



Chemicals of concern in plastic toys

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ABSTRACT

We present a list of Chemicals of Concern (CoCs) in plastic toys. We started from available studies reporting chemical composition of toys to group plastic materials, as well as to gather mass fractions and function of chemicals in these materials. Chemical emissions from plastic toys and subsequent human exposures were then estimated using a series of models and a coupled near-field and far-field exposure assessment framework. Comparing human doses with reference doses shows high Hazard Quotients of up to 387 and cancer risk calculated using cancer slope factors of up to 0.0005. Plasticizers in soft plastic materials show the highest risk, with 31 out of the 126 chemicals identified as CoCs, with sum of Hazard Quotients >1 or child cancer risk >10⁻⁶. Our results indicate that a relevant amount of chemicals used in plastic toy materials may pose a non-negligible health risk to children, calling for more refined investigations and more human- and eco-friendly alternatives. The 126 chemicals identified as CoCs were compared with other existing regulatory prioritization lists. While some of our chemicals appear in other lists, we also identified additional priority chemicals that are not yet covered elsewhere and thus require further attention. We finally derive for all considered chemicals the maximum Acceptable Chemical Content (ACC) in the grouped toy plastic materials as powerful green chemistry tool to check whether chemical alternatives could create substantial risks.

1. Introduction

A wide range of chemical additives are used in plastic products, including children's toys, to obtain or optimize specific product properties, such as material hardness or elasticity (Andrady and Rajapakse, 2019; Becker et al., 2010). Widely applied types of additives are used as plasticizers or softeners (to increase plasticity or decrease viscosity), flame retardants (to prevent or inhibit ignition), surface-active substances (e.g., to create foam with specific properties), stabilizers, colorants and fragrances (Geyer et al., 2017; Groh et al., 2019). Public concerns continue to emerge about the possibility of plastic toys containing chemical substances that are harmful to humans (Ionas et al., 2014; Negev et al., 2018b). This includes phthalate plasticizers (Ejaredar et al., 2015; McCombie et al., 2017; Schmidt, 2008), brominated flame retardants (Chen et al., 2009; Gallen et al., 2014; Guzzonato et al., 2017), bisphenol A (BPA) (Negev et al., 2018b; Rochester, 2013), odorants (Wiedmer and Buettner, 2019), colorants and stabilizers containing metals (Guney and Zagury, 2013; Omolaoye et al., 2010), as well as non-intentionally added substances (NIAS) (Bignardi et al., 2017;

Zimmermann et al., 2019). Several of these chemical constituents may pose negative health effects on humans, including children, either individually or in combination from a single or multiple sources (e.g., Fantke et al., 2018). Generally, infants and young children are considered particularly sensitive to chemical exposure for various reasons, including their fast metabolic rate, high surface area to body weight ratio, and fast growth of organs and tissues (Ionas et al., 2016; Trasande et al., 2018; Turner, 2018).

Numerous regulations are in force worldwide for limiting and controlling the application of harmful additives and more generally potentially toxic chemicals in plastic toys. In Europe, for example, chemicals in toys and childcare products are regulated by the Toy Safety Directive 2009/48/EC (European Parliament, 2009), under which the usage of >70 substances (e.g., phthalates, allergic fragrances, reducing agents) is restricted or prohibited. In North America, with the Consumer Product Safety Act in Canada (CMJ, 2018) and the Consumer Product Safety Improvement Act (CPSIA) in the U.S. (Lee, 2009), phthalates plasticizers are regulated. Similarly, regulations focusing on phthalate additives are in force also in some other countries, such as Japan and

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Egypt (MHLW, 2010; GIFTD, 2013). However, a consistent international approach for globally regulating chemicals in children's products and toys is lacking (Negev et al., 2018a). Existing regulations usually focus on particular chemicals (e.g., phthalates, brominated flame retardants and metals), while currently not covering the broad range of chemical substances that are found in plastic toys. In addition, some toxic and banned additives are still found in plastic toys also on regulated markets, for example in case of recycling contaminated plastics, unawareness by producers or absence of regulations in the producing country (Borling et al., 2006; Ionas et al., 2014; McCombie et al., 2017). Throughout the present text, the term "toy materials" refers to any material including plastic and non-plastic materials, while "plastic toy materials" refers specifically to plastic polymer matrices.

To compare the various chemicals in plastic toys for their potential exposure and risk, chemical risk screening approaches developed for alternatives assessment and chemical substitution are a suitable starting point (Fantke and Illner, 2019; Jolliet et al., 2020). However, existing tools lack efficient methods to quantify exposure for the thousands of marketed chemical-material combinations (Fantke et al., 2016; Greggs et al., 2019). To quantitatively estimate exposure to chemicals in various toy materials, high-throughput screening approaches might be applied instead (Csiszar et al., 2016; Ernststoff et al., 2017; Fantke et al., 2020b).

To address these needs, our overall aim is to develop an approach to screen the various chemicals found in plastic toys for both their potential exposure and health effects, building on high-throughput exposure modeling, and highlighting possible Chemicals of Concern (CoCs), which we identify based on defined prioritization criteria. To achieve this aim, we focus on the following specific objectives: (a) to collect data on reported chemicals in toys, their function in products and amount of plastic toys used per child, (b) to define prioritization criteria and characterize exposure and toxicity effects of chemicals in plastic toys, (c) to evaluate the magnitude of potential risks of chemicals in toys, identify CoCs above a given risk level, and compare our results with existing regulatory prioritization lists and, (d) to estimate the mass fraction above which chemicals become a concern. This can inform decision makers and toy companies to pinpoint relevant priority chemicals and focus future development of safer chemicals and toy materials.

2. Methods

2.1. Toy composition and amount of toys used per child

Chemical composition data for plastic toys are scarce (Groh et al., 2019), since manufacturers often do not disclose this information and toy composition databases are currently not available. For building a dataset of chemicals found in plastic toys, we extracted chemical testing information for specific toys from 25 peer-reviewed studies. The number and material type of toys tested, and the number and classes of chemicals detected or focused on in each study, is summarized in [Supplementary Materials](#) (SM, Table S1). For building the dataset, we checked and harmonized where needed the reported chemical names, CAS numbers, and chemical functions. Chemicals were classified according to their specific function in plastic materials based on the information reported in the considered studies. Wherever such information was missing, we retrieved the function from other studies (e.g., Isaacs et al., 2016). Furthermore, we checked that the reported chemical concentrations were within the maximum plausible ranges for the specific chemical function, e.g., for plasticizers ranging up to 70% w/w (Hahladakis et al., 2018).

Since detailed plastic property data were usually not reported, and our focus is on the chemicals constituents rather than on the different plastic types, we simplified the characterization of the wide range of available plastic toys on the market by grouping plastic materials into three main categories, namely "hard", "soft" and "foam" plastic. Where the plastic material was not specified, we defined as soft plastic all materials with a mass fraction of plasticizers higher than 20%, else we

defined them as hard plastic (McCombie et al., 2017). We finally grouped all other toy materials (e.g., wood, textile) into "non-plastic".

The information reported in the identified testing studies does not allow for evaluating actual exposure of children in specific regions to actual toys. Instead, the available information allows us to identify potential chemicals of concern by providing exposure and risk estimates of all chemicals found in plastic toy materials based on grouping the various distinct toy materials into three main material categories with defined characteristics (see SM, Table S2). To characterize exposure of children to chemicals found in plastic toy materials, we estimated an average annual mass of 18.3 kg plastic toys introduced into a household per child in western countries (kg/child/year), see SM (Section S1) for more details.

2.2. Estimating exposure for chemicals in plastic toy materials

For calculating human exposure to chemicals in plastic toy materials, we adapted the recently proposed Product Intake Fraction (PIF) framework (Fantke et al., 2016). This matrix-based framework starts from a set of direct chemical mass transfer fractions from a given product compartment (e.g., plastic toys) to and between various near-field and far-field environmental and human receptor compartments. By matrix inversion, we obtain a set of cumulative chemical mass transfer fractions for the given product. Cumulative transfer fractions reaching the human receptors' respiratory tract (via inhalation exposure), gastrointestinal tract (via ingestion exposure) and epidermis (via dermal exposure) are defined as product intake fractions expressed as chemical mass taken in via a particular exposure route per unit mass in the given product application. Aggregating exposure routes yields the total product intake fraction as mass fraction of a chemical in a product that is cumulatively taken in by humans via all routes (Rosenbaum et al., 2011). Since this framework allows to distinguish receptor groups, we derive, in our case, product intake fractions relating the chemical mass taken in by children via different exposure routes and underlying pathways per chemical mass unit within a given plastic toy material expressed in mg chemical intake per mg chemical in toy material.

