Dermal absorption of semivolatile organic compounds from the gas phase: Sensitivity of exposure assessment by steady state modeling to key parameters

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Maud Pelletier[1,2], Nathalie Bonvallot[1,2], Olivier Ramalho[3], Olivier Blanchard[1,2], Fabien Mercier[1,2,4], Corinne Mandin[2,3,4], Barbara Le Bot[1,2,4], Philippe Glorennec[1,2*]

[1]EHESP-School of Public Health, Sorbonne Paris Cité, Rennes, France

[2]INSERM-U1085, Irset-Research Institute for Environmental and Occupational Health, Rennes, France

[3]University of Paris-Est, Scientific and Technical Center for Building (CSTB), Health and Comfort Department, French Indoor Air Quality Observatory (OQAI), 84 Avenue Jean Jaurès, Champs sur Marne, 77447 Marne la Vallée Cedex 2, France

[4]LERES-Environment and Health Research Laboratory (Irset and EHESP Technologic Platform), Rennes, France

[*]Corresponding author:

INSERM-U1085, Irset-Research Institute for Environmental and Occupational Health, Rennes, France. EHESP-School of Public Health, Sorbonne Paris Cité, Rennes, France.

Tel.: +33-2 99 02 26 80.

E-mail address: philippe.glorennec@ehesp.fr

ABSTRACT

Recent research has demonstrated the importance of dermal exposure for some semivolatile organic compounds (SVOCs) present in the gas phase of indoor air. Though models for estimating dermal intake from gaseous SVOCs exist, their predictions can be subject to variations in input parameters, which can lead to large variation in exposure estimations. In this sensitivity analysis for a steady state model, we aimed to assess these variations and their determinants using probabilistic Monte Carlo sampling for 8 SVOCs from different chemical families: phthalates, bisphenols, polycyclic aromatic hydrocarbons (PAHs), organophosphorus (OPs), organochlorines (OCs), synthetic musks, polychlorinated biphenyls (PCBs) and polybromodiphenylethers (PBDEs). Indoor SVOC concentrations were found to be the most influential parameters. Both Henry's law constant (H) and octanol/water partition coefficient (K_{ow}) uncertainty also had significant influence. While exposure media properties such as volume fraction of organic matter in the particle phase ($f_{om\text{-}part}$), particle density (ρ_{part}), concentration ([TSP]) and transport coefficient (γ_d) had a slight influence for some compounds, human parameters such as body weight (W), body surface area (A) and daily exposure (t) make a marginal or null contribution to the variance of dermal intake for a given age group. Inclusion of a parameter sensitivity analysis appears essential to reporting uncertainties in dermal exposure assessment.

KEY WORDS

Percutaneous, indoor air, chemical, contact, sensitivity analysis, Monte Carlo.

HIGHLIGHTS

- Sensitivity analysis was conducted for 8 SVOCs with MC simulations.
- SVOC air concentration is the most influential variable parameter.

- Octanol-water partition coefficient and Henry's law constant are influent uncertain parameters.
- Influence of airborne particles characteristics and human parameters is minimal.

ABBREVIATIONS

A Body surface area (m^2)

C_a SVOC total concentration in indoor air (C_g+F) (ng/m^3)

C_g SVOC concentration in the gas phase (ng/m^3)

$DI_{dermal\text{-}gas}$ Daily intake by dermal exposure through the gas phase (micrograms per kilogram of body weight per day, µg/kg-bw/d)

F SVOC concentration in the particulate phase (ng/m^3 of air)

$f_{om\text{-}part}$ Volume fraction of organic matter associated with airborne particles

H Henry's law constant ($Pa.m^3/mol$)

K_{oa} Octanol/air partition coefficient

K_{ow} Octanol/water partition coefficient

K_p Gas/particle distribution coefficient ($m^3/µg$)

k_{pg} Indoor air transdermal permeability coefficient, describing the transport of a gas phase SVOC from bulk indoor air to dermal capillaries, through the boundary layer adjacent to skin, the stratum corneum and viable epidermis composite (m/h)

MW SVOC molecular weight (g/mol)

P_s SVOC vapor pressure (Pa)

