  
35 input parameters are most influential to characterization results, and use this information to help  
36 prioritize experimental research agenda. Our results suggest that focusing experimental resources on  
37 improving data for suspended solids partitioning behavior and multi-species toxicity indicators has the  
38 greatest potential to reduce uncertainty of current C<sub>60</sub> CF estimates. In this capacity, stochastic  
39 evaluation of impact assessment models to identify the most influential parameter uncertainties and  
40 inform future research agenda constitutes an example of *anticipatory* LCA (Wender et al. 2014a;  
41 Wender et al. 2014b).  
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46 The approach outlined in the present paper has potential for broader application to different LCIA  
47 models and other impact categories that use simplified fate and effect modeling based on variable  
48 substance properties. The controversy, parameter, and mechanistic uncertainty surrounding the  
49 environmental impacts of ENMs represent an opportunity to reevaluate LCIA estimates for  
50 commercially-available, well-studied chemicals. No midpoint impact assessment methods include  
51 formal uncertainty analysis, thus this approach could improve treatment and presentation of  
52 uncertainty for LCA of emerging and established technologies alike.  
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## 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 *Journal of Cleaner Production* 83:245-255 doi:<http://dx.doi.org/10.1016/j.jclepro.2014.07.024>
- Alvarez PJ, Colvin V, Lead J, Stone V (2009) Research priorities to advance eco-responsible nanotechnology *ACS nano* 3:1616-1619
- Andrievsky G, Klochkov V, Derevyanchenko L (2005) Is the C60 fullerene molecule toxic?! *Fullerenes, Nanotubes, and Carbon Nanostructures* 13:363-376
- Avanasi R, Jackson WA, Sherwin B, Mudge JF, Anderson TA (2014) C60 Fullerene Soil Sorption, Biodegradation, and Plant Uptake *Environmental Science & Technology* 48:2792-2797 doi:10.1021/es405306w
- Bare J, Young D, QAM S, Hopton M, Chief SAB (2012) Tool for the Reduction and Assessment of Chemical and other Environmental Impacts (TRACI)
- Benn TM, Westerhoff P, Herckes P (2011) Detection of fullerenes (C 60 and C 70) in commercial cosmetics *Environmental Pollution* 159:1334-1342
- Cellura M, Longo S, Mistretta M (2011) Sensitivity analysis to quantify uncertainty in Life Cycle Assessment: The case study of an Italian tile *Renewable and Sustainable Energy Reviews* 15:4697-4705 doi:<http://dx.doi.org/10.1016/j.rser.2011.07.082>
- Chen C-Y, Jafvert CT (2009) Sorption of Buckminsterfullerene (C60) to Saturated Soils *Environmental Science & Technology* 43:7370-7375 doi:10.1021/es900989m
- CIREP (2005) Cosmetic Ingredient Review Expert Panel Final Report of the Safety Assessment of Niacinamide and Niacin *International Journal of Toxicology* 24:1-31 doi:10.1080/10915810500434183
- Cohen Y, Rallo R, Liu R, Liu HH (2013) In Silico Analysis of Nanomaterials Hazard and Risk Accounts of Chemical Research 46:802-812 doi:10.1021/ar300049e
- Cucurachi S, Heijungs R (2014) Characterisation factors for life cycle impact assessment of sound emissions *Science of The Total Environment* 468–469:280-291 doi:<http://dx.doi.org/10.1016/j.scitotenv.2013.07.080>
- Dale AL, Lowry GV, Casman EA (2015) Stream Dynamics and Chemical Transformations Control the Environmental Fate of Silver and Zinc Oxide Nanoparticles in a Watershed-Scale Model *Environmental Science & Technology* 49:7285-7293 doi:10.1021/acs.est.5b01205