While direct mass transfer fractions between compartments of the near- and far-field environments are USEtox compatible and explained in the framework description (Fantke et al., 2016; Rosenbaum et al., 2015), we describe in the following the direct transfer fractions from the plastic toy material to the indoor environment via volatilization, to the human epidermis via dermal contact, and to the human gastrointestinal tract via hand-to-mouth exposure. Two models are employed for describing direct transfer from toy material to indoor air depending on chemical-material properties, namely a diffusion-limited and a partition-limited model. The related direct mass transfer fractions from plastic material to indoor air, $TF_{\text{material} \rightarrow \text{air}}$ ($\text{mg}_{\text{in air}}/\text{mg}_{\text{in plastic}}$), is a function of the characteristics of the chemical, the toy and the indoor environment, as well as the exposure duration. The equations for diffusion-limited and partition-limited $TF_{\text{material} \rightarrow \text{air}}$ from toy material to humans, and for the direct transfer fractions for dermal and hand-to-mouth exposure are presented in details in SM, Sections S3 and S4 (Csiszar et al., 2017; Ernststoff et al., 2016; Huang and Jolliet, 2019a, 2016). Note that mouthing (object-to-mouth) as an exposure pathway is not directly incorporated in our modeling framework due to the lack of reliable models for deriving chemical and material-specific migration rates into saliva for the various relevant chemicals. To nonetheless consider mouthing exposure, we derive exposure estimates for mouthing for the substances for which experimental migration data are available in the literature, and compare them with the other exposure pathways considered in our analysis (see SM, Section S5, for more details).

The three key input parameters to determine the mass transfer fractions are the material diffusion coefficient D_m (m^2/s), the plastic material-air partitioning coefficient K_{ma} (–) and the toy material-water partitioning coefficient K_{mw} (–) and were estimated via quantitative property-property relationships (QPPRs) using chemical and plastic

material properties as inputs (Huang et al., 2017; Huang and Jolliet, 2019a, 2019b). Skin permeation was estimated using a dermal absorption model, considering both dermal gaseous uptake and direct dermal contact (Huang et al., 2019). For values for other parameters, including indoor characteristics and exposure factors, a typical OECD household was used as reference (Little et al., 2012; Rosenbaum et al., 2015; Wenger et al., 2012), while typical values for exposure factors for children were obtained from several sources (Leech et al., 2002; Little et al., 2012; U.S. EPA, 2011a). Input parameters for our three main plastic toy material categories are summarized in SM, Table S2. We used a default exposure duration of 3 years with 18.3 kg of plastic toys purchased per child per year, assuming that toys are on average kept for 3 years in the household. Additionally, a shorter exposure duration (50 days) and lower toy mass introduced (9.15 kg/child/event) were tested to assess effects associated with initial exposures following reception of toys at a given event such as a birthday, and to further differentiate between semi-volatile organic compounds (SVOCs) and volatile organic compounds (VOCs) (Huang et al., 2019; Huang and Jolliet, 2016).

In addition, a full sensitivity analysis was carried out on our exposure estimates with focus on the aspects in our model that affect the estimated PiFs. We identified eight exposure model input parameters with relevant uncertainties, covering chemical emissions from plastic materials, dermal gaseous uptake, dermal contact and dust ingestion. By categorizing the identified parameters, we constructed a set of 16 sensitivity scenarios covering a set of plausible parameter combinations (See SM, Section S6, for details).

Finally, human exposure doses (mg/kg_{BW}/d) were calculated for each exposure route by multiplying product intake fractions by the chemical content in toy material when introduced into the household. In the present study, the term 'exposure dose' refers to the daily amount of a chemical substance taken in by a human per kg body weight.

2.3. Combining exposure and toxicity for chemical prioritization

To rank chemicals in plastic toy materials according to their potential risk for humans, we combined these exposure estimates with toxicity values for cancer and non-cancer effects.

For non-cancer effects, exposure doses were compared to reported reference doses (*RfD*) per exposure route, which were either directly expressed into mg/kg_{BW}/d or converted from reference concentrations for inhalation, to determine potential health risks from exposure to toys. Where available, reference doses were obtained from databases containing experimental data (ATSDR, 2020; U.S. EPA, 2011b, 1997), or otherwise using quantitative structure–activity relationship (QSAR) predictions (Wignall et al., 2018). We applied route-to-route extrapolation from oral to dermal exposure. As a health risk metric relating exposure doses *D* (mg/kg_{BW}/d) to reference doses, we used the hazard index, *HI*, as sum over the exposure route specific hazard quotients (*HQ_x*):

$$HI = \sum_x HQ_x = \sum_x \frac{D_x}{RfD_x} \quad (1)$$

For a given exposure route, hazard quotients express the ratio of an exposure concentration to a reference concentration associated with observable adverse health effects (U.S. EPA, 2018).

For cancer effects, exposure doses were combined with cancer slope factors *CSF* (mg/kg_{BW}/d)^{−1} per exposure route. *CSF* were estimated from TD50 toxic dose data as described by the USEtox effect factors (Rosenbaum et al., 2011). Route-to-route extrapolation to dermal exposure and between ingestion and inhalation exposure was applied, wherever related TD50 values were missing (Rosenbaum et al., 2011). To customize *CSF* to children, we multiplied the *CSF* by an age-dependent adjustment factor (*ADAF* = 4), as an age-weighted factor between 0 and 2 years (*ADAF* = 10) and between 2 and 14 years (*ADAF* = 3) (U.S. EPA, 2005). Multiplying these by the exposure daily

dose (*D_x*) corrected for childhood exposure duration over lifetime (14 yr/70 yr) yields the incremental child cancer risks *CCR* per exposure route *x*. The overall child cancer risk, *CCR_{total}*, associated with a given ingredient or residue in toys is finally obtained by summing up risks across all exposure routes:

$$CCR_{total} = \sum_x CCR_x = \sum_x \left(D_x \times \frac{14yr}{70yr} \times CSF_x \times ADAF \right) \quad (2)$$

To rank chemicals based on exposure and toxicity in support of identifying Chemicals of Concern (CoCs), we applied different prioritization criteria. As CoCs, we define all chemicals with *HI* > 1 and/or *CCR* > 10^{−6}. Additionally, we matched all considered chemicals against existing (mostly regulatory) priority substances lists, to put our results into perspective of other prioritization efforts. The considered regulatory and other substance prioritization lists include—amongst others—lists from the European Toy Safety Directive 2009/48/EC (European Parliament, 2009), the European Candidate List of substances of very high concern for Authorisation (SVHC) (ECHA, 2019) the Cal-Safer Candidate list (CalSAFER, 2019), and the California Proposition 65 list (OEHHA, 2018).

Finally, since the same chemicals can be found at different mass fractions in distinct toys, we estimated the maximum acceptable chemical contents (ACCs) based on our above-listed CoC prioritization criteria. We define this maximum ACC as the material content of a chemical at which reference hazard index *HI_{ref}* = 1 and/or *CCR_{ref}* = 10^{−6}. ACCs for cancer and non-cancer effects are back-calculated from the exposure and toxicity results as follow:

$$ACC_{non-cancer} = \frac{m_x}{HI} \times HI_{ref} \quad (3)$$

$$ACC_{cancer} = \frac{m_x}{CCR_{total}} \times CCR_{ref} \quad (4)$$

where *m_x* (mg_{chemical}/mg_{product}) is the modelled chemical mass fraction in a given toy material.

3. Results

3.1. Reported chemicals in plastic toys

For each of the *n* = 3155 data points of chemicals found in toy materials in our dataset, SM Table S7 provides a substance identifier, the tested material category (hard plastic, soft plastic, foam plastic and non-plastic), the chemical function (if originally reported), and the chemical mass fraction in the tested material. More than one data point might be available for the same chemical or chemical-material combination, across the considered sources. For instance, for the plasticizer diisobutyl-phthalate (DiBP, CAS: 84-69-5), there are 18 data points for hard plastic, 10 for soft plastic and 8 for foam plastic.

