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Predicting transdermal uptake of phthalates and a paraben from cosmetic cream using the measured fugacity

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Abstract

Transdermal uptake models compliment in vitro and in vivo experiments in assessing risk of environmental exposures to semi-volatile organic compounds (SVOCs). A key parameter for mechanistic models is a chemical driving force for mass transfer from environmental media to human skin. In this research, we measure this driving force in the form of fugacity for chemicals in cosmetic cream and use it to model uptake from cosmetics as a surrogate for condensed environmental media. A simple cosmetic cream, containing no target analytes, was mixed with diethylphthalate (DEP), di-n-butylphthalate (DnBP), and butyl paraben (BP) and diluted to make creams with concentrations ranging from 0.025% to 6%. The fugacity, relative to the pure compound, was measured using solid-phase micro extraction (SPME). We found that the relationship between the concentration and fugacity is highly non-linear. The relative fugacity of

the chemicals for a 2% w/w formulation was used in a diffusion-based model to predict transdermal uptake of each chemical and compared with excretion data from a prior human subject study with the same formulation. Dynamic simulations of excretion are generally consistent with the results of the human subject experiment but sensitive to the input parameters, especially the time between cream application and showering.

TOC Art

KEYWORDS

Dermal uptake, cosmetics, Chemical activity, Exposure model, Skin, Personal care products

1. Introduction

Many semi-volatile organic compounds (SVOCs) we encounter in indoor environments are suspected, predicted, or confirmed endocrine disruptors^{1,2} and belong to classes of compounds used as pesticides, plasticizers and flame retardants. Sources include building materials, cleaning agents, pest control agents and personal care products.³⁻⁵ Recent studies suggest that transdermal uptake of indoor SVOCs can be comparable to or greater than intake associated with inhalation^{4,6} or other exposure pathways. However, the dermal pathway is relatively poorly characterized for contaminants of indoor origin. Therefore, validated, quantitative methods to directly assess or predict exposure to these species are needed.

To assess individual and population dermal exposure to SVOCs present in our environment, a variety of in vitro and in vivo methods have been developed.⁷⁻¹¹ Transdermal uptake models compliment in vitro and in vivo experiments in assessing risk of environmental exposure and dose. Modeling is a particularly powerful tool if the models are representative and model parameters are

well-characterized. Transdermal exposure models often make predictions based on available information such as contact frequency, concentration of SVOCs in media, contact area and duration, and transfer efficiency or fractional dose. While semi-empirical approaches such as these can be rapidly and widely applied to many exposure scenarios, they are often limited by the need to derive media-specific parameters such as transfer efficiency or permeability. Chemical activity based mechanistic exposure models often require less information about the source media. They instead rely on a measure or estimate of a chemical activity gradient, or fugacity gradient, that acts as the driving force controlling transfer from sources to occupant.

The fugacity is a powerful concept that has been used to characterize contaminant transport among many disciplines. The fugacity can be regarded as the partial pressure (Pa) exerted by a compound within a medium on the surrounding environment and is a convenient measure of chemical activity when referenced to the pure compound. The steady state permeation rate for a membrane such as skin is proportional to the fugacity gradient across that membrane.¹² Fugacity affects both the direction of diffusion and the rate of diffusion.^{13–15} Net transfer continues from regions of higher fugacity to regions of lower fugacity until a condition of equal fugacity, or equilibrium, is achieved. The concept of fugacity has long been used in the field of chemical engineering in designing processes such as distillation, gas absorption, solvent extraction, etc.^{15–20} The importance of fugacity as an index of toxicity was later discussed by Ferguson.²¹ Mackay²² expanded on the concept of fugacity in mass transfer models in environmental exposure studies. From then, fugacity has been used extensively for modeling the transfer of chemicals among environmental media and across biological membranes in environmental toxicology and risk assessment.^{23–41}

There are relatively few controlled human subject experiments that provide direct, quantitative, measurements of transdermal uptake from environmental compartments that provide sufficient information to allow for testing of fugacity based models. Some examples include transdermal uptake of SVOCs from air and clothing^{6,42–44} and halogenated organics from water during bathing and swimming.⁴⁵ Fortunately, there are excellent experiments in the cosmetics literature that can be used as a proxy for contact with condensed environmental media.^{7–10} These experiments include large numbers of human subjects, application of cosmetic products over large areas of the body and measurements of urine and blood concentrations of target chemicals and their metabolites. They also provide sufficient information about the composition of the cosmetic product so that product

can be reproduced and the fugacity can be measured. From this measurement, we can determine if the fugacity, in combination with mechanistic models, can reproduce the human subject experimental results.

Personal care products (PCPs) are an important source of chemical exposure in the home microenvironment. Dermal exposure to multiple endocrine disrupting chemicals (EDCs) through daily application of lotions and creams is of concern.^{10,11,46–51} Sakhi et al.⁵² detected eleven different metabolites of phthalates (a group of SVOCs) commonly used in personal care products in urine samples of Norwegian mothers and children. They observed diurnally elevated concentrations of urinary EDC biomarkers, which can be due to morning and evening use of personal care products. This kind of diurnal pattern of metabolite concentrations in urine, an indirect measure of exposure to EDCs from use of PCPs, has been observed in other studies.^{53,54} Janjua et al.^{8,9} experimentally confirmed such an association with human subjects. They monitored transdermal uptake of diethyl phthalate (DEP), dibutyl phthalate (DnBP) and butyl paraben (BP) from dosed creams during whole-body topical application on a daily basis for a week on 26 male subjects that acted as their own controls. They observed a significant increase in urine and plasma concentrations of metabolites for all the chemicals after application of the dosed cream.⁹ A analogous study was conducted for chemical UV filters known to be used in sunscreens,¹⁰ with similar results.