63 R Ideal gas constant (=8.314 Pa.m^3/mol.K)

64 ρ_{part} Density of airborne particles (g/m^3)

65 *SVOC* Semivolatile organic compound

66 t Daily exposure duration (h/d)

67 T Temperature (K)

68 *[TSP]* Total suspended particle concentration (µg/m^3)

69 W Body weight (kg)

70 γ_d Coefficient describing the external transport of a gas phase SVOC from the bulk
71 indoor air to the boundary layer adjacent to the skin (m/h)

72 **INTRODUCTION**

73 People spend more than 80% of their time in enclosed spaces, largely in dwellings in which
74 they are exposed to an increasing number of chemicals from various sources and via different
75 exposure routes. In addition to other pollutants found in indoor environments (radon, carbon
76 monoxide, formaldehyde and other volatile organic compounds), semivolatile organic
77 compounds (SVOCs) have received a great deal of attention, due to a rise in their use in
78 consumer products as well as improved analytical techniques that have shown their ubiquity
79 in dwellings (Rudel et al., 2003; Weschler and Nazaroff, 2008).

80 SVOCs include organic molecules from many different chemical families (phthalates,
81 bisphenols, polycyclic aromatic hydrocarbons (PAHs), organophosphorus (OPs),
82 organochlorines (OCs), synthetic musks, polychlorinated biphenyls (PCBs),
83 polybromodiphenylethers (PBDEs), etc.). They are emitted from multiple household sources:
84 flooring and wall materials, furniture, cosmetics, cleaning products, combustion products,

packaging, etc. Due to their physical-chemical properties, they are able to migrate to, and partition between, different indoor compartments, including gas phase and airborne particles and settled dust (Weschler and Nazaroff, 2008), as well as other available surfaces such as walls, ceiling and flooring materials – or human skin and clothing. The scientific community's growing interest in studying exposure to these compounds is motivated by suspicion of reprotoxic, (Rubin, 2011; Moreau-Guigon and Chevreuil, 2014), neurotoxic (Baldi et al., 2001; Elbaz et al., 2009; Blanc-Lapierre et al., 2012; Zaganas et al., 2013) and carcinogenic (Armstrong et al., 2004; IARC, 2010a, 2010b) health effects, as well as the acknowledged presence of these compounds and their metabolites in human biological fluids (blood and urine) (NHANES, 2015). This interest is even more pronounced with regard to pregnant women and young children, considered more sensitive to these toxic effects (Grandjean et al., 2008).

At home, in addition to food ingestion (the main exposure pathway for many SVOCs), people are exposed through a variety of pathways: direct contact with the SVOC source, inhalation and contact with indoor air (gaseous and particulate phases), ingestion and contact with settled dust (on floor and furniture). Young children are more exposed than the rest of the population due to their more frequent contact with the ground and deposited dust, carrying objects in their mouths, etc. Though dust ingestion and inhalation of gaseous and particulate phases are the two best-documented exposure pathways in the literature, dermal absorption is rarely assessed in the course of environmental exposure assessments, because it is presumed to be negligible. Nevertheless, recent research has hypothesized the significance of dermal exposure (Weschler and Nazaroff, 2012; Gong et al. 2014) and more recently Weschler et al. (2015) and Morrison et al. (2016) have corroborated these findings via experimental human dermal exposure to two gaseous phthalates: diethyl phthalate (DEP) and di-n-butyl phthalate (DnBP). The results confirm that transdermal uptake directly from air can be a meaningful

exposure pathway for DEP and DnBP, and that direct dermal absorption from air is also expected to be significant for other SVOCs, where the molecular weight and K_{ow} are in a similar range. Bekö et al. (2013) estimated daily intakes resulting from four different indoor exposure pathways: dust ingestion, inhalation and dermal exposure through gas phase and through dust adhering to skin, based on phthalates' metabolites levels in urine samples of DEP, DnBP, di(isobutyl) phthalate (DiBP), butyl benzyl phthalate (BBzP) and di(2-ethylhexyl) phthalate (DEHP) and their concentration in dust samples collected at the same time. They found that gas phase dermal absorption was the major exposure pathway for the more volatile compounds, in comparison with the other pathways involved. They also found that intake through dermal contact with dust contributed only very slightly to total intake for all studied phthalates. In order to assess SVOC gas phase dermal exposure, some authors have adapted and used a model based on mass-transfer resistance to calculate an indoor air transdermal permeability coefficient $k_{p\text{-}g}$ (Weschler and Nazaroff, 2012; Bekö et al., 2013). This mass-transfer model describes the transport of a gas phase SVOC from bulk indoor air to dermal capillaries, through the boundary layer adjacent to skin, the stratum corneum and the viable epidermis composite.

