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Sensitivity analysis for research prioritization through stochastic characterization modeling

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Abstract

Purpose Product developers using life cycle toxicity impact assessment models to understand potential impacts of material substitutions face serious challenges related to large data demands and high uncertainty. This motivates greater focus on model sensitivity toward input parameter variability, particularly in the context of emerging contaminants like engineered nanomaterials (ENMs), to guide future efforts in data refinement and design of experiments. This study presents a Monte Carlo tool designed for use with USEtox 1.0 that allows researchers to rapidly prioritize data needs according to influence on characterization factors (CFs).

Methods Using Monte Carlo analysis we demonstrate a sensitivity-based approach to prioritize research through a case study comparing aquatic ecotoxicity CFs for the ENM C_{60} and the vitamin B derivative niacinamide, two antioxidants used in personal care products. We calculate CFs via 10,000 iterations assuming plus-or-minus one order of magnitude variance for fate and exposure-relevant inputs. Spearman Rank Correlation Indices are used for all variable inputs to identify parameters with the largest influence on CFs, which we prioritize for data refinement and future experimental investigation. Based on the importance of aggregate multi-species toxicity (average log EC_{50}) and studies suggesting solvent residues may yield erroneous toxicity estimates, we recalculate C_{60} CFs omitting all studies using solvents in sample preparation.

Results and discussion For emissions to freshwater, the C_{60} CF is log-normally distributed with a geometric mean of 280 and geometric standard deviation (GSD) of 2.1 PAF m^3 day/kg compared to 2.6 with a GSD=1.8 PAF m^3 day/kg for niacinamide. C_{60} CFs are most sensitive to varied suspended solids partitioning coefficients (Kpss) and average log EC_{50}, whereas variation of other substance parameters has comparatively little effect on model results. Insufficient experimental evidence hampers to revise assumptions for Kpss, and we suggest prioritizing future experiments that elucidate C_{60} interactions with suspended solids. Recalculating C_{60} CFs without toxicity studies that use solvents reduces the geometric mean by more than a factor of ten. This reinforces the importance of thorough characterization of released ENMs, in this case regarding the presence of solvent residues.

Conclusion Calculating stochastic CFs allows sensitivity-based prioritization of data needs and future experiments, which is particularly helpful in the context of emerging contaminants like C_{60}. Researchers can conserve resources and address parameter uncertainty by applying our approach when developing new or refining existing CFs for the inventory items that contribute most to toxicity impacts. The Monte Carlo tool can be applied to current toxicity characterization models like USEtox and is freely available at https://www.dropbox.com/home/MC%20USETox/Interface/20151222

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 ≈ 10,000 substances included in the latest Ecoinvent inventory library (Weidema 2013) and the ≈ 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

potential toxicity-related impacts associated with emissions of ENMs galvanized an active research community and produced volumes of published data that demonstrates high variability between published parameter estimates (NSTCCT 2014). The suitability of human and ecotoxicity LCIA models for ENMs is a known issue (Klopffer 2007) and relatively well covered in recent literature (Gilbertson et al. 2015; Miseljic and Olsen 2014b; Salieri et al. 2015). Less emphasized are critical data-related challenges include:

1) The large number of commercially-relevant ENMs and possible permutations made through alternative surface coatings leaves comprehensive characterization and collection of sufficient data for all ENM emissions impracticable (Alvarez et al. 2009; Cohen et al. 2013; Grieger et al. 2010),
2) Material heterogeneity within even narrow classes of ENMs – for example carbon nanotubes with differing lengths, number of walls, chirality – results in high variability in risk-relevant parameters reported in the literature (Hendren et al. 2015; Saleh et al. 2015; Seager and Linkov 2008), and
3) Computational approaches to estimating substance properties for ENMs are nascent (Alvarez et al. 2009; Cohen et al. 2013; Eisenberg 2015) and QSARs designed for conventional chemical pollutants may be inapplicable. For example, EPI Suite does not apply to the ENM C_{60} because the closed-cage structure is incomparable to other carbonaceous materials.