- Dawson DA, Wilke TS (1991) Evaluation of the frog embryo teratogenesis assay: *Xenopus* (FETAX) as a model system for mixture toxicity hazard assessment *Environmental Toxicology and Chemistry* 10:941-948 doi:10.1002/etc.5620100710
- EC (2011) International reference life cycle data system (ILCD) handbook - Recommendations for life cycle impact assessment in the European context. First edition edn. Office of the European Union, Luxemburg
- Eckelman MJ, Mauter MS, Isaacs JA, Elimelech M (2012) New Perspectives on Nanomaterial Aquatic Ecotoxicity: Production Impacts Exceed Direct Exposure Impacts for Carbon Nanotubes *Environmental Science & Technology* 46:2902-2910 doi:10.1021/es203409a
- Eisenberg DG, K; Hristozov, D; Bates, M and Linkov, I (2015) Risk Assessment, Life Cycle Assessment, and Decision Methods for Nanomaterials. In: Satinder Kaur Brar TCZ, Mausam Verma, Rao Y. Surampalli, and Rajeshwar D. Tyagi (ed) *Nanomaterials in the Environment*. American Society of Civil Engineers, Reston, Virginia, pp 383-419. doi:10.1061/9780784414088.ch15
- Fagerland MW, Sandvik L (2009) Performance of five two-sample location tests for skewed distributions with unequal variances *Contemporary Clinical Trials* 30:490-496 doi:<http://dx.doi.org/10.1016/j.cct.2009.06.007>

- 1  
2  
3  
4 Fantke P, Gillespie BW, Juraske R, Jolliet O (2014) Estimating Half-Lives for Pesticide Dissipation from  
5 Plants Environmental Science & Technology 48:8588-8602 doi:10.1021/es500434p  
6 Fantke P, Jolliet O (2015) Life cycle human health impacts of 875 pesticides. The International Journal of  
7 Life Cycle Assessment, doi:10.1007/s11367-11015-10910-y  
8 Fantke P, Weber R, Scheringer M (2015) From incremental to fundamental substitution in chemical  
9 alternatives assessment. Sustainable Chemistry and Pharmacy 1:1-8 doi:  
10 10.1016/j.scp.2015.08.001  
11  
12 Fantke P, Wieland P, Juraske R, Shaddick G, Itoiz ES, Friedrich R, Jolliet O (2012) Parameterization  
13 Models for Pesticide Exposure via Crop Consumption Environmental Science & Technology  
14 46:12864-12872 doi:10.1021/es301509u  
15  
16 Gauthier TD (2001) Detecting Trends Using Spearman's Rank Correlation Coefficient Environmental  
17 Forensics 2:359-362  
18  
19 Gavankar S, Suh S, Keller AF (2012) Life cycle assessment at nanoscale: review and recommendations  
20 The International Journal of Life Cycle Assessment 17:295-303 doi:10.1007/s11367-011-0368-5  
21  
22 Gelca R, Anderson TA, Cox SB (2012) The Effect of Cluster Size on the Breakdown of C<sub>60</sub>  
23 Water Suspensions Into Toxic Compounds Advanced Science, Engineering and Medicine 4:205-  
24 210 doi:10.1166/ase.2012.1181  
25  
26 Gilbertson L, Wender B, Zimmerman J, Eckelman MJ (2015) Coordinating Modeling and Experimental  
27 Research of Engineered Nanomaterials to Improve Life Cycle Assessment Studies Environmental  
28 Science: Nano doi:10.1039/c5en00097a  
29  
30 Golsteijn L, Hendriks HWM, van Zelm R, Ragas AMJ, Huijbregts MAJ (2012) Do interspecies correlation  
31 estimations increase the reliability of toxicity estimates for wildlife? Ecotoxicology and  
32 Environmental Safety 80:238-243 doi:<http://dx.doi.org/10.1016/j.ecoenv.2012.03.005>  
33  
34 Grieger K, Baun A, Owen R (2010) Redefining risk research priorities for nanomaterials Journal of  
35 Nanoparticle Research 12:383-392 doi:10.1007/s11051-009-9829-1  
36  
37 Gust KA, Collier ZA, Mayo M, Stanley JK, Gong P, Chappell M (2015) Limitations of toxicity  
38 characterization in life cycle assessment—can adverse outcome pathways provide a new  
39 foundation? Integrated Environmental Assessment and Management  
40  
41 Hauschild M (2007) Evaluation of Ecotoxicity Effect Indicators for Use in LCIA (10+4 pp) The International  
42 Journal of Life Cycle Assessment 12:24-33 doi:10.1065/lca2006.12.287  