At equilibrium and due to their physical-chemical properties, especially K_{oa}, SVOCs partition between the gas and particle phases of indoor air (Finizio et al., 1997; Pankow, 1998; Weschler and Nazaroff, 2008). When assessing gaseous SVOC dermal exposure, concentration in the gas phase (C_g) is required and could be either measured or modeled from total concentration in indoor air (C_a) - which is the sum of gas and particulate (F) phases ($C_g+F=C_a$). Salthammer and Schripp (2015) have highlighted the importance of taking parameter uncertainty and variability into account when assessing SVOC partitioning and exposure. Weschler and Nazaroff (2014) have already assessed the sensitivity of $k_{p\text{-}g}$ and other partitioning coefficient calculations, such as K_p, to the octanol/water partition

coefficient (K_{ow}), the octanol/air partition coefficient (K_{oa}) and Henry's law constant (H) uncertainties. We would like to continue this work here by evaluating the sensitivity of dermal intake, i.e. the mass of pollutant entering the body per kg of body weight and unit of time, to these parameters using a steady-state model.

The objective of this sensitivity analysis is to evaluate dermal intake variation caused by the uncertainty and variability of input parameters when using the model described by Weschler and Nazaroff (2012) for dermal absorption of gas phase SVOCs. We chose the study by Blanchard et al. (2014), in which 57 indoor SVOCs of health interest (Bonvallot et al., 2010) were measured with separation of their gas phase and airborne particle concentrations, as a starting study. We selected eight compounds from different chemical families having varied K_{oa} and volatility to represent contrasting situations: dimethyl phthalate (DMP), phenanthrene, galaxolide (HHCB), PCB 105, diazinon, permethrin, bisphenol A (BPA) and BDE 154.

METHODS

1. Equation tested for dermal intake modeling

For a given human, chronic daily intake of gas phase SVOC via the dermal pathway, $DI_{dermal-gas}$, can be estimated in steady-state conditions using the following equation adapted by Bekö et al. (2013).

$$DI_{dermal-gas} = \frac{\frac{C_g \times k_{p-g} \times A \times t}{1000}}{W} \quad (1)$$

Where C_g is the SVOC gas phase concentration (ng/m^3), A is the body surface area (m²), t is the daily duration of exposure (h/d), W is the body weight (kg), k_{p-g} is the SVOC transdermal permeability coefficient (m/h) and $DI_{dermal-gas}$ is expressed in µg/kg-bw/d.

The indoor air transdermal permeability coefficient ($k_{p\text{-}g}$) can be estimated using the steady-state model adapted by Weschler and Nazaroff (2012, 2014), (see supplementary material for the intermediate equations used to derive Equation 2):

$$k_{p-g} = 1/(\frac{1}{\gamma_d} + (\frac{H}{RT} / \frac{10^{(0.7\times\log(K_{ow})-0.0722\times MW^{2/3}-5.252)} \times 3600 \times 10^{-2}}{1 + (10^{(0.7\times\log(K_{ow})-0.0722\times MW^{2/3}-5.252)} \times MW^{0.5} \times 3600/2.6)})) \quad (2)$$

Where K_{ow} is the SVOC octanol-water partition coefficient, MW is the SVOC molecular weight (g/mol), H is the Henry's law constant (Pa.m^3/mol), R is the ideal gas constant (8.314 Pa.m^3/mol.K), T is the air temperature (K) and γ_d is the coefficient that describes the external transport of an SVOC from the gas phase in the core of a room through the boundary layer adjacent to the skin (m/h).