Predicting the fugacity of PCPs can be challenging because, like many other environmental media, PCP formulations can be quite complex. These mixtures or emulsions can be comprised of water, oils, salts, polymers, solids and nanoparticles.^{55–58} Given the complexity and sometimes high concentrations of target SVOCs, the mixtures may exhibit non-ideal behaviour and it may not (currently) be possible to predict the chemical activity or fugacity from the composition. Therefore, an independent measure of fugacity is valuable as media-independent input for mechanistic models.

Our goal in this research is to demonstrate the applicability of using the directly-measured relative fugacity as input to models of transdermal uptake of chemicals from complex environmental media such as personal care products. Specific objectives include 1) measure fugacities of the three target chemicals in the cosmetic cream formulation used in Janjua human subject study^{8,9} 2) assess the

linearity of fugacity with respect to the concentration of chemicals in the cream mixtures, 3) use the measured fugacities to predict transdermal uptake of the chemicals using an existing model⁵⁹ and 4) compare the predicted transdermal uptakes to Janjua human subject excretion data.⁹

2. Materials and Methods

2.1. Materials

WELLSKIN Glaxal Base (identical to the base cream used in the human subject studies by Janjua et al.^{8,9}) was purchased through Amazon. Ingredients as reported on its label are water, petrolatum, cetearyl alcohol, paraffinum liquidum, cereareth-20, sodium phosphate and p-chloro-m-cresol. Diethyl phthalate (DEP), di-n-butyl phthalate (DnBP) and butyl paraben (BP) with purity of 99% were purchased from Sigma-Aldrich. Screw cap clear glass vials (20 ml) and screw caps with 18 mm PTFE coated silicone septa were obtained from SUPELCO, USA. A 7 μ m polydimethylsiloxane (PDMS) SPME fiber (fused silica, 23 Ga, green) was obtained from SUPELCO for SPME analysis of cream samples.

2.2. Cream preparation

Four different initial stock mixtures were prepared as follows: 6% (w/w) DEP in Glaxal Base, 6% DnBP in Glaxal Base, 6% BP in Glaxal Base (single-component creams), and 6% each of DEP, DnBP, and BP combined in Glaxal Base (three-component creams). Once the compounds were added to the Glaxal Base, the creams were manually stirred for 2 minutes, 3-5 times a day for one week, using a glass rod. At this time, we observed that mixture appeared (visually) to be uniform and we considered each mixture to be fully mixed. We also checked the headspace SPME peak area (see method in section 2.3) of three separate samples of each cream mixture to ensure that the signal was the similar across these samples before making dilutions. Each of four stock creams were sequentially diluted by factors of three, for final concentrations that ranged from 0.025% to 6%. Of these, the 2% three-component cream formula was identical to the one used in Janjua human subject study.^{8,9} Between 0.5 to 0.6 gram of each diluted cream was added to a 20 ml glass vial that was then be sealed with a septa cap (triplicate of each concentration). Before being capped, the mixture was spread over the entire inner surface of the headspace vial (excluding neck and cap) using a glass stir rod to increase the exposed surface area of the mixture. This reduces

variability in subsequent SPME sampling and reduces the time required for the cream mixture and the air in the vial to reach equilibrium.

A vial of pure, unaltered base cream was prepared as a blank. Vials of pure DEP, DnBP and BP were also prepared as fugacity references. To do this, a small volume of DEP and DnBP – enough to coat the walls of the vial – were transferred to headspace vials. For BP, which is solid at room temperature, about 0.5 g was added to a headspace vial, capped, and heated until it melted. The inner walls were coated with melted BP and then allowed to cool so that a thin layer of solid BP coated the inner surface of the vial.

2.3. Relative fugacity measurement

Vapor-liquid phase equilibrium data have been commonly used to estimate fugacity of a compound in a substrate.^{60,61} SPME (our chosen method) has been used for equilibrium sampling and chemical activity measuring of environmental media in environmental toxicology and exposure studies.^{62–68}

An Agilent Technologies 7890A gas chromatograph with a flame ionization detector (GC-FID) system was used for headspace sample analysis. The GC column was a 30 m HP-5 5% Phenyl Methyl Siloxane capillary (30 m × 320 µm inner diameter × 0.25 µm film thickness). The sample, via the SPME fiber, was injected to the GC inlet at a temperature of 260 °C and in splitless mode. The carrier gas was nitrogen at a pressure of 6 psi and a total flowrate of 50 ml/min. The initial oven temperature was 40 °C, held for 1 min, then raised to 180 °C at 15 °/min, held for 3 minutes, then raised to a final temperature of 220 °C at 5 °C/min for the total GC run of 26.3 min.

Automatic SPME headspace sampling of the vials was carried out at 32 °C using a 7 µm PDMS SPME fiber (fused silica, 23 Ga, green, suitable for extraction of SVOCs). The GC was equipped with a Combi PAL auto sampler and all the steps of incubating, sampling, and injecting to GC were performed automatically. The autosampler was programmed for 30 minute incubation period of 32 °C. After testing different extraction times (SPME headspace sampling times) that ranged from 7 to 60 minutes, a method was developed using a 14 minute extraction time and 7 minute SPME desorption time. The headspace extraction time was chosen to result in sufficient sensitivity and also maintain the system in the linear, kinetically limited absorption range; i.e. not an

