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Attributing population-scale human exposure to various source categories: Merging exposure models and biomonitoring data

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ABSTRACT

Information about the distribution of chemical-production mass with respect to use and release is a major and unavailable input for calculating population-scale exposure estimates. Based on exposure models and biomonitoring data, this study evaluates the distribution of total production volumes (and environmental releases if applicable) for a suite of organic compounds. We used Bayesian approaches that take the total intake from our exposure models as the prior intake distribution and the intake inferred from measured biomarker concentrations in the NHANES survey as the basis for updating. By carrying out a generalized sensitivity analysis, we separated the input parameters for which the modeled range of the total intake is within a factor of 2 of the intake inferred from biomonitoring data and those that result in a range greater than a factor of 2 of the intake. This analysis allows us to find the most sensitive (or important) parameters and the likelihood of emission rates for various source emission categories. Pie charts of contribution from each exposure pathway indicate that chemical properties are a primary determinant of the relative contribution of each exposure pathway within a given class of compounds. For compounds with relatively high octanol–water partition coefficients (K_{ow}) such as di-2-ethylhexyl phthalate (DEHP), pyrene, 2,2′,4,4′-tetrabromodiphenyl ether (PBDE-47), and 2,2′,4,4′,5,5′-hexabromodiphenyl ether (PBDE-153), more than 80% of exposure derives from outdoor food ingestion and/or indoor dust ingestion. In contrast, for diethyl phthalate (DEP), di-iso-butyl phthalate (DiBP), di-n-butyl phthalate (DnBP), butylbenzyl phthalate (BBP), and naphthalene, all relatively volatile compounds, either inhalation (indoor and outdoor) or dermal uptake from direct consumer use is the dominant exposure pathway. The approach of this study provides insights on confronting data gaps to improve population-scale exposure estimates used for high-throughput chemical prioritization.

1. Introduction

The environmental health community has growing concerns about many of the commercially available chemicals introduced into residential environments, resulting in exposure to these compounds and their transformation products. Information about potential exposure and adverse health effects in humans from residential uses is limited for most chemicals. Therefore, there has been a growing need for research to screen chemicals that may have potential health hazards, based on exposure and toxicity, among tens of thousands of available commercial chemicals (Cohen Hubal et al., 2010; Egeghy et al., 2011). Methods for conducting rapid toxicological assessments are currently being utilized to help evaluate potential hazards (Dix et al., 2007; Judson et al., 2011; Wetmore et al., 2012). Similar methods for estimating exposure levels for comparison with toxicity levels are needed to evaluate and prioritize large numbers of compounds in a rapid and efficient manner.

Three primary types of information are required to parameterize models used to estimate population-scale exposure levels: (1) chemical properties, (2) chemical emission rates and/or total production volumes, and (3) information about the mass of chemicals consumed in each use and release category. Chemical properties can be estimated using quantitative structure–activity (property) relationship (QSA(P)R) models. The U.S. Environmental Protection Agency (EPA) Estimation Program Interface Suite (EPI Suite™) is one of the publicly available software programs that allows one to compute chemical properties using a unique chemical abstracts service (CAS) registry number or simplified molecular-input line-entry system (SMILES) (U.S. EPA, 2014a). For chemical emission rates and total production volumes, three available databases of the U.S. EPA provide limited chemical emissions rates, including the National-Scale Air Toxics Assessments (NATA) (U.S. EPA, 2009), the Toxics Release Inventory (TRI) Program (U.S. EPA, 2014b), and the National Emissions Inventory (NEI) (U.S. EPA, 2014c). Total production volumes are available in the U.S. EPA's Inventory Update

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Reporting (IUR) (U.S. EPA, 2008) or Chemical Data Reporting (CDR) system (U.S. EPA, 2014d), but are rather uncertain as they are recorded in "bins", spanning several orders of magnitude for a given chemical. Also scarce are both information and databases about how chemicals are introduced to consumer products (e.g., food additives, personal care products, or pesticides) and environments (e.g., indoors or outdoors). This gap is a major impediment to generating exposure estimates for high-throughput screening (Arnot et al., 2012; Mitchell et al., 2013; Shin et al., 2012).

Accurate source inputs in high-throughput exposure models are critical for estimating population-scale exposure levels. One key need is the calculation of intake fraction (iF), the integrated intake of a compound per unit of emission, which varies by several orders of magnitude depending on the release scenario or the product use type (Bennett et al., 2002). For example, given the same amount of release, the intake rate of benzene from cigarette smoking is several orders of magnitude higher than that from outdoor inhalation due to releases from automobiles (Bennett et al., 2002). In addition, even with equivalent amounts of use, the magnitude of exposure to phthalates commonly used in both personal care products and vinyl flooring (e.g., di-n-butyl phthalate, di-iso-butyl phthalate) has also been shown to vary greatly depending on the product use type (Guo and Kannan, 2013). The information needed regarding the distribution of total production volumes to each use and release category was also addressed in evaluating the exposure to naphthalene inferred from measured concentrations in urine, finding that estimated exposure is primarily determined by the proportion of total production volumes emitted to the indoor environment, even though the estimated magnitude of indoor emissions is much smaller (0.3%) than that of outdoor emissions (99.7%) (Shin et al., 2013a; Wambaugh et al., 2013).