When estimating dermal intake from the gas phase (see Equations 1 and 2), exposure assessors may face two situations which can be distinguished in terms of availability of the C_g value: A) C_g is measured experimentally or B) C_g is calculated from total indoor air concentration (C_a). Assuming that SVOCs are in equilibrium between gas and particulate phases, C_g can be estimated from C_a using the partitioning model proposed by Weschler and Nazaroff (2010) and can be expressed as follows (see supplementary material for the detailed calculation):

$$C_g = \frac{C_a}{1 + ([TSP] \times \frac{f_{om-part} \times K_{ow} \times R \times T}{\rho_{part} \times 10^6 \times H})} \quad (3)$$

Where [TSP] is the total suspended particle concentration (μg/m^3), $f_{om\text{-}part}$ is the volume fraction of organic matter associated with airborne particles and ρ_{part} is the density of airborne particles.

2. Parameter estimation

178 The impact of uncertainty or variability of equation parameters on $DI_{dermal\text{-}gas}$ variability was
179 assessed. Parameter distributions were constructed or retrieved from the literature as detailed
180 below. For a given group of occupants in a given indoor setting, some of these parameters
181 will be the same for all SVOCs (γ_d, [TSP], $f_{om\text{-}part}$, ρ_{part}, W, A and t) while others will vary
182 from one compound to another (K_{ow}, H, C_g and C_a).

183 *Physical-chemical parameters*

184 For each SVOC, measured or estimated values of log (K_{ow}) and Henry's law constant (H) at
185 25°C were retrieved from: online databases - Hazardous Substances Data Bank (HSBD) and
186 ChemIDplus (http://toxnet.nlm.nih.gov/), Chemspider (http://www.chemspider.com/), and
187 Chemicalize (http://www.chemicalize.org/); toxicological and environmental data sheets from
188 the French National Competence Centre for Industrial Safety and Environmental Protection
189 (INERIS) (http://www.ineris.fr/substances/fr/page/21); online calculators - Chemexper
190 (https://www.chemexper.com/) and ACD/Labs (http://www.acdlabs.com/); EPI Suite software
191 (US EPA, v4.1) and the Handbook of Physical-Chemical Properties and Environment Fate for
192 Organic Chemicals (Mackay et al., 2010a, 2010b, 2010c, 2010d). Only values at 25°C
193 (reference temperature) were selected, in order to be consistent and to estimate $DI_{dermal\text{-}gas}$ at a
194 constant temperature. For each SVOC, where at least 15 values for their log (K_{ow}) and H were
195 retrieved from the sources mentioned above, distributions were fitted – and otherwise we used
196 triangular distributions (between minimum, average and maximum values). Corresponding
197 distributions are displayed in Table 1.

198 *Contamination data*

199 In situation A (C_g measured): SVOC gas phase concentration values (C_g) were retrieved from
200 Blanchard et al. (2014). When 100% (i.e. in 30 out of 30 dwellings) of the data were > the
201 limit of quantification (LOQ), log-normal distributions were fitted. When 100% of the values

were < LOQ, uniform distributions between 0 and LOQ were used. Lastly when single values were > LOQ, custom distributions were constructed, related to their probabilities of occurrence, with continuous range between 0 and LOQ and discrete ranges for the values > LOQ. In situation B (C_g measured from C_a): SVOC indoor air concentration values (C_a) were retrieved from the literature (Fromme et al., 2004; Fromme et al., 2009 and Rudel et al., 2010). Log-normal distributions were fitted where possible; otherwise custom distributions were constructed, related to their probabilities of occurrence, with continuous ranges from 0 to LOQ and from LOQ to maximum value, or triangular distributions between minimum, average and maximum values. Corresponding distributions are displayed in Table 1.

Human parameters

We considered a 4-year-old male child to be representative of the sensitive population in terms of the identified toxicological effects and exposure behavior. As an example we searched literature for body weight (W), surface area (A), and time spent in dwellings (t) for a child living in France. Log-normal distributions were used for weight and body surface area. Normal distribution was used for the space-time-budget. Corresponding distributions are displayed in Table 1.