Together these challenges limit the applicability of existing human and ecotoxicity LCIA models to ENMs, and to date there are no CFs for ENMs included in any commercial LCA software package or database. Nanomaterial LCA review articles identified the lack of ENM-specific CFs as preventing quantification of toxicity impacts associated with ENM emissions (Gavankar et al. 2012; Hischier and Walser 2012; Miseljic and Olsen 2014a). In the literature fewer than five studies have developed aquatic ecotoxicity CFs for ENMs, predominantly through innovative modifications of USEtox including: development of realistic and worst-case scenarios for the ENM's CF (Eckelman et al. 2012), precautionary assumptions (Miseljic and Olsen 2014a), qualitative discussion of uncertainty (Rodriguez-Garcia et al. 2014), and development of simplified colloidal transport models within USEtox (Salieri et al. 2015). Only Eckelman et al (2012) conducts a thorough Monte Carlo sensitivity analysis on substance properties, but the emphasis was on comparing the magnitude of cumulative upstream ecotoxicity impacts with those directly from ENM releases, and therefor did not include the relative influence of variable substance data on characterization results.

The present paper introduces a Monte Carlo tool that can be combined with USEtox 1.01 to specify substance data as variable distributions, as opposed to point value estimates, and presents resulting CFs as frequency distributions. We apply the tool to compare aquatic ecotoxicity CFs of the ENM C_{60} (CAS 99685-96-8) and the vitamin B derivative niacinamide (CAS 98-92-0), both of which are used at low concentrations in commercial personal care products because of their antioxidant properties (Benn et al. 2011; Lens 2009; PEN 2013). The comparison represents a hypothetical decision context in which personal care product developers are considering the emerging material C_{60} as an alternative for a conventional chemical providing the same function. Given high environmental and regulatory uncertainty regarding ENMs, product developers are unsure of potential toxicity impacts and what further research is necessary to improve confidence in the material comparison. Differences in performance, which are often the motivation for adoption of new materials, would be reflected in functional unit definition and differences in emitted mass are tracked in the life cycle inventory, both of

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^3 d/$kg_{emitted}$), and interpreted as the product of a fate factor matrix (**FF**, $kg_{in\ compartment}$ per $kg_{emitted}$/d), an exposure factor matrix (**XF**, $kg_{bioavailable}/kg_{in\ compartment}$), and an effect factor matrix (**EF**, PAF $m^3/kg_{bioavailable}$) (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):

$$\mathbf{CF} = \mathbf{EF}\ \mathbf{XF}\ \mathbf{FF} \qquad \text{Eq. 1}$$

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_{60} 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_{60} 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_{60}

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

Kow	Octanol-water partitioning coefficient	L/L	4.6×10^{6}	 $4.6x10^{5}$ - $4.6x10^{7}$	Jafvert & Kulkarni, 2008
Koc	Organic carbon partitioning coefficient	L/kg	1.2×10^{7} 5×10^{3}	 $5x10^{3}$ - $1.2x10^{7}$	Chen & Jafvert, 2009 Avanasi et al, 2014
Kh	Henry's law constant	Pa m^3/mol	1×10^{-20}	 $1x10^{-20}$	USEtox manual
Pvap	Vapor pressure	Pa	6×10^{-4} 1×10^{-20}	 $1x10^{-20}$ - $6.6x10^{-4}$	SES Research, 2010 USEtox manual
Sol	Solubility in water	mg/L	2-8 x 10^{-6} <100 nC_{60}	 $5x10^{-6}$ - $1x10^{2}$	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	3.2×10^{4}	 $3.2x10^{3}$ - $3.2x10^{5}$	USEtox regression: Kdoc=0.08*Kow Assume Kdoc = Kpss = Kpsl = Kpsd
kdeg, air	Degradation rate in air	1/s	1×10^{-20} 2×10^{-5}	 $1x10^{-20}$ - $2x10^{-5}$	USEtox manual, Tiwari et al, 2014
kdeg, water	Degradation rate in water		4.5×10^{-8}	 $4.5x10^{-9}$ - $4.5x10^{-7}$	Avanasi et al, 2014 USEtox manual
kdeg, soil	Degradation rate in soil		2.25×10^{-8}	 $2.2x10^{-9}$ - $2.2x10^{-7}$	
kdeg, sed	Degradation rate in sediment		5×10^{-9}	 $5x10^{-10}$ - $5x10^{-8}$	
BAF fish	Bioaccumulation factor in fish	L/kg	3.2×10^{4} 5.12×10^{5}	 $5x10^{4}$ - $5x10^{6}$	Li et al, 2010 Jafvert & Kulkarni, 2008