equilibrium measurement. This was chosen because we anticipated that the target compounds were present at a large fraction of their saturation concentration (in air and mixtures), and therefore, there was a risk of non-linear absorption into the SPME coating. Similarly, a PDMS coating was chosen because it operates primarily by absorption, which exhibits more linear partitioning behavior at high-concentration conditions than coatings that are adsorptive. In determining the GC desorption time, we performed repeated injections of the same fiber to experimentally confirm that there was minimal carry-over (less than the limit of detection) of analytes to the following sample. The measured relative fugacity of species i , $\hat{F}_i$, is defined as the GC-FID peak area for the cream headspace sample, $FID_{cream,i}$, divided by the headspace peak area for the pure compound, $FID_{pure,i}$. The fugacity is then defined as $\hat{F}_i$ multiplied by the vapor pressure of the pure liquid species i , $P_{v,i}$ (Pa), at that temperature. In the cream mixture, the *liquid* vapor pressure is necessary to calculate relative fugacity. Since BP is a solid at 32 °C, the relative fugacity is corrected by the ratio of the predicted liquid and solid phase vapor pressures, $P_{v,BP,liquid}$ and $P_{v,BP,solid}$:

$$\hat{F}_{BP} = \left(\frac{FID_{cream,BP}}{FID_{pure,BP}} \right) \left(\frac{P_{v,BP,solid}}{P_{v,BP,liquid}} \right) \quad (1)$$

where⁶⁹,

$$\frac{P_{v,BP,solid}}{P_{v,BP,liquid}} = -\frac{\Delta H_{fus}}{RT_{mp}} \left(1 - \frac{T_{mp}}{T} \right) \quad (2)$$

R is the gas constant (8.314 J/mol K), and the enthalpy of fusion, ΔH_{fus} (26.3 kJ/mol) and melting point temperature T_{mp} (340K) are taken from Umnahant & Chickos.⁷⁰

2.4. Relative fugacity based on Raoult's law

We also compared the results to predictions resulting from the application of Raoult's law. We applied Raoult's law to predict the relative fugacity, $\hat{F}_{R,i}$, of the active chemicals assuming a well-mixed mixture of the three compounds in the oily medium where there is no phase separation among the organic/oily components and the activity coefficient is 1. The oily fraction of the cream was assumed to be 0.35 by weight, based on the mass change after drying the base cream in an oven (~60 °C). We also assumed no partitioning of the compounds into the water phase and that the oily component of the cream is "petrolatum" or "trimethylbenzen[e]indole" with a molecular

weight of 209 g/mol. The relative fugacity based on Raoult's law is given by the mole fraction of chemical in a mixture containing equal masses of DEP, DnBP, BP and petrolatum while the mass of cream change :

$$\dot{F}_{R,i} = \frac{M_i/MW_i}{0.35 * M_{cream}/MW_{petrolatum} + M_{DEP}/MW_{DEP} + M_{DnBP}/MW_{DnBP} + M_{BP}/MW_{BP}} \quad (3)$$

where M_i is the mass of each component in the mixture and MW_i is the molecular weight for subscripted species (g/mol).

2.5. Quality Assurance/Quality Control (QA/QC)

Only glass dishes, rods, and vials were used in all steps of sample preparation, mixing, and storage. All of the glassware was washed and rinsed with methanol then dried in an oven at 150 °C prior to use. The headspace was sampled using the same PDMS fiber throughout the experiments. The SPME fiber was baked two to three times prior to headspace sampling. Vials of pure DEP, DnBP, and BP were analyzed as SPME headspace references and as a regular check of the instrument sensitivity. Analytical blanks were analyzed at the beginning and during the experiment (between samples) to check for contamination and carry-over. No target compounds were observed in headspace analysis of the undosed cream. Blank analysis showed no carry-over at low or mid concentrations but there was a maximum carry-over of 0.45% of the prior injection of a high-concentration DEP sample. Triplicate samples of each concentrations were prepared for headspace SPME analysis. The limit of detection (LOD) and limit of quantification (LOQ) were determined based on the average and standard deviation of replicates of blank samples. In order to calculate LOD and LOQ, we converted the SPME signals to headspace concentration using the measurement-based vapor pressure (see

Table 2) and the peak area of headspace samples over the pure compounds. Method LODs of 10, 11, and 21 µg/m³ and LOQs of 20, 22, and 50 µg/m³ were obtained for headspace gas concentrations of DEP, DnBP, and BP, respectively. All concentrations of DEP and DnBP in both single compound creams and mixture had signals higher than the LOD. The two lowest concentrations of BP (0.025 and 0.074 %W/W) in both single compound creams and mixture had signals lower than the LOD.

2.6. Simulations of transdermal uptake from applied creams

2.6.1. Basis of simulation: human subject experiments by Janjua et al.⁹

In the human subject study by Janjua et al.,⁹ 26 caucasian male participants were given a whole-body treatment of a cream containing 2% (w/w) of DEP, DnBP and BP once a day for 5 days. The applied coverage was 2 mg/cm² of cream and the average treatment area per subject was 2 m². They were told they could shower after 4 hours but the time interval between application and showering was not recorded. All urine was collected and analyzed for metabolites of DEP (mono-ethyl phthalate, MEP), DnBP (mono-butyl phthalate, MnBP) and BP. These compounds are present in urine in both free and conjugated forms (conjugation converts lipophilic compounds to hydrophilic compounds which are more readily excreted) and samples were therefore treated (deconjugated) to maximize quantification of uptake via excreted total mass. The average 24-h clearance of free and unconjugated metabolites in urine voids on the last day was 41.5 mg, 12.5 mg and 2.7 mg for MEP, MnBP and BP respectively.

2.6.2. Model framework

The model by Morrison et al.⁵⁹ was applied to simulate transdermal uptake of DEP, DnBP and BP in human subjects described by Janjua et al.⁹ The simulation is applied to a “typical” subject, with cream application in the morning, a shower later in the day (timing is varied in the simulation as described below) and repeated for 5 days. Details of the parameters used in the model and the simulation schedule are found in Supporting Information.

