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Multi-pathway exposure modelling of chemicals in cosmetics with application to shampoo

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Abstract

We present a novel multi-pathway, mass balance based, fate and exposure model compatible with life cycle and high-throughput screening assessments of chemicals in cosmetic products. The exposures through product use as well as post-use emissions and environmental media were quantified based on the chemical mass originally applied via a product, multiplied by the product intake fractions (PiF, the fraction of a chemical in a product that is taken in by exposed persons) to yield intake rates. The average PiFs for the evaluated chemicals in shampoo ranged from 3×10^{-4} up to 0.3 for rapidly absorbed ingredients. Average intake rates ranged between nano- and micrograms per kilogram bodyweight per day; the order of chemical prioritization was strongly affected by the ingredient concentration in shampoo. Dermal intake and inhalation (for 20% of the evaluated chemicals) during use dominated exposure, while the skin permeation coefficient dominated the estimated uncertainties. The fraction of chemical taken in by a shampoo user often exceeded, by orders of magnitude, the aggregated fraction taken in by the population through post-use environmental emissions. Chemicals with relatively high octanol-water partitioning and/or volatility, and low molecular weight tended to have higher use stage exposure. Chemicals with low intakes during use (<1%) and subsequent high post-use emissions, however, may yield comparable intake for a member of the general population. The presented PiF based framework offers a novel and critical advancement for life cycle assessments and high-throughput exposure screening of chemicals in cosmetic products demonstrating the importance of consistent consideration of near- and far-field multi-pathway exposures.

Keywords: exposure; life cycle assessment; high-throughput screening; cosmetics; personal care products

1. Introduction

Using cosmetics can lead to consumer exposure to chemical ingredients during use or general population exposure to chemicals emitted post-use to the environment (Bergfeld et al., 2005 and Boxall et al., 2012). With limited human exposure data available for cosmetics (e.g. Koch et al., 2014), and potential for health risks associated with chemical exposures, modeling tools are needed to assess multi-pathway exposure to the variety of chemical-cosmetic combinations.

High-throughput screening (HTS) of exposures to chemicals, such as those used in cosmetics, is a risk prioritization strategy responding to the millions of product-chemical combinations on the market. In order to evaluate dozens to thousands of chemicals at a time, HTS relies on lower-tier models with high computational speed, interpretation of uncertainty, and readily available data such as national emission statistics (Isaacs et al., 2014, Shin et al., 2015 and Wambaugh et al., 2013). SHEDS-HT (Isaacs et al., 2014) for example offers a comprehensive platform for exposure screening of consumer products including cosmetics. Unlike platforms such as Crème RIFM (Safford et al., 2015) and the Targeted Risk Assessment (TRA) tool (<http://www.ecetoc.org/tra>) that assume dermal exposure leads to 100% dermal absorption, SHEDS-HT estimates absorption based on a simplified linear scaling of the chemical-specific skin permeation coefficient without consistently coupling all exposure pathways in a mass balance equation system (i.e. probabilistic mass transfers and exposures are forced to unity in post-processing). Skin permeation coefficients are also used in the dermal exposure models of ConsExpo (Delmaar et al., 2005) and PACEM (Delmaar et al., 2014; Dudzina et al., 2015a), which can estimate aggregated exposure fractions for

chemicals in cosmetics per unit mass of product used (Dudzina et al., 2015a) or per unit mass of chemical applied via a product (Delmaar et al., 2014). Platforms such as TRA, SHEDS-HT, ConsExpo, and PACEM can consider multiple exposure pathways and are suitable for risk-based assessment approaches. For comparative assessments based on multi-media, mass-balance exposure models (Hauschild et al., 2008; Wambaugh et al., 2013) there is a need to consistently integrate multiple exposure pathways and mechanistically consider the competition between different transfer and loss processes. For cosmetic exposure in particular, the chemical mass permeating the skin and the mass volatilizing that leads to inhalation are interdependent. Accounting for simultaneous volatilization and dermal permeation has been demonstrated as an important consideration by models that focus on dermal exposure (e.g. Kasting and Miller, 2006), but is currently missing from multi-pathway exposure screening assessments. Such dermal exposure models are not suitable for implementation in HTS or life cycle assessment (LCA) because of computational complexity (e.g. requiring numeric solutions) and unsuitable exposure metrics. Furthermore, none of the aforementioned exposure models have been used to estimate post-use emissions, which lead to ubiquitous contamination of aquatic environments including sources of drinking water (Kolpin et al., 2002 and Pal et al., 2014), and subsequent environmental exposure pathways.

LCA—a common quantitative assessment technique to inform environmental risk minimization and sustainable production and consumption—generally accounts for post-use environmental emissions of cosmetic ingredients, and often assumes that a fixed fraction (e.g. 100%) of ingredients is emitted to freshwater (Koehler and Wildbolz, 2009). Life cycle impact assessment (LCIA) models used in LCA, estimate potential impacts on humans and ecosystems mediated by environmental *emissions* along product life cycle stages (e.g. manufacturing, use, disposal). Recent advances in HTS of exposures to environmental

chemicals have also employed LCIA mass balance models (Shin et al., 2015 and Wambaugh et al., 2013), thus underscoring the utility of models compatible with both HTS and LCIA despite their different goals. LCA-compatible methods to evaluate exposures occurring during product use are, however, not yet available, although exposure during use is a predominate exposure pathway for consumer products like cosmetics (Jolliet and Fantke, 2015). Recently, Jolliet et al. (2015) presented and illustrated examples of the product-specific chemical intake fraction (PiF) metric, which represents all incurred exposures per unit of chemical mass applied via a product, as the first necessary step towards developing methods for LCIA to include consumer product exposure. Models to estimate PiF have however not yet been operationalized to account for multi-pathway exposures to multiple chemicals. Existing modeling platforms are not appropriate for estimating PiF, because they are not mass balance-based across exposure pathways, they do not mechanistically account for volatilization as a competing process with dermal permeation, and they do not estimate post-use emissions and subsequent exposures. Further development of lower-tier mechanistic, mass balance-based, exposure models compatible with LCIA as well as HTS is needed to better assess potential impacts and risks related to chemical fate and exposure pathways originating from chemicals in cosmetic products (Jolliet and Fantke, 2015).