In this study, we compared exposures inferred from biomarkers to exposures estimated from fate and transport models to explore the uncertainties associated with modeled iF and our lack of knowledge regarding the distribution of total production volumes to each use and release category for a suite of organic compounds. The exposure pathways for the modeled exposures include dermal uptake from direct consumer use, indoor inhalation, indoor dermal uptake, indoor dust ingestion, outdoor inhalation, and outdoor food ingestion. We assumed that the total production volumes are distributed to direct dermal application (e.g., fragrance, cosmetics), indoor residential consumer use resulting in indoor emissions (e.g., couch, vinyl flooring), and outdoor emissions. We then compared modeled exposure with estimated exposure inferred from biomarkers collected in the National Health and Nutrition Examination Survey (NHANES) (CDC, 2005, 2009). We identified critical uncertainties of model inputs (i.e., individual modeled iF and the distribution of total production volumes) via a generalized sensitivity analysis (Guven and Howard, 2007; Spear and Hornberger, 1980). This analysis addresses the critical need to obtain accurate information of source emission distribution in generating exposure estimates for high-throughput screening.

The objective of this study is to understand the importance of chemical properties and the distribution of total production volumes among different use and release categories on the magnitude of resulting human exposures. In addition, we explain how source inputs can be disaggregated to compute population-scale human exposure using exposure models and biomonitoring data and how critical input parameters can be identified via a generalized sensitivity analysis.

2. Materials and methods

2.1. Overview

The overall approach involves four steps to develop and evaluate our modeling methods. We first outline the information available for each domain of the model including biomarkers. Second, we describe how we modeled exposure levels for each exposure pathway. Third, we explain how a generalized sensitivity analysis is applied to identify critical inputs of modeled exposures. Last, we revise and evaluate the likelihood of emission rates for various source emission categories. The overview of source-to-exposure models used in this study is also depicted in Fig. 1.

Population-scale exposure levels or intake rates can be calculated in two ways. For each release environment, we can use standard exposure models that account for cumulative intake based on human exposure factors (e.g., inhalation/ingestion rates and time spent in microenvironments) to estimate iF. Then, the mass introduced to a specific mode of entry can be multiplied by iF for each release compartment and the total intake then obtained by summing the intake from all possible release compartments. Another method is to back-calculate the intake rate from biomonitoring data as the concentrations in biological media are likely to reflect actual body burden (Asimakopoulos et al., 2013; Guo et al., 2013; Lorber and Egeghy, 2011; Ma et al., 2013; Shin et al., 2013a). The intake rates from two approaches allow determining the likely source emission distribution using Bayesian principles that take the intake from our exposure models as the prior estimate of iF and the intake from measured concentrations in the NHANES survey as the updating datum.

2.2. Data sources

2.2.1. Selected compounds

We selected nine organic compounds for analysis based on the availability of both biomarker data in the NHANES survey and emissions/total production data in the EPA databases during the period of 2001–2004. The selected compounds include one phthalate [diethyl phthalate (DEP)] primarily associated with direct consumer use such as fragrance or cosmetics, one phthalate [di-iso-butyl phthalate (DiBP)] often used in both polyvinyl chloride (PVC) products and personal care products, three phthalates [di-n-butyl phthalate (DnBP), butylbenzyl phthalate (BBP), di-2-ethylhexyl phthalate (DEHP)] with emissions from vinyl flooring and PVC plastics directly to the air compartment of the indoor environment (Dodson et al., 2012; Hauser and Calafat, 2005; Heudorf et al., 2007), two polycyclic aromatic hydrocarbons (PAHs) [naphthalene (Nap), pyrene (Pyr)] with both indoor and outdoor emission sources (Jia and Batterman, 2010; U.S. EPA, 2014e), and two polybrominated diphenyl ethers (PBDEs) [2,2′,4,4′-tetrabromodiphenyl ether (PBDE-47), 2,2′,4,4′,5,5′-hexabromodiphenyl ether (PBDE-153)] used as flame retardants resulting in continuous emissions to the home (Rahman et al., 2001). The selected compounds represent a range of chemical properties, spanning from relatively volatile compounds (e.g. DEP, Nap) to those with a high affinity for organic materials and thus likely to exhibit bioaccumulation (e.g. DEHP, PBDE-153). Chemical properties for these nine studied compounds are listed in Table A1 in the Appendix.

2.2.2. Total production volumes and outdoor emissions

For five phthalates and two PAHs, we obtained total production volume data from the U.S. EPA's 2002 IUR system (U.S. EPA, 2008). The production data in the IUR system are reported as a range, with maximum values being 2 to 50 times greater than minimum values. To address this variance, we used the geometric mean of the end points of the range to model exposures. For DnBP, DEHP, Nap, and Pyr, we obtained additional emission rate estimates from the 2002 NATA database (U.S. EPA, 2009).

For PBDE-47 and PBDE-153, neither total production volumes nor outdoor emission rates are available in the EPA databases. Thus, we used the reported production volume of PentaBDE and OctaBDE along with percent mass composition of PBDEs in PentaBDE and OctaBDE products to estimate the total production volumes of PBDE-47 and PBDE-153. PBDE-47 is a major PBDE-congener in PentaBDE and PBDE-153 is used in both PentaBDE and OctaBDE products. Based on market demand, the estimate of PentaBDE total production volume in the Americas (i.e., North, Central, and South America) is 7100 metric tons in 2001 (Birnbaum and Staskal, 2004; UNEP, 2007a). The global production for OctaBDE was