43  
44 Hauschild M et al. (2013) Identifying best existing practice for characterization modeling in life cycle  
45 impact assessment The International Journal of Life Cycle Assessment 18:683-697  
46 doi:10.1007/s11367-012-0489-5  
47  
48 Hauschild MZ et al. (2008) Building a Model Based on Scientific Consensus for Life Cycle Impact  
49 Assessment of Chemicals: The Search for Harmony and Parsimony Environmental Science &  
50 Technology 42:7032-7037 doi:10.1021/es703145t  
51  
52 Hauschild MZ, Huijbregts MA (2015) Life Cycle Impact Assessment LCA Compendium—The Complete  
53 World of Life Cycle Assessment (  
54  
55 Henderson A et al. (2011) USEtox fate and ecotoxicity factors for comparative assessment of toxic  
56 emissions in life cycle analysis: sensitivity to key chemical properties The International Journal of  
57 Life Cycle Assessment 16:701-709 doi:10.1007/s11367-011-0294-6  
58  
59 Hendren CO, Lowry GV, Unrine JM, Wiesner MR (2015) A functional assay-based strategy for  
60 nanomaterial risk forecasting Science of The Total Environment 536:1029-1037  
61 doi:<http://dx.doi.org/10.1016/j.scitotenv.2015.06.100>  
62  
63 Henry TB, Petersen EJ, Compton RN (2011) Aqueous fullerene aggregates (nC60) generate minimal  
64 reactive oxygen species and are of low toxicity in fish: a revision of previous reports Current  
65 Opinion in Biotechnology 22:533-537 doi:<http://dx.doi.org/10.1016/j.copbio.2011.05.511>

- 1  
2  
3  
4 Hischier R, Walser T (2012) Life cycle assessment of engineered nanomaterials: State of the art and  
5 strategies to overcome existing gaps *Science of The Total Environment* 425:271-282  
6 doi:<http://dx.doi.org/10.1016/j.scitotenv.2012.03.001>  
7  
8 Huijbregts MA, Hauschild, M. Jolliet, O., Margni, M., McKone, T., Rosenbaum, R.K., and van de Meent, D.  
9 (2010a) USEtox User Manual.  
10  
11 Huijbregts MAJ, Rombouts LJA, Ragas AMJ, van de Meent D (2005) Human-toxicological effect and  
12 damage factors of carcinogenic and noncarcinogenic chemicals for life cycle impact assessment  
13 *Integrated Environmental Assessment and Management* 1:181-244 doi:10.1897/2004-007R.1  
14  
15 Huijbregts MM, M; van de Meent, D; Jolliet, O; Rosenbaum, RK; McKone, T and Hauschild, M. (2010b)  
16 USEtox chemical-specific database: Organics.  
17  
18 Huijbregts MM, M; van de Meent, D; Jolliet, O; Rosenbaum, RK; McKone, T and Hauschild, M. (2010c)  
19 USEtoxTM Chemical-specific database: organics  
20  
21 Jafvert CT, Kulkarni PP (2008) Buckminsterfullerene's (C60) Octanol–Water Partition Coefficient (Kow)  
22 and Aqueous Solubility *Environmental Science & Technology* 42:5945-5950  
23 doi:10.1021/es702809a  
24  
25 Ji K-h, Kim J-k, Choi K-h (2014) Sunlight Enhances Toxicity of Fullerene (C 60) to Freshwater Invertebrates  
26 *Daphnia magna* and *Moina macrocopa* *The Korean Journal of Public Health* 51:35-45  
27  
28 Jolliet O, Fantke P (2015) Human Toxicity. In: *Life Cycle Impact Assessment*. Springer, pp 75-96  
29  
30 Kiser MA, Ryu H, Jang H, Hristovski K, Westerhoff P (2010) Biosorption of nanoparticles to heterotrophic  
31 wastewater biomass *Water research* 44:4105-4114  
32 doi:<http://dx.doi.org/10.1016/j.watres.2010.05.036>  
33  
34 Klopffer W, Curran, M.A., Frankl, P., Heijung, R., Kohler, A., and Olsen, S.I. (2007) Nanotechnology and  
35 life cycle assessment: A systems approach to nanotechnology and the environment. Woodrow  
36 Wilson International Center for Scholars,  
37  
38 Kolosnjaj J, Swarc H, Moussa F (2007) Toxicity Studies of Fullerenes and Derivatives. In: Chan WW (ed)  
39 *Bio-Applications of Nanoparticles*, vol 620. *Advances in Experimental Medicine and Biology*.  
