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High Throughput Risk and Impact Screening of Chemicals in Consumer Products

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The ubiquitous presence of more than 80,000 chemicals in thousands of consumer products used on a daily basis stresses the need for screening a broader set of chemicals than the traditional well-studied suspect chemicals. This high-throughput screening combines stochastic chemical-product usage with mass balance-based exposure models and toxicity data to prioritize risks associated with household products. We first characterize product usage using the stochastic SHEDS-HT model and chemical content in common household products from the CPDat database, the chemical amounts applied daily varying over more than six orders of magnitude, from mg to kg. We then estimate multi-pathways near- and far-field exposures for 5,500 chemical-product combinations, applying an extended USEtox model to calculate product intake fractions ranging from 0.001 to ∼1, and exposure doses varying over more than nine orders of magnitude. Combining exposure doses with chemical-specific dose–responses and reference doses shows that risks can be substantial for multiple home maintenance products, such as paints or paint strippers, for some home-applied pesticides, leave-on personal care products, and cleaning products. Sixty percent of the chemical-product combinations have hazard quotients exceeding 1, and 9% of the combinations have lifetime cancer risks exceeding 10^{-4}. Population-level impacts of household products ingredients can be substantial, representing 5 to 100 minutes of healthy life lost per day, with users' exposures up to 10^3 minutes per day. To address this issue, present mass balance-based models are already able to provide exposure estimates for both users and populations. This screening study shows large variations of up to 10 orders of magnitude in impact across both chemicals and product combinations, demonstrating that prioritization based on hazard only is not acceptable, since it would neglect orders of magnitude variations in both product usage and exposure that need to be quantified. To address this, the USEtox suite of mass balance-based models is already able to provide exposure estimates for thousands of product-chemical combinations for both users and populations. The present study calls for more scrutiny of most impacting chemical-product combinations, fully ensuring from a regulatory perspective consumer product safety for high-end users and using protective measures for users.

KEY WORDS: Chemical ingredients; high throughput exposure and risk screening; household products

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1. INTRODUCTION

Chemicals are ubiquitously present in thousands of consumer products used on a daily basis. It is estimated that approximately 30,000–80,000 different chemicals are commonly used, but good quality and regulatory toxicity data are only available for a few thousand chemicals, and the product- and user-specific nature of exposure states that many decisions are often taken on hazard-based data only (Greggs et al., 2019). Wambaugh et al. (2014) showed

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that chemicals found at the highest concentrations in serum and urine human biomonitoring data are associated with chemical usage in consumer products, whereas chemicals only used in industrial processes or active ingredients in pesticides are generally associated with lower exposure levels. This stresses the need for screening a broader set of chemicals than the traditional well-studied suspect chemicals, accounting for both exposure and hazard, and considering both chemical and product properties.

Recent developments in the assessment of near-field exposures (i.e., exposure pathways in the vicinity of product use) (Huang & Jolliet, 2016, Isaacs et al., 2014; Jolliet, Ernstoff, Csiszar, & Fantke, 2015) have framed the field towards a consistent inclusion of near-field human health assessment that is product-chemical combination specific into high-throughput risk and impact assessment studies. Data are becoming increasingly available to assess chemical content in products (Dionisio, Phillips, Price, Biryol, & Isaacs, 2018; Isaacs, Phillips, Biryol, Dionisio, & Price, 2018; Phillips, Wambaugh, Grulke, Dionisio, & Isaacs, 2017), and stochastic methods have been developed to predict population product usage patterns for many product categories (Isaacs et al., 2014). These data and product usage methods have been used within a screening-level exposure model to inform chemical prioritization (Isaacs et al., 2014), which had some limitations on the exposure side, including lower-tier conservative assumptions that do not account for the mass balance nature of competing processes, such as volatilization and dermal uptake on skin surface. On the other hand, more elaborate, higher tier mass balance-based models have been developed to estimate transport, fate, exposure associated with multiple chemical emissions, and usage along the life cycles of products and services (Csiszar, Ernstoff, Fantke, Meyer, & Jolliet, 2016; Fantke, Ernstoff, Huang, Csiszar, & Jolliet, 2016; Fantke, Huang, Overcash, Griffing, & Jolliet, 2020) for high-throughput screening of cosmetics, and have been consolidated within an extended USEtox near-field and far-field model, but to date have incorporated relatively limited data on chemical and product usage.

The present paper aims to combine stochastic estimates of chemical-product usage with product-chemical mass balance-based exposure models and toxicity data to inform High Throughput Screening (HTS) of chemical risks associated with commonly used household products. More specifically, we aim to (i) characterize the product usage and chemical content in commonly used household products, (ii) estimate multi-pathways near- and far-field exposures for thousands of chemical-product combinations, and (iii) screen and prioritize risk and health impact to identify products and substances of concern, using the estimated exposures in concert with available toxicity data and high-throughput toxicity estimates. This work demonstrates the feasibility of combining HTS stochastic estimates for chemical usage, exposure models, and toxicity to identify and prioritize chemicals of concern that require further scrutiny, as well as main product usage that might lead to substantial exposures and impacts. This approach could be used in the context of either receptor-oriented methods like screening-level risk assessment (RA) to assess the order of magnitude of risks for product users and the general population, or of product-oriented methods, such as life cycle assessment (LCA) and chemical alternatives assessment to identify substances that matter most during the product use life cycle stage.

2. METHODS

2.1. Assessment Framework

High throughput quantitative exposure assessment is performed according to the product intake fraction (PiF) framework (Fantke et al., 2016; Fantke, Huang et al. 2020; Jolliet et al., 2015) and its implementation within the USEtox model, successively determining the amount of chemical applied in product per user and per day, the corresponding exposure in mg/kg/d and the associated risks, hazard quotients, or health impacts (Fig. 1). It aims to determine the incremental or marginal increase in exposure and risks due to the considered household products and therefore does not include background exposures from environmental emissions or other products. This overall assessment framework is in line with current recommendations for characterizing chemical-related toxicity impacts (Fantke et al., 2018), and is executed according to the following stepwise procedure:

2.1.1. Chemical Used in Product

We first quantify the chemical mass of each substance i ($m_{i,p}$, $\mathrm{kg_{chemical}}$/person/d) that is used daily by a user of a specific product p:

$$m_{i,p}^{\mathrm{user}} = M_p^{\mathrm{user}} \times wf_{i,p} \quad (1)$$

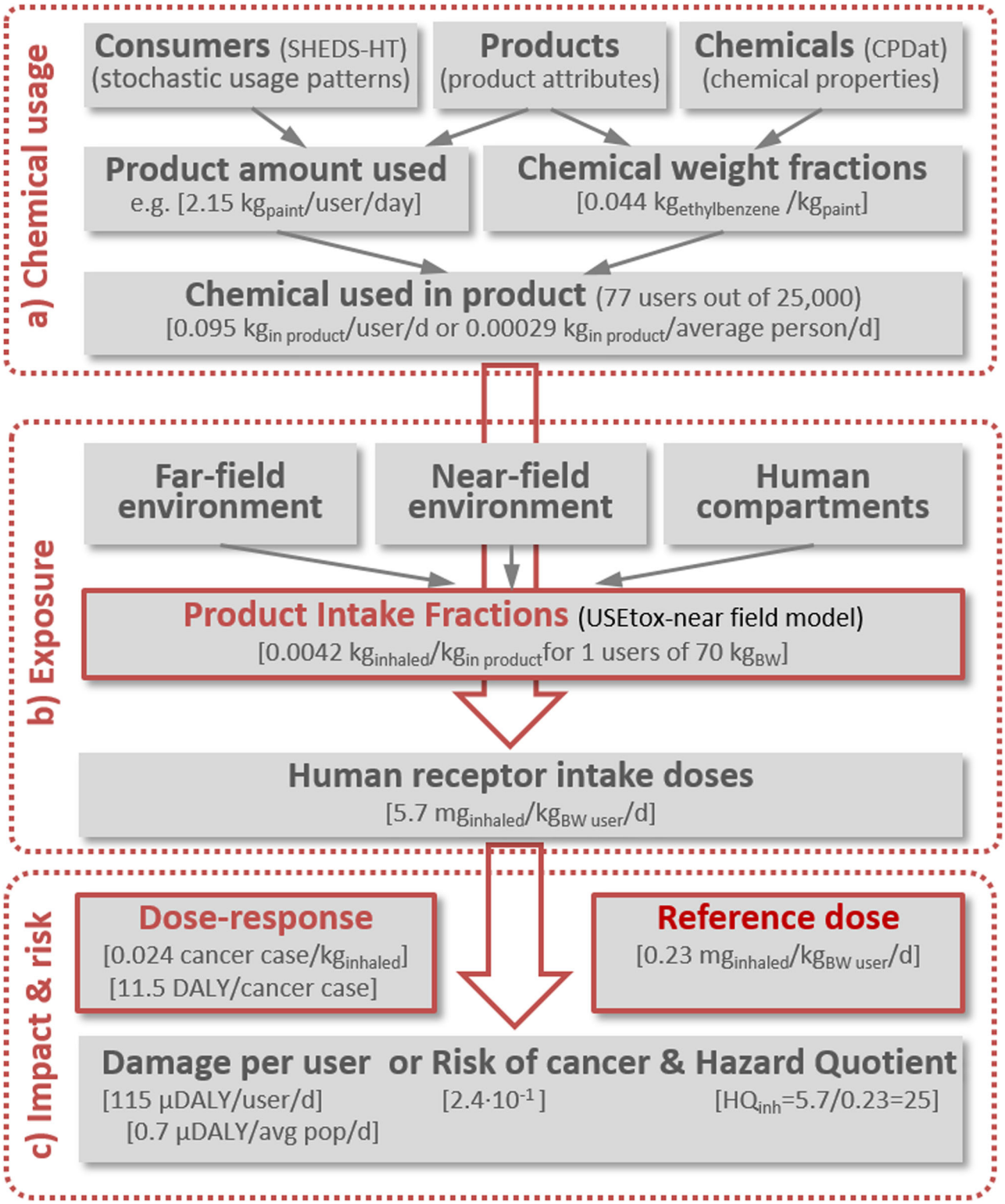

Fig 1. Schematic description of the assessment framework and impact pathways, from mass in product to risk and impacts, illustrated with the example of ethylbenzene in paint.

where M_p^{user}($kg_{product}$/person/d) is the daily amount of product used by a user of this product, estimated with the high-throughput stochastic human exposure and dose simulation model (SHEDS-HT, Isaacs et al., 2014), and $wf_{i,p}$ ($kg_{chemical}/kg_{product}$) is the content of chemical i in product p taken from the U.S. Environmental Protection Agency's (EPA) Chemicals and Products Database (CPDat, Dionisio et al., 2018).

Chemicals in product applied enter a defined compartment of entry, that is, the compartment into which or within which a chemical is first applied or used within the considered product (e.g., 'skin surface' for an ingredient in personal care products). The mass used is calculated both for one person using the product ($m_{i,p} = m_{i,p}^{\text{user}}$), and for the average population, accounting for the SHEDS-HT predicted fraction of the population using this product per day ($m_{i,p}^{\text{average pop}} = m_{i,p}^{\text{user}} \times N_p^{\text{user}}/N^{\text{pop}} = m_{i,p}^{\text{user}} \times f_p^{\text{user}}$).

2.1.2. User and Population Exposure

Second, the framework captures the multipathway transport and fate processes transferring chemicals among compartments in the near- and far-field environments, until finally reaching humans. Multimedia transfers are structured in a matrix of direct inter-compartmental transfer fractions (Fantke et al., 2016). By matrix inversion, we quantify cumulative multimedia transfer fractions and exposure route-specific (x: inhalation, ingestion, dermal) product intake fractions defined as chemical mass taken in ($I_{i,p,h,e}$, kg/d) via multiple exposure pathways e (e.g., dust ingestion, dermal contact) by exposed humans h per unit mass of chemical in a product (Jolliet et al., 2015): $PiF_{i.p,h,x} = \sum_{e \in x} I_{i,p,h,e}/m_{i,p}^{\text{user}}$. Combining product intake fractions with chemical mass in the product, multiplying by the 1,000,000 *kg_to_ mg* conversion factor and dividing by the number of exposed humans in the considered subpopulation (N_h, persons) of users, nonuser household members, or general population, and an average human body weight (BW_h, kg_{BW}/person) yields intake doses for exposure route x ($D_{i,p,h,x}$, $mg/kg_{BW}/d$) as exposure estimates:

$$D_{i,p,h,x} = \frac{m_{i,p}^{\text{user}} \times PiF_{i,p,h,x} \times kg\_to\_mg}{N_h \times BW_h} \tag{2}$$

2.1.3. Risk Characterization

The third step is to assess and compare the risks and impacts associated with each of the chemical-product combinations, combining exposure doses with toxicity data. First, carcinogenic risks ($R_{i,h}$, in probability of cancer for a lifetime exposure of user h by route x) are calculated by multiplying the dose by a route-specific cancer slope factor ($CSF_{i,x}$, in incidence/($mg/kg_{BW}/d$)), taken from the carcinogenic potency database, see Equation 6 below):

$$R_{i,p,h} = \sum_x D_{i,p,h,x} \times CSF_{i,x} \tag{3}$$

This risk probability can then be compared to the acceptable lifetime cancer risk limit of 10^{-4} to 10^{-6} for the general population depending on the jurisdiction. Noncarcinogenic risks are characterized by comparing the dose with a reference dose ($RfD_{i,x}$, $mg/kg_{BW}/d$, from Wignall et al., 2018) and calculating the dimensionless cumulative hazard quotient as:

$$HQ_{i,p,h} = \sum_x D_{i,p,h,x}/RfD_{i,x} \tag{4}$$

The cumulative hazard quotient should not be interpreted as a risk, but an HQ >1 (exposure dose higher than reference dose) may indicate potentially harmful chemicals that require further scrutiny.

2.1.4. Impact Characterization

In addition to the risk screening, we also calculate comparative impact scores for both cancer and noncancer toxicity impacts, according to latest LCA approaches, i.e, multiplying the inventory flows by the substance intake fraction (fate and exposure factor in $kg_{intake}/kg_{emitted}$), the USEtox dose–response factors (DRFs, incidence/kg_{intake}) and severity factors (SF, DALY/incidence). For the specific case of chemicals in consumer products, the cumulative impacts resulting from a daily usage of a mass of chemical in product ($m_{i,p}$, kg/person/d) and ($IS_{i,p}$, DALY/person/d for both cancer or noncancer effects e) via exposure route x is given by (Jolliet et al., 2015):

$$IS_{i,p} = m_{i,p}^{\text{user}} \times \sum_{h,x,e} (PiF_{i,p,h,x} \times DRF_{i,x,e} \times SF_e) \tag{5}$$

Where the sum on h is calculated considering the direct adult (or child) product user exposed, the other humans in the household, composed by default of two adults and one child in total, as well as the general exposed background human population.

Risk and impact are first determined for the product user and then extrapolated to an average risk or impact for the entire population ac-

counting for the fraction of the population using this product. This impact-oriented representation enables us to analyze results either from a product perspective, summing up impacts for all chemicals in a given product, or from a substance perspective, summing up impacts for all products containing a given chemical. The next sections detail the data and models used for each of these three main steps.

2.2. Chemical Used in Product: The SHEDS-HT Model

For determining daily chemical usage by product user and for the general population, we used the SHEDS-HT model (Isaacs et al., 2014), an integrated probabilistic exposure model for prioritizing exposures to chemicals. The model is run for 1,777 unique chemicals in 289 individual product categories, including arts and crafts, auto, cleaning, home maintenance, home office, lawn and yard, personal care, pet, and home pesticide products; this results in 9,700 product-chemical combinations. The SHEDS-HT input data include empirical chemical weight fraction distributions developed from EPA's CPDat database (Dionisio et al., 2018) and use variables for individual product categories (e.g., population prevalence, frequency of use, mass per use) developed from a review of existing data sources or assumed where necessary (Isaacs, 2019; Isaacs et al., 2014). A population of 25,000 individuals is simulated; distributions and means of the mass of product and mass of chemical used per day per person are obtained (i) per user for product users only and (ii) per person for the entire population of simulated individuals, accounting for the SHEDS-HT predicted fraction of the population using this product per day.

