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UPTAKE OF CHEMICALS FROM INDOOR AIR: PATHWAYS AND HEALTH EFFECTS

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ABSTRACT

Building occupants are exposed to manufactured chemicals. Exposure in the indoor environment can occur via non-dietary ingestion (e.g. indoor dust), inhalation and dermal absorption including dermal uptake directly from air. The extent of dermal uptake from air has been previously studied for volatile organic compounds (VOC). Not much is however known about its role for semivolatile organics (SVOC) and therefore this exposure pathway is often neglected in exposure assessments. Dermal uptake received attention with regards to contact transfer from contaminated surfaces. Recent modeling efforts however indicate that direct uptake of certain semivolatile organic compounds from air may occur. Experimental verification of this hypothesis is emerging. Recent studies have demonstrated that dermal uptake of certain phthalates directly from air can be comparable to or larger than the corresponding intake from inhalation. Further experiments have been conducted with nicotine and the results are similar. Some of the SVOCs present indoors may have adverse health effects or are categorized as potential endocrine-disrupting compounds. It has been suggested that the health effects of a chemical may depend on the pathway of exposure. However, studies that investigate the health consequences of dermal uptake of SVOCs from air are lacking.

Keywords: Exposure pathways, Indoor environment, Endocrine disrupting chemicals

1. BACKGROUND

Certain semivolatile organic compounds (SVOC) are known to be developmental and reproductive toxicants. Indications exist that they may impact genital development, semen quality, children's neurodevelopment, thyroid function, onset of puberty in females and other health endpoints (Jurewicz and Hanke, 2011; Whyatt et al., 2012). Dietary ingestion and inhalation have long been assumed to constitute the major routes of exposure to these chemicals. For example, while dietary ingestion has been believed to constitute the major source of exposure to high molecular weight phthalates, recent studies indicate that diet is not the dominant exposure pathway for lower molecular weight phthalates. Koch et al. (2013) measured the urinary phthalate metabolites of human subjects over a 48 hour period of strict fasting. They concluded that non-dietary pathways were the major exposure pathways for lower molecular weight phthalates. The same conclusion was drawn by Fromme et al. (2013). The pathways of exposure in the indoor environment are non-dietary ingestion, inhalation and dermal absorption. Dermal exposure through the use of personal care products and dermal contact can add to the total intake of certain SVOCs (Wormuth et al., 2006; Guo and Kannan, 2011). For example, systematic uptake of phthalates through skin after topical application was shown to be an important route of exposure (Janjua et al., 2007; 2008). However, direct air-to-skin transdermal uptake has been overlooked until recently. There is a limited number of experiments from the past decades that focused on direct uptake of

chemicals through the skin. These studies investigated the transdermal exposure to vapors of *volatile* organic compounds.

Earlier experiments include cases in which the whole body of a human subject has been exposed and cases in which only an arm or hand has been exposed. Dutkiewicz and Piotrowski (1961) estimated that dermal absorption of aniline vapors accounted for 47-64% of a resting person's aggregate aniline intake. Piotrowski (1967) more fully described experiments in which both naked and dressed men were exposed to nitrobenzene vapors in a chamber while breathing clean air. About half as much vapor was absorbed through the skin as through the lungs. Piotrowski (1971) conducted similar chamber experiments in which the entire bodies of seven men were exposed to phenol vapors; the dermal absorption rate averaged 70% of the inhalation rate. Kežić et al. (1997) report a study in which five volunteers had their forearm enclosed in a cylinder containing vapors of either 2-methoxyethanol or 2-ethoxyethanol. Based on the urine concentrations of the metabolites, the authors estimated that skin uptake would be approximately 120% of inhalation uptake for 2-methoxyethanol and 70% of inhalation uptake for 2-ethoxyethanol. Johanson and Boman (1991) exposed volunteers to 50 ppm 2-butoxyethanol (BE) vapor. During the first two hours period the subjects were exposed by mouth only via a respiratory valve connected by tubes to the exposure chamber. During the second exposure period the men were exposed by skin only while sitting inside the exposure chamber, naked except for shorts, and wearing a respiratory protection mask supplied with compressed air. The calculated uptake rate for BE was about three to four times higher during dermal exposure than during inhalation exposure. The authors suggested that dermal uptake of BE accounts for about 75% of the total uptake during whole body exposure. These studies however focused on volatile organic compounds, not semivolatiles, which are of increasing concern in the indoor environment.