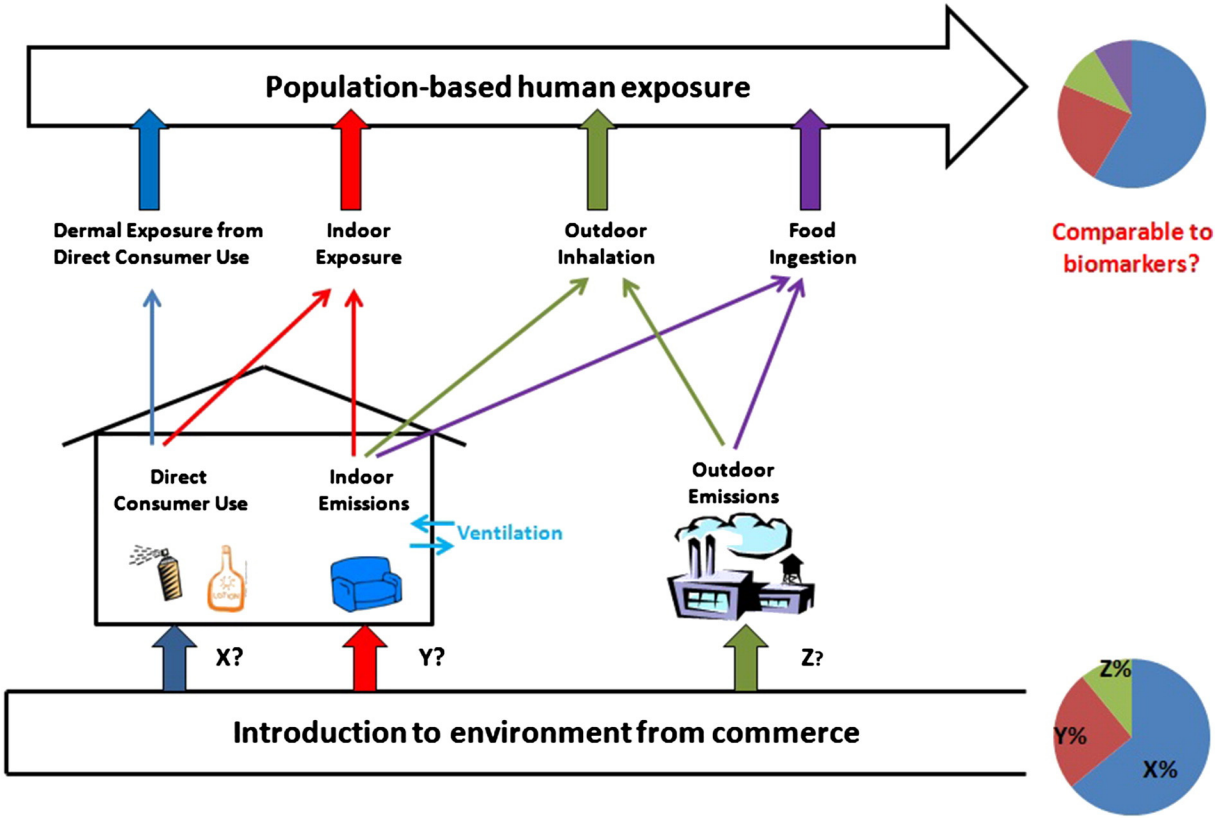

Fig. 1. Overview of source-to-exposure models used in this study.

reported to be smaller than 4000 metric tons in early 2000s (UNEP, 2007b). No country-based information is available for production volumes of either BDE. The U.S. EPA has estimated that the amounts of total production and import of PentaBDE in the U.S. were between 4500 and 23,000 tons in 2002 (U.S. EPA, 2005). Thus, we assumed that 5800 tons of PentaBDE (average of 4500 and 7100 tons) and 3200 tons of OctaBDE (80% are consumed in the U.S.) were consumed in the U.S. in 2001, respectively, acknowledging that this assumption might result in over- or under-estimation of total production volumes for both PBDEs. Reported PentaBDE and OctaBDE congener composition varies among different studies. We used the average composition values of PBDE-47 in PentaBDE (31%) and PBDE-153 in PentaBDE (4%) and OctaBDE (7.5%) products from a U.S. EPA report, which integrates results from eight published studies of PBDE composition (U.S. EPA, 2010). Total production volumes and emission rates used in this study are summarized in Table A2 in the Appendix.

The total production volume estimates are not equal to the actual emission rate estimates for all compounds. In other words, for some of the compounds, not all of the mass in consumer products is available for emissions. For example, compounds commonly used as plasticizers (e.g., DnBP, BBP, and DEHP) or flame retardants (e.g., PBDE-47 and PBDE-153) are formulated in the products and slowly released over a long period of time. Therefore, we first computed the total intake rate by multiplying the lowest iF among all possible exposure scenarios by the selected total production volume. For example, outdoor iF is the lowest for all compounds. Then, we adjusted the percent mass available for emissions until the modeled total intake rate meets the intake rate inferred from the NHANES biomonitoring data. If the modeled intake rate is smaller than the intake rate from the biomonitoring data, we then assumed that 100% of the compound is available for emissions. We also assumed that the total U.S. population is 300 million and that there are 3 residents per household and that all chemicals were used and released equally in all homes for the population.

2.2.3. Biomarkers and biological half-lives

Over the last decade, the Centers for Disease Control and Prevention (CDC), as part of the National Health and Nutrition Examination Survey (NHANES), has been collecting biological samples (e.g., urine, serum, lipid) from the U.S. population of 6 years old and older to provide an ongoing assessment of exposure to environmental contaminants based on biomonitoring data (CDC, 2005, 2009). These biomonitoring data have been used to derive intake rates of environmental chemicals for the general U.S. population (Asimakopoulos et al., 2013; Guo et al., 2013; Lorber and Egeghy, 2011; Ma et al., 2013; Shin et al., 2013a). For the current study, we used biomonitoring data for individuals 20 years of age and older obtained from the 2003–2004 NHANES survey. The distribution of biomonitoring data is available in Table A3 in the Appendix. For compounds with relatively short biologic half-lives on the order of hours or days such as for Nap, Pyr, and phthalates, the measurements of urinary metabolites likely reflect exposures to parent compounds that have occurred in the last day or two. Thus, we used the following equation to estimate the daily intake rate (μg/day) from the NHANES urine concentrations (Guo et al., 2013; Nazaroff et al., 2012; Shin et al., 2013a; Wittassek et al., 2007, 2011):