In this study, we address these research gaps and aim to (1) develop a consistent, LCA-compatible, mass balance framework coupling multi-pathway fate and exposures to chemicals in dermally applied cosmetics; (2) analyze fate and exposure pathways during and after use for an exposure duration relevant for cosmetic use; (3) quantify product intake fractions (*PiFs*) and intake rates for a case study of chemicals in a shampoo product and account for uncertainty propagation; and (4) apply the model to determine exposure to

multiple chemicals in shampoo and to identify predominant exposure pathways and data gaps.

2. Methods

2.1 Cosmetic product intake fraction framework and exposure pathways

The presented framework is applicable to non-medical, dermally-applied products regardless of their functions (e.g., beautification, hygiene, etc.), referred to as cosmetics (European Union, 2009). We built the framework based on the product intake fraction (PiF , Jolliet et al., 2015) metric to quantify consumer exposure to chemicals in cosmetics via use and general population exposure mediated by post-use environmental emissions (Table 1). PiF is defined as the fraction of the *chemical mass* applied in a cosmetic product that is eventually taken in by all exposed persons, with the dimensionless units of kilogram chemical taken in versus kilogram chemical initially applied via the cosmetic. Thereby, PiF accounts for exposures during the use stage that are missing in LCIA methods (Jolliet et al., 2015) which are restricted to estimating the emissions-based intake fraction, iF (Bennett et al., 2002). The modeling strategy for PiF is determined by the nature of the product (e.g. if applied on the skin), and like iF , model results are dependent on chemical behavior (e.g. volatility), meaning each chemical has its own PiF and iF . Consistent with iF , but for the amount of chemical applied rather than emitted, PiF multiplies the amount of chemical applied in a product to yield the human *intake* (not *uptake*) at the exposure interface—for example, permeation into the stratum corneum, not uptake into the blood stream. As the outermost epidermal barrier, stratum corneum intake is recommended for exposure assessments (Cleek and Bunge, 1993).

To preserve versatility of application and model flexibility and to enable comparison across exposure pathways, the total PiF (PiF^{tot}) was differentiated into five components discerning life cycle stages as well as exposure pathways and routes (indicated by superscripts); Eq. (1) follows as

$$PiF^{tot} = \underbrace{PiF^{use, d, aq} + PiF^{use, inh} + PiF^{use, d, g}}_{\text{use stage, } PiF^{use}} + \underbrace{PiF^{dis, inh} + PiF^{dis, ing}}_{\text{disposal stage, } PiF^{dis}} \quad (1)$$

Three exposure pathways were considered for the product use stage (near-field), i.e dermal permeation originating from the aqueous solution on the skin surface ($PiF^{use, d, aq}$), and if volatilized from the skin surface, inhalation ($PiF^{use, inh}$) and dermal permeation via transfer from the gaseous phase ($PiF^{use, d, g}$). Two environmentally-mediated pathways (far-field) were considered for the disposal stage (i.e. after product use), i.e. inhalation of ambient air ($PiF^{dis, inh}$) and ingestion of freshwater, fish and other food items ($PiF^{dis, ing}$), aggregated for all members of the general population. *Far-field* refers to indirect exposure to post-use emissions mediated through environmental pathways, which includes exposures via food, water, and air. *Near-field* refers to direct (dermal permeation via application on skin) and indirect (e.g. inhalation) exposures to chemical ingredients through product use. Representing all intakes by different individuals, each PiF component is normalized to the same initial mass of a given chemical in an applied cosmetic. Depending on the desired application of the metric, each PiF can be kept separate (e.g. with respect to life cycle stage, exposure route, or exposure pathway) or summed within Eq. (1).

2.2 Mass balance based models for product intake fractions

PiF was derived by first establishing the mass balance for a chemical applied via the cosmetic which advances dermal exposure models based on ConsExpo (Delmaar et al.,

2005), by including volatilization as a competing process with dermal permeation. The change in mass m (kg) of a chemical c remaining on the skin surface over the exposure duration t (h) is described in Eq. (2)

$$\frac{dm_c(t)}{dt} = - \underbrace{k_{p,a} \times m_c(t)}_{\text{volatilization}} - \underbrace{k_{p,s} \times m_c(t)}_{\text{dermal intake}} \quad (2)$$

The rate constants $k_{p,s}$ (h^{-1}) and $k_{p,a}$ (h^{-1}) respectively account for the losses due to mass transfer from the product (p) on the skin surface to air (a) and into the stratum corneum (s) and are described in Section 2.3.

The mass fraction of chemical permeating into the skin during exposure can be expressed by the time-integrated mass of chemical intake into the stratum corneum, $m_{c,s}$, divided by the initial mass of chemical applied to the skin, $m_{c,0}$, shown in Eq. (3)

$$PIF^{\text{use,d,aq}} = \frac{m_{c,s}}{m_{c,0}} = \frac{\int_0^{t_d} k_{p,s} \times m_c(t) \times dt}{m_{c,0}} \quad (3)$$

where t_d is the product-specific exposure duration. Solving Eq. (2) for m_c and introducing into Eq. (3) yields the solution Eq. (4) (Table 1) as recently applied in Csiszar et al., (2016). The first term of Eq. (4) expresses the chemical mass fraction transferred into the skin as a competitive process between dermal intake and volatilization. The second term expresses the total fraction of mass removed from the skin surface via both volatilization and dermal intake. The fraction volatilized from the product to the air $f_{p,a}$, Eq. (7) (Table 1), was derived in a similar manner to Eq. (4) and satisfying mass balance principles the sum of the fraction taken in, Eq. (4), and the fraction volatilized, Eq. (7), during use is always ≤ 1 .