In total, we found *n* = 613 unique chemical-material category combinations covering 419 different substances. Fig. 1 presents an overview of the chemical-material category combinations, their average reported chemical mass fractions and corresponding ranges across available data points. Data are ranked according to increasing average chemical mass fractions. Data on the right side of Fig. 1 are more likely to be actual chemical additives fulfilling a specific function in the given material as compared to detected residual concentrations of unintentionally added chemicals (left side). For example, in some considered studies, recycled plastic was tested, which sometimes contained several reported low-concentration substances (e.g., NIAS) (Bignardi et al., 2017; Zimmermann et al., 2019). For the same chemical-material category combination, we found that reported chemical mass fractions can range over several orders of magnitude. For example, the plasticizer di(2-ethylhexyl) terephthalate (DOTP, CAS: 6422-86-2) was found in soft plastic in the range between 0.6% and 20% across 37 data points, and the plasticizer diisodecyl phthalate (DiDP, CAS: 26761-40-0) was found

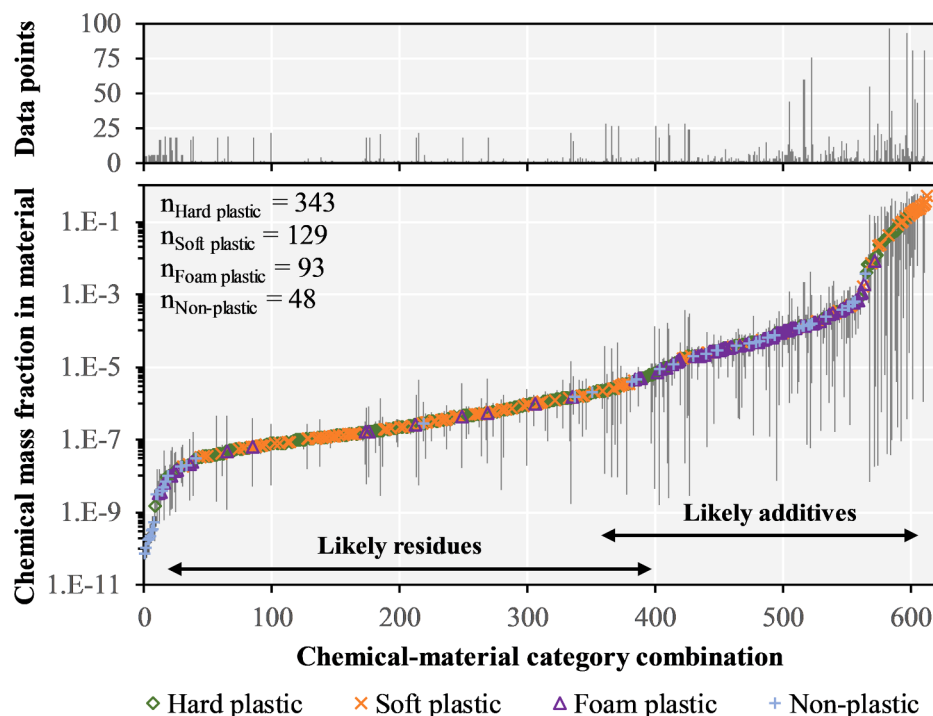


Fig. 1. Chemical mass fractions of the reported chemical-material category combinations in the toy materials dataset, ranked according to increasing average chemical mass fraction across available data points ($n = 613$ chemical-material combinations from 25 studies covering 419 chemicals in 4 tested toy material categories). For each combination, error bars indicate the range of chemical mass fraction while grey bars indicate the number of data points available. The likelihood of a chemical concentration to be an additive or a residue depends on the typical concentration ranges of the specific function that the chemical fulfills in a given material (Hahladakis et al., 2018).

in hard plastic in the range between 0.0003% and 30% across 11 data points. The two chemicals with highest mass fractions found are plasticizers in soft plastic materials: di-2-ethylhexyl hexahydrophthalate (CAS: 84-71-9) with a mass fraction of up to 60%, and di-2-ethylhexyl phthalate (DEHP, CAS: 28553-12-0) with a mass fraction of up to 68%.

3.2. Exposure and toxicity for chemicals in plastic materials

For estimating exposure to chemicals in plastic toy materials, we focused exclusively on the three defined material categories and organic chemicals, since models for characterizing exposure to inorganic substances are currently lacking (Kirchhübel and Fantke, 2019). As starting point for estimating exposure, we used the 95th percentile across reported mass fractions per chemical-material category combination, since this will target chemical ingredients rather than residues that can cover a wide range on the negative side of the error bars, while also avoiding extreme outliers. For single reported data points, we assume that the reported value corresponds to the upper-end of the 95th CI. Exposure and toxicity results across the remaining 456 chemical-material category combinations (only considering organic substances and plastic materials) are summarized in Fig. 2 and SM (Fig. S3). Unless specified otherwise, all results are presented for the standard exposure scenario (i.e., three years of exposure and 18.3 kg of plastic toys purchased per child per year).

Fig. 2A-D presents all data ranked according to increasing hazard indices for non-cancer risk. Fig. 2A shows estimated daily chemical mass applied via plastic toys per child, aggregated according to main plastic material and chemical functions, differentiating plasticizers, flame retardants and fragrances (e.g., perfumers, flavorants), from all “other” functions. We focus on these three chemical functions due to the specific attention that they receive in the literature as common additives of concern (Guzzonato et al., 2017; McCombie et al., 2017). Applied chemical mass ranges widely from 0.01 μg to 50 g per child and day, strongly influenced by chemical mass fraction and chemical function. Thereby, plasticizers show highest daily mass applied (top part of the graph), especially in soft plastics, where plasticizers can reach up to 70% of the toy material mass (Hahladakis et al., 2018; McCombie et al., 2017).

Fig. 2B presents for each chemical-material category combination the total product intake fraction (i.e., cumulatively over all considered exposure routes) and the contribution of each exposure route. For dermal exposure, we distinguished two pathways, namely direct dermal contact and gaseous dermal uptake. For most chemicals, inhalation is the main exposure contributor, followed by ingestion (hand-to-mouth). More specifically, for substances with high octanol–air partition coefficients ($K_{OA} > 10^6$), such as the brominated flame retardant decabromodiphenyl ether (DBDE, CAS: 1163–19-5), hand-to-mouth dust ingestion was usually the predominant exposure pathway. In contrast, inhalation was the main pathway contributing to exposure for volatile substances, which is in line with previous findings (Li et al., 2019). Numerous chemical-material category combinations show a PiF of around 3×10^{-3} (Fig. 2B). For these combinations, almost 100% of the chemical present in the material is emitted during the considered 3 years of exposure; thus, the PiFs are entirely driven by the indoor air intake fraction, derived from the volume of air inhaled by the child per total volume of air in the household. It is important to note that exposure mediated via air and inhalation is more relevant when looking at all toys per household, while transfer to hands and mouth become important when assessing a single toy that a child is actively playing with. Across chemical-material category combinations, total product intake fractions range from 4×10^{-5} for DBDE to 0.01 for the propylene glycol solvent (CAS: 57-55-6), meaning that for the latter chemical, 1% of the mass in the considered plastic toy materials are taken in by children via all exposure routes.

Multiplying the total product intake fractions with corresponding chemical mass fractions in plastic toy materials and the total amount of toys used yields average daily exposure doses per child. Exposure doses are presented in Fig. 2C for both exposure scenarios (i.e., 3 years and 50 days exposure duration), differentiating chemicals according to their volatilization potential from the plastic materials into indoor air. For rapidly emitted substances (i.e., VOCs), we observe that when considering only 50 days of exposure, the average daily dose for the exposed child is systematically higher than in the 3 years exposure duration scenario and will, hence, also yield higher hazard indices. In contrast, when considering slowly emitted substances (i.e., SVOCs), an exposure duration of three years yields moderately higher average daily doses