Morrison’s model simulates dynamic transdermal uptake of chemicals assuming Fickian diffusion through distinct physical layers of skin (skin lipids, stratum corneum, and viable epidermis). In this study, skin lipids were assumed to mix into the cream and the cream replaced the “skin oil” layer in the Morrison et al. model.⁵⁹ More detail on the model framework and the equations applied can be found in Supporting Information. To directly use the measured fugacity in the model, we assume the cream composition does not change upon whole-body application (due to immediate evaporation of volatile ingredients or target compounds mixing with skin oil or sweat). However, we do account for changes in the composition that are the result of absorption and evaporation of target compounds. We also assume that the target compounds are at equilibrium throughout the cream. This means that the chemical activity in different phases of an emulsion (if any) are equal

and that the fugacity at the cream-skin interface is the same as that measured in vitro. The model framework is equivalent to that of Cleek & Bunge⁷¹ except that the compounds in the cream can volatilize to air or transfer to clothing. The measured relative fugacity, and that predicted by Raoult's law, of each chemical combined with the vapor pressure of the chemical at the temperature of skin (see Model Parameters for values) was used to calculate the near skin gas phase concentration of the chemical ($C_{g,i}$).

$$C_{g,i} = \frac{\dot{F}_i P_{v,i} MW_i}{RT} \quad (4)$$

where, MW_i is the molecular weight of species i . Octanol/air partition coefficient of the chemical was used to relate the $C_{g,i}$ to concentration of the chemical in skin lipids. After a subject showers, the cream layer is set to a skin lipid layer of a defined thickness and the concentration of the target chemical in this layer is set to zero. This skin lipid layer is allowed to equilibrate with the top layer of the stratum corneum (SC) as well as the overlying air in the manner outlined Morrison et al.⁵⁹ That is, in the first time-step after a shower, the lipid layer concentration is set to zero, but the concentration in the adjacent stratum corneum layer is not equal to zero. At the next time step, the lipid layer accumulates chemicals from the stratum corneum to achieve equilibrium and also equilibrates with the overlying air. For each chemical, the initial equilibrium air concentration, adjacent to the cream, was calculated by multiplying the vapour pressure of the chemical by its relative fugacity in the 2% mixture and converting to appropriate concentration units. In this model, we assume that absorbed DEP, DnBP, and BP are rapidly metabolized; metabolites accumulate in urine and are excreted with each urination. The model uses available experimental toxicokinetic factors to compare the simulated excreted mass to the measured excreted mass of Janjua human subject experiment data over the same time period. To make this comparison, we apply toxicokinetic parameters determined by single oral dose methods for BP⁷² and DnBP⁷³ for different modes of action such as hydrolyzation, oxidation and/or conjugation. Assuming that the metabolism of DEP is similar to that of DnBP, we set the DEP excretion fraction equal to that for DnBP. Specifically, the amount of BP, MnBP and MEP excreted is equal to 0.056, 0.84 and 0.84 times the amount of BP, DnBP and DEP absorbed in the simulation, respectively. The model was solved using a finite-difference approach in Microsoft Excel.

2.6.3. Model parameters

Simulations are run for 120 hours starting with the whole-body cream application on the first day and a shower later in the day; cream application and showering are repeated for 5 days to match Janjua human subject study. Participants of the whole-body topical application in Janjua study were asked to shower no sooner than 4 hours after the experiment, but the actual time between application and showering was not recorded.⁹ Since the participants were treated at the same time each day, we assumed a maximum of 20 hours between treatment and showering. Therefore, we set the minimum and maximum time interval between application and showering to 4 and 20 h, respectively, and assigned a base-case value of 8 hours (8-hour scenario).

Base-case skin penetration parameters (see Table 2) required for the model were calculated based on the analyses and parameters discussed by Gong et al.⁷⁴ and Morrison et al.⁵⁹ Basic chemical-physical properties of DEP, DnBP, and BP at 32°C (such as molecular weight (g/mol), density (g/cm³), molar volume (cm³/mol), and Henry's constant (H_{cp} , atm m³/mol)) were obtained from SPARC online calculator (

Table 1) and were used to calculate other transdermal uptake model input parameters as follows (See Supporting Information). The stratum corneum/air partition coefficient (K_{sc-g}) for the partially hydrated condition was based on previous methods,^{3,74,75} which primarily use the octanol/water partition coefficient (K_{ow}) and Henry's law constant (H_{cp}) as input parameters. Equations derived by Wang et al.⁷⁶ were used to calculate the effective diffusion coefficient in partially hydrated stratum corneum (D_{sc} , m²/s). Equations in Appendix D of Dancik et al.⁷⁷ were used to estimate effective diffusion coefficients of chemicals in the viable epidermis (D_{ve} , m²/s) and the viable epidermis/water partition coefficient (K_{ve-w}) and, finally, viable epidermis/air partition coefficient (K_{ve-g}). The stratum corneum's thickness (L_{sc}) of 23 μm and viable epidermis's thickness (L_{ve}) of 100 μm were chosen based on the average skin layers' thicknesses measured and discussed in previous papers.^{59,71,74,78-82} Discussion of the vapor pressure (P_v) is found in the the Supporting Information. A screenshot of the spreadsheet which was prepared for calculation of the transdermal

uptake model input parameters is also found in the Supporting Information. The spreadsheet is available from the authors upon request.

