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High-throughput exposure modeling to support prioritization of chemicals in personal care products

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HIGHLIGHTS

- A high-throughput (HT) exposure model for personal care products is presented.
- Exposure is modeled using the product intake fraction and product chemical content.
- The model is demonstrated for hundreds of chemicals in PCPs.
- Intakes depend on chemical and product properties and span orders of magnitude.
- Intakes were combined with HT toxicity data to demonstrate risk screening.

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ABSTRACT

We demonstrate the application of a high-throughput modeling framework to estimate exposure to chemicals used in personal care products (PCPs). As a basis for estimating exposure, we use the product intake fraction (PiF), defined as the mass of chemical taken by an individual or population per mass of a given chemical used in a product. We calculated use- and disposal- stage PiFs for 518 chemicals for five PCP archetypes. Across all product archetypes the use- and disposal- stage PiFs ranged from 10^{-5} to 1 and 0 to 10^{-3}, respectively. There is a distinction between the use-stage PiF for leave-on and wash-off products which had median PiFs of 0.5 and 0.02 across the 518 chemicals, respectively. The PiF is a function of product characteristics and physico-chemical properties and is maximized when skin permeability is high and volatility is low such that there is no competition between skin and air losses from the applied product. PCP chemical contents (i.e. concentrations) were available for 325 chemicals and were combined with PCP usage characteristics and PiF yielding intakes summed across a demonstrative set of products ranging from 10^{-8}–30 mg/kg/d, with a median of 0.1 mg/kg/d. The highest intakes were associated with body lotion. Bioactive doses derived from high-throughput *in vitro* toxicity data were combined with the estimated PiFs to demonstrate an approach to estimate bioactive equivalent chemical content and to screen chemicals for risk.

1. Introduction

There are potentially thousands of chemicals used in personal care products (PCP) and cosmetics (Egeghy et al., 2011) and estimating exposure to all these chemicals is not possible based on empirical techniques alone. Biomonitoring data, for example, are only available for a subset of compounds through programs such as NHANES (CDC, 2009) in the United States. Computational exposure models can be used to estimate chemical intake due to the use of

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PCPs based on physico-chemical properties, product composition, and product usage characteristics for chemicals in the absence of emperical data.

There are several examples of high-throughput (HT) exposure models for chemical prioritization and screening (Wambaugh et al., 2013; Isaacs et al., 2014; Shin et al., 2015). These HT exposure estimates are being combined with HT screening toxicity data, for example *in vitro* bioactivities from the U.S. EPA ToxCast program (Kavlock et al., 2012), to screen and prioritize chemicals for risk (Cohen Hubal, 2010; Shin et al., 2015; Wetmore et al., 2015). These efforts have highlighted the need to better understand chemical exposure from consumer products (Wambaugh et al., 2013, 2014; Shin et al., 2015). PCPs are a product class for which emperical studies have found that usage is correlated with chemical exposures (Sandanger et al., 2011; Parlett et al., 2013).

Jolliet et al. (2015) have proposed the *product intake fraction* (PiF) metric to quantity the amount of chemical taken in by the exposed population per mass of chemical used in a consumer product. Shin et al. (2015) combined the PiF with chemical production volumes (PVs) to estimate dermal exposure to chemicals in PCPs using body lotion as a sentinel product. PVs, however, do not inform what proportion of the PV is used in any given product type or process nor on how many members of the population use a given chemical (Nazaroff et al., 2012; Shin et al., 2015). Dudzina et al. (2015) modeled route specific exposure fractions to PCP chemicals, however, this method was applied to a single chemical and has yet to be applied to several PCP chemicals at once. Recently, Csiszar et al. (2016) applied the PiF to estimate dermal and inhalation exposure to parabens in several PCP types using chemical fractional content (i.e., concentrations) with exposure estimates which compared well to biomonitoring data. The PiF can also be used to estimate environmentally mediated exposures to post-use emissions (referred to as disposal-stage) (Jolliet et al., 2015) although this has also yet to be performed in an HT study.

In this paper, we combine PiFs with product usage and fractional chemical content data to develop an HT exposure and risk screening approach to estimate use- and disposal-stage exposures to hundreds of PCP-chemical combinations. The goals of this study are to: (i) demonstrate the use of PiF to estimate exposure to hundreds of PCP chemicals, (ii) understand chemical and product specific factors affecting PiF, and (iii) within a risk screening context, use bioactive doses derived from *in vitro* screening toxicity data (Wetmore et al., 2012, 2015) to demonstrate how bioactive chemical contents can be back-calculated and compared with actual chemical contents being used in PCPs (Goldsmith et al., 2014).