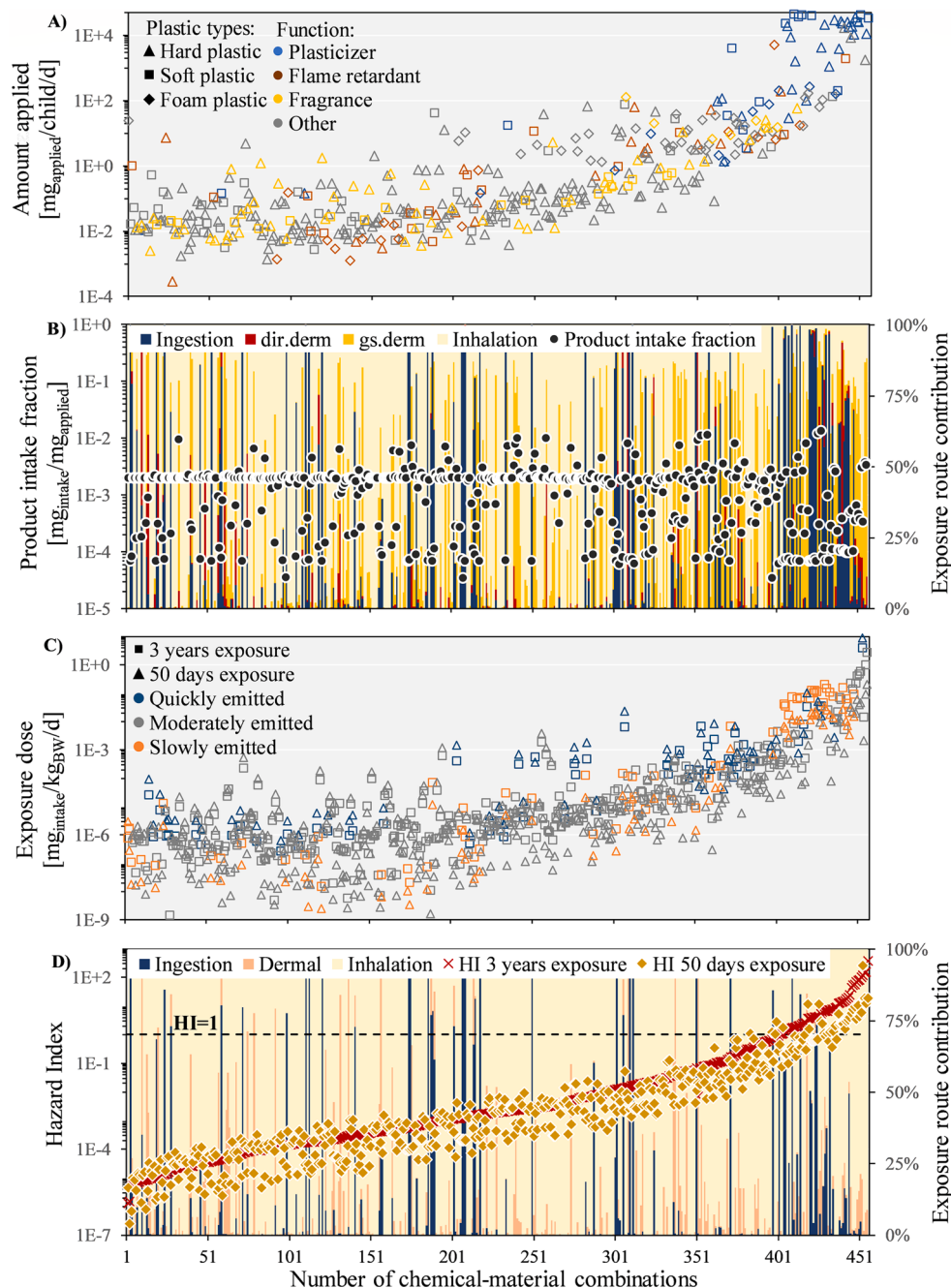


Fig. 2. Amounts of chemical applied (A), product intake fraction (B), exposure doses (C) and resulting Hazard Index for the 3 years exposure duration scenario. In plot A, material types are indicated by symbols and chemical function classes by colors of the symbols, and in plot C, different symbols indicate different exposure duration scenarios, and colors indicate volatilization potential from the plastic materials into indoor air. Chemicals are defined as quickly emitted if >70% of the initial mass migrates into indoor air after 50 days, while they are defined as slowly emitted if less than 10% migrates into indoor air after 3 years. C and D also display results for the 50 days exposure duration scenario. All plots are ranked according to increasing hazard indices in D. In B, dermal exposure is split into direct dermal contact (dir.derm) and gaseous dermal uptake (gs.derm).

than the 50 days exposure with reduced toys quantity associated with a single event. This trend is consistent with previous findings (Huang et al., 2019).

Finally, the ratio of estimated exposure doses for both exposure duration scenarios divided by reference doses for non-cancer effects, and aggregated across exposure pathways yields a single hazard index per chemical-material category combination (Fig. 2D, left axis). Hazard indices based on an average daily dose over 50 days exposure (i.e., first 50 days after introducing new toys into the household) are within an order of magnitude of the average daily dose over 3 years. For both exposure scenarios, we find the highest hazard indices for plasticizers, especially in soft plastic toy materials. For the majority of flame retardants and fragrances, no hazard indices higher than 1 were estimated. For example, the SVOC dibutyl phthalate (DBP, CAS: 84-74-2) shows one of the highest $\text{HI} = 69.8$ (3 years exposure scenario) and $\text{HI} = 1.5$ (50 days exposure scenario). Other SVOC plasticizers are slightly lower,

but found in the same range, including Diisononyl phthalate (DINP, CAS: 28553-12-0) and DiDP. The right axis of this figure displays the contribution of exposure routes to the hazard index, showing that inhalation is generally the main contributor across most chemical-material category combinations, with ingestion being dominant for certain of these categories.

To provide an overview of exposure and toxicity results per exposure route and effect type, we contrast in SM (Fig. S3) average daily exposure doses against reference doses for non-cancer effects and against adjusted cancer slope factors for cancer effects. Combining exposure and toxicity yields in this figure on diagonal iso-lines hazard quotients for all 456 chemical-material category combinations and incremental child cancer risks for 47 chemical-material category combinations, for which cancer effect data were available. As a general trend, we observe that across exposure routes, the majority of substances with $\text{HQ} > 1$ and $\text{CCR} > 10^{-6}$ are plasticizers, followed by flame retardants and very few

Table 1

Overview of Chemicals of Concern (CoCs) in plastic toys. The reported hazard index (HI) and child cancer risk (CCR) for each substance represent the maximum values across the three defined plastic materials. The number of references column (N Ref) represents the number of studies detecting and reporting the substance. The substances are separated into four categories based on being included in regulatory lists of concern as well as on risk-based criteria with color code as : $HI > 10$ or $CCR > 10^{-5}$, : $1 < HI \leq 10$ or $10^{-5} < CCR \leq 10^{-6}$, : $0.1 < HI \leq 1$ or $10^{-7} < CCR \leq 10^{-6}$, and : $HI \leq 0.1$ or $CCR \leq 10^{-7}$.

Substance Name	CAS RN	Function	Regulatory list	HI	CCR	N Ref
Category I – Substances of concern according to our and other studies						
Substances included in regulatory lists of concern with $HI > 1$ and/or $CCR > 10^{-6}$						
Mono(2-ethylhexyl) phthalate	4376-20-9	Metabolite	l	3.87×10^2	n/a	1
Triphenyl phosphate [TPHP]	115-86-6	Flame retardant; plasticizer	j, l-n	1.51×10^2	n/a	1
Diisobutyl-phthalate [DiBP]	84-69-5	Plasticizer	d, e, h-j, l-n	8.25×10^1	n/a	10
Dibutyl-phthalate [DBP]	84-74-2	Plasticizer	d-f, h-n	6.98×10^1	n/a	13
Dioctyl phthalate [DNOP]	117-84-0	Plasticizer	d, f, i, j, l, m	5.79×10^1	n/a	7
Di(2-ethylhexyl) adipate [DEHA]	103-23-1	Plasticizer	l	2.04×10^1	8.99×10^{-5}	4
Di-(2-ethylhexyl)-phthalate [DEHP]	117-81-7	Plasticizer	d-n	1.78×10^1	5.08×10^{-4}	14
Tricresyl Phosphate	1330-78-5	Flame retardant	l, m	1.55×10^1	n/a	1
Bisphenol A [BPA]	80-05-7	Crosslinking agent	d, f, h, i, k-m	1.43×10^1	n/a	3
Di-(2-ethylhexyl)-terephthalate [DEHTP]	6422-86-2	Plasticizer	l	1.35×10^1	n/a	4
1,2-Benzenedicarboxylic acid, butyl cyclohexyl ester	84-64-0	Plasticizer	d	1.27×10^1	n/a	1
Diethyl phthalate [DEP]	84-66-2	Plasticizer	d, i, j, l, m	8.89×10^0	n/a	5
Diisononyl phthalate [DINP]	28553-12-0	Plasticizer	d, f, i, l, m	6.53×10^0	n/a	8
Pentamethyldiethylenetriamine	3030-47-5	n.d.	g	6.15×10^0	n/a	1
Bis[2-(dimethylamino) ethyl] ether	3033-62-3	n.d.	g	4.31×10^0	n/a	1
1,2-Benzenedicarboxylic acid, bis(2-propylheptyl) ester [DPHP]	53306-54-0	Plasticizer	d, l	3.89×10^0	n/a	1
Butyl benzyl phthalate [BBP]	85-68-7	Plasticizer	d-f, h-n	3.79×10^0	6.29×10^{-6}	5
1,4- Diazabicyclo [2.2.2]octane	280-57-9	Catalyst	g	3.77×10^0	n/a	1
2-Ethylhexyl diphenyl phosphate [EHDPP]	1241-94-7	Plasticizer	m	2.59×10^0	n/a	2
Diisodecyl phthalate [DiDP]	26761-40-0	Plasticizer	d, f, i-m	2.18×10^0	n/a	5
diisooctyl phthalate [DiOP]	27554-26-3	Plasticizer	d	1.31×10^0	n/a	2
Tris(2-chloroethyl) phosphate	115-96-8	Flame retardant	f, h, i, k-n	1.09×10^0	9.85×10^{-6}	1
Hexabromocyclododecane [HBCD]	3194-55-6	Flame retardant	a, b, h, i, l	1.03×10^0	n/a	1
Decabromodiphenyl oxide [DBDE]	1163-19-5	Flame retardant	a, h, i, l, m	7.08×10^{-1}	2.40×10^{-6}	4
Tributyl phosphate [TnBP]	126-73-8	Plasticizer	m	4.89×10^{-1}	1.33×10^{-5}	2
Styrene	100-42-5	Monomer	g, k-m	2.99×10^{-3}	1.53×10^{-4}	2
Ethylbenzene	100-41-4	Solvent	g, k-m	9.75×10^{-4}	2.39×10^{-5}	2
Category II – Substances of concern according to our study						
Substances not included in regulatory lists of concern with $HI > 1$ and/or $CCR > 10^{-6}$						
2,2-Dimethylpropane-1,3-diol	126-30-7	Plasticizer	-	1.17×10^2	n/a	1
2,2,4-Trimethyl-1,3-pentanediol diisobutyrate [TXIB]	6846-50-0	Plasticizer	-	1.05×10^2	n/a	5
2,4-Bis(1-methyl-1-phenylethyl) phenol	2772-45-4	n.d.	-	2.47×10^1	n/a	1
Acetyl-tributyl-citrate [ATBC]	77-90-7	Plasticizer	-	7.89×10^0	n/a	5
Diisobutyl adipate	141-04-8	Plasticizer	-	7.19×10^0	n/a	1
di-2-ethylhexyl hexahydrophthalate	84-71-9	Plasticizer	-	6.73×10^0	n/a	1
Tributyl citrate	77-94-1	Plasticizer	-	6.61×10^0	n/a	1
Diethylene glycol dibenzoate	120-55-8	Plasticizer	-	5.38×10^0	n/a	1
1,2,3-Propanetriol, diacetate	102-62-5	Solvent	-	2.51×10^0	n/a	1
Triethyl phosphate	78-40-0	Flame retardant	-	2.09×10^0	n/a	1
Diisononyl-adipate [DINA]	33703-08-1	Plasticizer	-	1.93×10^0	n/a	2
Hexadecanoic acid	57-10-3	Fragrance	-	1.87×10^0	n/a	1
Dipropylene glycol dibenzoate	27138-31-4	Plasticizer	-	1.82×10^0	n/a	1
Tri-(2-ethylhexyl)-trimellitate	3319-31-1	Plasticizer	-	1.74×10^0	n/a	2
Trioctyl trimellitate	89-04-3	Plasticizer	-	1.64×10^0	n/a	1
Diethylene glycol	111-46-6	n.d.	-	2.04×10^{-1}	4.62×10^{-6}	1