2. INITIAL STUDIES INDICATING DERMAL UPTAKE OF SVOCS FROM AIR

Few studies indicate the importance of the dermal pathway for a subset of SVOCs based on estimates derived from mechanistic models (Xu et al. 2009; 2010). Weschler and Nazaroff (2012; 2014) have estimated transdermal uptake of various organic compounds from the gas phase using idealized mass transport considerations. They have concluded that air-to-skin transdermal uptake is a potentially important pathway for lower molecular weight semivolatile compounds.

Using the approach described by Weschler and Nazaroff (2012), Bekö et al. (2013) calculated for 431 Danish children between 3 and 6 years old the total daily intakes of selected phthalate esters based on levels of phthalate metabolites measured in their urine. Additionally, for each child the intakes attributable to exposures in the indoor environment via dust ingestion, inhalation and dermal absorption were estimated from the phthalate levels in the dust collected from the child's home and daycare center. It was concluded that dermal absorption was the major pathway by which diethyl phthalate (DEP), di(n-butyl) phthalate (DnBP) and di(isobutyl) phthalate (DiBP) entered the bodies of the children, while inhalation was roughly 1/10th the dermal pathway and dust ingestion contributed even less. Dermal absorption also constituted a substantial fraction of the total intake derived from urinary metabolite levels. Furthermore, the authors estimated that transdermal exposure to DiBP alone may exceed tolerable daily intake levels (TDI set by the European Food Safety Authority) for a number of the children. These results illustrate the potential significance of dermal exposure to phthalates in the indoor environment (Figure 1).

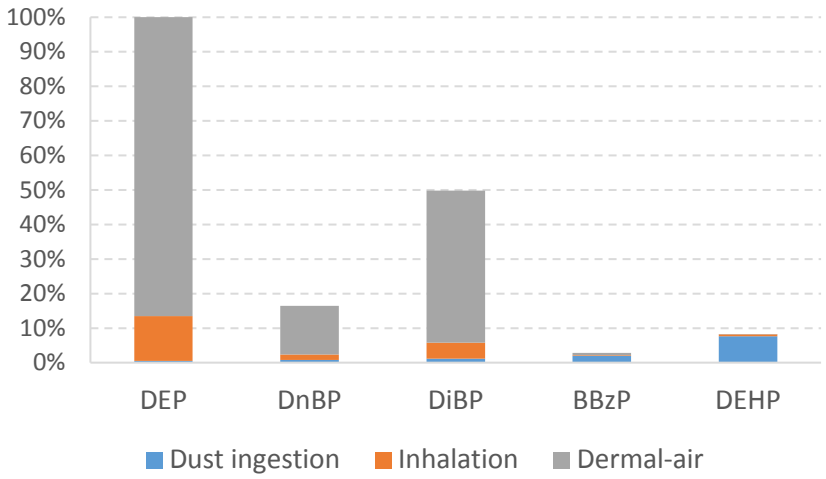

Figure 1. Contribution of each exposure pathway in the indoor environment to the total daily intake estimated from urinary metabolite concentrations (adapted from Bekö et al., 2013).

Gaspar et al. (2014) concluded that dermal absorption of gas-phase dibutyl phthalate (DBP) was the dominant route of exposure, with median percent contribution to nondietary exposure between 80 and 86%, depending on the age group. Inhalation was the second most dominant route of exposure (median percent contribution = 11−14%), with nondietary ingestion and dermal absorption via dust adhered to skin playing smaller roles. Gas-phase absorption was not significant for DEHP exposure.

Gong et al. (2015) concurrently collected handwipes and urine samples from 39 Beijing children (5–9 years). They measured the levels of five phthalates in the handwipes and the concentrations of eight corresponding metabolites in urine. Significant associations were found between the parent phthalates in handwipes and their monoester metabolites in urine for DiBP, DnBP, BBzP (butyl benzyl phthalate) and DEHP (di(2-ethylhexyl) phthalate). The authors estimated that dermal absorption contributed between ~5% and ~20% to total uptake.