2.3. User and Population Exposure

To estimate product intake fractions, we build on the USEtox mass balance-based model (Rosenbaum et al., 2008) and extend it to the near-field environment to create an extended version of the USEtox compartment system that includes exposure to chemicals in consumer products. We first populate a multimedia transfer matrix $\mathbf{T}$ $(n \times n)$ with direct intercompartmental transfer fractions from each column to each row. The first column of direct transfer fractions characterizes transfers from the product compartment of entry in the near-field environment (e.g., an "object surface" for cleaning products) to the neighboring compartments (e.g., to indoor air via volatilization, and to human epidermis via direct dermal contact between the user and the object surface) using the near-field models described in Table I. The other columns of the transfer matrix contain the direct transfer fractions from 17 compartments to their neighboring environmental compartments and to an additional 28 human exposure compartments. The environmental compartments include near-person air (a 1 m^3 compartment to receive the fraction volatilized in direct proximity of the user), indoor air (for volatilization to the rest of the user household air), as well as the already existing 11 USEtox outdoor environmental compartments of urban, continental, and global air, continental and global freshwater, continental coastal marine water, and global deep ocean, and continental and global agricultural and natural soils. For these compartments, direct transfer fractions are calculated as the ratio of the intercompartment transfer rate constant divided by the total removal rate constant of the respective column compartment. The human compartments correspond to a combination of intake compartments and exposure pathways (respiratory tract for inhalation, gastrointestinal tract for ingestion of food and drinking water, and for dust ingestion via hand to mouth, epidermis for gaseous and direct dermal exposure) for four subpopulations, namely one adult user, a second nonuser adult, one child (optionally being a user) in the user household, and the general population of one billion people (with 10 intake compartments/exposure pathways differentiated).

As demonstrated by Fantke et al. (2016), the compartments are then combined and the cumulative transfers accounting for all subsequent higher order transfers obtained by inverting the difference between the identity matrix $\mathbf{I}$ (with ones in the main diagonal and zeroes elsewhere) and $\mathbf{T}$, yielding the cumulative transfers matrix $\mathbf{T}_{\text{cum}} = (\mathbf{I} - \mathbf{T})^{-1}$. The first column of matrix $\mathbf{T}_{\mathbf{cum}}$ provides the cumulative chemical transfer fractions from the product to both the other indoor and outdoor compartments and to the different human compartments. The cumulative transfers to these human compartments directly correspond to the product intake fractions associated with different exposure pathways.

An example of matrices $\mathbf{T}$ and $\mathbf{T}_{\mathbf{cum}}$ is presented for our example chemical-product combination—ethylbenzene in paint—in the SI2 tab of the Supporting Information SI. In the first matrix, the first

Table I. Selected Underlying USEtox Near-Field Exposure Models with Main Direct Transfer Fractions from Compartment of Entry, Exposure Pathways, Model Mechanisms, Key Parameters, and Example Products Covered to Determine Product Intake Fractions

Model	Compartment of entry and main transfers and compartments considered	Direct exposure pathways	Model mechanism	Key parameters	Product example
Direct emission (based on USEtox 2.2)	Emissions to near-person, indoor, urban or continental air, to surface water, agricultural and natural soil, WWTP[1] and STP[2]	Inhalation and gaseous dermal uptake, ingestion pathways via drinking water, above ground produce, below ground produce, meat, milk and dairy products, and fish	Direct transfer fraction is the chemical mass emitted to a certain compartment divided by the original mass in product and is calculated as the ratio of transfer rate constant to total removal rate, using the USEtox rate constant K matrix (Henderson et al., 2011; Rosenbaum et al., 2008)	Half-lives and residence time in each environmental compartment. Bioaccumulation factors	All chemical emissions to indoor and outdoor environmental compartments
Article interior	Transfers from chemicals in article interior to near-person air or indoor air, to human epidermis via dermal contact, to human gastrointestinal tract via dust ingestion and to STP[2] at its end-of-life.	Dermal contact with article surface, dust ingestion in addition to inhalation and gaseous dermal uptake	Diffusion-limited (for e.g., VOCs[3]) or partition-limited model (for e.g., SVOCs[4]) for the transfer from article interior to indoor air. The diffusion-limited model accounts for the chemical's internal diffusion inside the article via Fick's second Law, but does not need to account for the restricted long-term chemical's sorption on other indoor surfaces, yielding a two exponential model applicable to most VOCs (Huang & Jolliet, 2016). The partition-limited model accounts for indoor sorption, but assumes the chemical is always evenly distributed inside the article since surface partitioning is limiting. The air is assumed in quasi steady state with the different surfaces. This yields a parsimonious two-compartment mass balance-model for article and indoor surfaces applicable to most SVOCs, solved into a two exponential explicit equation using eigenvalues and eigenvectors	Diffusion coefficient inside the article D_m, solid material-air partition coefficient K_{ma}, material-water partition coefficient K_{mw}, which are predicted by Huang, Fantke, Ernstoff, and Jolliet (2017), Huang and Jolliet (2019a, 2019b), respectively.	Chemicals encapsulated in article interior (e.g., building materials, furniture, toys, or arts and crafts)

(*Continued*)

Table I (Continued)

Model	Compartment of entry and main transfers and compartments considered	Direct exposure pathways	Model mechanism	Key parameters	Product example
Skin-surface layer	Transfer from skin surface layer to near-person air, to human epidermis, and to WWTP[1]	Direct dermal aqueous uptake in addition to inhalation and gaseous dermal uptake	The model uses a three-compartment mass balance, whose compartments include skin, indoor air, and the product applied on the skin. The model assumes that volatilization and skin permeation are two competing loss processes for chemicals in the product applied on skin. (Csiszar, Ernstoff, Fantke, & Jolliet, 2017; Ernstoff et al., 2016). The fraction remaining on the skin at the end of the exposure period is washed-off to waste-water treatment plant	Skin permeation coefficient via aqueous solution K_{p_aq}, total gaseous-skin permeation coefficient $K_{p\_gas\_total}$, which are calculated by the methods used by ten Berge (2009) as applied by Csiszar et al. (2017).	Personal care products, hand dishwashing
Object surface	Transfer from object surface to near-person air, and indoor air, to human epidermis and to WWTP[1]	Dermal contact in addition to inhalation and gaseous dermal uptake	The model is a simplified version of the model from Earnest and Corsi (2013), as developed by Wang, Huang, Nguyen, and Jolliet (2016), which uses a four-compartment mass balance, whose compartments include near-person surface, near-person air, far-person surface and far-person air. In this model, a transfer rate constant between near-person surface and the rest of the surface (far-person surface) is used to simulate the movement of the person when cleaning surfaces	Air-water partition coefficient K_{aw}, taken from the OPERA QSARs[5] (Mansouri et al., 2018).	Surface cleaner detergents

[1]Wastewater treatment plant,
[2]Solid waste treatment plant such as landfill or incinerator,
[3]Volatile organic compounds.
[4]Semi-volatile organic compounds.
[5]Quantitative structure-activity relationships.

column indicates that 20% of ethylbenzene entering the household environment as a thin coating is volatilized in the near-person compartment during the painting process, that 0.18% is transferred to the user epidermis during painting and that the remaining 79.82% are volatilized to the rest of the indoor air over the 15 years defined exposure period. The near-person air column indicates that 99.77% of the chemical is transferred to the rest of the household, whereas 0.33% is inhaled by the user. The first column of the second, cumulative transfer matrix indicates that 0.42% of the applied ethylbenzene are inhaled by the user (thus a PiF of 0.0042), another 0.35% are inhaled by the second household adult, and 0.20% by the household child, whereas a negligible fraction of only 0.0011% is inhaled by the one billion persons of the continent's general population.