Table 1 (continued)

Substance Name	CAS RN	Function	Regulatory list	HI	CCR	N Ref
Tris(2-ethylhexyl) phosphate	78-42-2	Flame retardant	-	1.77×10^{-2}	1.65×10^{-6}	2
Category III – Substances of concern according to other studies						
Substances included in regulatory lists of concern with $HI \leq 1$ and $CCR \leq 10^{-6}$						
Benzophenone	119-61-9	UV absorber	k, l	6.18×10^{-1}	n/a	2
Dimethyl phthalate [DMP]	131-11-3	Plasticizer	d, l	2.78×10^{-1}	n/a	2
Linalool	78-70-6	Fragrance	f, g	1.45×10^{-1}	n/a	1
Decanedioic acid, dibutyl ester	109-43-3	Plasticizer	n	1.03×10^{-1}	n/a	1
Dimethylformamide	68-12-2	Solvent	g, h, k, l	9.46×10^{-2}	n/a	1
Benzene, 1,1-oxybis-, octabromo [BDE-203]	32536-52-0	Flame retardant	i, l	8.48×10^{-2}	n/a	2
2,2',3,4,4',5',6-Heptabromodiphenyl ether [BDE-183]	207122-16-5	Flame retardant	i	6.81×10^{-2}	n/a	2
Butylated hydroxytoluene	128-37-0	Antioxidant	g, j	5.27×10^{-2}	2.67×10^{-7}	2
Bis(2-hydroxypropyl) ether	110-98-5	n.d.	n	4.91×10^{-2}	n/a	1
4,4'-methylenebis benzenamine	101-77-9	Pigment agent; curing agent	g-i, k, l	4.64×10^{-2}	n/a	1
Salicylic acid, benzyl ester	118-58-1	Flavoring agent	f	1.92×10^{-2}	n/a	1
1,2-Bis(2,4,6-tribromophenoxy)ethane	37853-59-1	Flame retardant	l	1.47×10^{-2}	n/a	1
4,4'-Diphenylmethane diisocyanate	101-68-8	Intermediate	i, l	8.36×10^{-3}	n/a	1
2,2',4,4',5,5'-Hexabromodiphenyl ether [BDE-153]	68631-49-2	Flame retardant	i, l	7.42×10^{-3}	n/a	2
1,4-Dioxane	123-91-1	Intermediate	g, k-m	6.65×10^{-3}	7.97×10^{-7}	1
Acetophenone	98-86-2	Fragrance	l	3.33×10^{-3}	n/a	1
Phenol	108-95-2	Monomer	f, g, l, m	2.85×10^{-3}	n/a	1
2-(2-Butoxyethoxy)ethanol	112-34-5	Film forming agent	i	2.13×10^{-3}	n/a	1
Benzene, (1-methylpropyl)-	135-98-8	n.d.	l	2.06×10^{-3}	n/a	1
Tris(dichloropropyl)-phosphate [TDCPP]	13674-87-8	Flame retardant	f, k-m	1.59×10^{-3}	2.03×10^{-7}	1
Ethylene glycol	107-21-1	n.d.	k-m	1.17×10^{-3}	n/a	1
Pentabromophenoxybenzene [BDE-99]	60348-60-9	Flame retardant	l	1.16×10^{-3}	n/a	2
Naphthalene	91-20-3	Colorant	k, l	1.11×10^{-3}	2.60×10^{-7}	1
4-Vinylcyclohexene	100-40-3	n.d.	k, l	9.49×10^{-4}	1.18×10^{-7}	1
2,2',4,4'-Tetrabromodiphenylether	5436-43-1	Flame retardant	a, i, l	9.36×10^{-4}	n/a	2
Biphenyl	92-52-4	Fragrance	l	6.76×10^{-4}	n/a	1
2,2',4,4',5,6'-Hexabromodiphenyl ether [BDE-154]	207122-15-4	Flame retardant	i	5.87×10^{-4}	n/a	2
Diethyl propanedioate	105-53-3	Fragrance	n	5.53×10^{-4}	n/a	1
1,2,4-Trimethylbenzene	95-63-6	Solvent	l	5.11×10^{-4}	9.9×10^{-10}	2
Cumene	98-82-8	Catalyst	k, l	3.88×10^{-4}	n/a	2
4-Methoxyphenol	150-76-5	Antioxidant	f	2.42×10^{-4}	3.81×10^{-8}	1
Styrene oxide	96-09-3	n.d.	k, l	2.09×10^{-4}	5.73×10^{-8}	1
Bisphenol AF [BPAF]	1478-61-1	Crosslinking agent	l	1.88×10^{-4}	n/a	1
1,3-Dichlorobenzene	541-73-1	n.d.	l	1.84×10^{-4}	n/a	1
Diphenyl phthalate [DPP]	131-18-0	Plasticizer	d, h, l, m	1.70×10^{-4}	n/a	1
Propylbenzene	103-65-1	Fragrance	l	9.23×10^{-5}	n/a	2
1,1,2,2-Tetrachloroethane	79-34-5	Solvent	i, k-m	8.91×10^{-5}	6.43×10^{-8}	1
Toluene	108-88-3	Precursor	g, i, k-m	7.65×10^{-5}	3.40×10^{-9}	2
1,4-Dichlorobenzene	78-59-1	Flavoring agent; solvent	l	4.85×10^{-5}	6.60×10^{-8}	1
Methylparaben	99-76-3	Fragrance	j, l, m	4.52×10^{-5}	n/a	1
2-Butoxyethanol	106-46-7	Colorant	i, k, l, n	1.37×10^{-5}	8.45×10^{-8}	1
Decabromodiphenyl ethane [DBDPE]	84852-53-9	Flame retardant	l, m	1.29×10^{-5}	n/a	1
Propylparaben	94-13-3	Fragrance	j, l, m	8.44×10^{-6}	n/a	1
Methyl methacrylate	95-50-1	Colorant	l, n	3.37×10^{-6}	n/a	1

(continued on next page)

Table 1 (continued)