Table 1 Chemical-physical properties of DEP, DnBP, and BP at 32°C (303.15 K)

compound	CAS	MW (g/mol)	Density (g/cm ³)	Volume (cm ³ /mol)	log (K _{ow})	Hcp Pa m ³ /mol	P_v Pa
DEP	84-66-2	222.2	1.13	197.3	2.55	8.83×10^{-3}	0.210
DnBP	84-74-2	278.3	1.05	266.1	4.56	2.49×10^{-2}	0.012
BP	94-26-8	194.2	1.08	179.7	3.39	8.05×10^{-3}	0.0036*

*Vapor pressure of pure *solid* BP

Table 2 Base-case and derived transdermal uptake model parameters at 32°C a

compound	L_{sc} (μm)	L_{ve} (μm)	$K_{ve/w}$	$K_{ssl/g}$	$K_{sc/g}$	$K_{ve/g}$	D_{sc} m ² /s	D_{ve} m ² /s	h_m m/h
DEP	23	100	2.19	1.0×10^8	7.1×10^6	6.3×10^5	2.4×10^{-15}	6.2×10^{-11}	25
DnBP	23	100	32.6	3.7×10^9	2.7×10^7	3.3×10^6	4.0×10^{-15}	6.4×10^{-12}	25
BP	23	100	5.25	7.7×10^8	1.8×10^7	1.7×10^6	8.3×10^{-15}	3.2×10^{-11}	25

^a Method details and all other supporting parameters can be found in Supporting Information

The average body surface area of 2 m² was obtained from Janjua human subject study.⁹ The cream thickness of 20 μm was calculated based on the mass of cream which was used in Janjua human subject study for each participant and the assumption of cream density equal to 1 g/cm³. The skin lipid thickness, after showering, is set to 1.2 μm . The gas-side mass transfer coefficient, h_m , was set to 25 m/h, reflecting a high value associated with wearing clothing after application of the cream.⁸² We do not consider transfer of cream to clothing. If some of the cream has transferred to clothing, it is still “near” the skin and we assume it is effectively “on” the skin. However, ignoring transfer onto clothing could result in an overestimate of transdermal uptake, since there may be an increased mass-transfer resistance between cream (on clothing) and the stratum corneum.

2.6.4. Conversion and plotting of human subject data and model output

To make a direct comparison of the Janjua human subject study⁹ to the model, the raw urine concentration results were converted to a mass-rate of excretion. Total excretion mass (free + unconjugated metabolite) per hour for each participant at each urine sample collection time is

$$\dot{M}_{total} = \frac{VC}{t} \quad (5)$$

where $\dot{M}_{total}$ is the total excretion mass per hour ($\mu\text{g/h}$), V is the urine sample volume (ml), C is the concentration of the metabolite of the chemical in the urine sample ($\mu\text{g/ml}$), and t is the time interval between the previous and current urine sample (h).

The urination time obtained from Janjua human subject study was used to plot minimum, mean $\pm$ standard deviation, and maximum of excretion rates for all subjects at each time point between 0 to 120 hours after the start of the experiment. Model excretion rate was calculated based on a urination frequency of every 5 hours during the first 24 h; after that, the model results are reported as 24h pooled urine samples to be consistent with Janjua human subject study.⁹ Modeled excretion rates of metabolites were adjusted by the toxicokinetic excretion ratios (see section 2.6.2) and molecular weights.

2.6.5. Sensitivity analysis

In addition to the base-case values (Table 2) the influence of stratum corneum thickness, shower time, skin temperature, vapor pressure, and partition coefficients were evaluated. The stratum corneum thickness (L_{sc}) not only varies with age, sex, skin health status (for example eczema), but also varies among different parts of the body and can depend on skin hydration. We used lower and upper values of 15 and 30 μm for L_{sc} .^{59,71,79,81} We also evaluated the effect of elapsed time between the cream application and showering (4-20 hours). Like the stratum corneum thickness, skin temperature also varies with sex, age, body mass index (BMI), percent of body fat (PBF), and skeletal muscle mass (SMM).^{83,84} Studies also have measured different skin temperatures for different parts of the body.⁸³ In addition to endogenous factors, skin temperature is influenced by the surrounding environment such as air temperature, wind, and humidity.⁸⁵ A wide range of skin temperatures have been observed for different body locations for female and male subjects at moderate and severe environmental

conditions.^{85–87} We chose a skin temperature range of 25–37 °C for the sensitivity analysis. To evaluate the influence of vapor pressure, we set the upper and lower bounds to be twice and half the model base-case values; respectively. To evaluate the influence of partition coefficients, we assumed half and double of the base-case partition coefficients, and we assumed diffusion coefficients vary inversely with the partition coefficients.⁵⁹

3. Results and Discussion

3.1. Headspace analysis of creams

Figure 1 visualizes the results of SPME headspace analysis of each single-component creams and three-component creams for DEP, DnBP, and BP. Results are reported as the peak area of the chemical in the mixture normalized by the peak area of the pure compound (relative fugacity, $\hat{F}_i$) vs the mass fraction of the compound in the mixture. In addition to the experimental data, each chemical's relative fugacity, as predicted by Raoult's law (Equation 3), has been added to each plot. This curve illustrates the relative fugacity of each compound assuming a homogeneous solution of the three compounds in the petrolatum of the cream. There are four main observations from these results. First, for either the single-component creams or three-component creams, the relative fugacity is greater than the weight fraction of the component in the cream. For example, $\hat{F}_i$ for a 2% (w/w) mixture is greater than 2% of the pure chemical's headspace peak area. For the single component mixtures, each at 2% by weight, $\hat{F}_i$ of DEP, DnBP, and BP are 0.72, 0.37, and 0.46, respectively. Second, for a given mass fraction in the cream, the relative fugacity of each chemical is greater in a single-component cream than in the three-component cream. For the three-component mixture, each at 2% by weight, $\hat{F}_i$ of DEP, DnBP, and BP are 0.33, 0.14, and 0.30; respectively. This suggest that the additional lipophilic mass fraction of the active ingredients (DEP+DnBP+BP) suppresses the vapor pressure of each compound. Third, these values are mostly greater than the relative fugacity based on an application of Raoult's law for mixtures of the three compounds in the oily medium of cream. The Raoult-based estimate approaches (or crosses) the measured results at the highest cream concentration. Extrapolating the data to the point where only the three chemicals are present (each representing 1/3 of the mixture without base cream), the fugacity appears to be reasonably predicted by Raoult's law (where the curve ends at the right side of the Figure 1). Finally, the relationship between relative fugacity and concentration is highly