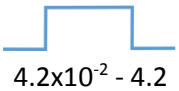
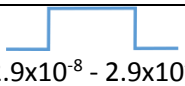
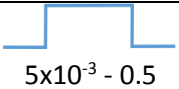
A growing weight of evidence suggests that C_{60} released to water partitions to natural organic matter, biological membranes, and settles to sediment rapidly (PubChem 2015a; Pycke et al. 2012; USEPA 2010). Nonetheless some fate-relevant parameters published data show high variability, for example Chen and Jafvert (2009) reported the first estimate of an organic carbon-water partitioning coefficient (Koc) of ≈ 1.2×10^{7} mL/g, whereas five years later Avanasi et al. (2014) report Koc values as low as 5×10^{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-

stable aggregates (Avanasi et al. 2014), which we model as uniform between 5 x 10^{-6} and 100 mg/L. Similarly, atmospheric degradation rates (kdeg, air) of 2 x 10^{-5} 1/s by environmentally-relevant ozone concentrations was shown in Tiwari et al. (2014), although other carbon nanomaterials have been modeled as resistant to degradation (e.g., 1 x 10^{-20} 1/s) (Rodriguez-Garcia et al. 2014). Thus we model kdeg, air as uniform between these two values. In part the variability in fate and exposure relevant substance data for C_{60} is related to the large number of publications on the ENM, as compared to the less-studies niacinamide. Thus, future efforts can incorporate the number of studies into estimates of parameter uncertainty or variability as has recently been demonstrated for pesticide dissipation half lives in plants (Fantke et al. 2014) and related CFs for human exposure to pesticide residues in crops (Fantke and Jolliet 2015).

Fate and exposure relevant parameters for which only point values are reported in literature or available from QSAR programs were assumed to have an arbitrary baseline scenario of uniform variable distributions of plus-or-minus one order of magnitude from the midpoint value. The USEtox 1.01 manual describes a simple regression to estimate the dissolved organic carbon partitioning coefficient (Kdoc) as 0.08 x Kow, giving the midpoint value of 3.2 x 10^4 L/kg. In the absence of experimental data, we assume Kdoc is equal to the suspended solids partitioning (Kpss), sediment particle partitioning (Kpsd), and soil particle partitioning (Kpsl) coefficients (Eckelman et al. 2012). Based on the classification of C_{60} as recalcitrant (Avanasi et al. 2014; Kümmerer et al. 2011) and the USEtox manual (Huijbregts 2010b), we model the aquatic degradation rate (kdeg, water) as 4.5 x 10^{-8} 1/s, and the soil and sediment degradation rates as 1/2 and 1/9 of kdeg, water respectively. Bioaccumulation factors for fish (BAF fish) have been reported as ≈ 3 x 10^4 L/kg (Li et al. 2010) and 5 x 10^5 L/kg (Jafvert and Kulkarni 2008), which is less than the assumed baseline variability, thus we model BAF fish as uniform between 5 x 10^4 and 5 x 10^6 L/kg.

The conventional antioxidant niacinamide that C_{60} may replace is the subject of relatively fewer studies, which is why we rely primarily on EPISuite (USEPA 2015b) and supplement with available literature as summarized in Table 2.

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	 122	Chemical formula
Kow	Octanol-water partitioning coefficient	L/L	0.42	 4.2x10^{-2} - 4.2	OECD SIDS
Koc	Organic carbon partitioning coefficient	L/kg	8.5	 0.85 - 85	EPISuite, Kocwin
Kh	Henry's law constant	Pa m^3/mol	2.9 x 10^{-7} 6.45 x10^{-6}	 2.9x10^{-8} - 2.9x10^{-6}	PubChem database USEtox Guidance
Pvap	Vapor pressure	Pa	0.026 0.05	 5x10^{-3} - 0.5	EPISuite, MPBPVP PubChem database

Solubility	Solubility in water	mg/L	5e5 6.9-10 x 10^5	 $5x10^4$ - $5x10^6$	EPISuite, exper. OECD SIDS
kdeg, air	Degradation rate in air	1/s	1.8 x 10^{-6}	 $1.8x10^{-7}$ - $1.8x10^{-5}$	EPISuite, AOPWin USEtox manual
kdeg, water	Degradation rate in water		2.1 x 10^{-7}	 $2.1x10^{-8}$ - $2.1x10^{-6}$	EPISuite, Biowin USEtox manual
kdeg, soil	Degradation rate in soil		1 x 10^{-7}	 $1x10^{-8}$ - $1x10^{-6}$	
kdeg, sed	Degradation rate in sediment		2.3 x 10^{-8}	 $2.3x10^{-9}$ - $2.3x10^{-7}$	
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 10^5 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^{-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 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_{60} and niacinamide – typically reported as the concentration at which 50 percent of the exposed organisms over background exhibit the studied effect (EC_{50}), inhibited growth (IC_{50}), or lethality (LC_{50}) – was taken from available literature and is summarized in Table 3 and Table 4, respectively.