Substance Name	CAS RN	Function	Regulatory list	HI	CCR	N Ref
Isophorone	80-62-6	Precursor	l	2.45×10^{-6}	n/a	1
Category IV – Substances that could not be characterized in our study						
Substances included in regulatory lists of concern but without exposure/toxicity estimates						
Lead	7439-92-1	n.d.	d, e, h, i, k, l	n/a	n/a	7
Antimony	7440-36-0	n.d.	l, m	n/a	n/a	6
Cadmium	7440-43-9	n.d.	d, e, h, i, l, m	n/a	n/a	6
Manganese	7439-96-5	n.d.	l	n/a	n/a	3
Nickel	7440-02-0	n.d.	i, k, l	n/a	n/a	3
Tin	7440-31-5	n.d.	l	n/a	n/a	3
Arsenic	7440-38-2	n.d.	d, i, l, m	n/a	n/a	3
Copper	7440-50-8	n.d.	l	n/a	n/a	3
Cobalt	7440-48-4	n.d.	k-m	n/a	n/a	2
Zinc	7440-66-6	n.d.	l	n/a	n/a	2
Caprolactam	105-60-2	Catalyst	l	n/a	n/a	2
Decamethylcyclotetrasiloxane	541-02-6	Emollient	h,i, l	n/a	n/a	2
octamethylcyclotetrasiloxane	556-67-2	Emollient	g-i, l	n/a	n/a	2
Benzyl alcohol	100-51-6	n.d.	f	n/a	n/a	1
Acrolein	107-02-8	n.d.	l	n/a	n/a	1
Ethan, 1,2-dichloro-	107-06-2	n.d.	b, h, k, l, n	n/a	n/a	1
Mesitylene	108-67-8	n.d.	l	n/a	n/a	1
Benzene, chloro-	108-90-7	n.d.	l	n/a	n/a	1
Ethanamine, N,N-diethyl-	121-44-8	n.d.	l	n/a	n/a	1
Propanale	123-38-6	n.d.	l	n/a	n/a	1
Heptane	142-82-5	n.d.	l	n/a	n/a	1
1,1-Dichloro-1-fluoroethane	1717-00-6	n.d.	c	n/a	n/a	1
Naphthalene, 1-methyl-	25154-52-3	Plasticizer	h-j, l, m	n/a	n/a	1
Formaldehyde	50-00-0	n.d.	i, k-n	n/a	n/a	1
1,2-Dichlorobenzene	540-97-6	n.d.	h, l	n/a	n/a	1
D-Limonene	5989-27-5	n.d.	f, g	n/a	n/a	1
Trichloromethane	67-66-3	n.d.	i, k, l	n/a	n/a	1
Benzene	71-43-2	n.d.	f, i, k-m	n/a	n/a	1
Acetaldehyde (ethanal)	75-07-0	n.d.	k-m	n/a	n/a	1
Methylene chloride	75-09-2	n.d.	g, i, k-m	n/a	n/a	1
Ethan, 1,1-dichloro-	75-34-3	n.d.	k, l, n	n/a	n/a	1
Ethene, 1,1-dichloro-	75-35-4	n.d.	i, k, l	n/a	n/a	1
Propane, 1,2-dichloro-	78-87-5	n.d.	k, l, n	n/a	n/a	1
2-butanon	78-93-3	n.d.	l, m	n/a	n/a	1
Mercury	7439-97-6	n.d.	o	n/a	n/a	1
Tris(2-chloro-1-methylethyl) phosphate	13674-84-5	Flame retardant	o	n/a	n/a	1
2,2',4,5'-tetrabromodiphenylether [BDE-47]	243982-82-3	Flame retardant	o	n/a	n/a	1

“n.d.”: not defined.

^aStockholm Convention on Persistent Organic Pollutants (Stockholm Convention, 2009).

^bRotterdam Convention (Mashimba, 2011).

^cMontreal Protocol (Montreal Protocol, 1987).

^dGlobal Chemicals Outlook II (UN Environment, 2019).

^eRestriction of Hazardous Substances (RoHS) Directive 2002/95/CE (European Commission, 2011).

^fToy Safety Directive 2009/48/EC (European Parliament, 2009).

^gKlinke et al. (2018).

^hCandidate List of substances of very high concern for Authorisation (SVHC) (ECHA, 2019).

ⁱREACH ANNEX XVII (European Commission, 2006).

^jUN Environment (2016).

^kCalifornia Proposition 65 list of chemicals (OEHA, 2018).

^lCalSAFER – Safer consumer products management system (CalSAFER, 2019).

^mWashington State Children's Safe Product Act (CSPA) (Washington State Department of Ecology, 2016).

ⁿU.S. EPA – Chemical Substances Undergoing Prioritization (U.S. EPA, 2019).

^oState of Washington Department of Ecology's Product Testing Database (<https://apps.ecology.wa.gov/ptdbreporting/>).

fragrances, especially in soft plastic toys. The detailed results for all 456 chemical-material category combinations are provided in SM, Table S8.

3.3. Identified chemicals of concern (CoCs)

We apply the two prioritization criteria (i.e., $HI > 1$ and $CCR > 10^{-6}$) to our risk estimates (Fig. 2D) for children exposed to chemicals in plastic toy materials in order to identify a list of chemicals of concern (CoCs) resulting from this risk screening. We then compare the composition of this list to chemicals found in (mostly) regulatory prioritization lists. The proposed CoCs were grouped into four

categories: I) substances included in regulatory lists of concern and high risk estimates, II) substances not included in regulatory lists of concern but high risk estimates, III) substances included in regulatory lists of concern and low risk estimates, and IV) substances included in regulatory lists of concern but without exposure/toxicity estimates. The resulting list of CoCs in plastic toy materials is provided in Table 1, with substances being ranked according to decreasing hazard index. For substances in category IV, it was not possible to estimate non-cancer or cancer risks, either due to model limitations (inorganic substances) or due to missing reported chemical mass fractions. Nevertheless, these chemicals are included as they have been reported as priority chemicals

elsewhere, and have been found in plastic toys. Out of 126 CoCs, we found 31 plasticizer, 18 flame retardants and 8 fragrances. Since chemicals from different classes can be used for the same function (e.g., phthalates, phosphates and adipates can all be used as plasticizers), and the chemical function determines the amount of a chemical used in plastic materials, we classified our evaluated chemicals by their function rather than by chemical class.

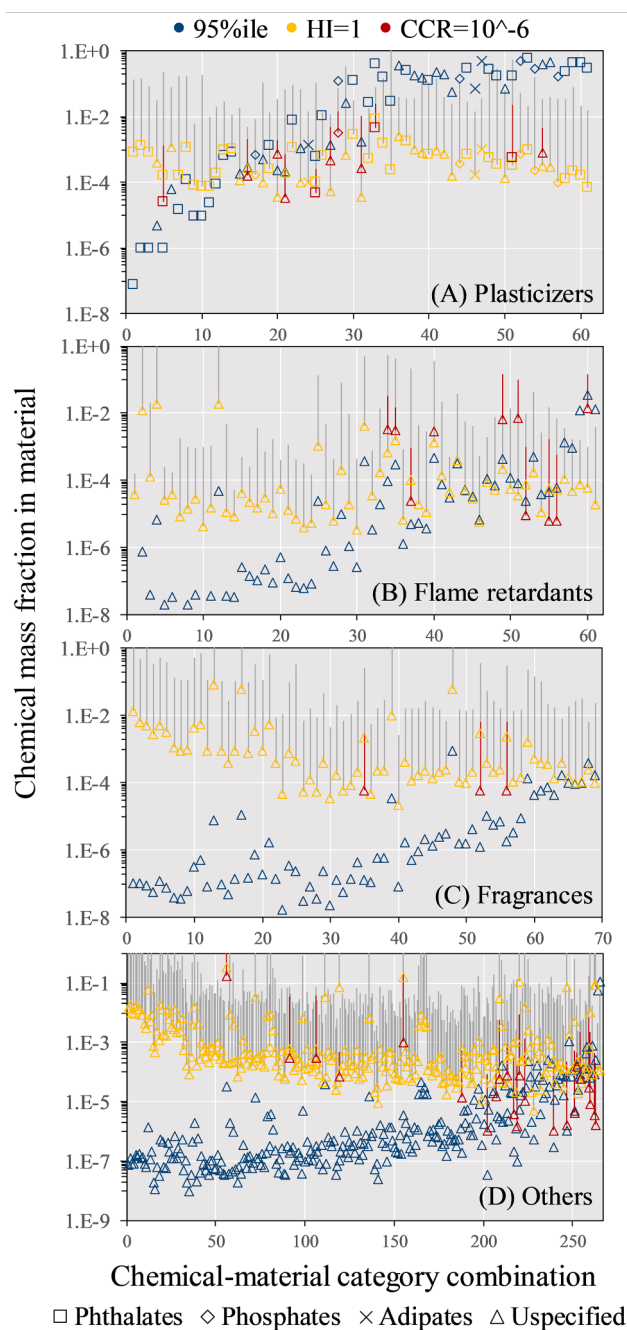


Fig. 3. Estimated maximum acceptable chemical contents (ACCs) considering both non-cancer in yellow (HI) and cancer effects in red (CCR) compared to 95th percentile of reported mass fractions in blue, for all chemical-material combinations, grouped by chemical function: plasticizers (A), flame retardants (B), fragrances (C) and others (D). The data points represent values estimated for the standard scenario of 18.3 kg toys per year, while the error bars represent resulting ranges considering a scenario with a single toy. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.4. Identified maximum acceptable chemical contents (ACCs)