Table 1. Calculation of the cosmetic product intake fraction (*PiF*) for the relevant exposure pathways with respect to life cycle stages.

Life cycle stage	Exposure pathways	Equation
use	dermal, aqueous	$PiF^{use, d, aq} = \frac{k_{p,s}}{k_{p,s} + k_{p,a}} \times \left[1 - e^{-(k_{p,s} + k_{p,a}) \times t_d} \right] \quad (4)$
	inhalation	$PiF^{use, inh} = f_{p,a} \times iF_a^{inh} \quad (5)$
	dermal, gas	$PiF^{use, d, g} = f_{p,a} \times iF_a^{d, g} \quad (6)$
where		$f_{p,a} = \frac{k_{p,a}}{k_{p,s} + k_{p,a}} \times \left[1 - e^{-(k_{p,s} + k_{p,a}) \times t_d} \right] \quad (7)$
disposal	inhalation	$PiF^{dis, inh} = \sum_{j=1}^n (f_{p,j} \times iF_j^{inh}) \quad (8)$
	ingestion	$PiF^{dis, ing} = \sum_{j=1}^n (f_{p,j} \times iF_j^{ing}) \quad (9)$

$k_{p,s}$ (h^{-1}), product-to-skin transfer rate constant, is a function of the skin permeation coefficient, K_p^{aq} ($m h^{-1}$) (SI Section S1), transfer through the aqueous film, φ_w ($m h^{-1}$) (SI Section S2), and the product thickness, h (m), where $k_{p,s} = (h / K_p^{aq} + h / \varphi_w)^{-1}$; $k_{p,a}$ (h^{-1}), product to indoor air transfer rate constant, is a function of φ_w ($m h^{-1}$) and the transfer from the aqueous film to the air, φ_a ($m h^{-1}$) (SI Section S2), and product thickness h (m), where $k_{p,a} = (h / \varphi_a + h / \varphi_w)^{-1}$; t (h), exposure duration prior to wash-off; $f_{p,a}$ (—), emitted fraction from the product to indoor air; iF_a^{inh} (—), intake fraction due to inhalation of indoor air (SI eq S3a); $iF_a^{d, g}$ (—), intake fraction due to dermal permeation from contact with the gaseous phase in indoor air (SI eq S3b); $f_{p,j}$ (—), emitted fraction from the product to environmental compartment j (SI Section S3), where emission to freshwater is a function of the remaining amount washed-off after use and sent to the treatment plant, $f_{p,tp} = \exp(-(k_{p,s} + k_{p,a}) \times t_d)$; iF_j^{inh} (—), inhalation intake fraction estimated by USEtox for releases to environmental compartment j (SI Section S3); iF_j^{ing} (—), ingestion intake fraction estimated by USEtox for releases to environmental compartment j (SI Section S3).

199

200 $PiF^{use, d, g}$ and $PiF^{use, d, inh}$, Eq. (5)-(6) (Table 1) are calculated as a function of the fraction
201 volatilized $f_{p,a}$ combined with indoor intake fractions, iFs (SI Section S3). Chemical
202 removal in indoor air via sorption and degradation were not considered due to limited
203 information and limited expected reductions in exposure (Rosenbaum et al., 2015 and
204 Wenger et al., 2012).

205 Post-use (disposal stage) emission fractions are directly linked to the use stage via the
206 conservation of mass. The fraction of chemical mass remaining on the skin surface at the end
207 of the exposure duration was assumed to be washed-off down the household drain and
208 thereby transferred to a conventional wastewater treatment plant, from where environmental
209 emissions occurred according to treatment efficiency estimates (US EPA, 2012). The
210 remaining volatilized fraction that was not taken in via inhalation or dermal permeation was
211 assumed to be directly ventilated outdoors to urban air. The disposal stage $PiFs$, Eqs. (8)-(9)
212 (Table 1), are a function of the emitted fraction of the applied chemical and of the far-field
213 iFs (SI Section S3) capturing population-scale exposure and accounting for environmental
214 intermedia transfers and degradation processes as estimated by USEtox 1.01 the United
215 Nations Environment Program, Society for Environmental Toxicology and Chemistry
216 consensus model (Hauschild et al., 2008; Rosenbaum et al., 2008).

217 **2.3 Estimating transfer rates and skin permeation coefficient**

218 Mass transfer from the product-to-skin and product-to-air was modeled based on the
219 conventional two film theory where it is assumed that the steady-state transfer rate through a
220 two-phase interface (i.e., solution-skin and solution-gas) is controlled by transfer processes
221 specific to each phase and boundary layer and the equilibrium concentration occurs at the

interface. The overall rate constant describing transfer from the product solution to the skin, $k_{p,s}$, is a function of the rate of passage through the boundary layer of the aqueous cosmetic solution (φ_w , SI Section S2) and through the stratum corneum determined by the skin permeation coefficient (K_p^{aq} , SI Section S1), and the solution thickness, h . The rate constant describing transfer from the product solution to the air, $k_{p,a}$, was estimated as a two-sided boundary layer series as a function of the rate of passage through the cosmetic solution (φ_w , SI Section S2), the rate of transfer to the air based on volatility (φ_a , SI Section S2), and the solution thickness, h . The skin permeation coefficient K_p^{aq} is an essential consideration for dermal permeation modeling, and due to lacking empirical data we selected a QSAR to model K_p^{aq} according to the methods below.