Table 3 Data from individual ecotoxicity studies of C_{60}

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

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

		5d Chronic EC_{50} Fin malformation	0.15 mg/L		0.15 mg/L
Zhu et al, 2007	*D. rerio*	96h Chronic EC_{50} developmental	1.5 mg/L	C_{60} in THF then evaporated	1.5 mg/L
			50 mg/L (NOEC)	$C_{60}(OH)_{24}$	450 mg/L

*Although USEtox manual specifies EC_{50} 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_{50} 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_{60} 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_{50} 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_{60}. Reported toxicity data for niacinamide are consistently greater than C_{60} 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 eqiv. EC_{50} value
Producers				
OECD SIDS, 2002	*S. subspicatus*	72h Acute EC_{50}	>1000 mg/L	500 mg/L
	Algae - generic	QSAR, 96h Accute EC_{50}	8,934 mg/L	4,500 mg/L
Primary consumers				
	D. magna	24h Acute EC_{50}	>1000 mg/L	500 mg/L

OECD SIDS, 2002	Daphnid - generic	48h Acute EC_{50}, QSAR	16,456 mg/L	8,000 mg/L
Secondary consumers				
OECD SIDS, 2002	*P. reticulata*	96h Acute LC_{50}	>1000 mg/L	500 mg/L
	Fish - generic	96h Acute LC_{50}, QSAR	18,189 mg/L	9,000 mg/L
ECOTox database*	*X. laevis*	96h Acute EC_{50}, embryonic	0.34 mg/L	0.17 mg/L

*Misclassified data point contained in ECOTox database.

Consistent with our treatment of C_{60} 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_{50}. 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 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 10^5 PAF m³ 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_{50}) estimation and standard error on the mean (SEM) calculation is significant (SI 2.3.1).

To calculate aveLog EC_{50} 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_{50} values, and is 0.43 and 3.2 log mg/L for C_{60} and niacinamide respectively. We calculate the SEM from the log EC_{50} data, which is 0.12 for C_{60} and 0.04 for niacinamide (SI 2.3.2). Uncertainty in the average toxicity ($\overline{ave\ Log}$) follows a Student's t distribution (Golsteijn et al. 2012; Van Zelm et al. 2007) centered around aveLog EC_{50} and scaled by the SEM, shown in Eq. 2:

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

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_{60} 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 $\overline{ave\ Log}$ 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

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

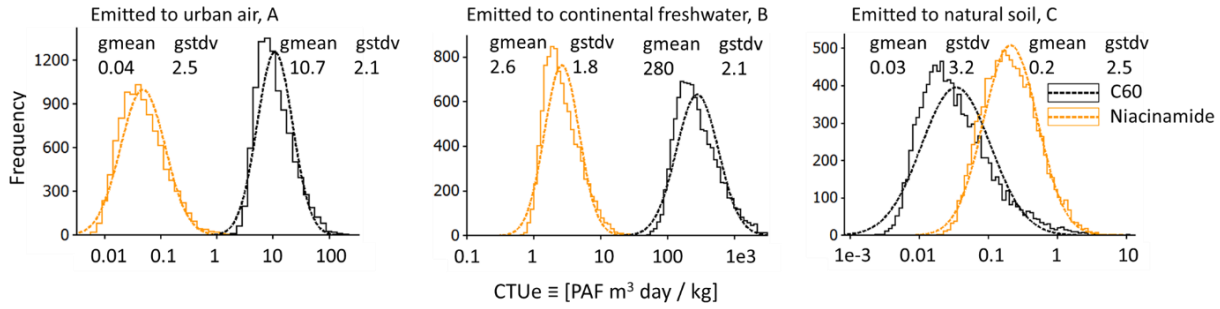


Fig 1 Stochastic aquatic ecotoxicity CFs for C_{60} (black) and niacinamide (orange) antioxidants emitted to urban air (A), freshwater (B), and natural soil (C) compartments. Solid lines are frequency distributions from 10,000 Monte Carlo runs and dashed lines are normal distributions fit to the log-transformed data (i.e., CFs are log normal distributions).