3. RECENT EXPERIMENTS

Improved understanding of metabolism and elimination of SVOCs allows us to estimate total daily intakes, from all pathways and sources, based on concentrations of parent compounds or their metabolites in urine. Studies often use human biomonitoring to determine the total intake or intake from a specific source such as diet or personal care products (Rudel et al., 2011; Romero-Franco et al., 2011). Using human subject experiments under controlled laboratory conditions coupled with biomonitoring, the fraction of the total SVOC intake attributable to a specific exposure pathway can be isolated. Such studies are however rare.

Weschler et al. (2015) recently conducted the first experimental study investigating the contribution of transdermal exposure to total intake of two SVOCs – the phthalates DEP and DnBP. Six human subjects were exposed for six hours in a chamber to air containing known concentrations of DEP and DnBP. In one set of experiments the subjects, clothed in only shorts, wore a hood and breathed phthalate free air. In another set of experiments the subjects were exposed without wearing a hood. Metabolites of DEP and DnBP were measured in urine. The study experimentally demonstrated for the first time that dermal uptake directly from air can be a meaningful exposure pathway for phthalates. For DEP, the median

normalized dermal uptake directly from air was 4.0 μg/(μg/m^3 in air) compared with an inhalation intake of 3.8 μg/(μg/m^3 in air). For DnBP, the median dermal uptake from air was 3.1 μg/(μg/m^3 in air) compared with an inhalation intake of 3.9 μg/(μg/m^3 in air). This study has demonstrated that for human participants following a 6-hr dermal-only exposure to elevated gas-phase concentrations of DEP and DnBP, the levels of the metabolites MEP (metabolite of DEP), MnBP, and 3OH-MnBP (both metabolites of DnBP) in urine samples collected over the next 2 days were roughly half those measured in urine samples following a 6-hr dermal plus inhalation exposure.

Although the urine concentrations of MEP, MnBP, and 3OH-MnBP peaked shortly after the participants left the chamber, the urine concentrations were still two or more times greater than background 40 hr after leaving the chamber. This indicated a lag between dermal absorption and uptake into the blood, which would not be anticipated for ingestion or inhalation. Additionally, the ratios of dermal uptake to inhalation intake for DEP and DnBP in Weschler et al. (2015) were smaller than obtained in the modeling studies of Bekö et al. (2013) and Gaspar et al. (2014), which used the steady-state approach. This has been attributed to the fact that the participants were exposed to elevated levels of DEP and DnBP for only 6 hr, whereas dynamic modeling indicates that much longer time would be required to reach steady-state and maximal uptake via the dermal pathway in comparison to the inhalation pathway. Moreover, at the time the participants left the chamber, a large fraction of the DEP and DnBP absorbed by the skin was predicted to be still in the skin. These compounds in the skin can desorb to air and the clothing the participants wore after exposure. Bathing can also remove some fraction of the phthalates on the skin.

Direct absorption from air is also anticipated to be significant for other semivolatile organic compounds whose molecular weight and skin lipid/air partition coefficient are in the appropriate range. In a preliminary study Bekö et al. (2016) exposed two subjects wearing only shorts to environmental tobacco smoke (ETS), generated by mechanically "smoking" cigarettes, for three hours in a chamber while breathing clean air via breathing hoods. The average nicotine concentration in the chamber was comparable to the highest levels reported for smoking sections of pubs. Urine samples were collected immediately before exposure and 60-h post exposure. The urine samples were analyzed for nicotine and two metabolites - cotinine and 3OH-cotinine. Peak urinary cotinine and 3OH-cotinine concentrations were comparable to levels measured among non-smokers in hospitality environments before smoking bans. The study demonstrated meaningful dermal uptake of nicotine directly from air. The authors concluded that these findings may be especially relevant for children in homes with smoking and in environments where vaping occurs. The latter is especially of concern, since vaping e-cigarettes is increasingly popular and unregulated in many countries.

4. THE ROLE OF CLOTHING

The uptake of organic compounds by transfer from treated fabrics has been recognized for decades. For example, Blum et al. (1978) observed metabolites in the urine of children who had worn clothing treated with a flame retardant. Forestry workers wearing permethrin-treated tick-proof pants were shown to have significantly increased urinary permethrin metabolite levels (Rossbach et al., 2016). It has been also suggested that certain chemicals can transfer from a work site to the worker's home via clothing (Knishkowy and Baker, 1986), and even into the family member's clothing while laundering the contaminated clothes together with clean fabrics (Faulde et al., 2006). Fewer studies have evaluated how clothing may influence dermal uptake of organic compounds from air. These studies have only examined a few chemicals. For example, Piotrowski (1967) found that clothing reduced dermal uptake

of airborne nitrobenzene by about 20-30% but had no observable effect on phenol absorption.