We tested 8 QSAR models recommended for dermal exposure studies (SI Table S1) by comparing their estimated skin permeation coefficients to a list of *in vitro* human skin permeation data we compiled from the literature (Chen et al., 2010; Flynn, 1990; Hadgraft, 2002; Lian et al., 2008; Williams, 2004); these data are available in a supplementary spreadsheet described in SI Section S6. The QSARs by ten Berge, 2009 and Robinson presented by Wilschut et al., 1995 most accurately predicted the compiled *in vitro* skin permeation coefficient data among the 8 considered models (SI Table S1), both with squared geometric standard deviations of $GSD^2 \approx 20$ and standard error of $SE \approx 0.65$. The skin permeation coefficient QSARs were developed on diverse training sets, but parameterization was restricted to molecular weight (MW) and the octanol-water partition coefficient (K_{ow}), which contributes to the uncertainty of the QSARs. The range of suggested applicability is constrained by these parameters, e.g. $18 \text{ g/mol} < MW < 585 \text{ g/mol}$ and $-3.7 < \log K_{ow} < 5.49$ (ten

Berge, 2009; SI Table S1), and not by other molecular descriptors (e.g. shape) or substance function (e.g. surfactant).

2.4 Estimating intake rates

The absolute mass taken in per day by an individual product user is the product of the *PiFs* and the mass of chemical initially applied. Specifically, the individual daily intake rate for a product user, IR ($\mu\text{g kg}^{-1} \text{d}^{-1}$), in micrograms of chemical taken in per kilogram body weight per day, was estimated as

$$IR = (PiF^{\text{use}} + PiF^{\text{dis}} \times N^{\text{use}} / N^{\text{pop}}) \times S_c / BW \quad (10)$$

which accounts for exposures during use PiF^{use} (sum of use stage *PiFs*) and mediated by post-use emissions PiF^{dis} (sum of disposal stage *PiFs*), assuming an average daily use of a cosmetic by all users. Bodyweight (BW) was fixed at $70 \text{ kg capita}^{-1}$. The source of chemical mass, S_c ($\mu\text{g capita}^{-1} \text{d}^{-1}$), was determined as the mass of cosmetic product applied per person per day, S_p ($\text{kg capita}^{-1} \text{d}^{-1}$), multiplied by the concentration (w/w) of chemical in the product, f_c ($\mu\text{g kg}^{-1}$). To obtain the individual average dose taken in from the disposal of product used, PiF^{dis} must be multiplied by the fraction of the population using the product, i.e. the ratio of the total number of product users to the overall receptor population size considered in the PiF^{dis} calculation ($N^{\text{use}} / N^{\text{pop}}$).

2.5 Shampoo case study

The *PiF* equations listed in Table 1 were determined for a case study product and chemical ingredients. Shampoo was selected for a case study on a commonly used cosmetic, washed-off directly after use. Ingredients and formulation vary greatly, e.g., pH 3-9 (Gavazzoni Dias et al., 2014 and Goldsmith et al., 2014). Shampoo is typically >2/3 water

and subsequently diluted six-fold during use (Bremmer, et al., 2006). Five exemplary chemicals were first selected from the CPCat (Dionisio et al., 2015) or Household Products (<http://householdproducts.nlm.nih.gov>) databases. Chemicals were selected to span a representative range of physicochemical properties (i.e. molecular weight, octanol- and air-water partition coefficients) (SI Figure S2) to demonstrate model behavior, and toxicological relevance was not a selection criterion. The selected chemicals by name and by Chemical Abstracts Service (CAS) number were: benzyl benzoate (CAS 120-51-4), isopropyl alcohol (CAS 67-63-0), propylene glycol (CAS 57-55-6), sodium lauryl sulfate (CAS 151-21-3), and quinoline yellow (CAS 8004-92-0). Average concentrations of these chemicals in shampoo were reported (Bremmer et al., 2006 and Goldsmith et al., 2014) below water saturation as indicated in the USEtox 1.01 database. *PiF* was evaluated based on an average use scenario (SI Table S2) for men and women with an exposure duration of 4 minutes (0.065 h), after which the solution is washed-off (Bremmer et al., 2006, Hall et al., 2007 and Loretz et al., 2006).

To characterize ranges in *PiF* estimates for a larger number of substances, we also identified 414 additional chemicals based on inquiry of “personal_care cosmetics shampoo” within the CPCat database (Dionisio et al., 2015). We then obtained all the chemical-specific parameters required for both the near- and far-field models by using the USEtox 1.01 substance database (downloadable at <http://usetox.org>). The properties required for the near-field *PiF* models, Eqs. (4)-(7), are MW, Kow, Kaw, and the properties required for the far-field *iF* model are listed in the USEtox documentation. The resulting list of 118 chemicals was then restricted to the applicability range of the skin permeation QSAR model (ten Berge, 2009), $18 \text{ g/mol} < \text{MW} < 585 \text{ g/mol}$ and $-3.7 < \log \text{Kow} < 5.49$. The wastewater treatment plant efficiencies were extracted for each chemical when available in STPWIN (EPI Suite v4.11),

and then combined with the USEtox far field intake fractions, iF , to estimate the far-field PiF based on post-use environmental emissions (Eqs. (8)-(9); SI section S3). The remaining 69 chemicals (listed in the supplementary spreadsheet described in SI S-6) spanned the QSAR applicability range for physicochemical properties offering a robust case study of model behavior. Additional chemicals could be modeled if their required properties are obtained (e.g. from EPI Suite). In addition to $PiFs$, IRs were estimated when the chemical concentrations in shampoo ($\mu\text{g kg}^{-1}$) were available in Goldsmith et al., 2014 and non-zero values were averaged; 53 chemicals had sufficient data to estimate IRs . Benzyl benzoate concentration was unavailable and was thus estimated from the shampoo preservative concentration range (Bremmer, et al., 2006). The number of daily users was set equivalent to the USEtox 1.01 continental population of 1 billion people thus $N^{\text{use}} / N^{\text{pop}} = 1$ in Eq. (10).