The direct transfer fractions from the compartment of entry to other various near-field environmental compartments, to the USEtox far-field environmental compartments and to the three human receptor compartments (respiratory tract, gastro-intestinal tract, and epidermis, corresponding to the three exposure routes) are calculated using a series of complementary underlying models. Depending on the product application and the compartment of entry in the near-field environment, four main models are included into our framework for calculating direct transfer fractions, namely "Direct emission," "Article interior," "Skin surface layer," and "Object surface." Table I summarizes the direct transfer fractions that are determined by each model and the respective exposure pathways. Each of these models is then parametrized adapting required model parameters (such as thickness of applied chemical on skin, surface applied, number of adults and children exposed, and adult and child specific exposure factors e.g., for hand-to-mouth dust ingestion) to the SHEDS-HT product category. The underlying models required chemical property estimates, which are obtained from EPA's OPEn structure-activity relationship app (OPERA) quantitative structure-activity relationship (QSAR) models (Mansouri, Grulke, Judson, & Williams, 2018). The availability of chemical properties restricts results to 5,500 of the 9,700 chemical-product combinations. The Supporting Information provides the list of the 5,500 product-chemical combinations characterized, together with their usage characteristics, and the main resulting exposures, risks, and impacts.

2.4. Toxicity data, Risk Characterization and Impacts

2.4.1. Cancer Slope Factor

For cancer risks, cancer slope factors are calculated based on the Carcinogenic potency database (CPDB: https://files.toxplanet.com/cpdb/index.html) and its implementation for LCA in USEtox (Rosenbaum et al., 2011), starting from the lowest (across animal species—after correction by the extrapolation factor for interspecies differences) harmonic mean of tumorigenic doses generating an additional risk of 50% over background in a chronic lifetime cancer test ($TD50_{a,i,x}$, $mg/kg_{BW}/d$):

$$CSF_{i,x} = \frac{0.5 \times f_a \times f_t}{TD50_{a,i,x}}, \quad \text{in}(mg/kg_{BW}/d)^{-1} \qquad (6)$$

where f_a (dimensionless) is the extrapolation factor for interspecies differences between animal species a and humans (Rosenbaum et al., 2011, Table S3), and f_t (dimensionless) is the extrapolation factor for differences in time of exposure, that is, a factor of 2 for subchronic to chronic exposure and a factor of 5 for subacute to chronic exposure (Huijbregts, Rombouts, Ragas, & Van de Meent, 2005). Route-specific harmonic means are determined separately when available for both ingestion and inhalation. In case no data are available for a specific exposure route, a route-to-route extrapolation is carried out, assuming equal slope factor between inhalation and ingestion route, and between dermal and ingestion route. Rosenbaum et al. (2011, SI section S3.2) indicates that cancer slope factors by inhalation might be underestimated, when (i) the primary target site is specifically related to the route of entry (case of formaldehyde linked to nasal cancer), and (ii) when the expected fraction absorbed via inhalation is expected to be much higher than the fraction absorbed via ingestion with octanol–water partition coefficients K_{ow} smaller than 2.5×10^{-2} or K_{ow} larger than 10^{10}. The slope factors for acrylonitrile, arsenic, benzene, benzidine, beryllium, 1,3-butadiene, cadmium, chromium (VI), and nickel by inhalation are directly taken from the human based data available via the IRIS database (http://www.epa.gov/iris/).

2.4.2. Reference Doses

For noncancer risk characterization, for ingestion, Reference Doses (*RfD*) are determined starting from a point of departure and dividing them by the product of three uncertainty factors for animal

to human extrapolation, interindividual variability, and uncertainty: $RfD_x = POD_x / \prod_i UF_i$. For calculating the *RfD*s, the points of departure are in general no-observed adverse effect levels (NOAEL) or lowest observed adverse effect levels (LOAEL) taken from IRIS or other regulatory oriented databases, retaining the *RfD*s used as training set by Wignall et al. (2018), collected from IRIS, Office of Pesticide Programs (OPP), Superfund Regional Screening Level Tables (RSLs)], California EPA, Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profiles, U.S. EPA Provisional Peer Reviewed Toxicity Values (PPRTV), and U.S. EPA Health Effects Assessment Summary Tables (HEAST)). When not available, we use the *in silico* conditional toxicity value (CTV) predictors from Wignall et al. (2018)) to predict quantitative estimates of ingestion *RfD*s (also used by default for dermal uptake) and inhalation reference concentrations (RfCs). Inhalation *RfD*s are then derived from multiplying RfCs by by an average breathing rate of 16 m^3/person/d for a middle age adult (USEPA, 2011) and dividing by a standard human adult body weight of 70 kg/person. Predicted *RfD*s are only retained if they are within the QSAR model applicability domain (Wignall's quality indicator lower than or equal to three, as reported in the Supporting Information), that is for 344 chemicals representing 2,888 chemical-product combinations for inhalation-based *RfD*s and for 477 chemicals representing 3,495 chemical-product combinations for ingestion *RfD*s.

2.4.3. Dose–response and Severity Factors

For determining carcinogenic impacts, the *DRF*s are taken from the USEtox database as described by Rosenbaum et al. (2011)): $DRF_{i,\text{cancer},x} = \frac{0.5 \times f_a \times f_i \times 10^6}{TD50_{i,a,\text{cancer},x} \times N_d \times BW \times LT}$, where BW is the average body weight of human adults, LT is the average lifetime of humans (70 years), and N_d is the number of days per year (365.25 d/year). An average cancer severity factor of 11.5 DALY/incidence (Huijbregts et al., 2005) is taken as average over various cancer types.

For noncancer impacts, *DRF*s are also taken from the USEtox database as described by Rosenbaum et al., 2011): $DRF_{i,\text{noncancer},x} = \frac{0.5 \times f_a \times f_i \times 10^6}{TD50_{i,a,\text{noncancer},x} \times N_d \times BW \times LT}$ where $TD50_{a,i,x}$ is the toxic dose extrapolated either from NOAEL ($TD50_{i,a,x} = 9 \times NOAEL$, $\text{mg/kg}_{\text{BW}}\text{/d}$) or from LOAEL ($TD50_{i,a,x} = 2.25 \times LOAEL$, $\text{mg/kg}_{\text{BW}}\text{/d}$). An average noncancer severity factor of 2.7 DALY/incidence (Huijbregts et al., 2005) is taken as average over various noncancer effects. Since there is 31.5 million seconds in a year, a μDALY could be interpreted as 31.5 second or 0.53 minutes of healthy life lost per day.

3. RESULTS AND DISCUSSION

3.1. Chemical and Product Usage

From SHEDS-HT, the mean total amount of chemical used per day per person is calculated as the multiplication of three model output statistics: the mean amount of product used per day by a user, the mean chemical content or weight fraction in products used, and the fraction of the population using this product for calculating an average daily chemical usage at population level. Taking the example of ethylbenzene used in paint (Fig. 1), a user will apply 2.15 kg_{paint}/user/d, which contains an average value of 0.042 $\text{kg}_{\text{ethylbenzene}}$/ kg_{paint}, thus an application of 0.095 $\text{kg}_{\text{ethylbenzene in paint}}$/user/d. Considering that on a given day only 77 persons out of 25,000 are using this product, this corresponds to a population average chemical application of 0.00029 $\text{kg}_{\text{ethylbenzene in paint}}$/person/d. Fig. 2a shows the fraction of users, that is, fraction of the population, using a given product-chemical combination per day. It varies from close to 1 (almost everybody uses it on a daily basis) for several cosmetics and cleaning products, down to 1 user out of 25,000 for some home maintenance products that tend to be used by a smaller fraction of the population compared to other products. The following sections first focus on the user and the other members of the household in which the product is used, to characterize risks associated with individual product-chemical usage. Average population applications are considered in a second stage to provide insights on the magnitude of the population-level burden of disease.