$$I_{UC} = Output \cdot \sum_{i=1}^{n} C_{m,i} \cdot \left(MW_p / MW_{m,i}\right) \cdot 1/f_{UE} \quad (1)$$

where I_{UC} is the estimated daily average intake rate of parent compounds derived from the metabolite urinary concentrations, *Output* is the average urine output per day (= 1.5 L/day), $C_{m,i}$ is the urine concentration of metabolite i from the NHANES survey (μg/L), n is the number of metabolite compounds of the corresponding parent compound, MW_p and $MW_{m,i}$ are the molecular weights of the parent and metabolite compound i, respectively (μg/μmol), and f_{UE} is the ratio of metabolites excreted in urine relative to the total exposure dose (unitless). The ratio, f_{UE}, of 1 and 0.068 is used for naphthalene and pyrene, respectively

(Guo et al., 2013; Li et al., 2012) and that for all phthalates is from Anderson et al. (2001) and Koch et al. (2005) and is available in Table A3. Example calculation for the daily intake rate of DiBP using the NHANES urinary concentrations is provided in the Appendix.

For PBDE-47 and -153, which have terminal elimination half-lives in the human body of 3.0 and 11.7 years, respectively (Geyer et al., 2004), the PBDE-47 and -153 concentrations in serum likely result from cumulative exposure over the recent months to years. Thus, we used the following one-compartment pharmacokinetic model, which estimates time-dependent serum concentrations, to back-calculate intake rates from the measured serum concentration (Bartell, 2003; Shin et al., 2011).

$$C_{serum,t} = C_{serum,t-1} \cdot e^{-k} + \left(1 - e^{-k}\right) \frac{f}{k \cdot m_f} I_t \quad (2)$$

where $C_{serum,t}$ is the serum concentration of the compound at time t (μg/g of lipid), k is the elimination rate constant of the compound (1/day), f is the fraction of the ingested compound present in the blood after absorption across the gastrointestinal tract and distribution throughout the body (unitless), m_f is the body fat mass (kg), and I_t is the intake rate of the compound at time t (μg/day). Assuming that $C_{serum,t-1}$ is equal to $C_{serum,t}$, Eq. (2) becomes

$$C_{serum,t}\left(1 - e^{-k}\right) = \left(1 - e^{-k}\right) \frac{f}{k \cdot m_f} I_t. \quad (3)$$

Rearranging Eq. (3) in terms of the intake rate, I_t, results in the following equation.

$$I_t = C_{serum,t} \frac{k \cdot m_f}{f} \times \frac{1000\ g}{kg}. \quad (4)$$

In this model, the elimination rate constant, k, can be expressed as $(\ln 2) / t_{1/2}$ where $t_{1/2}$ is the half-life of the compound in blood. The average body fat percentage (kg of fat / kg of body weight) of adult women and men is 0.28 and 0.21, respectively (ACE, 2009). The average body weight for adult women and men is 74.7 and 88.3 kg, respectively (U.S. EPA, 2011). In applying this model, we used the weighted average fat mass for all adults, 19.7 kg. The congener-specific oral absorption fraction, f, is 0.96 and 0.90 for PBDE-47 and -153, respectively (Geyer et al., 2004). Because the congener-specific absorption fractions for other routes including inhalation, dust ingestion, and dermal uptake are not available, we applied the same absorption fraction for other routes as for the oral route, acknowledging that this assumption might result in over- or under-estimation of intake rates of PBDE-47 and -153. The distribution of intake rates derived from the above two methods is summarized in Table A4 in the Appendix.

2.3. Modeled intake fractions (iFs)

We provide here an overview of the exposure models we use to estimate iF for each release compartment. Details on model structure and input parameters have been presented previously (Bennett and Furtaw, 2004; McKone, 1993). Prediction uncertainty resulting from uncertainties in reported and estimated values of chemical properties, environmental parameters, and exposure factors has been estimated to be relatively small (within one order of magnitude) (Arnot et al., 2012). This contrasts to the uncertainty about the total production volume (up to a factor of 50) and the uncertainty resulting from the insufficient information on how this production is distributed into different emissions and uses (Breivik et al., 2012). Therefore, we focused our evaluation on relatively large uncertainty in the distribution of total production volumes by determining the sensitivity of the estimated intake rate to the selected combination of iF for each release compartment (i.e., indoor air releases, outdoor air releases, and direct dermal application) and the distribution of total production volume/emission rates to each release compartment.

2.3.1. iF for indoor air releases

In order to estimate exposure to chemicals released indoors, we used our previously developed and applied fugacity-based indoor exposure model (Bennett and Furtaw, 2004) to simulate the fate, transport, and human exposure for indoor chemical sources. This model and others based on it have been widely used in indoor exposure assessment (Bennett and Furtaw, 2004; Shin et al., 2012; Zhang et al., 2009, 2011). Here, fugacity can be regarded physically as the partial pressure or the tendency of a chemical to leave or escape from a given state or compartment (Bennett and Furtaw, 2004). The indoor model is comprised of four compartments that serve as potential reservoirs of a chemical: air, carpet, vinyl flooring, and walls. Each compartment is comprised of multiple phases, such as gases and particles in the air. The total fugacity capacity of each compartment is volume-weighted sum of all subphase fugacity capacities. We quantify both diffusive mass transport using a fugacity-based mass-transfer coefficient and advective mass transport driven by particle resuspension and deposition. The details of the indoor fugacity model are described elsewhere (Bennett and Furtaw, 2004; Shin et al., 2012, 2013b). This indoor exposure model has been improved over time primarily by revisions to better account for size-specific dust removal rates from surface cleaning (Shin et al., 2013c). For all of the candidate compounds, we calculated iF for inhalation, dust ingestion, and dermal uptake following an assumed release to indoor air. We modeled indoor dermal uptake iF using Cohen Hubal's surface contact transfer method (2000) and the Weschler and Nazaroff's air-to-skin transdermal uptake method (2012). For dust ingestion, we multiplied the surface dust concentration (C_{dust}, μg/g) from the indoor fugacity model by the adult dust ingestion rate (=30 mg/day or 0.03 g/day) recommended by the U.S. EPA Exposure Factors Handbook (U.S. EPA, 2011). We acknowledge that for some chemicals within building materials, release to the indoor environment may be driven by the abrasion or weathering processes (Webster et al., 2009).