2.6 Sensitivity, uncertainty, and variability analyses

To identify potentially important parameters, model sensitivity was evaluated for the values of PiF^{use} for all chemicals, as the change in the resulting model output divided by the change in an input parameter, fixed at 10%, with all other parameters fixed. Further, the uncertainty distribution of product intake fractions as estimated by Eqs. (4)-(9) (Table 1) were determined using a Monte Carlo (MC) simulation in Matlab[®] based on 10^6 randomly permuted points for each parameter considering log-normal distributions except for room ventilation (McKone and Bogen, 1992) (SI Table S2 and Section S4). Uncertainty was also estimated with respect to environmental fate and intake fractions (SI Section S4). MC determines the stochastic propagation of parameter uncertainty and variability, and was also used to evaluate the contribution of parameters to the overall distribution. We further investigated variability with respect to the exposure duration and the distribution of shampoo

mass typically applied by consumers (Hall et al., 2007) whereas the average concentration of chemicals in shampoo was fixed, due to a lack of data on realistic concentration distributions. Results are therefore indicative of intake rates for the considered concentrations, whereas PiF s are concentration independent.

2.1 Results

3.1 Use stage exposure to chemicals in shampoo

PiF^{use} and relative contributions of exposure pathways varied greatly for the five chemicals studied, ranging in total from ≈ 0.0003 (quinoline yellow) to ≈ 0.3 (benzyl benzoate) with the dimensionless units of kilogram chemical taken in versus kilogram chemical initially applied in shampoo. Due to $K_{ow} > 10^3$ and $K_{aw} > 10^{-3}$, relatively fast transfer rates to skin and to air $> 1 \text{ h}^{-1}$ were estimated for benzyl benzoate, resulting in rapid use stage intake and a high $PiF^{use} > 0.1$, despite the short shampoo exposure duration of 4 minutes (0.065 h) (Bremmer et al., 2006). Considering the high volatility of isopropyl alcohol and minimal dermal intake associated with $K_{ow} \approx 1$, $PiF^{use, inh}$ is high (3.3×10^{-2}) and superior to $PiF^{use, d, aq}$. Sodium lauryl sulfate and quinoline yellow, with $K_{ow} < 100$, $MW > 200 \text{ (g mol}^{-1}\text{)}$ and negligible volatility with a $K_{aw} < 10^{-10}$, were estimated to have low-end exposure during use ($PiF^{use} < 0.001$).

3.2 Influence of exposure duration on exposure and post-use emissions

As demonstrated in Figure 1A-D, PiF^{use} is a function of exposure duration (0-10 h). For volatile case study chemicals (i.e. benzyl benzoate and isopropyl alcohol), an exposure duration exceeding one hour does not influence PiF^{use} any further; after this point, the chemical on the skin surface has been completely removed from the skin surface via volatilization and dermal permeation. For such chemicals, our modeling predicts that a

maximum PiF^{use} occurs within an hour and plateaued well below 1 (e.g. 0.3) (see Figure 1D). In contrast, other compounds with lower volatility, such as sodium lauryl sulfate, quinoline yellow or propylene glycol, can potentially approach $PiF=1$ intake if they remain on the skin for an extended duration (i.e. >10 h). Figure 1E-H also demonstrate that post-use emissions are a direct function of the fate and exposures during the use stage which is especially important to consider for chemicals with fast skin permeation and/or volatility. Post-use emissions also influence the exposure pathways in the far-field as demonstrated in Figure G-H for ingestion due to emission to freshwater and inhalation due to emission to urban air.

Figure 1 A-H. Evolution of use stage product intake fractions through the exposure duration for (A) dermal take of the aqueous solution on the skin, (B) dermal intake of the gaseous phase, and (C) inhalation of the gaseous phase, and (D) the sum of all use stage routes (A-C). Evolution of post-use emissions and disposal stage product intake fractions as a result of the exposure duration during use for (E) wash-off to the wastewater treatment plant, $f_{p,wp}$, (F) ventilated to urban air, $f_{p,a}$, (G) ingestion via foods and water due to emissions to freshwater (H) inhalation due to emissions to urban air. The grey vertical line represents the shampoo case study exposure duration of 0.065 hours (i.e. 4 minutes).

3.3 Comparison between use and disposal stage exposures

Main results and model parameters are presented in Table 2, with further details provided in SI Tables S2-4. Estimated PiF s for all exposure pathways (Figure 2) demonstrated that in most cases PiF^{use} dominated. However, when considering uncertainty, quinoline yellow had PiF^{dis} close to $PiF^{use} \approx 10^{-4}$, predominated by ingestion of drinking water. By definition, PiF^{dis} is always a function post-use emissions (SI Section S3). Thereby when consumer exposure is low, (e.g. <0.001) the post-use emission fraction approaches 1, and the magnitude of PiF^{dis} is only controlled by the far-field intake fraction, iF (Rosenbaum et al., 2008). Near- and far-field models shared mechanistic basis on physicochemical properties (K_{ow} , K_{aw} , MW), therefore chemicals with $PiF^{use} > 0.1$ attributable to a high K_{ow} may in addition have a relatively high environmental iF of emissions, e.g. $>10^{-4}$ due to bioaccumulation in the food chain.

370

371 Table 2. Physicochemical properties, key model parameters, and resulting product intake
 372 fractions and individual intake rates for a user using a shampoo containing the five exemplary
 373 chemicals.