40 Springer New York, pp 168-180. doi:10.1007/978-0-387-76713-0\_13  
41  
42 Kovoichich M et al. (2009) Comparative Toxicity of C60 Aggregates toward Mammalian Cells: Role of  
43 Tetrahydrofuran (THF) Decomposition *Environmental Science & Technology* 43:6378-6384  
44 doi:10.1021/es900990d  
45  
46 Kümmerer K, Menz J, Schubert T, Thielemans W (2011) Biodegradability of organic nanoparticles in the  
47 aqueous environment *Chemosphere* 82:1387-1392  
48 doi:<http://dx.doi.org/10.1016/j.chemosphere.2010.11.069>  
49  
50 Lens M (2009) Use of Fullerenes in Cosmetics *Recent Patents on Biotechnology* 3:118-123  
51 doi:10.2174/187220809788700166  
52  
53 Li D, Fortner JD, Johnson DR, Chen C, Li Q, Alvarez PJJ (2010) Bioaccumulation of 14C60 by the  
54 Earthworm *Eisenia fetida* *Environmental Science & Technology* 44:9170-9175  
55 doi:10.1021/es1024405  
56  
57 Lloyd SM, Ries R (2007) Characterizing, Propagating, and Analyzing Uncertainty in Life-Cycle Assessment:  
58 A Survey of Quantitative Approaches *Journal of Industrial Ecology* 11:161-179  
59 doi:10.1162/jiec.2007.1136  
60  
61 Lovern SB, Klaper R (2006) *Daphnia magna* mortality when exposed to titanium dioxide and fullerene  
62 (C60) nanoparticles *Environmental Toxicology and Chemistry* 25:1132-1137  
63  
64 Miseljic M, Olsen S (2014a) Life-cycle assessment of engineered nanomaterials: a literature review of  
65 assessment status *Journal of Nanoparticle Research* 16:1-33 doi:10.1007/s11051-014-2427-x  
66  
67 Miseljic M, Olsen SI (2014b) Life-cycle assessment of engineered nanomaterials: a literature review of  
68 assessment status *Journal of Nanoparticle Research* 16:1-33

- 1  
2  
3  
4 NSTCCT (2014) Progress review on the coordinated implementation of the national nanotechnology  
5 initiative 2011 environmental, health, and safety research strategy. Washington, DC  
6 PEN (2013) Consumer Products Inventory. Project on Emerging Nanotechnologies.  
7 <http://www.nanotechproject.org/cpi>. Accessed Spetember 2015  
8  
9 Pennington DW (2003) Extrapolating ecotoxicological measures from small data sets Ecotoxicology and  
10 Environmental Safety 56:238-250 doi:[http://dx.doi.org/10.1016/S0147-6513\(02\)00089-1](http://dx.doi.org/10.1016/S0147-6513(02)00089-1)  
11 Pennington DW, Margni M, Ammann C, Jolliet O (2005) Multimedia Fate and Human Intake Modeling:  
12 Spatial versus Nonspatial Insights for Chemical Emissions in Western Europe Environmental  
13 Science & Technology 39:1119-1128 doi:10.1021/es034598x  
14 Petersen EJ et al. (2015) Adapting OECD Aquatic Toxicity Tests for Use with Manufactured  
15 Nanomaterials: Key Issues and Consensus Recommendations Environmental Science &  
16 Technology 49:9532-9547 doi:10.1021/acs.est.5b00997  
17  
18 PubChem (2015a) Compound Summary for Buckminsterfullerene. National Center for Biotechnology  
19 Information. <https://pubchem.ncbi.nlm.nih.gov/compound/123591>. Accessed October 27 2015  
20 PubChem (2015b) Compound Summary for Nicotinamide. National Center for Biotechnology  
21 Information. <https://pubchem.ncbi.nlm.nih.gov/compound/936>. Accessed September 9 2015  
22  
23 Pycke BF, Chao T-C, Herckes P, Westerhoff P, Halden RU (2012) Beyond nC60: strategies for  
24 identification of transformation products of fullerene oxidation in aquatic and biological samples  
25 Analytical and bioanalytical chemistry 404:2583-2595  
26  
27 e-ToxBase (2015) National Institute for Public Health and the Environment.  