To assess the influence of clothing on dermal uptake of semi-volatile organic compounds (SVOCs) from air, Morrison et al. (2016a) measured uptake of selected airborne phthalates for an individual wearing clean clothes or air-exposed clothes and compared these results with dermal uptake for bare-skinned individuals under otherwise identical experimental conditions. An individual was exposed to known concentrations of DEP and DnBP for 6 hours in a climate chamber while breathing clean air through a breathing hood. Urinary metabolites of the two phthalates were measured. The individual wore either fresh clean cotton clothes or cotton clothes that had been exposed to the same chamber air concentrations for 9 days. When compared against the average results for bare-skinned participants (Weschler et al., 2015), clean clothes were protective, decreasing the uptake 3.2 to 5.6 times. Exposed clothes increased dermal uptake for DEP and DnBP by factors of 3.3 and 6.5, respectively. The authors concluded that wearing clothing that has adsorbed/absorbed indoor air pollutants can increase dermal uptake of SVOCs by substantial amounts relative to bare skin.

In a similar study Bekö et al. (2016) investigated the dermal uptake of nicotine from air while wearing clean cotton clothes or an identical set of clothes that included a shirt that had been exposed for five days to elevated nicotine levels. The subject was exposed to environmental tobacco smoke in an experimental chamber for three hours while breathing clean air from a breathing hood. Urine samples were collected for 24-h after the first exposure (clean clothes). The subject then entered the chamber for another three-hour exposure wearing the clothes including the contaminated shirt. Urine was collected for 60 hours. The urine samples were analyzed for nicotine and two metabolites - cotinine and 3OH-cotinine. Clean clothes significantly reduced uptake relative to bare skin, but the excretion was greater than background levels. Nicotine absorbed was estimated to be about 20 µg (compared to 570 µg for the bare-skinned subjects). Substantially larger uptake, 80 µg, was observed when the subject wore a shirt previously exposed to nicotine.

5. MODELING DERMAL UPTAKE FROM AIR

Weschler and Nazaroff (2012, 2014) developed a steady-state model of transdermal uptake of SVOCs from air and predicted that dermal uptake would be important for many indoor-relevant SVOCs. Gong et al. (2014) developed a transient model to predict dermal absorption of gas-phase chemicals via direct air-to-skin-to-blood transport under non-steady-state conditions. They showed that for time periods less than those required to reach steady state, a substantial amount of SVOC may reside in the skin before diffusing to the dermal capillaries or back out of the skin to air. The results further supported the fact that dermal intake can be comparable to or larger than inhalation intake for DEP, DiBP, DnBP, and BBzP. However, the Gong et al. model still overpredicted uptake when applied to the subjects of an actual experiment described in Weschler et al. (2015). To more accurately predict dynamic transdermal uptake of SVOCs, Morrison et al. (2016b) modified the Gong et al. model to include a layer of skin surface lipids (SSL). Addition of SSL increases the overall resistance to uptake of SVOCs from air but also allows for rapid transfer of SVOCs to sinks like clothing or clean air. This improved model predicted total uptake values that were consistent with the measured values. Simulations that included transfer of skin oil to clothing further improved model predictions.

6. POTENTIAL HEALTH EFFECTS

Absorption, distribution, and elimination of a chemical in the body may differ between the various

exposure pathways (Needham et al., 2007). Ingested compounds pass through the intestines and liver before entering the blood. Inhaled contaminants first pass through the lungs where they may be transferred directly to capillary blood. Chemicals penetrating the skin can directly enter the blood. However, they are first absorbed at the surface of the stratum corneum, they diffuse through the cell layers, entering the viable epidermis, then the papillary dermis and then reaching the capillary. Therefore the half-life of contaminants for these routes are different (Nomiyama et al., 2000). Moreover, for nominally comparable exposures, the resulting biologically effective dose to various organs can differ between exposure routes. Mielke et al. (2011) modeled the concentration of bisphenol-A in the liver and kidney from a given oral or identical dermal dose. For oral intake, about two times higher peak concentrations were obtained in the liver, compared to kidney. Peak concentrations were however about an order of magnitude higher in the kidney compared to liver after an identical dermal dose. In the liver, exposure (area under the curve) by the oral route was two-fold higher and peak concentrations 10 times higher than after dermal exposure.