Variable	Unit	benzyl benzoate	isopropyl alcohol	propylene glycol	sodium lauryl sulfate	quinoline yellow
MW	g mol^{-1}	212.3	60.1	76.1	288.38	353.35
K_{ow}	—	9.3×10^3	1.1	0.12	40	11
K_{aw}	—	3.0×10^{-4}	5.8×10^{-4}	9.2×10^{-7}	4.9×10^{-16}	7.5×10^{-17}
f_c	$\mu\text{g kg}^{-1}$	1.5×10^3	1.0×10^7	9.8×10^7	4.7×10^7	2.8×10^6
$k_{p,s}$	h^{-1}	3.9	6.9×10^{-2}	1.6×10^{-2}	2.4×10^{-2}	4.1×10^{-3}
$k_{p,a}$	h^{-1}	13	26	5.0×10^{-2}	2.6×10^{-11}	4.1×10^{-12}
$f_{p,a}$	—	0.53	0.82	3.2×10^{-3}	1.7×10^{-12}	2.6×10^{-13}
$f_{p,tp}$	—	0.32	0.18	0.99	0.99	1.0
iF_a^{inh}	—	3.1×10^{-2}	4.0×10^{-2}	3.0×10^{-2}	1.7×10^{-2}	1.7×10^{-2}
$iF_a^{\text{d,g}}$	—	0.23	3.3×10^{-3}	0.26	0.59	0.59
$PiF^{\text{use,d,aq}}$	—	0.15	2.1×10^{-3}	1.0×10^{-3}	1.5×10^{-3}	2.7×10^{-4}
$PiF^{\text{use,d,g}}$	—	0.12	2.7×10^{-3}	8.5×10^{-4}	1.0×10^{-12}	1.5×10^{-13}
$PiF^{\text{use,inh}}$	—	1.6×10^{-2}	3.3×10^{-2}	9.5×10^{-5}	2.8×10^{-14}	4.4×10^{-15}
$PiF^{\text{dis,inh}}$	—	9.9×10^{-6}	2.1×10^{-5}	5.3×10^{-8}	2.5×10^{-9}	2.9×10^{-18}
$PiF^{\text{dis,ing}}$	—	1.9×10^{-5}	5.5×10^{-6}	2.4×10^{-5}	6.0×10^{-5}	8.1×10^{-5}
PiF^{total}	—	0.29	3.8×10^{-2}	2.0×10^{-3}	1.6×10^{-3}	3.5×10^{-4}
IR	$\mu\text{g kg}^{-1} \text{ d}^{-1}$	3.1×10^{-2}	27	14	5.4	7.0×10^{-2}

Grey shading indicates greater than 10% relative contribution to total PiF ; MW , molecular weight; K_{ow} , octanol-water partition coefficient; K_{aw} , air-water partition coefficient, adjusted for average skin temperature of 34 °C (SI Section S2); f_c , fraction of chemical originally in shampoo; $k_{p,s}$, product to skin transfer rate constant; $k_{p,a}$, product to air transfer rate constant; $f_{p,a}$, fraction volatilized from product to indoor air, dimensionless units of kilogram chemical emitted to indoor air per kilogram chemical initially applied; $f_{p,tp}$, fraction transferred from product to wastewater treatment plant, dimensionless units of kilogram chemical transferred to treatment plant per kilogram chemical initially applied; iF_a^{inh} , indoor air intake fraction due to inhalation and $iF_a^{d,g}$, indoor air intake fraction due to dermal contact with volatilized gas-phase chemicals, both with dimensionless units of kilogram taken in per kilogram emitted indoors to the shower stall; all $PiFs$ (see Table 1) have dimensionless units of kilogram chemical taken in versus kilogram chemical initially applied; IR , intake rate as a function of PiF and mass applied. The disposal (dis) stage $PiFs$ are aggregated for all emission compartments (emissions to air, water, and soil).

3.4 Sensitivity, variability, and uncertainty

Monte Carlo (MC) simulations accounting for uncertainty and variability according to parameter distributions within SI Table S2, demonstrated that PiF^{use} varied by one to three orders of magnitude, with an upper limit of $PiF \leq 1$ due to mass balance principles (see 95th CI, Figure 2). Due to non-linearity, sensitivity on PiF^{use} was chemical-specific but the case study chemicals were usually most sensitive to the skin permeation coefficient, except for benzyl benzoate with the highest estimated K_p^{aq} ($> 10^{-4} \text{ m h}^{-1}$) which was most sensitive to the thickness of the solution applied on the skin surface and the resistance of the aqueous boundary layer. Further investigation of K_p^{aq} 's role in the propagated results distribution can be found with SI Figures S3-4. The influence of K_p^{aq} emphasizes the importance of obtaining good quality experimental data or at least selecting the best available predictive model, i.e the QSARs by ten Berge (2009) or Robinson presented by Wilschut et al. (1995). When removing variabilities in consumer behaviors and use scenarios (exposure duration, mass applied, body surface areas, indoor ventilation rates, breathing rates) the 95% CI interval was

reduced by 16-22% for all example chemicals but for benzyl benzoate for which only a 4% change was seen (difference between Figure 2, where all uncertainties and variabilities are accounted for, and SI Figure S5 where only uncertainties on estimated parameters are considered).

Figure 2. Ranges of PiF^{use} (white) and PiF^{dis} (grey) for the considered exposure pathways and routes: use stage dermal permeation due to the aqueous solution on the skin surface (use, d, aq) and due to the gaseous phase (use, d, g), inhalation (inh), and ingestion (ing) both during the use stage and due to the disposal (dis) stage (via post-use emissions). Calculated values (based on means of input variables) are marked with a star.