28 <http://www.ru.nl/environmentalscience/research/themes-0/risk-assessment/e-toxbase/>.  
29  
30 Rodriguez-Garcia G, Zimmermann B, Weil M (2014) Nanotoxicity and Life Cycle Assessment: First  
31 attempt towards the determination of characterization factors for carbon nanotubes IOP  
32 Conference Series: Materials Science and Engineering 64:012029  
33  
34 Rosenbaum R et al. (2008) USEtox—the UNEP-SETAC toxicity model: recommended characterisation  
35 factors for human toxicity and freshwater ecotoxicity in life cycle impact assessment The  
36 International Journal of Life Cycle Assessment 13:532-546 doi:10.1007/s11367-008-0038-4  
37  
38 Rosenbaum RK (2015) Ecotoxicity. In: Life Cycle Impact Assessment. Springer, pp 139-162  
39  
40 Saleh NB, Aich N, Plazas-Tuttle J, Lead JR, Lowry GV (2015) Research strategy to determine when novel  
41 nanohybrids pose unique environmental risks Environmental Science: Nano 2:11-18  
42 doi:10.1039/c4en00104d  
43  
44 Salieri B, Righi S, Pasteris A, Olsen SI (2015) Freshwater ecotoxicity characterisation factor for metal  
45 oxide nanoparticles: A case study on titanium dioxide nanoparticle Science of The Total  
46 Environment 505:494-502 doi:<http://dx.doi.org/10.1016/j.scitotenv.2014.09.107>  
47  
48 Saltelli A et al. (2008) Global sensitivity analysis: the primer. John Wiley & Sons,  
49  
50 Seager TP, Linkov I (2008) Coupling multicriteria decision analysis and life cycle assessment for  
51 nanomaterials Journal of Industrial Ecology 12:282-285  
52  
53 Seki MF, S; Gondo, Y; Inoue, Y; Nozaka, T and Takatsuki, M (2008) Acute toxicity of fullerene C60 in  
54 aquatic organisms Environmental Science (Japan) 21:53-62  
55  
56 Sonnemann GW, Schuhmacher M, Castells F (2003) Uncertainty assessment by a Monte Carlo simulation  
57 in a life cycle inventory of electricity produced by a waste incinerator Journal of Cleaner  
58 Production 11:279-292 doi:[http://dx.doi.org/10.1016/S0959-6526\(02\)00028-8](http://dx.doi.org/10.1016/S0959-6526(02)00028-8)  
59  
60 Tiwari AJ, Morris JR, Vejerano EP, Hochella MF, Marr LC (2014) Oxidation of C60 Aerosols by  
61 Atmospherically Relevant Levels of O3 Environmental Science & Technology 48:2706-2714  
62 doi:10.1021/es4045693  
63  
64 UNEP (2002) OECD SIDS Initial Assessment Report - nicotinamide.  
65  
66 Usenko CY, Harper SL, Tanguay RL (2007) In vivo evaluation of carbon fullerene toxicity using embryonic  
67 zebrafish Carbon 45:1891-1898 doi:<http://dx.doi.org/10.1016/j.carbon.2007.04.021>