Exposure assessment is often based on the concentration of a compound or its metabolites in a biological matrix, most often urine or blood. The intake of a compound can be estimated from these concentrations if information on its metabolism and elimination is available. However, concentrations of a compound or its metabolites obtained from biomonitoring represent the total intake, irrespective of the exposure pathway. If a given pathway (e.g. diet) overwhelmingly dominates total exposure, then urinary metabolite concentrations or the estimated total intake could fail to reveal an association between the fraction entering the body through a different exposure pathway and the development of a disease. Understanding the contribution of each pathway to the total intake may well be important from a health-effects perspective. However, the relationship between dermal uptake of SVOCs from air and health effects has not been studied. Moreover, current exposure limit values are mainly based on oral intake. Limit values for intake via other pathways do not exist for SVOCs typically present in indoor air.

Studies that use intakes back-calculated from urinary metabolite concentrations rely on the often limited information on metabolism and elimination of a given compound. For example, the number of controlled studies on the metabolism of phthalates in humans is small (Koch et al., 2005). Different urinary excretion factors (the fraction of an administered dose excreted in urine) are reported in the literature. For some of the phthalates, these factors have been obtained from studies with only a few adult volunteers. The urinary excretion factors have been determined from excretion over a short time period after controlled oral administration. Studies assume that the fraction of a given phthalate excreted in urine is identical for all exposure pathways. Whether the fraction excreted after inhalation or dermal absorption is the same as that following ingestion (the only pathway studied until now) is currently not known. This is the case for most of the common indoor SVOCs.

Bekö et al. (2015) examined the associations between phthalate exposure indicators (mass fractions in dust from children's homes and daycares, metabolites in urine, and estimated daily indoor intakes from dust ingestion, inhalation and dermal absorption) and allergic sensitization in a large group of 3-5 year old children: 300 random controls and 200 cases with asthma, rhinoconjunctivitis or atopic dermatitis. Among children with disease, there were significant positive associations between non-dietary exposures to DnBP, BBzP and DEHP in the indoor environment (mass fractions in dust or daily indoor intake fractions from dust ingestion, inhalation or dermal absorption) and allergic sensitization. Some exposure pathways were more strongly associated with sensitization than others. No significant

associations were observed between phthalate metabolites in urine, which reflected total exposure (diet as well as indoor pathways), and allergic sensitization. To our knowledge this is the only study investigating the link between phthalate exposure via different pathways and health effects. The results therefore warrant confirmation.

Another study that deserves attention looked at the association between filaggrin deficiency and urinary phthalate metabolites (Joensen et al., 2014). Filaggrin is an epidermal protein that is crucial for skin barrier function. Filaggrin deficiency due to the presence of one or more loss-of-function variants in the filaggrin gene is observed in approximately 10% of lightly pigmented Europeans and in a slightly lower proportion of Asians. Permeation of allergens seems to be increased in filaggrin-depleted skin and an increased risk of atopic dermatitis, asthma, rhinitis has been observed. The study found that carriers of such filaggrin variants had significantly higher urinary concentrations of several phthalate metabolites, including a 33% higher concentration of MnBP. The authors concluded that a likely explanation is increased transepidermal absorption. Transdermal absorption of chemicals from air in populations with filaggrin loss-of-function variants in the filaggrin gene warrant further attention.

7. CONCLUSION

There is a need to better understand this potentially very important exposure pathway. It is an area that has received little attention. The field of dermal exposure to SVOCs is however gaining awareness internationally. Significantly more research is needed before we can fully understand the metabolism, elimination and health effects related the dermal uptake of commonly encountered semivolatile organic compounds in indoor air and thus appreciate the importance of this pathway. Increasing knowledge regarding this previously neglected pathway is anticipated to influence future policies (e.g., on building materials, e-cigarettes, use of personal care products, storage of clothing), ventilation strategies, air cleaning and other mitigation strategies in residential, educational, public and occupational settings.

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