2.3.2. iF for outdoor air releases

To estimate iF for outdoor air releases, we used the CalTOX model (McKone, 1993). Because indoor released compounds are also transported outdoors through ventilation, we computed the percent of mass ventilated outdoors from the indoor model and applied to the CalTOX model to estimate iF to account for the mass ventilated outdoors. The CalTOX model is a mature and widely used multimedia fate, transport, and exposure model and provides a broad assessment of the partitioning of chemicals between the air, water, soil, and biota. CalTOX derives environmental concentrations by determining the likelihood of competing processes by which chemicals (a) accumulate within the compartment of origin, (b) are physically, chemically, or biologically transformed within this compartment (i.e., hydrolysis, oxidation, etc.), or (c) are transported to other compartments by cross-media transfers that involve dispersion or advection (i.e., volatilization, precipitation, etc.) (McKone, 1993). CalTOX uses a level III multimedia chemical partitioning model to characterize mass-transfer processes between compartments and transformation within compartments. The CalTOX model considers chemical transformation in the environment (see Table A5 in the Appendix for the environmental degradation half-lives used in the CalTOX model) and uses biotransfer and bioconcentration factors, including partition coefficients between soil and plants; between air and plants; between animal feed intake and animal-based food products; and between surface water and fish (Hsieh et al., 1994) (see Table A6 in the Appendix for the biotransfer and bioconcentration factors used in the CalTOX model). For two PBDEs, gut absorption efficiencies in fish (0.45 for PBDE-47 and 0.40 for PBDE-153) are also applied when calculating ingestion exposure through fish consumption (Bhavsar et al., 2008). The model calculates inhalation exposure from releases to outdoor air and exposure from

food or water ingestion attributable to outdoor releases. Therefore, we calculated iF of inhalation and food ingestion resulting from releases to outdoor air using the CalTOX model. In order to evaluate the model performance in food exposure estimation, we compare in Table A7 in the Appendix the predicted food intake rates from the CalTOX model with reported food intake rates from the literature (Falco et al., 2003; Marti-Cid et al., 2008; Martorell et al., 2010; Schecter et al., 2007, 2013).

2.3.3. iF for direct dermal application

Chemicals with significant use in consumer products, particularly those applied to skin, require a dermal-based iF assessment. For example, DEP is often used in a variety of personal care products such as fragrance, cosmetics, lotion, and sunscreen and DiBP is used in nail polish and other personal care products such as fragrance and make-up foundation (Dodson et al., 2012; Hauser and Calafat, 2005; Heudorf et al., 2007). The intake rate through skin per unit of direct dermal application is a key determinant for total intake of these compounds. For estimating iF from direct dermal application, we used the fraction of applied dose absorbed through skin for adults (Elsisi et al., 1989; McKee et al., 2002; Wormuth et al., 2006). This fraction is derived from rat skin measurements and extrapolated to human adult skin based on the observation that the absorption rate through rat skin is 7 to 10 times greater than that through human skin (Koniecki et al., 2011; Mint et al., 1994). The dermal iF used in the study is 0.021 and 0.012 for DEP and DiBP, respectively. We acknowledge that the absorption fraction used in this study is only representative for leave-on personal care products, and could be an over-estimate for other product types.

2.4. A generalized sensitivity analysis

A generalized sensitivity analysis provides a process to determine the plausible distribution of total production volumes and then find the most important input parameters (with respect to uncertainty) for simulating exposure levels that correspond to exposures inferred from biomarkers. Our approach to the generalized sensitivity analysis is to run a Monte Carlo assessment and classify the result of each Monte Carlo simulation as either representative (behavior, B) or not representative (non-behavior, $\overline{B}$) based on the classification criterion. For example, we classify the result as "behavior" if resulting intake rates are within a factor of 2 of the intake rates from biomarkers and as "non-behavior" for others. We then test the null hypothesis that two vectors of a parameter categorized as behavior and non-behavior are from the same continuous distribution (Guven and Howard, 2007; Spear and Hornberger, 1980). Important parameters in simulating exposures that correspond to the observed exposures from biomarkers can be determined based on the degree of separation between cumulative distribution curves of behavior and non-behavior. To assess the degree of separation, we used the Kolmogorov–Smirnov two sample test to determine the statistic, $d_{m,n}$, as the maximum vertical distance between cumulative distribution functions of behavior and non-behavior

$$d_{m,n} = \sup|S_n(x) - S_m(x)| \quad (5)$$

where S_n and S_m are the sample distribution functions corresponding to n behaviors and m non-behaviors, respectively. Because S_n and S_m are the estimates of parameter distributions for behavior and non-behavior, respectively, the test statistic is sensitive not only to differences in central tendency, but to any difference in the distribution functions (Guven and Howard, 2007; Spear and Hornberger, 1980). We then determined and ranked important parameters for simulating the exposures based on the degree of $d_{m,n}$.