2. Methods

2.1. Product intake fraction for PCPs

We considered four exposure pathways for calculating PiF due to the application of PCPs to the skin. Dermal aqueous uptake ($PiF^{derm,aq}$), inhalation ($PiF^{use,inh}$), and dermal gaseous uptake ($PiF^{derm,g}$), comprise the use-stage PiF and can be summed as $PiF^{use,tot}$. The fourth pathway is an aggregated intake via outdoor environmental exposure pathways (PiF^{disp}). The sum of all four pathways is PiF^{tot}. Following Csiszar et al. (2016) and Ernstoff et al. (2016) for a product that is applied to skin, a mass-balance can be analytically solved to calculate the fraction of chemical lost from the product via transfer into the skin or volatilization to air (f^{volat}). The fraction that is transferred to skin from the product is also the fraction of dermal aqueous uptake, i.e. $PiF^{derm,aq}$ and the solution is

$$PiF^{derm,aq} = \frac{k_{ps}}{k_{ps}+k_{pa}}\left(1-e^{-(k_{ps}+k_{pa})\,t}\right);\ f^{volat} = \frac{k_{pa}}{k_{ps}+k_{pa}}\left(1-e^{-(k_{ps}+k_{pa})\,t}\right) \quad (1)$$

where k_{ps} and k_{pa} are the product-to-skin and product-to-air transfer rates (h^{-1}), respectively, and t is the application duration (h) (see Supplementary Information (SI) for more information). The k_{ps} is a function of the aqueous skin permeation coefficient, K_p^{aq} (m/h) which was calculated using the relationship of ten Berge (2009) based on molecular weight (MW) and octanol-water partition coefficient (K_{ow}). The k_{pa} is a function of air-water mass transfer coefficient and depends on the air-water partition coefficient, K_{aw}. The fraction of chemical that volatilizes to air becomes available for inhalation and gaseous dermal uptake and transfer to outdoor air. We assumed that chemicals volatilize to a near-person area of 1 m^3 (Isaacs et al., 2014) and then transfers to a larger well-mixed indoor air compartment. After the exposure duration, t, the fraction of chemical remaining in the applied product (i.e., on the skin surface) is assumed to be washed down the drain to a waste water treatment plant (WWTP) resulting in subsequent fractions emitted to air, water, and soil. To estimate PiF^{disp} we multiplied the emission fractions to WWTPs and outdoor air with their respective outdoor mediated intake fractions (mass of chemical taken in per mass of chemical emitted) for release to air, water, and soil calculated using the USEtox model (Rosenbaum et al., 2008). These processes are summarized in Fig. S1 and equations are listed in Tables S1 and S2 in the SI.

Product and exposure characteristics (i.e., irrespective of chemical properties) which determine the PiF include product use duration, product thickness, room ventilation rates, inhalation rates, and surface area of skin in contact with air (Csiszar et al., 2016). Product characteristics were grouped into five different product archetypes: 'leave-on'; 'leave-on, spray'; 'shampoo'; 'body wash'; 'face wash'; with distinguishing parameters summarized in Table S3 and based on Csiszar et al. (2016). Incidental ingestion, for example, from hand-to-mouth contact can also be an exposure pathway for PCP chemicals. We did not model this pathway for most products since we assumed that it was negligible for wash-off products and small compared to dermal uptake for leave-on products. This pathway is likely most important for products with lip application. To address this, we included a 1% ingestion of product irrespective of chemical properties (Isaacs et al., 2014) and the remaining 99% treated as the 'leave-on' archetype. This method or more elaborate hand to mouth models based on contact frequency could also be used to include incidental ingestion for other product types, especially for chemicals which have small PiFs for the other considered pathways.

2.2. Intake and risk screening

The PiF can be combined with chemical content and product use information to estimate chemical intakes following Csiszar et al. (2016). The intake (mg/kg/d) of a chemical, c, due to the use of a single PCP, p, can be calculated as

$$I_{c,p} = \frac{P_p f_{c,p} PiF_{c,p}^{tot}}{BW} \quad (2)$$

where P_p is the mass of product p used per person per day (mg/d), $f_{c,p}$ is the fractional chemical content in a given product, and BW (kg) is body weight. In this paper, aggregate PCP exposure to one chemical refers to the sum of intakes across the eleven products types that chemical was found to be used in (referred to as relevant