Fig. 2b illustrates the variability in chemical usage across users. The amount of chemical used per user per day for a given product-chemical application varies by more than six orders of magnitude, from mg to kg; across all applications, where the highest quantities used per user are for home maintenance products.

3.2. Product Intake Fractions and User Exposures

Product intake fractions and exposures were characterized for 846 chemicals in 270 unique

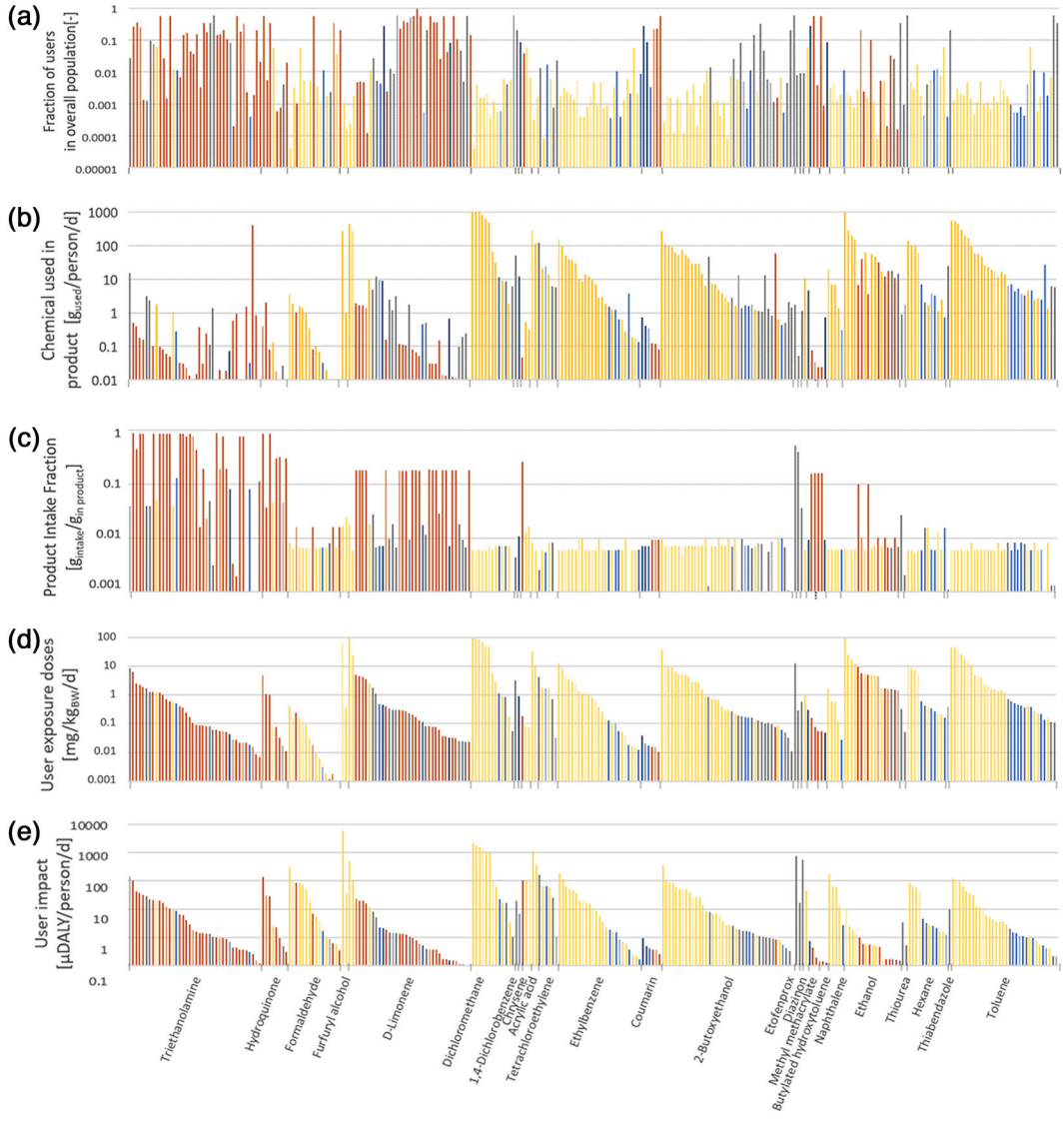

Fig 2. Fraction of users (a), chemical and product usage (b), product intake fractions (c), exposure doses (d), and health impacts (e) on the product user, for multiple product-chemicals combinations of the 23 chemicals generating the highest cumulative impacts at population level.

products, for a total of 5,465 product-chemical combinations.

3.2.1. Product Intake Fractions

Applying the USEtox-compatible PiF exposure modeling framework for each of the product-chemical combination yields the product intake fraction (PiF). In the case of ethylbenzene in paint, the inhalation PiF for the adult user amounts to 0.0042 $kg_{intake}/kg_{ethylbenzene\ in\ paint}$. This means that for 1 g of ethylbenzene used in product, 4.2 mg is taken in by the user. The dermal PiF for the user is twice lower than for inhalation, at 0.0018 $kg_{intake}/kg_{ethylbenzene\ in\ paint}$. In addition, the inhalation PiF for the second adult and the child in the household are still slightly lower than for the user but still substantial with values of 0.0035 and 0.0020, respectively. In contrast, the inhalation PiF for the general population is restricted to 1.1×10^{-5} for a billion exposed people. Fig. 2c shows that user PiFs typically vary by a factor of 1,000 between the various products considered, ranging from 1/1,000 for inhalation exposure to ingredients of many home maintenance

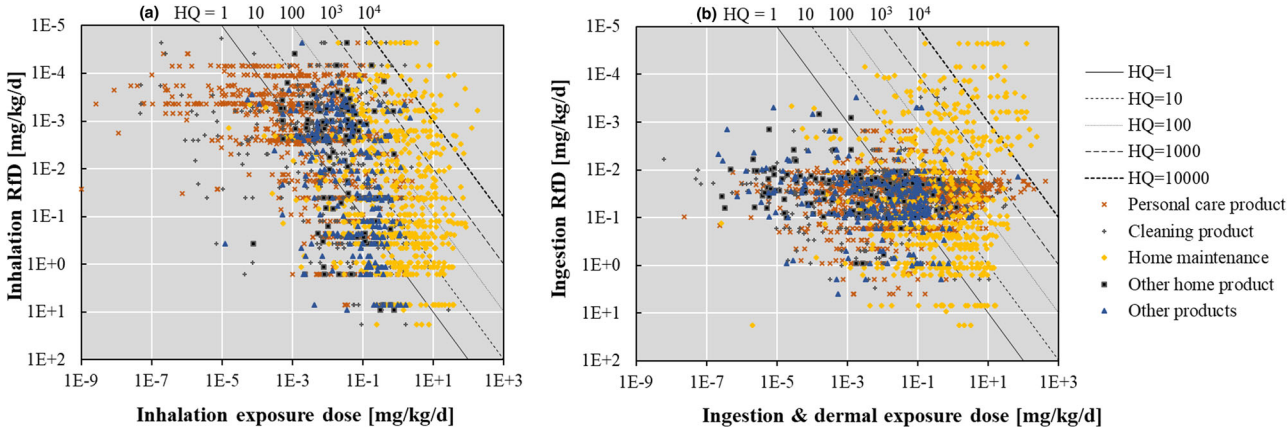

Fig 3. Hazard quotient (HQ) represented as diagonal lines determined as the product of exposure dose for (a) inhalation, and (b) the sum of ingestion and dermal exposure of the adult user on the *x*-axis, multiplied by the inverse of reference doses (reversed values on the *y*-axis), for multiple product-chemical combinations.

products such as paint or paint stripper, up to close to 1 for dermal exposure to ingredients of leave-on personal care products such as body or face lotion. Population exposure outside of the household remains minimal, on the order of 1 to 10 ppm.