Initial iF values and % ventilation included in the generalized sensitivity analysis are predicted from exposure models. Other input parameters include % mass available for emissions, % total production volumes (TPV) consumed in direct consumer use (DCU), % TPV that results in indoor emissions (IE), and % TPV that results in outdoor emissions (OE). Table 1 provides a list of the initial mean values of input variables (i.e., iF and the distribution of total production volume/emission rates to each release compartment) used for the Monte Carlo simulations. For each input variable, variance is represented with the probability distributions provided in Table A8 in the Appendix along with the coefficient of variation (CV) for lognormal distributions and minimum and maximum values for uniform distributions.

3. Results and discussion

3.1. Distribution of total production volumes

The results summarized below present our estimated distribution of total production volumes among different use and release categories from the generalized sensitivity analysis using initial values of iFs from exposure models and total production volumes, and the NHANES biomarkers. For the nine studied compounds, Table 2 provides the relative rank of parameters that reject the null hypothesis based on the test statistic, $d_{m,n}$. These compounds were grouped into three categories according to the order of importance of their input parameters. In the first category, iF for dermal uptake from direct consumer use (DCU DM) is an important parameter in simulating exposures for compounds associated with dermal uptake from direct consumer use such as DEP and DiBP. In the second category, the percentage of total production volumes to indoor emissions (% TPV IE) and iF for indoor or outdoor inhalation are important parameters in simulating exposures. The compounds in this second category are DnBP, BBP, and Nap, which are relatively volatile compared to the rest of compounds and are not used in personal care products. In the third category, iF for outdoor food ingestion (OUT FD) and/or indoor dust ingestion (IND Dust) contributes significantly to the

Table 1
Mean of initial input parameters used in Monte Carlo simulation.

Parameters	DEP	DiBP	DnBP	BBP	DEHP	Nap	Pyr	PBDE-47	PBDE-153
% mass available for emissions [a]	100%	100%	53%	80%	3.6%	100%	100%	0.16%	0.08%
% ventilation	85%	85%	67%	67%	63%	99%	61%	63%	62%
% TPV to DCU [b]	33%	33%	–	–	–	–	–	–	–
% TPV to IE [b]	33%	33%	25%	25%	25%	0.5%	0.1%	25%	25%
% TPV to OE [b]	33%	33%	75%	75%	75%	99.5%	99.9%	75%	75%
Indoor inhalation iF	1.8E−03	1.8E−03	1.4E−03	1.4E−03	9.8E−04	2.1E−03	1.3E−03	1.2E−03	9.5E−04
Indoor dermal iF	6.9E−07	2.7E−05	2.0E−06	2.6E−06	2.3E−04	1.4E−08	5.0E−07	2.1E−05	1.5E−04
Indoor dust ingestion iF	3.1E−05	7.1E−04	5.0E−05	5.7E−05	5.4E−03	7.7E−07	2.5E−05	5.9E−04	1.2E−03
Outdoor inhalation iF	1.2E−13	7.0E−14	7.6E−14	6.3E−14	3.1E−14	4.9E−14	2.2E−14	8.7E−14	7.0E−14
Outdoor food ingestion iF	1.5E−13	6.6E−13	7.2E−13	8.2E−13	5.6E−12	1.0E−15	3.1E−13	1.9E−11	1.9E−11
DCU dermal iF	2.1E−02	1.2E−02	–	–	–	–	–	–	–

[a] The total production volume estimates are not equal to the actual emission rate estimates for all compounds because plasticizers (DnBP, BBP, DEHP) and flame retardants (PBDE-47 and -153) are formulated in products and slowly released over a long period of time. The listed values are our initial values based on matching model results to NHANES biomonitoring data.
[b] TPV: total production volume, DCU: direct consumer use, IE: indoor emissions, OE: outdoor emissions.

Table 2
Order of parameters that reject the null hypothesis based on ranking at the level of 0.1% significance.

Rank	DEP	DiBP	DnBP	BBP	DEHP	Nap	Pyr	PBDE-47	PBDE-153
1	DCU DM	% TPV OE	% TPV IE	% TPV IE	% TPV IE	% TPV IE	OUT Food	OUT Food	OUT Food
2	% TPV DCU	DCU DM	% TPV OE	% TPV OE	% TPV OE	% TPV OE		% TPV IE	% TPV IE
3	% TPV OE	IND INH	IND INH	OUT Food	IND Dust	OUT INH		% TPV OE	% TPV OE
4	% TPV to IE	% TPV DCU	OUT Food	IND INH	OUT Food	IND INH		IND INH	
5		% TPV IE			IND INH			IND Dust	
6		IND Dust							

DCU: direct consumer use, DM: dermal uptake iF, TPV: total production volume, IE: indoor emissions, OE: outdoor emissions, IND: indoor, OUT: outdoor, INH: inhalation iF, Food: food ingestion iF, Dust: dust ingestion iF.

results in simulating exposures for compounds with relatively high octanol–water partition coefficients (K_{ow}) such as DEHP, Pyr, PBDE-47, and PBDE-153. We found that indoor dermal uptake estimated from either Cohen Hubal's surface contact transfer method (2000) or Weschler and Nazaroff's air-to-skin transdermal uptake method (2012) was not important for any of the compounds, indicating that dermal uptake is not an influential exposure pathway for the studied compounds (see Table A9 in the Appendix for indoor iF of each exposure pathway). The test statistics ($d_{m,n}$) for all input parameters are also available in Table A10 in the Appendix.

We also determined how much input parameters were changed after the sensitivity analysis in Table 3. Overall, the input parameters that are ranked high in Table 2 resulted in large changes. The updated medians of input parameters that are only classified as a behavior (B) are presented in Table A11 in the Appendix. For DEP, updated medians of iF for DCU DM are about a factor of 2 smaller than initial values. For DnBP, BBP, and Nap, updated medians of % TPV IE came out to be about a factor of 5 smaller than initial conditions. For DEHP, Pyr, PBDE-47, and PBDE-153, the magnitude of changes in iF for OUT FD or IND Dust is the biggest except for PBDE-153.