For all the considered chemical-material category combinations we back-calculated the maximum acceptable chemical contents (ACCs) based on our prioritization criteria (i.e., $HI > 1$ and $CCR > 10^{-6}$) according to Eqs. (3) and (4) from the exposure and toxicity factors. Fig. 3A-D compares the ACCs to the 95th percentile of the reported mass fractions per chemical-material combination used in our exposure estimates, differentiating between groups of chemical function. Results are sorted within each chemical function group by increasing ratio between the 95th percentile contents and the identified ACCs, expressing increasing risks from left to right. For plasticizers (Fig. 3A), the ACCs show a relatively narrow range of two orders of magnitude variation, i.e., mass fractions between 4×10^{-5} and 8×10^{-3} . The observed toy contents (95th percentile) are higher than the estimated ACCs for 47 out of 61 combinations, confirming the generally high risk for chemicals used as plasticizers. The differentiation of plasticizer by chemical class markers of phthalates, phosphates, adipates and others yields the highest risk for phthalates (Fig. 3A, top right corner), but also that this high risk is not restricted to phthalates. All plasticizers with chemical mass fractions higher than 3×10^{-2} lead to important risk exceedance, suggesting that non-phthalate alternatives are not substantially better. For flame retardants and other chemicals, despite often lower ACCs than for the plasticizers, only few chemical contents exceed the identified ACCs, for example DBDE in Fig. 3B or BPA in Fig. 3D (top-right corner). None of the fragrances yield a substantial risk (Fig. 3C).

4. Discussion

4.1. Comparison with other priority chemicals lists

The 27 substances identified in category I, correspond well to chemicals present in other prioritization lists. For example, widely regulated phthalates are also identified as CoCs in the present study. These phthalates include DEHP, DINP, DBP, DiDP, di-(n-octyl)-phthalate (DNOP, CAS: 117-84-0), and benzyl butyl phthalate (BBP, CAS: 85-68-7). In addition, five flame retardants that we identified as CoCs appear in various priority lists. This includes triphenyl phosphate (CAS: 115-86-6) and DBDE, of which the former is identified as potential endocrine disrupting chemical, while the latter is currently listed in the European SVHC list.

The 17 chemicals found in category II are identified as CoCs in the present study, but do not appear in other considered priority lists for plastic toys. Hence, these chemicals should receive more attention and require further research. For example, the two plasticizers 2,2,4-trimethyl-1,3-pentanediol diisobutyrate (TXIB, CAS: 6846-50-0) and acetyl tributyl citrate (ATBC, CAS: 77-90-7) are part of the portfolio of commercialized alternative plasticizers to some regulated phthalates. Nonetheless, these alternatives show high hazard indices. These substances should be further assessed to avoid “regrettable substitutions”, focusing on providing consistent toxicity data.

In category III, we listed 45 substances which do not appear as CoCs according to our prioritization criteria but appear as priority substances in other lists. This means that for these substances, the observed chemical content from the literature review was below the acceptable chemical contents (ACCs) identified in Fig. 3. An example is the allergenic fragrance linalool (CAS: 78-70-6), which according to the European Toy Safety Directive 2009/48/EC (European Parliament, 2009) shall be listed if used in toys in concentrations above 100 mg/kg. For substances listed in this category, there is a need to refine exposure estimates and toxicity data based on the possible concern expressed in other lists by also considering additional risk criteria not included in our study (e.g., allergies) and to systematically check for new toys whether the chemical content might exceeds the ACCs.

Finally, we found 37 substances that appear in our category IV,

which contains substances that appear in other priority lists, but for which we were not able to quantify any risk. This includes the allergenic fragrance d-Limonene (CAS: 5989-27-5), which was detected in toys but for which we could not quantify exposure without any reported mass fraction, as well as eleven inorganic substances (all metals). For metals constituents, which all have migration limits in place (European Parliament, 2009), the present approach is not suitable to estimate exposures, and further research is needed to e.g., account for metal speciation inside plastic materials. There is a need to develop exposure models consistent with our applied approach, since metals are generally considered as hazardous and thus require special attention.

4.2. Applicability and limitations of the followed approach

Our exposure and risk screening estimates for chemicals in plastic toy materials are widely applicable, demonstrating that considering exposure in addition to toxicity is crucial for adequate chemical prioritization (Fantke et al., 2020c). Our results represent an initial step to identify (and further assess) potentially suitable alternatives to harmful substances of concern for chemical substitution (Fantke et al., 2015), to help introducing consumer-related health impacts into product life cycle assessment (LCA) (Ernststoff et al., 2019; Fantke et al., 2020b, 2016) and most importantly to systematically identify chemicals of concern for research and policy prioritization (Shin et al., 2015). It is important to specify that in our study we systematically look at chemicals actually found in toy materials and screen their risk for children, which goes beyond individual chemical assessments in current regulatory lists. Our approach can, hence, inform further assessments to complement regulatory lists as well as focus higher tier risk assessments for individual chemical-material combinations.

Our proposed framework also comes with several limitations. One of the main limitations is related to missing chemical composition data for plastic toys. Databases such as the Database of Chemicals associated with Plastic Packaging (CPPdb) (Groh et al., 2019) are required for toys to identify and evaluate the broad range of chemicals used in plastic toy materials. The sources used in the present study (SM, Table S1) were often focusing on selected and known plasticizers and/or flame retardants, but did not usually analyze the entire chemical composition of the tested toy materials. In the compiled database (SM, Table S7), only one data point was available across the considered sources for several chemical-material combinations, introducing additional uncertainty to the results for these substances. In the future, a dedicated study should be carried out to analyze the distribution of concentrations, differentiating residues and additives, and considering at the same time also the function of the chemicals.

In our study, we assess each chemical-material combination separately, without indicating a particular chemical composition of an actual toy. With that, our estimates focus on the chemicals rather than on specific toy materials. Whether children are exposed to a particular chemical-material combination will depend on the use of a chemical in material used for specific toys that are ultimately purchased. As a result, we are currently unable to evaluate risk at the level of actual toys or toy materials, instead we provide information at the level of chemical-material category combination. Since there are various additional chemical constituents found in toy materials for which exposure and risks are currently not characterized, we might underestimate overall risks at the toy material level.

In addition, due to the large variability in plastic toy materials and their different specific properties, we used generic plastic material categories with reference properties. However, this introduces uncertainty related to the estimation of material-(and chemical)-specific diffusion and partitioning coefficients in our exposure results. To overcome this limitation, we suggest to increase the number of tested plastic material categories, characterizing in detail both chemical and material properties studied, to then develop targeted prediction tools of diffusion and partition coefficient, based on relevant material key properties for the

considered exposure pathways rather than experimentally derived fixed material coefficients.

Our estimates are valid for the defined exposure scenarios, using an average annual amount of plastic toys of 18.3 kg introduced in a household per child and an average use duration of three years (i.e., the time that toys are kept in the household). We compared our exposure estimates with daily phthalate intake back-calculated from measured urinary metabolite levels (Lioy et al., 2015). Our results fall within or are close to the high end of the reported ranges for DBP, BBP, DEHP and diethyl phthalate (DEP, CAS: 84-66-2), while being a factor of 24 and 12 higher for DiBP and DINP, respectively. To compare our results with biomarker studies, information about market penetration is needed but largely lacking. Hence, we assume in our screening scenarios an equal market penetration across chemical-material category combinations and consider a high-end user with large amounts of plastic toys purchased per child. Furthermore, we acknowledge that our results are based on various simplifying assumptions to allow for a broad screening of chemicals in toy materials in support of informing higher tier exposure assessments, where our assumptions should be refined and exposure settings be modeled in greater detail (e.g., how children play with toys, or considering specific manufacturing processes).

The results of the sensitivity analysis carried out on our exposure estimates with focus on the aspects in our model that affect the estimated product intake fractions are detailed in SM (Section S6). In summary, when comparing the results of the sensitivity scenarios for our default settings of 18.3 kg toys per year and a single toy, the estimated total product intake fractions fall within one order of magnitude across the 16 sensitivity scenarios (SM, Fig. S2). Analyzing the specific exposure pathways individually, estimated product intake fractions for a typical SVOC vary up to 4 orders of magnitude for dermal contact, and less than one order of magnitude for dust ingestion. In contrast, estimated product intake fractions for a typical VOC vary up to 6 orders of magnitude for dermal contact and less than one for inhalation.