3.2.2. *User Exposure Doses*

User exposure doses for each exposure route are obtained by combining the chemical mass in the product with the product intake fractions. Multiplying the amount of chemical used per day of 0.095 $kg_{ethylbenzene\ in\ paint}$/user/d by the inhalation PiF for the adult user of 0.0042 $kg_{inhaled}/kg_{ethylbenzene\ in\ paint}$ and dividing by 70 kg_{BW}, we obtain for ethylbenzene a daily inhalation dose of 5.7 mg/kg_{BW}/d for the adult user, plus a dermal exposure of 2.4 mg/kg_{BW}/d. This is slightly higher than the exposure of the second adult nonuser household member (4.8 mg/kg_{BW}/d) and lower than the per kg body dose for the child in the household (13.5 mg/kg_{BW}/d), but much higher than the daily exposure dose for the background population, which amounts to 1.4×10^{-11} mg/kg_{BW}/d, due to the low PiF and high number of exposed adults in the background population. Fig. 2d shows that depending on the considered product-chemical combination, exposure doses vary by more than five orders of magnitude, from 0.001 to 1,000 mg/kg_{BW}/d for a user using the product, with especially high doses when applying home maintenance products the entire working day. The contribution of each exposure route and subpopulation is further detailed for each of the 5,500 chemical-product combinations in the SI1 tab of the Supporting Information file.

3.3. Risk Characterization

3.3.1. *Risk Characterization for Users*

Risks were characterized for 665 chemicals in 228 unique products, for a total of 4229 product-chemical combinations (Fig. 3). Predicted *RfD*s within the QSAR model applicability domain were used for 344 chemicals representing 2,888 chemical-product combinations for inhalation-based *RfD*s and for 477 chemicals representing 3,495 chemical-product combinations for ingestion *RfD*s. For the noncancer characterization of the illustrative example of ethylbenzene in paint (Fig. 1), the user dose of 5.7 mg/kg_{BW}/d is divided by a *RfD* of 0.23 mg/kg_{BW}/d (derived from a RfC of 1 mg/m^3), yielding a Hazard Quotient of 25 for inhalation. Fig. 3 presents the noncancer hazard quotients in diagonal line, expressed as the ratio of the same exposure doses on the *x*-axis and the reference doses on the *y*-axis (reverse values). This prioritization exercise also identifies multiple combinations with hazard quotients substantially higher than one: for inhalation (Fig. 3a), the highest exposures and hazard quotients are observed for ingredients of home maintenance products, the product-chemical combinations with highest hazard quotient deserving further scrutiny in priority. The ingestion reference doses tend to be higher than those for inhalation for the majority of the considered chemicals (Fig. 3b, inversed value on the *y*-axis). Two product categories lead to the highest user hazard quotient: the

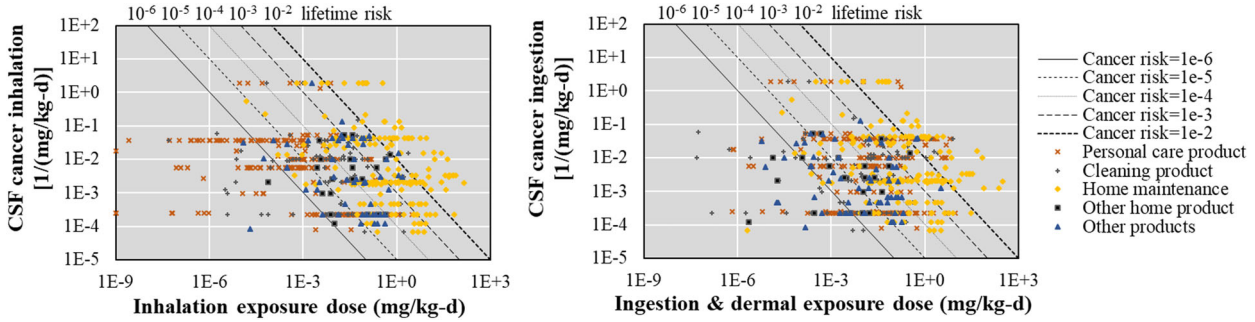

Fig 4. User lifetime cancer risks due to chemical exposures represented as diagonal lines (equi-cancer risks of 10^{-2} to 10^{-6}), determined as the product of exposure dose for inhalation (a), and the sum of ingestion and dermal exposure (b) of the adult user on the *x*-axis, multiplied by the cancer slope factor (CSF) on the *y*-axis.

ingredients of home maintenance products with low ingestion *RfD*s, and the ingredients of specific personal care products, such as body lotions, that have lower *RfD*s but are taken in dermally at higher doses. Overall, 60% and 12% of the chemical-product combinations have hazard quotients exceeding 1 and 100, respectively, up to more than 10^4.

For cancer, taking the example of ethylbenzene (Fig. 1), the user dose of 5.7 mg/kg$_{BW}$/d is multiplied by a cancer slope factor of 4.2×10^{-2} (mg/kg$_{BW}$/d)$^{-1}$ to yield a high cancer risk over lifetime of 2.4×10^{-1}, substantially higher than the commonly acceptable range at population level of 10^{-6} to 10^{-4}. Fig. 4a presents the resulting estimates of carcinogenic risks for a lifetime use of each product-chemical combination. Risks are shown as diagonal lines, representing for each considered product-chemical combination the cancer slope factors as a function of the corresponding exposure doses. This screening shows that for multiple products, continuous exposures to these chemicals in products can potentially yield high cancer risks for the user, exceeding 10^{-2} over lifetime, especially for inhalation and dermal exposures of ingredients in home maintenance and personal care products. Substances with the highest cancer slope factor of 1.5 to 4 (mg/kg$_{BW}$/d)$^{-1}$ are chrysene, formaldehyde, and 3,3'-dimethylbenzidine dihydrochloride. They can lead to substantial lifetime risks for both inhalation and ingestion up to or higher than 10^{-2} when used on a regular basis. But substances such as triethanolamine (CSF = 4.2×10^{-2}) or dichloromethane (CSF = 3.8×10^{-2}) with two to three orders of magnitude lower CSF can lead to similar risks due to two to three orders of magnitude higher exposure doses.

This high-throughput screening analysis indicates that exposure to chemicals in products might lead to high exposure for regular product users for multiple product-chemical combinations and enable us to identify chemical combinations inducing substantial risks and that deserve further scrutiny. At the same time, absolute user risks must be taken with care, since for chemicals with low usage at population level, it is unlikely that these products will be used on a daily basis over lifetime, apart from professional usage of for example paint strippers. Also, most dermal effect data are extrapolated from ingestion toxicity data and might overestimate real risks. Overall 14% and 9% of all the chemical-product combinations have user lifetime cancer risks exceeding 10^{-6} and 10^{-4}, respectively (up to 10^{-1}), but these proportions increase substantially to 94% and 60% when only considering the chemicals with available cancer data.

3.3.2. *Cancer Risk Characterization at Population Level*

Considering that only 77 persons are using ethylbenzene in paint out of the total considered population of 25,000, cancer risks are reduced at population level, in the order of 10^{-4}, which is still a relevant risk for an entire population. Since there are large variations in product usage and penetration in the population (Fig. 2), Fig. 5 analyses how the user cancer risks translate at population level as a function of the fraction of population using this product. It shows that the highest population risks are found for chemical usage in broadly used leave-on personal care products and in a lesser extent in cleaning products, due to the combination of intermediate chemical usage, high PiFs, and broad usage of these products in the population (right upper corner of Fig. 5, see list in Supporting Information, column AZ). The highest individual risks to the user tend to correspond to rarer product usages, that show lower risks at population level (left upper corner of Fig. 5).