non-linear. These results show that $\hat{F}_i$ in the cream may not be predicted solely from Raoult's law. It may be possible to apply Henry's law at the lower concentration range, as demonstrated recently for mixtures of oil soluble solutes in an oily medium.⁸⁸ However, the data in our study are insufficient to demonstrate linearity in the low concentration range. A version of Figure 1 with linear axes can be found in Supporting Information.

Figure 1. Measured relative fugacity, $\hat{F}_i$, (normalized SPME signals) vs. mass fraction of each chemical in single-component creams (○) and in three-component creams (●). The diamond symbol (◇) represents the result for the pure chemical without cream. Also shown is the relative fugacity prediction based on Raoult's law of the three chemicals in a well-mixed lipophilic fraction of the

cream (solid line). All BP results shown have been adjusted to account for the fact that the pure BP reference is solid at room temperature.

3.2. Model results

Figure 2 compares the results of excretion rates for each chemical from Janjua human subject data⁹ and the dynamic transdermal uptake simulation, using the base-case parameters (Table 2). Two simulations are shown for different time intervals between cream application and showering: an 8-h scenario and a 4-h scenario. Data from Janjua's human subject experiment is reported as the mean, plus-or-minus one standard deviation (SD), minimum and maximum. Dynamic simulations of excretion are qualitatively similar to the results of the human subject experiment. For the 8-h scenario, the simulated BP excretion rate after 1 day is within plus-or-minus one standard deviation of the human subject excretion rate. The simulated excretion rate for MEP and MnBP for the 8-h scenario is higher, but still within a factor of 3 of that for human subjects. The 8-h scenario simulations result in excretion rates that are almost twice that assuming a shorter, 4-h scenario; the amount absorbed and excreted is very sensitive to showering time. A comparison of the 24-h cumulative excretion after 120 h is shown in Figure S3 of Supporting Information for Janjua human subject experiment data, the model using measured relative fugacity and the model using the estimated relative fugacity based on Raoult's law (see section 2.4). The Raoult's law based predictions are closer to the human subject experiment than those based on measured fugacity for DEP and DnBP, but not BP (Supporting Information).

Similar to the results of Janjua human subject study, the simulation also predicts an increase in the excretion rate of MEP, MnBP and BP very soon after topical application. In both data obtained from the human experiment and in the simulation, the concentration of all chemicals peaked in urine 8-12 hours after whole-body application. Both the human experiment and simulation show higher absorption of DEP than the other two chemicals, which is consistent with its chemical properties.

Figure 2 Excretion rates of metabolites for a) BP-, b) DnBP and c) DEP. Shown in grey and black are the combined results from 26 human subjects in Janjua study.⁹ Grey shaded region represents $\pm$ one standard deviation. The blue solid line is the model output using an 8-h shower interval; the blue dashed line represents the model using a 4-h shower interval.

3.3. Cumulative urinary excretion: human experiment and model

Some insight into the differences between model analysis and human subject results can be obtained by comparing shapes of the dynamic cumulative uptake figures. Shown in Figure 3 is a comparison of the predicted and measured cumulative urinary excretion of metabolites for the first 24 h after the initial topical application. We only show the excretion data of the individuals with at least seven urinations during the first 24 h. The predicted cumulative urinary excretion is shown for elapsed times of 4, 8, and 20 h between the topical application and showering. Qualitatively, showering later lengthens the time over which cumulative uptake occurs, as anticipated. For a 4-h scenario, the accumulation begins to flatten out by about 8 to 12 h. For a 20-h scenario, uptake

431 increases during the whole period. Similar shapes can be discerned in the human subject data.
432 Early flattening of the curve, among all metabolites, for subject P9 may indicate an early shower.
433 The monotonic increase in excretion of MnBP and BP, exhibited by subject P22, may suggest a
434 late shower or poor removal of the cream during an earlier shower.

435 There is an inconsistency in the relative shapes of the modeled and measured curves. For MEP,
436 the cumulative excretion curves of the human subject flatten out sharply between 6 and 12 h. For
437 BP, this occurs later and less sharply. MnBP generally rises throughout the period with only a
438 modest flattening. These trends differ from those predicted by the model. It may be that during the
439 experiments the participants were more exposed to DnBP from additional sources compared with
440 DEP and BP. If this is not the case, this disagreement between measured and modeled results may
441 indicate that diffusivity predictions are inaccurate (even relative to one another). Diffusivity
442 predictions are further discussed in Section 3.4.

443 Another inconsistency is the lag time in the model compared to a fast increase in cumulative
444 urinary excretions of the human experiment data (mainly for MEP). This may be due to early
445 uptake through the hair follicles pathway resulting in a rapid rise of urinary metabolites; this
446 mechanism is also discussed in more detail in Section 3.4.

Figure 3 Estimated (graphs on left) and measured (graphs on right) cumulative urinary excretion of monoethyl phthalate (MEP), mono-n-butyl phthalate (MnBP), and butyl paraben (BP) within the first 24 h after the initial topical application of the cream.