3.5 Intake Rates

PiF is multiplied by the chemical mass applied to estimate IRs for an individual product user, see Eq. (9), and the chemical mass applied is estimated as the product of the mass of shampoo applied and the fraction of chemical mass f_c ($\mu\text{g kg}^{-1}$) in the shampoo

(Table 2). We found *IR* for shampoo applications of these five chemicals was on the order of nano- to several micrograms chemical intake per kilogram bodyweight per day, which is similar to other recent estimates (Delmaar et al., 2014, Dudzina et al., 2015a and Safford et al., 2015). Conservatively assuming that the number of product users was equal to the number of individuals in a population, we found that for the 53 chemicals with readily available data to estimate *IRs* in this study, the contribution of the far-field *IR* was a function of the magnitude of the near-field exposure; for example when the near-field *PiF* was greater than 0.01, the far-field exposure negligibly contributed to *IR* (<1%). The near- and far-field exposures contributed to 70% and 30% of the total intake rate of $0.07 \mu\text{g kg}^{-1} \text{d}^{-1}$ for quinoline yellow, respectively. Accounting for uncertainty ranges, these contributions were not significantly different.

Figure 3 demonstrates that the order of chemical prioritization changed when considering the ranking of *IR* compared to *PiF*. For example, benzyl benzoate had the highest *PiF*, but resulted in the lowest *IR* due to the assumed low concentration fraction in shampoo for such preservatives (0.00015%) (Bremmer et al., 2006). Increasing the mass of shampoo used across the range typically applied by consumers (Hall et al., 2007) resulted in decreasing *PiF* by approximately an order of magnitude due to a thicker solution on skin surface (when the applied surface area is assumed constant). However, *IR* remained relatively stable because the effects of increasing the mass of chemical applied were compensated by the decreasing *PiF*.

Figure 3. Total *PiF* and *IR* based on percentiles of shampoo mass applied (black solid line). Symbols indicate the calculated values based on the mean mass applied daily (5.05 g d⁻¹).

3.6 Screening of additional chemicals

Figure 4 shows the range in *PiFs* evaluated for the 69 chemicals in shampoo that had data readily available to enable screening. Direct dermal intake generally dominates exposure, but inhalation was greater than dermal permeation for 16 out of the 69 evaluated chemicals. These chemicals typically have a smaller octanol-air partition coefficient, K_{oa} , with log values between -1 and 6.5, versus 3.5 and 32.5 for chemicals where direct dermal exposure

dominated. Four chemicals had disposal stage *PiFs* greater than use stage *PiFs* (SI Figure S6).

Figure 4. Product intake fraction (*PiF*) and intake rate ranges (*IR*) for a subset of chemicals found in shampoo (n=69). Stars indicate geometric means across chemicals.

2.2 Discussion

4.1 Feasibility and Limitations

With a lack of empirical data on cosmetic exposure there have been many recent modeling attempts. Generally, our dermal exposure results fall in the same range, or even predict the same values to one significant digit, of other recent exposure models built on empirical evidence. For instance, a PACEM case study using the dermal exposure equation in Delmaar et al., 2005 predicted an exposure fraction of 0.02 for diethyl phthalate (DEP) in shampoo (Delmaar et al., 2014). Using our model, which added simultaneous volatilization to the Delmaar et al., 2005 equation, a value of $PiF^{use,d,aq}=0.02$ for DEP in shampoo was also obtained. Although generally important to consider for volatile or semi-volatile compounds, the low volatility of DEP led to negligible competition with dermal permeation, resulting in similar dermal exposure estimates to Delmaar et al., 2014. We also compared our dermal exposure and volatilization results with the Center for Disease Control (CDC) Finite Dose Skin Permeation Calculator which is based on a different mass balance approach but also uses physicochemical properties to estimate skin permeation and volatilization (Dancik et al., 2013 and Kasting and Miller, 2006). Using vapor pressures from 0.22-0.66 Pa (range from 25-32 °C) (US EPA, 2012) for DEP and a 6x dilution with water, the CDC model predicted a relatively low fraction of 1-3% of the original mass has volatilized after 4 minutes (the shampoo exposure duration), without water dilution the CDC model predicts DEP volatilization between 3-10%. Our model predicted comparable fraction emitted to indoor air $f_{p,a} \approx 5\%$. The CDC model has a different configuration from our model which complicates comparison for dermal exposure, for example the model assumes immediate uptake into the upper layers of the stratum corneum and volatilization and deeper permeation occurs from there (Kasting and Miller, 2006). Generally, inhalation is considered negligible

for dermally applied cosmetics with limited experimental verification of this assumption; our model predicted that inhalation can be an important exposure pathway for volatile chemicals applied dermally and this is corroborated with recent experimental evidence (Biesterbos et al., 2015; Dudzina et al., 2015b). Also recently, Csiszar et al., (2016) used Eq. (4) to estimate dermal exposure to parabens and modeled results compared reasonably well with national biomonitoring data, bolstering the feasibility of modeling approaches.

Through a Monte Carlo simulation, we estimated the propagation of uncertainty related to the parameters within the model set-up, and corroborated that the skin permeation coefficient, K_p^{aq} , is a main contributor to uncertainty in dermal exposure modeling (Bouwman et al., 2008). As a concentration-independent and steady-state approximation, the K_p^{aq} metric, which we estimated by QSAR, does not consider mixture effects (Megrab et al., 1995), thermodynamics (Williams and Barry, 2012), or non-steady-state dynamics resulting in faster intake into the stratum corneum at short exposure durations (ten Berge, 2009, Cleek and Bunge, 1993 and Grégoire et al., 2009). Furthermore, mixture formulations affect dermal permeation in a variety of ways. As commonly occurring examples for cosmetics, co-solvents, terpenes and surfactants can *increase* the flux of dermal chemical intake in comparison to aqueous solutions, for example due to thermodynamic alterations or disruption of the skin's natural permeability (Williams and Barry, 2012). Co-solvents specifically can increase solution concentrations above water saturation, which leads to higher mass transfer into the skin than occurring at maximum water concentration (Moser et al., 2001). In contrast, emulsions, crystallization and ionization can potentially *decrease* flux, e.g., due to partitioning out of the aqueous phase and adjustment of the effective K_{ow} (Grégoire et al., 2009 and Moser et al., 2001). 16 out of the 69 chemicals screened had concentrations in the