- 1  
2  
3  
4 Usenko CY, Harper SL, Tanguay RL (2008) Fullerene C60 exposure elicits an oxidative stress response in  
5 embryonic zebrafish Toxicology and Applied Pharmacology 229:44-55  
6 doi:<http://dx.doi.org/10.1016/j.taap.2007.12.030>  
7  
8 USEPA (2010) Interim Technical Guidance for Assessing Screening Level Environmental Fate and  
9 Transport of, and General Population, Consumer, and Environmental Exposure to  
10 Nanomaterials. United States Environmental Protection Agency,  
11 ECOTox User Guide: ECOTOX Database System. Version 4.0 (2015a) <http://www.epa.gov/ecotox>.  
12 USEPA (2015b) Estimation Programs Interface Suite™ for Microsoft® Windows, v 4.11. United State  
13 Environmental Protection Agency, Washington, DC, USA  
14  
15 Van Zelm R, Huijbregts MA, Harbers JV, Wintersen A, Struijs J, Posthuma L, Van de Meent D (2007)  
16 Uncertainty in msPAF-based ecotoxicological effect factors for freshwater ecosystems in life  
17 cycle impact assessment Integrated Environmental Assessment and Management 3:e6-e37  
18  
19 van Zelm R, Huijbregts MAJ (2013) Quantifying the Trade-off between Parameter and Model Structure  
20 Uncertainty in Life Cycle Impact Assessment Environmental Science & Technology 47:9274-9280  
21 doi:10.1021/es305107s  
22  
23 van Zelm R, Huijbregts MJ, van de Meent D (2009) USES-LCA 2.0—a global nested multi-media fate,  
24 exposure, and effects model The International Journal of Life Cycle Assessment 14:282-284  
25 doi:10.1007/s11367-009-0066-8  
26  
27 Weidema BPB, Ch.; Hischer, R.; Mutel, Ch.; Nemecek, T.; Reinhard, J.; Vadenbo, C.O.; Wernet, G (2013)  