3.2. Contribution of each exposure pathway to the total intake

In addition to determining the distribution of total production volumes, we used this evaluation to understand how each exposure pathway contributes to the total intake. Fig. 2 provides pie charts showing the distribution of total production volumes and the resulting contribution of each exposure pathway. In evaluating the results in Fig. 2, we observe that exposure to DEP and DiBP is primarily driven by both intake from direct consumer use and indoor inhalation from indoor emissions. For DnBP and BBP, total exposure is driven by indoor intake from indoor emissions and outdoor food ingestion from outdoor emissions although the percentage of total production volumes to indoor emissions (% TPV IE) is much smaller (6%) than that to outdoor emissions (94%). Similar to DnBP and BBP, DEHP is commonly used as a plasticizer, but total intake of DEHP is mainly driven by outdoor food ingestion (42%) and indoor dust ingestion (39%) as a result of its high K_{ow} compared to DnBP and BBP. The results on DEP and DEHP are in line with the findings in other studies (Guo et al., 2012; Wittassek et al., 2011). For the two PAHs considered, the estimated fraction of total production volumes to be released outdoors is similar (0.1%), but the primary exposure pathway for Nap and Pyr is outdoor inhalation from outdoor emissions (56%) and outdoor food ingestion from outdoor emissions (97%), respectively. This is consistent with the findings in other studies (Guo et al., 2013; Li et al., 2012; Viau et al., 2002). Our previous study (Shin et al., 2013a) also estimated total intake rates of Nap (8.1 μg/day) and Pyr (0.024 μg/day) and reported that the primary exposure pathway for both PAHs is indoor inhalation. This discrepancy from the current study is because our previous study used the measured indoor air concentrations collected from 10 houses in the Chicago area during 1994–1995 (900 ng/m^3 for Nap and 2 ng/m^3 for Pyr) — results that are much higher than predicted indoor air concentrations (40 ng/m^3 for Nap and 0.32 ng/m^3 for Pyr) derived from the total production volumes in 2002 and the number of U.S. households considered (100 million). For the two PBDEs considered, the contribution of outdoor food intake to total intake is the biggest among all exposure pathways. Compared to the findings in other studies (Johnson-Restrepo and Kannan, 2009; Jones-Otazo et al., 2005; Lorber, 2008; Roosens et al., 2009), the contribution of indoor dust ingestion to total intake is only 5% and 14% for PBDE-47 and PBDE-153, respectively. This is because our predicted outdoor food ingestion intake rates are about 2 to 3 factors larger than reported food intake rates (see Table A8 for comparison of estimated and reported food intake rates). In addition, we found that the estimated mass released indoors is highly correlated with inferred intake rates (see Fig. A1 in the Appendix). Individual intake rates with updated medians of input parameters are also provided in Table A12 in the Appendix.

3.3. Implications/limitations

This study has several implications for setting priorities on exposure information needed to assess high-throughput chemicals. Four key observations arise from the results. First, we find that formal methods

Table 3
Percent changes of input parameters. Data in bold are changes over 50%.

	DEP	DiBP	DnBP	BBP	DEHP	Nap	Pyr	PBDE-47	PBDE-153
% TPV to DCU	11%	4%	–	–	–	–	–	–	–
% TPV to IE	6%	6%	**75%**	**77%**	**58%**	**81%**	9%	14%	1%
% TPV to OE	5%	10%	25%	26%	19%	0%	0%	5%	0%
Indoor inhalation iF	11%	3%	30%	30%	14%	27%	11%	6%	9%
Indoor dermal iF	29%	28%	31%	28%	33%	31%	33%	**64%**	**60%**
Indoor dust ingestion iF	28%	24%	32%	32%	**56%**	29%	34%	23%	28%
Outdoor inhalation iF	31%	29%	31%	27%	33%	**61%**	30%	3%	29%
Outdoor food ingestion iF	40%	42%	**54%**	**58%**	**64%**	41%	**109%**	**98%**	12%
DCU dermal iF	**48%**	18%	–	–	–	–	–	–	–

TPV: total production volume, DCU: direct consumer use, IE: indoor emissions, OE: outdoor emissions.