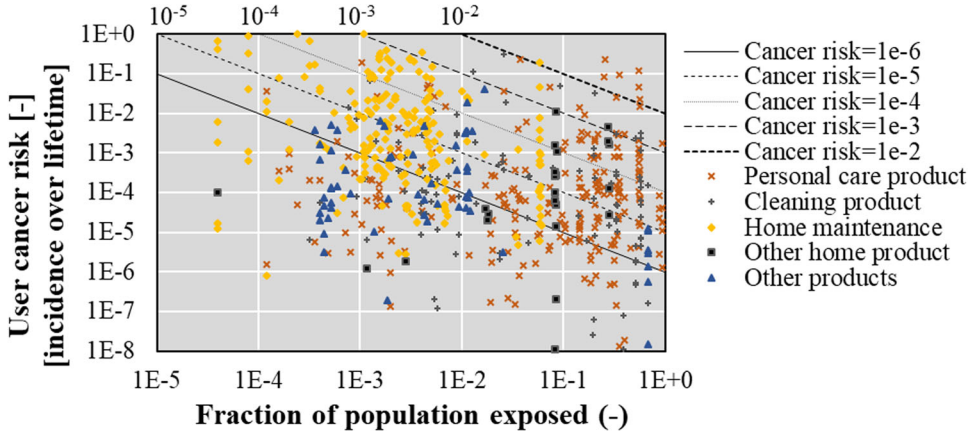

Fig 5. Population cancer risks (based on user exposure) represented as diagonal lines (equi-cancer risks of 10^{-2} to 10^{-6}), determined as the product of fraction of population using the product-chemical combination, multiplied by the user cancer risk associated with chemicals in household products.

3.4. Impact Characterization by Product

Impacts were estimated for 129 chemicals in 233 unique product, for a total of 1,148 product-chemical combinations.

3.4.1. Impacts on Users

Since exposure duration of users is not very well defined over lifetime, the impact-oriented approach of Equation 5 might be more adapted to look at impacts of single daily usage, enabling a first comparison between cancer and noncancer impacts. For ethylbenzene, the inhalation dose of 5.7 $mg/kg_{BW}/d$ is multiplied by a dose–response factor of 0.024 cancer incidence/kg_{intake}, a standard human body weight of 70 kg and an average cancer severity factor of 11.5 DALY/incidence (Fig. 1) to yield a daily carcinogenic impact by inhalation of 107.5 μDALY/user/d, whereas the dermal intake amounts only to 0.5 μDALY/user/d due to a two orders of magnitude lower dose–response factor of 2.6 10^{-4}. The corresponding noncancer impact amounts to 6.9 μDALY/user/d, yielding an overall user impact of 115 μDALY/user/d or 60 minutes of healthy life lost per day, and an average population impact of 0.35 μDALY/person/d for the main user, plus another 0.35 μDALY/person/d associated with the other adults and the child of the household assumed to be present in the home during painting.

Fig. 2e shows the product-chemical combination for the 23 chemicals with highest impacts, expressing the impacts in μDALY/user/d and selecting combinations with impacts higher than 0.1 μDALY/user/d. First, for a given chemical, impacts vary by more than three orders of magnitude depending on the product usage, emphasizing the importance to look at both chemical and product usage and properties. Second, while some of the usual suspect chemicals, such as formaldehyde, 1,4-dichlorobenzene, ethylbenzene, and toluene, were expected among the highest impacting chemical-product combinations, this high-throughput screening suggests that other broadly used chemicals, such as triethanolamine, hydroquinone, or D-limonene, could lead to substantial risks at user level and need further scrutiny. Third, though high-throughput screening tools are primarily designed for relative comparisons, analyzing the order of magnitude of the impacts is nevertheless of interest. Impacts of chemical-product combinations range here from 0.1 up to 100 μDALY/user/d or 50 minutes of healthy life potentially lost per user per day. This is in the same order of magnitude as other risk factors included in the global burden of disease study series, such as nutrition-related risks (e.g., 35 minutes of life lost per serving of processed meat—Stylianou et al., 2016; Stylianou, Fulgoni, & Jolliet, *submitted*).

Fig. 6a presents the impacts associated with the different ingredients of the 20 household products with the highest impacts on users. The products with the highest user impacts are home maintenance products such as adhesive remover, paint stripper, concrete cleaner, and home applied pesticides, with substantial impacts of the order of magnitude of 1000 μDALY/user/d or 500 minutes of healthy life lost per day. This emphasizes the importance of

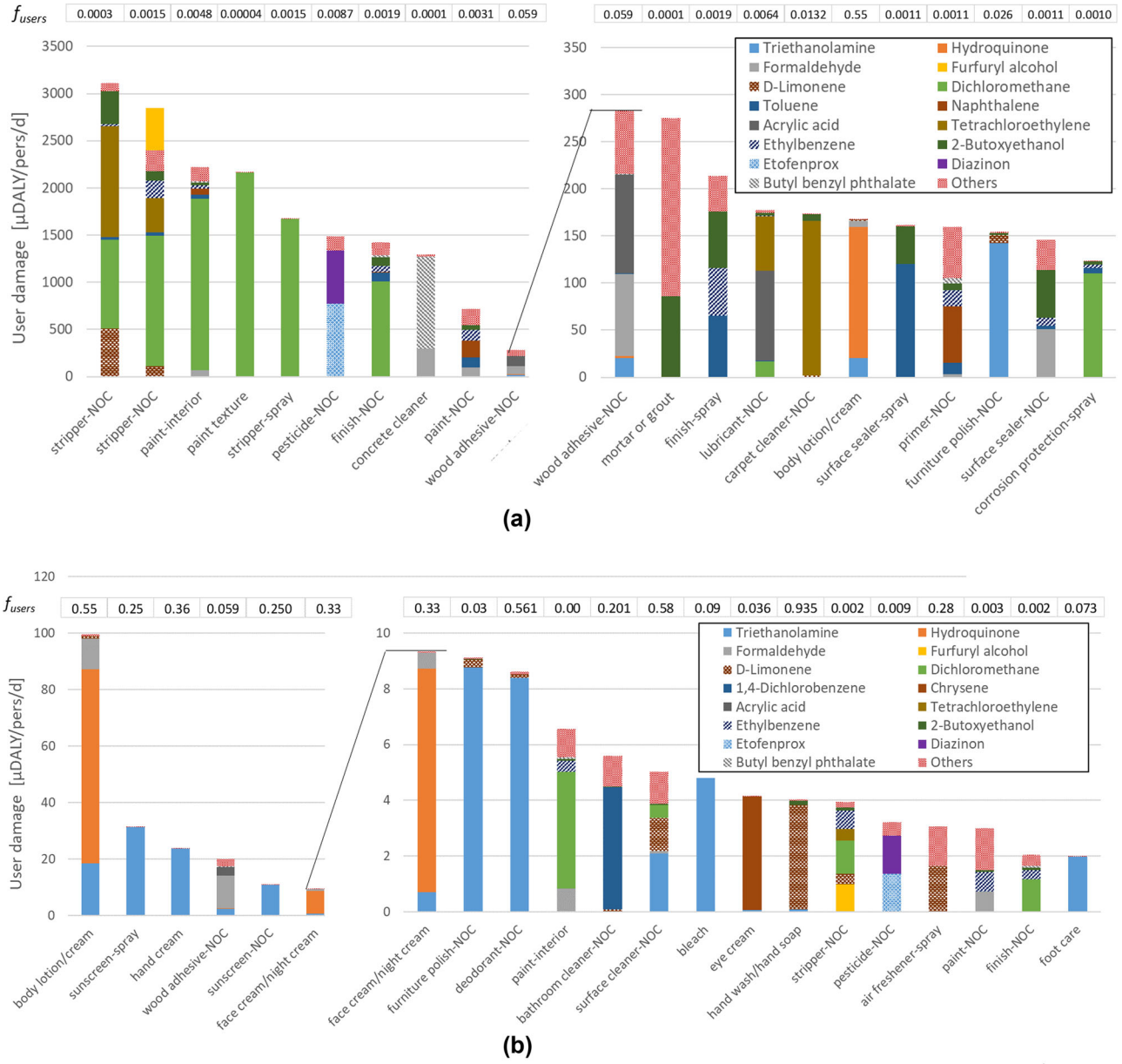

Fig 6. Cumulative impacts on human health associated with chemicals in household products, differentiated by main contributing chemicals of the 20 household products with highest impacts for (a) product user impacts and (b) average population impacts accounting for the fraction of users in the population. Note the change in scale between the first five products and the others.

using protective equipment for such home maintenance tasks to limit impacts. Personal care products and cleaning products are also found among the 23 most impacting chemicals on users, but rather in the order of a 100 μDALY/user/d or 50 minutes of healthy life lost per day. Fourteen main contributing chemicals are found in Fig. 6a and would deserve further investigation beyond the present screening, including tetrachloroethylene, dichloromethane, furfuryl alcohol, D-limonene, formaldehyde, butyl benzyl phthalate for home maintenance products, as well as diazinon and 1,4 dichlorobenzene for use of pesticides at home. Diazinon has been one of the most widely used insecticides in the U.S. for household but

was phased out for residential use in early 2000 and would rather represent usage of products kept over long period on consumers' shelves.