An exposure pathway that is not included in our modeling framework is mouthing. For the substances for which migration rates into saliva were available in the literature, we therefore estimated mouthing exposure based on reported migration rates and compared resulting exposure estimates with the other considered exposure pathways, differentiating between the standard scenario of 18.3 kg toys per year (Fig. 4A) and a single toy (Fig. 4B). From the comparison, we observe that for the 18.3 kg scenario, only in case of total exposure doses below 0.1 $\mu\text{g}/\text{kg}_{\text{BW}}/\text{d}$ mouthing becomes relevant for selected chemicals. As expected, when considering only a single toy, mouthing becomes the predominant pathway for 15% of chemicals with reported mouthing data. These results are currently restricted to 26 chemicals (predominantly phthalates and brominated flame retardants) with available experimental migration rates for 64 chemical-material combinations. Methods that are compatible with our proposed framework should hence be developed to properly estimate mouthing exposure across all relevant chemicals and toy materials.

Finally, in our assessment, we do not consider directly internal metabolism processes, such as chemical biotransformation and bioelimination, since at the interface between intake dose and toxicity level, internal metabolism is already considered in the RfDs and CSFs. Considering internal metabolism is crucial when using bioassays (*in vitro* tests) referring to internal concentration, while we used toxicity data based on *in vivo* tests at intake dose level. Since RfDs were collected from various sources and derived with different uncertainty factors, our hazard results are highly influenced by the considered toxicity data, which might add to the uncertainty in our results and influence the comparability across chemicals. For the majority of considered chemicals, RfDs were predicted using QSAR models, while only for 20% of chemicals experimental data were available.

For chemicals with empirical data, reference doses usually aim to account for the most sensitive endpoint per chemical. Hence, we would not expect to see many false negatives. However, we acknowledge that it

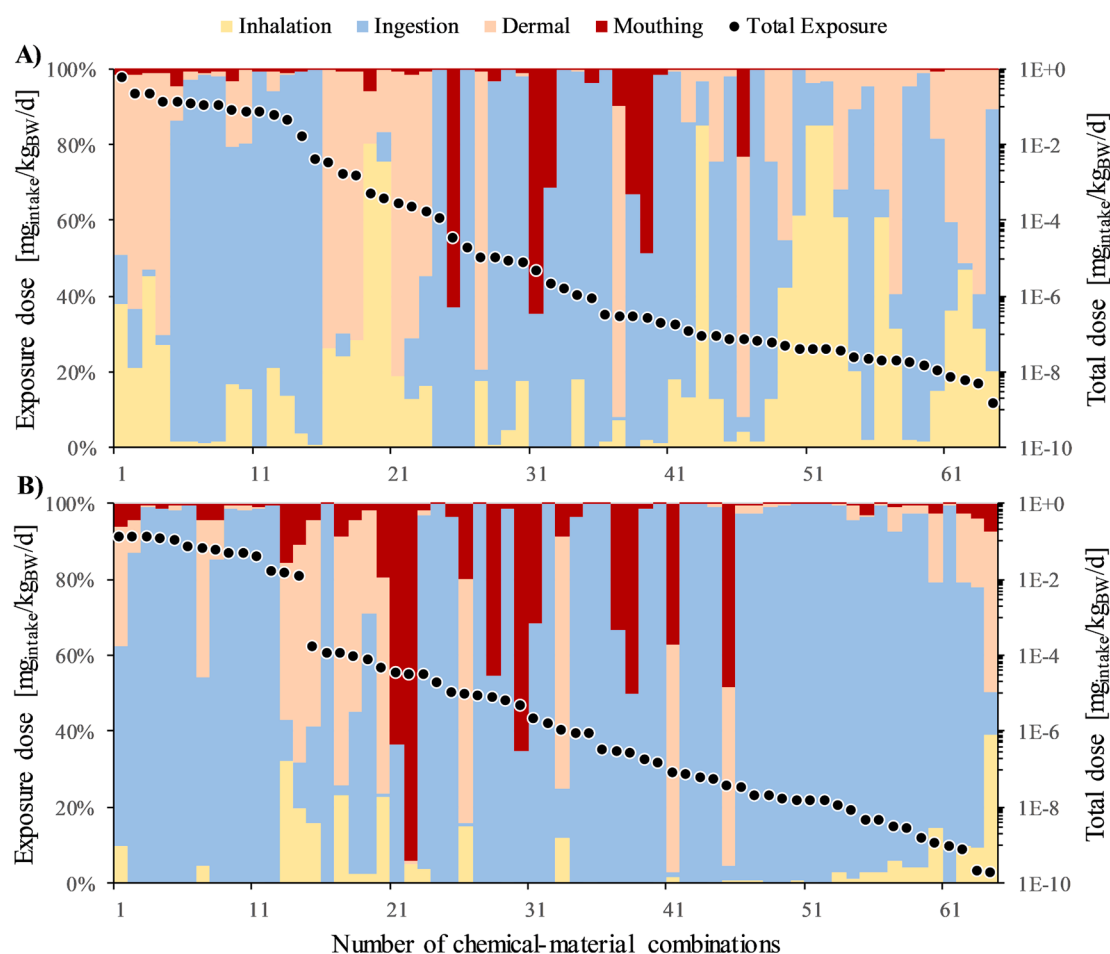


Fig. 4. Contribution of each exposure pathway to the total exposure including mouthing, considering both a standard scenario of 18.3 kg toys per year (A) and a single toy (B). Chemical-material combinations are ranked by total dose in decreasing order (2nd y-axis).

is usually not known whether the most sensitive endpoints have been tested, and further research is required to systematically and comprehensively identify the most sensitive endpoint per chemical. For higher tier assessments, we recommend to explore the use of more endpoint-specific toxicity data. For the majority of chemicals extrapolated with QSARs, it is fundamental to provide extended and higher-quality data and quality-related uncertainty information, both for the experimental-based training sets and for the QSAR screening-level approaches (Fantke et al., 2020a). This is especially true for the prediction of inhalation reference concentrations that were leading to substantially lower reference doses than for ingestion, yielding hazard ratios that might be overestimated for common substances like hexadecanoic acid (CAS: 57-10-3). While such data selection approaches are emerging for example to estimate ecotoxicity values (Aurisano et al., 2019), systematic methods for data curation and selection for human toxicity information is currently still lacking (Smith et al., 2019).

5. Conclusions

Nowadays, existing regulations mainly prioritize a small set of chemicals, and regulators struggle to keep up with the thousands of new chemicals entering the market every year. As recently highlighted by Sackmann et al. (2018) new chemistries and mitigation options are needed to combat regrettable substitution and identify fundamentally safer substances in toys and elsewhere. With our straightforward approach, we could demonstrate that high-throughput exposure screening methods combined with toxicity and chemical composition information can be used to systematically identify harmful chemicals in

plastic materials and evaluate potential alternatives. Nevertheless, we also highlight that an efficient and practical way to reduce exposure to priority chemicals present in plastic toys is to reduce the amount of new toys introduced into our households every year. This is also supported by a recent study showing that the quality of children play is negatively influenced by the abundance of toys, and that fewer toys may help toddlers to focus better and play more creatively (Dauch et al., 2018). Beyond the regulation of chemicals, thus, strategies to address (over-) consumption and/or lifestyles should be considered when designing approaches to Chemicals of Concern (CoCs). With these findings, policy should put focus on supporting the development of fundamentally different chemistries to known CoCs, while future research is needed to better understand plastic composition, exposure patterns and toxicity. Our findings also provide input to enhance the environmentally sound management of chemicals over their life cycle, as promoted by Target 12.4 of the UN Sustainable Development Goals; it is essential that the assessment of alternatives to CoCs considers toxicity impacts and other impacts along their life cycle to avoid unintended trade-offs. The determinations of maximum acceptable chemical contents for the different chemicals represents a powerful green chemistry tool in the hands of product designers to check whether the material content of newly proposed chemical alternatives could create substantial risks.

CCRediT authorship contribution statement

Nicolò Aurisano: Conceptualization, Investigation, Methodology, Formal analysis, Data curation, Visualization, Writing - original draft.
Lei Huang: Formal analysis, Data curation, Writing - review & editing.

Llorenç Milà i Canals: Writing - review & editing. **Olivier Jolliet:** Investigation, Methodology, Writing - review & editing. **Peter Fantke:** Conceptualization, Investigation, Methodology, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Additional methodology details, tables and figures, including sources used for the toys chemical composition, the calculation of the amount of plastic toys in households per child, toys chemical composition dataset, and detailed exposure and toxicity results. Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2020.106194>.

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