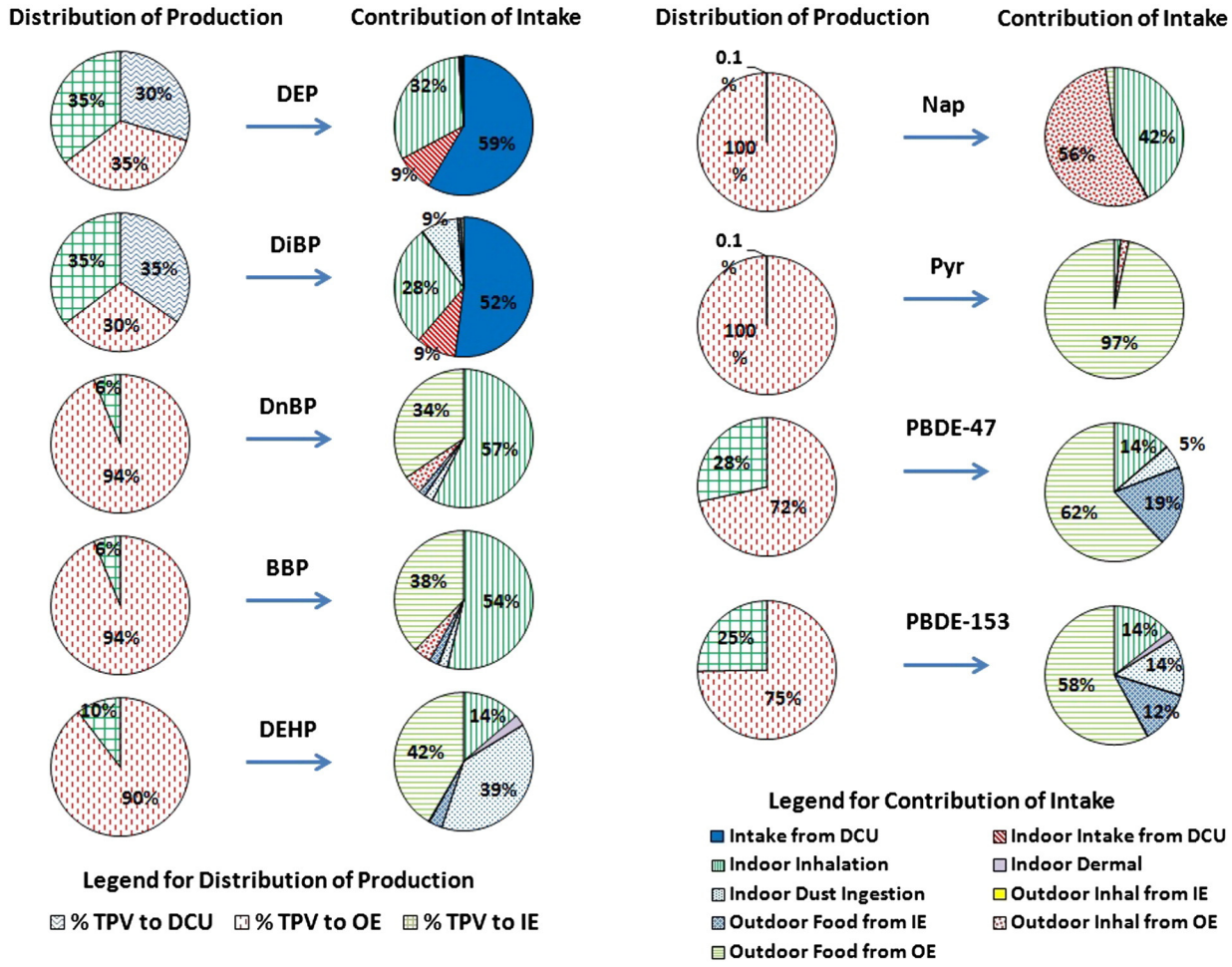

Fig. 2. Distribution of total production volume and resulting contribution of each exposure pathway to total intake. TPV = total production volume; DCU = direct consumer use; IE = indoor emissions; OE = outdoor emissions; Inhal = inhalation.

to disaggregate total production volumes to various use and release categories are very limited and present a very large information gap for those who need to assess chemical impacts. The result is that regulators and policy makers who need to rank chemicals must rely on conservative approaches in which one assumes for any compound that all of the mass produced is released and/or consumed in each of its use and release categories and then selects the maximum intake among the categories. The methods in this study provide a process for using Bayesian methods with exposure models and NHANES biomonitoring data to predict a more realistic mass distribution among sources and uses (i.e., application to skin and emissions to indoor and outdoor air). Second, we demonstrated that the contribution of exposure pathways to total intake is strongly dependent on the chemical properties within similar use categories (e.g., DnBP, BBP, and DEHP) and release scenarios (e.g., Nap, Pyr) of compounds. Third, a generalized sensitivity analysis provides a process to identify the most sensitive input parameter whose values can be altered within their plausible value range and to determine the exposure comparable to biomonitoring data when a full-scale uncertainty analysis is not applicable. Fourth, we also confirmed that not all of the compounds produced annually are available for emissions (see DnBP, BBP, DEHP, PBDE-47, and PBDE-153 in Table 1). Compounds used as plasticizers and flame retardants are slowly released from sources over a long period of time.

One of the limitations of this study is that the NHANES biomonitoring survey includes a limited list of chemical classes. This points to the value and opportunity for future NHANES surveys to include a broader spectrum of chemical classes, spanning chemical sets from volatile compounds to those with a high affinity for organic materials. Exposure to PBDE-47 and -153 in the office environment has been shown to contribute to PBDE body burden (Watkins et al., 2011). Thus, for compounds commonly found in occupational environments, model reliability would be improved if exposure from occupational settings was included in calculating total exposure. In addition, PBDEs are likely to have biotransformation and bioformation processes in food webs (Bhavsar et al., 2008; Kierkegaard et al., 1999; Tomy et al., 2004). However, the CalTOX model does not account for these processes and thus modeled food ingestion exposure of PBDE-47 and -153 from CalTOX is another limitation of this study. Phthalates are found in food products and packaging materials (Bi et al., 2013; Fierens et al., 2012a) and phthalate concentrations in foods have been observed to decline after cooking (Fierens et al., 2012b). Moreover, dietary ingestion of barbequed food can be an important exposure route for pyrene (Li et al., 2012; Viau et al., 2002). Thus, accounting for the exposure from cooking and food packaging would likely improve the reliability of exposure estimates. Other than use and release categories specified in this study, some compounds are categorized as food additives, pharmaceuticals, pesticides, colorants, etc. Therefore, future studies need to handle multiple use categories to disaggregate mass distribution based on biomonitoring data. Further, models that account for the difference between leave-on and wash-off consumer products also need to be included for source disaggregation. Non-dietary ingestion is found to be an important exposure pathway to young children for compounds with high K_{ow} values

(Lorber and Egeghy, 2011; Shin et al., 2012). This work only includes exposure pathways relevant to adults because the NHANES biomonitoring data is available for individuals 6 years of age and older. Thus, including the exposure pathways that are important to susceptible populations is an important opportunity for future work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.envint.2014.05.020.

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