3.4.2. Health Impacts at Population Level

Since the fractions of the population using each product vary widely depending on each household product and product category, we also study the products and chemicals contributing most to the population burden of disease. Multiplying impact per user per day by the fraction of the population using the product-chemical combination and summing up over all ingredients of a product yields the cumulative impacts at population level associated with the consumer use of that product (Fig. 6b).

In this screening assessment, products with the highest population burden of disease are primarily personal care products, and in particular body lotions and creams, due to the combination of high fraction of users in the population and high quantities of product applied directly on the skin. Home maintenance products and pesticides are also found among the 20 most impacting chemicals at population level, but with reduced impacts compared to user impacts due to their lower usage at population level. The chemicals that deserve further investigations include hydroquinone, triethanolamine as well the ingredients identified above for the user impacts of home maintenance products and home applied pesticides.

4. CONCLUSIONS, LIMITATIONS, AND RECOMMENDATIONS

This high-throughput screening of risks and impacts associated with chemicals in consumer products enables the identification of the chemical-product combinations with highest impacts to be further scrutinized in priority. It demonstrates large variations of up to 10 orders of magnitude in impact between both chemicals and product combinations, consumer products being responsible for high exposure, and risks for users and thus for the general population. It also shows that prioritization based on hazard only would neglect orders of magnitude variations in both product usage and exposure that need to be quantified. To address this issue, present mass balance-based models are already able to provide exposure estimates for both users and populations.

Results show that both individual and population exposures need to be considered when prioritizing chemicals. Prioritization mostly based on biomarker levels in the population (Ring et al., 2019; Wambaugh et al., 2014) might neglect substantial exposures of individuals using certain products that are only used by a small fraction of the population, which are unlikely to show up as being important when sampling the general population.

The present screening shows substantial risks and impacts for household users of several home maintenance, personal care, and cleaning products, whose exposure to their ingredients might exceed reference regulatory doses by several orders of magnitude. This is primarily related to the high intake doses experienced by users exposed to chemicals in consumer products rather than to toxicity level per unit dose: The median intrinsic toxicity of compounds in the considered household products being a factor 3 to10 lower than the median of USEtox chemicals, and the most toxic being a factor 10,000 less toxic than 2,3,7,8 tetrachlorodibenzodioxin (TCDD).

The scope of the present assessment is limited to screening and prioritization purposes and therefore suffers several limitations. First, the present study focuses on the incremental or marginal increase in exposure due to the considered household products, and does not include background exposures neither from environmental emissions, nor from other products (building products, food contact materials, articles, textiles, etc.), which could increase the absolute carcinogenic risks or noncarcinogenic hazard quotients. Second, for fate and exposure, the models are only presently applicable to organic substances, and their validity for polar or ionizable chemicals needs to be further investigated, along with developing methods for addressing inorganic chemicals, which cannot currently be characterized (Kirchhübel & Fantke, 2019). The present article focused on adult exposure, children being only considered for background exposures, with specific exposure parameters for contact to articles and building materials (Fantke et al., 2016). We however acknowledge the need to carry out dedicated studies on children exposure to chemicals in various children products, such as carried out by Aurisano, Huang, Mila I Canals, Jolliet, and Fantke (2020) for toys, which follow the same exposure framework as proposed in the present study. Further research is also needed to improve the quantitative estimates for several exposure pathways, in particular for child mouthing, dermal contact, and gaseous dermal exposures to chemicals in consumer products. Third, for more than half of the chemicals, human toxicological data were not available or

estimates were outside of the QSARs' applicability domain. These require additional research efforts as risk related to these chemicals is currently underestimated. The uncertainty on the toxicity QSAR is high, with mean value prediction absolute error of 1 order of magnitude for ingestions *RfD*s, and 1.5 orders of magnitude for RfCs (factor 30), for which less data are available to train the *in silico* model (Wignall et al., 2018). The route-to-route extrapolation is also associated with a factor 50 uncertainty (Rosenbaum et al., 2011), and has limited validity in case toxicokinetic and adsorption rate differ substantially by route, and ingestion reference doses and dose–response data were also used to evaluate dermal exposures. There is therefore a need to take advantage of the growing amount of toxicological data that are becoming available on the Comptox dashboard (https://comptox.epa.gov/dashboard) or at the European Chemical Agency (https://echa.europa.eu/information-on-chemicals) for example, and to derive best available values for comparative assessment. This might require additional efforts related to data interpretation, quality control and aggregation, since data from different sources come with different levels of quality, scrutiny, and details (Fantke, Aurisano et al., 2020). Fourth, further investigations are required for evaluating the impacts of products and chemicals identified by the present screening with the highest user and population impacts, analyzing in depth each steps of the impact pathway from product usage up to exposures and toxicity data. For example, high impacts are associated here with triethanolamine, due to carcinogenic effect since triethanolamine is found with positive cancer responses in mouse in the carcinogenic potency database (https://files.toxplanet.com/cpdb/index.html). Further investigation is however needed, since this chemical is considered as not classifiable as to its carcinogenicity to humans by the International Agency for Research on Cancer (IARC-Group 3). Main sources of uncertainties in this assessment include the market penetration of different ingredients for a given product, the chemical content inside the products, the exposure estimates for recently identified exposure pathways, such as gaseous dermal uptake, and the determination of chemical specific toxicological dose–responses for the large number of ingredients used here. This results in typical uncertainties of two to three orders of magnitude, which remains discriminant for prioritization purposes and for identifying product-chemical combination that needs further scrutiny, when considering the more than 10 orders of magnitude variation in risk across all chemical-product combinations considered in the present study.

The translation of impacts into μDALY/user/d and minutes of healthy life potentially lost per user per day also opens the possibility to compare impacts of chemicals in consumer products with other types of impacts associated with, for example air pollution, pesticides, nutrition, occupational exposure, or physical activity toward an exposome-based approach. The present study suggests that impacts due to exposure of users to chemicals in household products are substantial, in the order of 100 μDALY/user/d for personal care products to even a 1,000 μDALY/user/d for some home maintenance products. This is in the same range as the main risks factors from the global burden of disease, such as nutrition-related risks (e.g., 70 μDALY per serving of processed meat—Stylianou et al., 2016; Stylianou et al., submitted) or occupational risks (e.g., 200 to 1,000 μDALY/user/d—Kijko, Margni, Partovi Nia, & Jolliet, 2015), and substantially higher than the average impacts due to general population exposure to pesticides residues estimated at between 0.01 and maximum 5 μDALY/user/d (Fantke, Friedrich, & Jolliet, 2012). This emphasizes the importance to include the use of household consumer products in survey such as National Health and Nutrition Examination Survey, in order to be able to perform epidemiological studies of the impacts of their ingredients. It also calls for more scrutiny from a regulatory perspective, in order to ensure the same level of safety that has been implemented for limiting pesticide residues in products (in e.g., banning diazinon from residentially used products as discussed above), applying systematically alternatives assessment approaches (Fantke & Illner, 2019; Tickner et al., 2019) to substitute in priority chemicals with highest potential impacts. Finally, at the user level, the magnitude of potential impacts calls for the use of protective measures, such as the systematic usage of gloves when cleaning, the use of respiratory protective masks when using home maintenance products such as paint or paint strippers containing volatile organic compounds (VOCs), and the reduction of the applied quantities of chemicals as body lotions, by using more natural products such as coconut oil for moisturizing purposes, for example.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Supplemental Material