For emissions to air and freshwater, niacinamide is characterized by a lower toxicity potential per unit mass than C_{60}, as opposed to emissions to soil in which case C_{60} has a lower average CF due to its strong partitioning to soil over water. For emission to freshwater, stochastic CFs for C_{60} and niacinamide are log normally distributed with a geometric mean of 280 and 2.6 and geometric standard deviation of 2.1 and 1.8, respectively. All of these differences are significant (Welch's t-test $p < 0.001$), with the closest scenario (i.e., emission to soil) yielding a Welch's t-test statistic < 0.05 (SI 3.2) (Fagerland and Sandvik 2009). Although model uncertainty is relatively well studied and beyond the scope of this study, these differences are significant with respect to model uncertainty, and variability in CFs in the baseline scenario is smaller in magnitude than estimated model uncertainty (Rosenbaum et al. 2008) (SI 3.3). Given baseline scenario assumptions, the hypothetical product developers can conclude that C_{60} has greater potential for ecotoxicity impacts per unit mass than niacinamide,

3.1 Identifying the Most Influential Substance Parameters

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

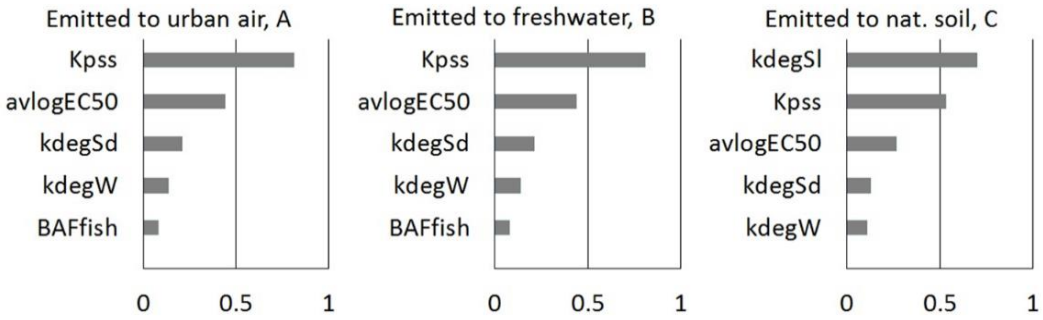


Fig 2 The five Spearman rank correlation indices with the greatest magnitude out of all variable inputs for three C_{60} aquatic ecotoxicity CFs. Greater magnitude indicates which input parameters have the greatest influence on CF variability for each emission compartment.

Figure 2 calls attention to the importance of variability in the suspended solids partitioning coefficient (Kpss), $\overline{ave\ Log}$ aggregate ecotoxicity, and to a lesser extent sediment, aquatic, and soil degradation rates (kdegSd, kdegW, kdegSl) as driving variance in C_{60} CF results. Uncertainty in $\overline{ave\ Log}$ 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_{60} 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_{60} Kpss and $\overline{ave\ Log}$ 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 $\overline{ave\ Log}$ (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.