3.4. Sensitivity analysis

To study the effects of model input uncertainties, Figure 4 compares the transdermal uptake model outputs (total steady state excretion mass) for a range of vapor pressure, shower times, stratum corneum thicknesses, and skin temperatures. The dashed lines show the total excretion mass of the chemicals using the base-case parameters. Figure 4 also compares the predictions with the range of excretion values of the 26 participants in Janjua study.⁹ The simulations for BP are consistent with the experimental results. For DEP and DnBP, use of base-case input parameters results in predictions that are greater than mean values from human subjects; however, use of a reasonable range of values (as defined in section 2.6.5) for vapor pressure, showering time, stratum corneum

thickness and skin temperature result in some predictions that are within the range of the human subject excretion mass for MnBP and MEP. Excretion mass is directly proportional, and therefore very sensitive, to the choice of vapor pressure.

Figure 4 Sensitivity of transdermal uptake model predictions of excretion mass to vapor pressure (P_v), showering time, stratum corneum thickness (L_{sc}) and skin temperature (Temp). For the Janjua human subject experiment, the line is the mean, the box is the upper and lower quartile (Q1 and Q3), and the whiskers are the maximum and minimum values.

The predicted excretion mass is also very sensitive to the time between cream application and showering, with the excretion mass increasing nearly linearly with the time before showering. The excretion mass of the chemicals using a stratum corneum thickness of $15\ \mu\text{m}$ is almost twice the mass using a thickness of $30\ \mu\text{m}$. Changing the partition coefficients did not result in significant changes in the model output (this is not shown in Figure 4); to be internally consistent with the methods used to determine skin parameters, doubling a partition coefficient results in halving the diffusivity, which in turn, results in a nearly constant permeability. However, changing the partition coefficient (e.g. K_{sc}) without altering the diffusivity, or vice versa, would strongly influence uptake. For example, doubling either K_{sc} or D_{sc} nearly doubles the mass absorbed.

Excretion mass increases with temperature, but only by a modest amount. In our model, this is because as temperature increases, the predicted chemical driving force (fugacity) increases while the stratum corneum-air partition coefficient, K_{sc-g} , decreases. For example, as temperature rises from 25 to $37\ ^\circ\text{C}$, the fugacity of DnBP increases by a factor of 4.8 but K_{sc-g} decreases by about a factor of 3.4 (see Table S3, S4, S5). There is a slight increase in diffusivity of DnBP: 3.91×10^{-15} to $4.11 \times 10^{-15}\ \text{m}^2/\text{s}$. In combination, the resulting steady-state flux increases by about 22%. This result may seem inconsistent with in-vitro studies that show permeability increasing with more substantially over the same temperature range.^{89–94} For many in-vitro studies, the permeability is based on the concentration in the vehicle at the saturation concentration of the permeant. Over a

small temperature range, the concentration in the vehicle only changes slightly, for hydrophobic compounds. As an example, Akomeah et al.⁹² observed that the saturation concentration of BP in an aqueous vehicle increased by about 20% from 23°C to 30°C. However, they do not account for the higher chemical activity or fugacity that would result at the higher temperature; we predict the fugacity of BP in their vehicle would have increased by nearly a factor of 3, accounting for much of the increase in observed permeability. That said, a major assumption in our model is that the relative fugacity of each component in the cream is not itself influenced by temperature; given the good match with Raoult's law for a high-concentration cream, this seems to be a reasonable assumption. But this assumption could also result in an over-prediction of fugacity for a complex solution at a lower temperature. Such qualitative differences in modeled vs experimental observations should be investigated more thoroughly.

Figure 2 shows that the dynamic simulations of excretion rate, that are based on fugacity measurements of cream, are qualitatively similar to the results for the human subjects, but are higher in magnitude for DEP and DnBP. The model, using base-case values, overestimated transdermal uptake of DEP and DnBP for even the human subject that had the highest apparent uptake (Figure 4). Quantitative deviations between the results of Janjua human subject experiment and our predictions may be due the model framework or, as demonstrated by the sensitivity analysis, the choice of parameters used to populate the model. In particular, vapor pressure and showering time are influential, but uncertain, variables. Further, we base our toxicokinetic factor on oral ingestion for all chemicals; better would be to apply a toxicokinetic factor based on skin absorption but this value has not, to our knowledge, been reported. We have no basis for setting upper and lower bounds on this value in the sensitivity analysis, but if the toxicokinetic factor is, for example, 20% lower for skin absorption than for oral ingestion, then the excretion rate would also be 20% lower since the excretion rate is linearly dependent on the toxicokinetic factor.

Skin temperature may have a bigger impact than we have shown. To estimate transdermal uptake of the active chemicals at different skin temperatures, we only rely on vapor pressure, diffusivities, and partition coefficients. In other words, we do not consider changes in the skin physiology such as changes in stratum corneum lipid structure and changes in effective diffusion length due to changes in skin temperature or skin hydration.^{95–97}

In our transdermal uptake estimation, we assumed the cream composition does not change as a result of the whole-body application and mixing with skin oil. This assumption allows us to use our measured fugacity directly in the model. Both the model and the Janjua human subject experiment⁹ show that only a small fraction of the compound are absorbed from the cream. This is considered a “high load” condition in which the load applied (mass per area) does not influence the rate of transdermal uptake. Increasing the amount of cream applied would not have increased metabolite excretion. Although we account for loss of target chemicals from the cream by absorption, the fact that the composition changes little, in a sense, simplifies the comparison because only fugacity and permeability are important. This is the advantage of using fugacity in transdermal uptake risk assessment over fixed absorption dose which depends on the load or mass amount of test chemical applied to the skin.^{98–100} It is possible that fugacity may change after application as, for example, water or other volatile ingredients evaporate from the applied cream. For the high-concentration cream used in Janjua et al.,⁹ this probably does not alter fugacity very much since gas-phase fugacity appears to be dominated by the fugacity of the three-component mixture, not the amount of base cream. However, as volatiles evaporate from a low-concentration cream, the active ingredients become more concentrated in the low-volatility oily components of the cream resulting in an altered, or perhaps even increased, fugacity. This suggests that future experiments should include in vivo measurement of fugacities after cream application to volunteer skin.