28 The ecoinvent database: Overview and methodology, Data quality guideline for the ecoinvent  
29 database version 3.  
30  
31 Wender BA et al. (2014a) Anticipatory life-cycle assessment for responsible research and innovation  
32 Journal of Responsible Innovation 1:200-207 doi:10.1080/23299460.2014.920121  
33  
34 Wender BA et al. (2014b) Illustrating Anticipatory Life Cycle Assessment for Emerging Photovoltaic  
35 Technologies Environmental Science & Technology 48:10531-10538 doi:10.1021/es5016923  
36  
37 Westh T, Hauschild M, Birkved M, Jørgensen M, Rosenbaum R, Fantke P (2015) The USEtox story: a  
38 survey of model developer visions and user requirements The International Journal of Life Cycle  
39 Assessment 20:299-310 doi:10.1007/s11367-014-0829-8  
40  
41 Yang Y, Wang Y, Hristovski K, Westerhoff P (2015) Simultaneous removal of nanosilver and fullerene in  
42 sequencing batch reactors for biological wastewater treatment Chemosphere 125:115-121  
43 doi:<http://dx.doi.org/10.1016/j.chemosphere.2014.12.003>  
44  
45 Zhu S, Oberdörster E, Haasch ML (2006) Toxicity of an engineered nanoparticle (fullerene, C60) in two  
46 aquatic species, Daphnia and fathead minnow Marine Environmental Research 62, Supplement  
47 1:S5-S9 doi:<http://dx.doi.org/10.1016/j.marenvres.2006.04.059>  
48  
49  
50  
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55  
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Figure 1

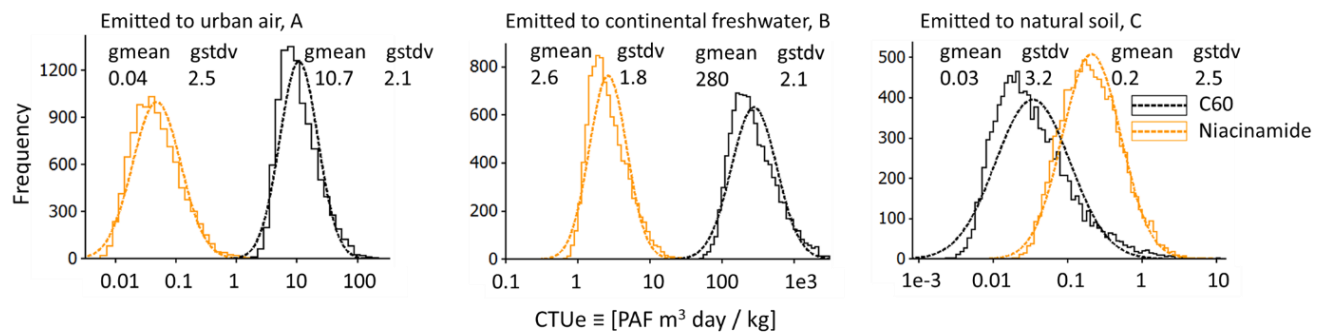


Figure2

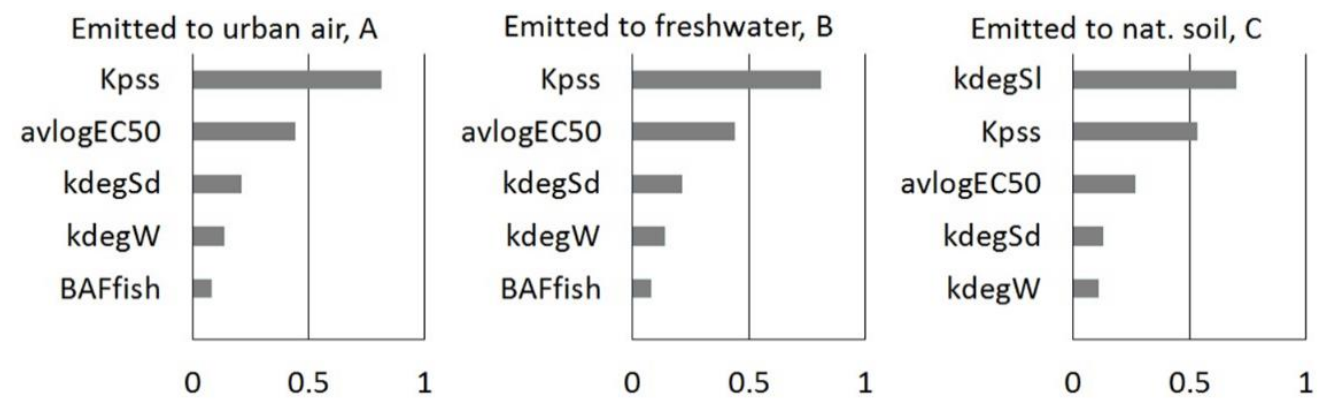




Figure3

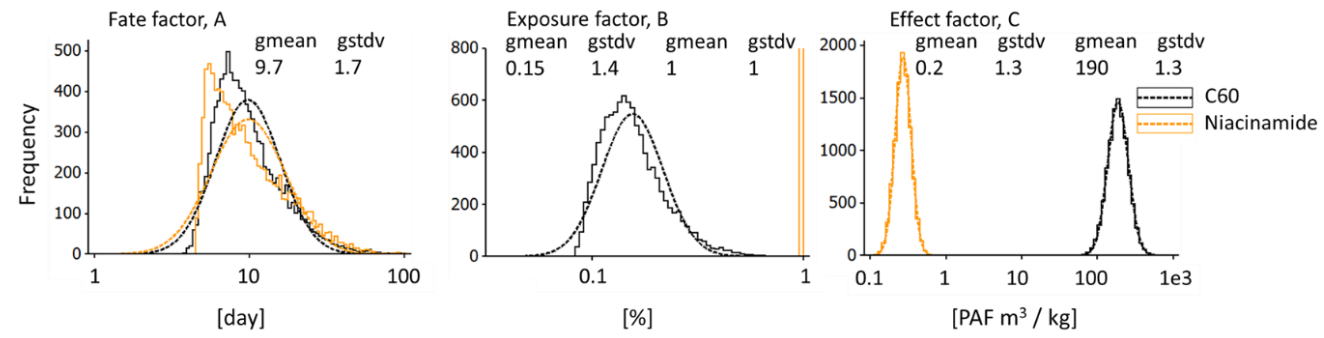


Figure4