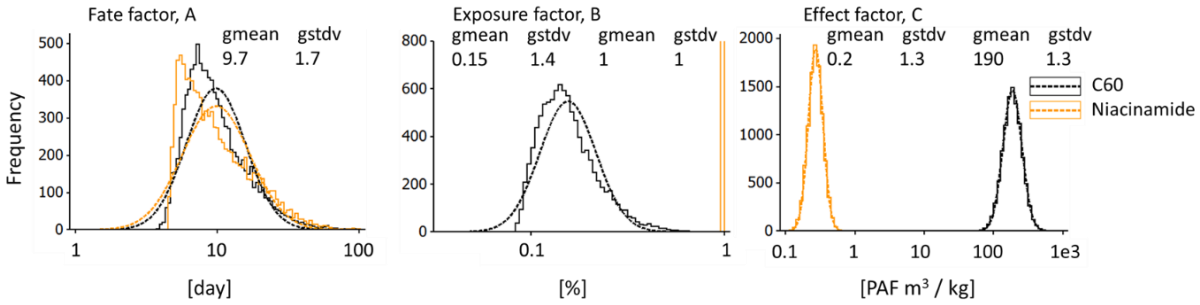


Fig 3 Component fate (A), exposure (B), and effect factors (C) for niacinamide (orange) and C_{60} (black) identify significant differences between the two antioxidants, specifically the high exposure and low toxicity of niacinamide compared to C_{60}. Solid lines are frequency distributions of 10,000 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_{60} and biodegradation dominant for niacinamide. XF for niacinamide is effectively 1 – representing 100 percent of the emission being bioavailable – whereas the C_{60} 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_{60} 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_{60} 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_{60} aquatic ecotoxicity CFs. In the case of direct emission to freshwater, the suspended solids partitioning coefficient (Kpss) and average toxicity (aveLog EC_{50}) are prioritized for data refinement and promising candidates for further experimental investigation. The assumed Kpss with uniform variability between 3×10^3 and 3×10^5 L/kg is based on the USEtox 1.01 regression for estimating Kdoc from Kow, which does not warrant reduction from our high-uncertainty baseline scenario even though experimental values for Kow are available. C_{60} is expected to exhibit strong partitioning to suspended solids based on reported Koc 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_{60} preparation methods (Kiser et al. 2010). Thus, further reduction of variability in Kpss requires identification of dominant preparation methods and experimental investigation of C_{60} partitioning to suspended solids with realistic compositions and concentrations.

Uncertainty in aveLog EC_{50} for C_{60} 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_{60}, uncertainty in aveLog EC_{50} 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_{60} 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_{60} EFs and CFs to preparation method, we exclude all studies in Table 3 that used solvents to stabilize C_{60} 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).

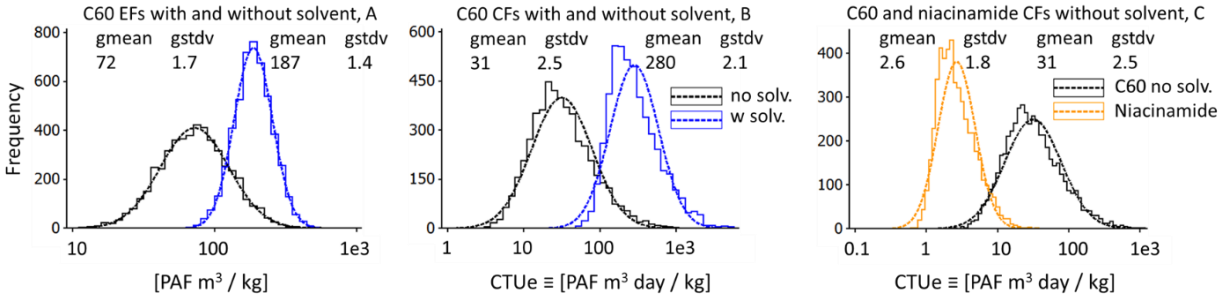


Fig 4 Removal of all ecotoxicity studies relying on solvents (black without, blue with) reduces the C_{60} effect factor (A) and characterization factor (B) by more than one order of magnitude. With no

solvents the toxicity potential of C_{60} is closer to niacinamide (orange) but still significantly different for emissions to freshwater (C).

The revised CF for C_{60} emissions to freshwater still exceeds niacinamide by an order of magnitude (4C) and is significantly different (Welch's t test $p < 0.001$). This suggests that, if solvent residues are not present in C_{60} emissions, the aquatic ecotoxicity potential is marginally greater than niacinamide for direct emission to freshwater. For emissions to rural and continental air, the geometric mean of the C_{60} CF is at least two orders of magnitude greater than niacinamide, whereas for emissions to natural soil, agricultural, and marine water niacinamide significantly exceeds C_{60} (SI 3.7). Thus, the order of preference for the materials depends on the emission compartment. Furthermore, there is a critical need to: 1) characterize the form of C_{60} released regarding the presence of solvent residues, and 2) to design new experiments to elucidate suspended solids partitioning behavior.

4.0 Conclusion

LCIA method developers can apply the Monte Carlo tool to expedite expansion and review of toxicity databases by identifying the most influential substance data for distinct chemical classes, and then focusing their efforts on reducing parameter uncertainty on these estimates by finding or providing experimental references. Analogous to the case shown above, it is likely that only a few model input parameters are significant for each chemical class, 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 the Monte Carlo tool to the life cycle inventory items that contribute most to ecotoxicity impacts to increase confidence in interpretation of LCIA results.

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 agenda. Our results suggest that focusing experimental resources on improving data for suspended solids partitioning behavior and multi-species toxicity indicators has the greatest potential to reduce uncertainty of current C_{60} CF estimates. In this capacity, stochastic evaluation of impact assessment models to identify the most influential parameter uncertainties and inform future research agenda constitutes an example of *anticipatory* LCA (Wender et al. 2014a; Wender et al. 2014b).