We also assumed that the target compounds are at equilibrium throughout the cream. If the cream is comprised of multiple phases (e.g. an emulsion) this may result in phase separation upon application to skin; more likely the oily components would preferentially mix with skin lipids. If the fugacity is not equal among phases, this would result in a different driving force at the cream-skin interface. However, a well-mixed cream with a large surface area between phases will come to equilibrium rapidly and the fugacity will be equal among phases, even if the oily phase would necessarily have a much higher concentration of lipophilic compounds. This means that the fugacity at the cream-skin interface would be the same as that measured in vitro even if the oily phase preferentially contacts the skin.

Skin hydration can significantly affect estimated transdermal uptakes, because an increase in the water content of the stratum corneum can alter partitioning and diffusivity. An increase in water

content can also result in an increase in stratum corneum thickness.⁷⁶ It has been observed in several *in vivo* and *in vitro* experiments that increases in skin hydration can lead to an increase in permeability of stratum corneum which could be the result of an increase in the fluid fraction of SC proteins and lipids.^{101–104} At higher skin hydration, a higher flux of both hydrophilic and lipophilic compounds have been observed.^{101,102,105,106} Spencer et al.¹⁰⁷ measured a maximum 60% increase in stratum corneum thickness after skin was exposed to water for 60 minutes. Lotion and moisturizers can change skin hydration.^{108,109} However, changes in skin hydration and stratum corneum thickness generally do not occur when applying lotions and moisturizers over short time intervals.^{108,109} Therefore, we feel comfortable with our assumption that the skin in the Janjua human subject experiment was “partially hydrated” and that the hydration condition was not significantly altered by cream application.

Penetration through the skin-follicle pathway may be the reason Janjua observed a fast increase in cumulative urinary excretion of target chemicals, most notably MEP, immediately after topical application of the creams in human subjects. Unlike a longer delay in absorption of chemicals from the stratum corneum, penetration through hair follicles occurs immediately after topical application.¹¹⁰ Frum et al.¹¹¹ showed that hair follicles are responsible for 34 to 60% of the penetration of chemicals (drugs) with intermediate and low octanol/water partition coefficients. However, they only contributed in 2 to 4% of transdermal uptake for more lipophilic molecules. DEP, DnBP, and BP are all lipophilic; DEP is the least lipophilic with an octanol/water partition coefficient about 100 and 7 times lower than DnBP and BP at 32 °C; respectively. Since our model only considers the stratum corneum pathway, the simulations do not capture this early rise in excretion rates (Figure 3). However, since most of the permeation occurs via the stratum corneum, the cumulative uptake is reasonably captured by the model.

4. Implications

In this paper, we show that dynamic simulations based on fugacity measurements of two phthalates and a paraben mixed in a cream are consistent with the results of human experiments conducted by Janjua et al.⁹ This supports the general principal that the concept of fugacity can be used to quantitatively estimate transdermal exposure from contact with environmental media. Cosmetics can serve as a valuable proxy for environmental media that allows for control of composition and

precise measurements of uptake and excretion in human subjects. There exist many other *in vivo* or *in vitro* measurements of transdermal uptake reported in the cosmetic and pharmaceutical literature that can be used to test models of uptake from environmental media. This may be especially valuable for exposure to substances present at relatively high concentrations, such as chemicals in paint,¹¹² PVC flooring,^{113,114} or from occupational exposures.¹¹⁵ Our results also support the use of fugacity instead of fixed absorption dose in transdermal uptake risk assessment. However, models like this must be used with caution since quantitative predictions are very sensitive to the choice of model parameters such as vapor pressure, diffusion coefficients, stratum corneum thickness, defective skin barrier function, skin temperature, and elapsed time between topical application and shower time. Despite these current limitations, we believe that the measured fugacity is a valuable tool for estimating exposure, dose and risk of chemicals in cosmetic products and environmental media.

We also show that the relationship between measured fugacity and cream composition is highly non-linear and even as low as 0.2% in solution, the solute exhibits non-ideal behavior. At low concentrations, linear extrapolation may be acceptable. Therefore, extrapolation from *in vivo* data at one concentration cannot be used to predict uptake and excretion at other concentrations for complex mixtures like cosmetics and personal care products with high solute concentrations of active ingredients. For exposure and risk assessment, linear extrapolation or fixed-absorption dose methods must be used with caution for such mixtures or other materials in contact with skin (e.g., clothing). For many chemicals in personal care products, we believe the application of the measured relative fugacity is superior to these dose-estimation methods: it is easy to measure and can be directly included in fundamental models of mass transfer through skin that make reasonable predictions of transdermal uptake.

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601 Supporting Information Available

- 602 • Vapor pressures of DEP, DnBP, and BP. Linear version of relative measured fugacity vs
603 mass fraction of each chemical in cream mixtures. Description of the transdermal uptake
604 model used in this study. Calculations of transdermal uptake model input parameters and
605 the parameters at temperature ranges between 25-37 °C.

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980

a) DEP

b) DnBP

c) BP

MEP (mg)

MnBP (mg)

BP (mg)