shampoo solution (even when considering 6x dilution) exceeding water saturation, indicating the presence of a co-solvent. Due to the uncertainty regarding saturation and co-solvent effects, these chemicals were flagged in the supplementary spreadsheet described in SI Section S6, and the saturation concentrations were included for reference. Furthermore, 17 out of the 69 of the chemicals in the extended shampoo case study had dissociation constants indicating potential ionization, and these chemicals are also flagged in the supplementary spreadsheet described in SI Section S6. Empirical and modeling studies to date generally limit focus to a subset of these effects and how they influence K_p^{aq} (Grégoire et al., 2009, Megrab et al., 1995 and Moser et al., 2001). Paradoxically, parameterizing K_p^{aq} models (e.g. QSARs) with respect to various formulation variables such as ionization may only partially resolve the uncertainty, which largely results from natural variation in skin and from difficult-to-estimate contributions, e.g. related to three-dimensional molecular shape (Akomeah et al., 2007, Cruciani et al., 2000 and Tadros et al., 2004).

Monte Carlo only considers the propagation of uncertainties of model parameters. For example, removal processes within indoor air were not parameterized in the model and therefore did not contribute to uncertainty distribution as estimated via Monte Carlo. The volatile compounds within the case study (benzyl benzoate, isopropyl alcohol) do not have ozone or nitrate degradation rates available to our knowledge (US EPA, 2012, Wenger et al., 2012) and sorption to surfaces within the bathroom or shower stall is likely limited (Won et al., 2001). Due to these data gaps removal processes within indoor air were not parameterized within our model but indoor degradation is unlikely to increase the removal rate by more than 20% (Rosenbaum et al., 2015) which could have an effect for chemicals with high inhalation. Additionally, the developed mass balance model was based on several assumptions, for

example that the thickness of the cosmetic on the skin was constant. In reality, some cosmetics formulations or long exposure durations may result in volatilization that substantially decreases the thickness on the skin surface, resulting in an increase of thermodynamic activity leading to increased dermal transfer, assuming no crystallization (Moser et al., 2001).

With significant hurdles to account mechanistically for the multitude of formulation effects, at least within lower-tier models appropriate for HTS and LCIA, a qualitative descriptor to identify chemical functions (e.g. surfactant, co-solvent) is an emerging, resourceful way forward to improve HTS of dermal exposure to cosmetics (Chevillotte et al., 2014). Additionally, as cosmetics may be intentionally formulated with specific properties to enhance or inhibit skin permeation, industrial knowledge may bring significant benefits to modeling improvements. The *PiF*-based framework presented in this study (Table 1) offers a novel and critical advancement to LCIA and HTS by building on accessible dermal exposure research, and offers a flexible framework which may be updated to account for improvements in dermal research, e.g. improved estimates of mass transfers in cosmetic mixtures.

4.2 Implications and future work

In this study, mass balance models enabled connecting, quantifying and comparing near- and far-field contributions to the product intake fraction (*PiF*) (Jolliet et al., 2015). The *PiF* framework is compatible with the *iF*-based framework established within the LCIA step of LCA. An example application in LCA is detailed in SI Section S5. The results of the shampoo case study corroborated the intuition that exposure during use of a cosmetic usually exceeds environmental exposures to post-use emissions of the product, at least for product users, and justifies including use stage exposure in LCIA of cosmetic products. Furthermore,

results demonstrated the importance of bridging, and simultaneously considering, multi-pathway exposures on a mass balance basis, as inhalation during use dominated over dermal intake for 20% of chemicals in the extended shampoo case study, and post-use far-field exposures can be comparable to exposure during use for chemicals with low permeation coefficients and high washed-off fractions. Such observations are a direct consequence of mechanistic consideration of physicochemical properties within the models and their connection on a mass balance basis. The chemicals considered in this study had a range of functions including fragrances, surfactants, and preservatives and physicochemical properties, but they cover only a fraction (<20%) of chemicals known to occur in shampoo (Dionisio et al., 2015). Complementary studies are therefore needed to systematically investigate the role of physicochemical properties in determining the magnitude of various exposure pathways, and emission magnitudes. SI Section S5 illustrates in a proof of concept case study how our models can be integrated and applied in an LCIA framework. It also shows that accounting for volatilization of volatile substances can lower the estimated ecotoxicity impacts by orders of magnitude when compared to the common conservative assumption of 100% washed-off to freshwater after use. With consideration of the limitations and strengths, the presented framework is deemed best applicable for future assessments that aim to compare relative magnitudes of population-scale chemical intakes, e.g. in LCA to support estimation of impact trade-offs or in HTS of exposures to prioritize chemicals and product combinations of concern.

Some of the greatest limitations to HTS and LCIA of cosmetics are data availability, both for model development and validation and uncertainty. Fortunately, recent works have focused on compiling lists of chemicals in cosmetics and consumer products (Dionisio et al., 2015), concentrations in cosmetics (Goldsmith et al., 2014), and cosmetic use patterns

(Comiskey et al., 2015) making HTS of exposures increasingly feasible. Despite efforts to estimate exposure, LCIA and risk-based HTS remain limited by the number of chemicals that have compiled toxicity information underscoring the importance of complementary research on high-throughput assays of bioactivity (Wetmore et al., 2015) and also implies an urgent need to mandate publically funded “open-access” platforms with toxicity information, such as TOXNET (<http://toxnet.nlm.nih.gov/>) and REACH dossiers (<http://echa.europa.eu/>), to be offered in more usable forms (e.g. spreadsheets).

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Supporting Information Available

Supporting information includes detailed equations, supplementary results, and a supplementary spreadsheet with all calculations as well as *in vitro* skin permeation data.

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