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. The controversy, parameter, and mechanistic uncertainty surrounding the environmental impacts of ENMs represent an opportunity to reevaluate LCIA estimates for commercially-available, well-studied chemicals. No midpoint impact assessment methods include formal uncertainty analysis, thus this approach could improve treatment and presentation of uncertainty for LCA of emerging and established technologies alike.

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Figure1

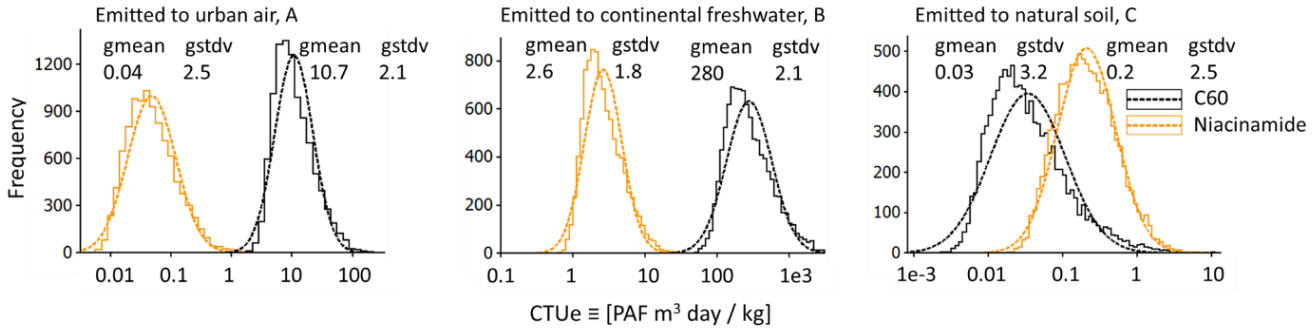

Emitted to urban air, A
gmean
0.04
gstdv
2.5
gmean
10.7
gstdv
2.1
Frequency
1200
900
600
300
0
0.01
0.1
1
10
100
Emitted to continental freshwater, B
gmean
2.6
gstdv
1.8
gmean
280
gstdv
2.1
800
600
400
200
0
0.1
1
10
100
1e3
Emitted to natural soil, C
gmean
0.03
gstdv
3.2
gmean
0.2
gstdv
2.5
C60
Niacinamide
500
400
300
200
100
0
1e-3
0.01
0.1
1
10
CTUe ≡ [PAF m³ day / kg]

Figure2

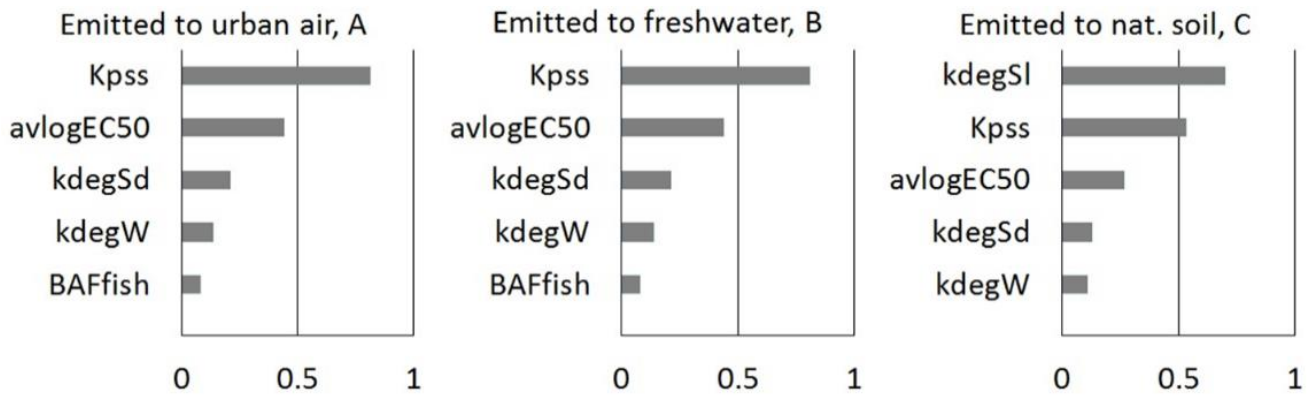

Emitted to urban air, A
Kpss
avlogEC50
kdegSd
kdegW
BAFfish
0
0.5
1
Emitted to freshwater, B
Kpss
avlogEC50
kdegSd
kdegW
BAFfish
0
0.5
1
Emitted to nat. soil, C
kdegSl
Kpss
avlogEC50
kdegSd
kdegW
0
0.5
1

Figure3

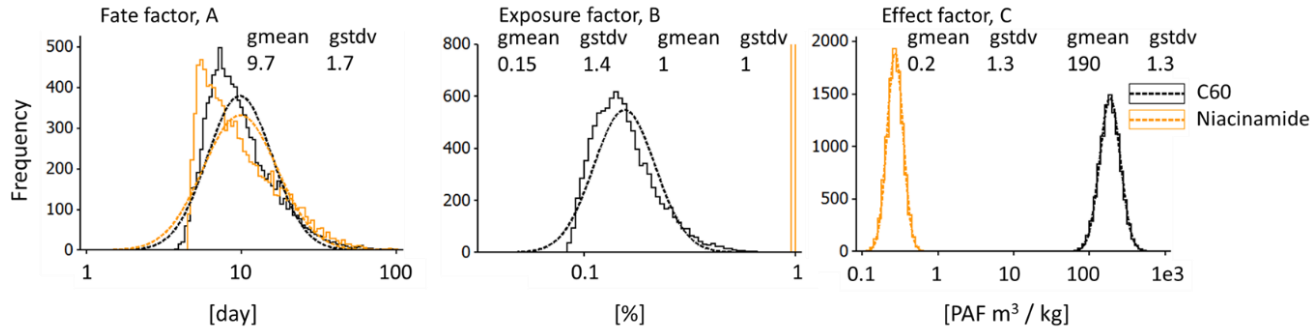
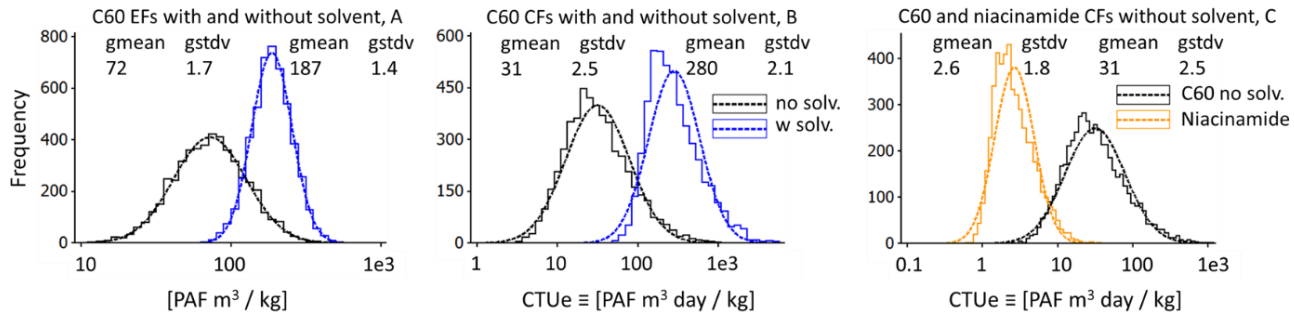

Fate factor, A
gmean
gstdv
9.7
1.7
Frequency
500
400
300
200
100
0
1
10
100
[day]
Exposure factor, B
gmean
gstdv
gmean
gstdv
0.15
1.4
1
1
800
600
400
200
0
0.1
1
[%]
Effect factor, C
gmean
gstdv
gmean
gstdv
0.2
1.3
190
1.3
2000
1500
1000
500
0
0.1
1
10
100
1e3
[PAF m3 / kg]
C60
Niacinamide

Figure4


C60 EFs with and without solvent, A
gmean gstdv gmean gstdv
72 1.7 187 1.4
Frequency
800
600
400
200
0
10
100
1e3
[PAF m³ / kg]
C60 CFs with and without solvent, B
gmean gstdv gmean gstdv
31 2.5 280 2.1
no solv.
w solv.
600
450
300
150
0
1
10
100
1e3
CTUe ≡ [PAF m³ day / kg]
C60 and niacinamide CFs without solvent, C
gmean gstdv gmean gstdv
2.6 1.8 31 2.5
C60 no solv.
Niacinamide
400
300
200
100
0
0.1
1
10
100
1e3
CTUe ≡ [PAF m³ day / kg]