Exposure media properties

The assessment of gas phase SVOC dermal transfer requires the use of exposure media properties such as γ_d, [TSP], $f_{om\text{-}part}$ and ρ_{part}. Triangular distribution was used for γ_d, using the minimum and maximum values found in the literature and the generally-assumed 6 m/h as the most likely value to occur. Log-normal distribution was used for [TSP] and $f_{om\text{-}part}$. Normal distribution was used for ρ_{part}. Corresponding distributions are displayed in Table 1.

3. Simulation

225 Dermal intake sensitivity analysis (Eq. 1) was performed using Crystal Ball® software
226 (Oracle©, version 11.1.1.3.00). For each SVOC and for each of the two situations regarding
227 C_g (A: C_g measured, B: C_g modeled), Latin Hypercube one-dimensional simulations were
228 carried out with 10^5 runs.

229 **Table 1:** Parameter distributions used in the dermal intake sensitivity analysis from gas phase for 8 SVOCs.

Parameter	DMP	Phenanthrene	HHCB	Permethrin	Diazinon	PCB105	BPA	BDE154	Sources
log (K_{ow})*	Log-normal min=1.35 μ=1.65 σ=0.14	Logistic μ=4.50 scale=0.09	Triangular min=3.42 μ=5.23 max=6.26	Minimum extreme likeliest=6.51 scale=0.73	Minimum extreme likeliest=3.74 scale=0.37	Minimum extreme likeliest=6.72 scale=0.35	Triangular min=3.32 μ=3.48 max=4.04	Triangular min=6.86 μ=7.89 max=8.83	Internet databases***, Chemexper, ACD/Labs calculators, EPI Suite software (US EPA, v4.1), Mackay et al., 2010a, 2010b, 2010c, 2010d.
H* ($Pa.m^3/mol$)	Triangular min=6.20E-3 μ=3.60E-2 max=1.11E-1	Triangular min=2.38 μ=3.74 max=5.55	Uniform min=7.66E-2 max=1.34E+1	Triangular min=2.33E-6 μ=5.34E-2 max=1.89E-1	Triangular min=7.00E-3 μ=4.25E-2 max=1.44E-1	Triangular min=2.43 μ=2.24E+1 max=8.36E+1	Triangular min=9.28E-7 μ=2.49E-6 max=4.05E-6	Triangular min=4.77E-2 μ=1.46E-1 max=2.40E-1	
C_g (ng/m^3)	Log-normal min=0 μ_g=8.57 σ_g=2.23	Log-normal min=4.16 μ_g=3.88 σ_g=2.98	Log-normal min=0 μ_g=6.67E+1 σ_g=2.57	Uniform [0 - 0.6(LOQ)]	Discrete (p=0.03) 2.45 Uniform (p=0.97) [0 - 0.6(LOQ)]	Discrete (p=0.03) 0.4 Uniform (p=0.97) [0 - 0.25(LOQ)]	Uniform [0 - 0.6(LOQ)]	Uniform [0 - 0.6(LOQ)]	Blanchard et al., 2014.
C_a (ng/m^3)	Log-normal μ=1.18E+3 p50=4.36E+2 p95=4.65E+3	Log-normal μ=6.1 p50=1.10E+1 p95=2.90E+1	Log-normal μ=1.19E+2 p50=1.01E+2 p95=2.45E+2	Uniform (p=0.92) [0 - 0.3(LOQ)] Uniform (p=0.08) [0.3(LOQ) - 2]	Uniform (p=0.98) [0 - 0.3 (LOQ)] Uniform (p=0.02) [0.3(LOQ) - 3.1E+1]	Uniform (p=0.88) [0 - 0.3 (LOQ)] Uniform (p=0.12) [0.3(LOQ) - 1.2]	Uniform (p=0.84) [0 - 0.8(LOQ)] Uniform (p=0.16) [0.8(LOQ) - 2.2E+1]	Triangular min=0 μ=6.20E-4 max=1.09E-2	Rudel et al., 2010 (phen, per, diaz, PCB105, BPA), Fromme et al., 2004 (DMP, HHCB), Fromme et al., 2009 (BDE154).
v_d (m/h)	Triangular min=5, likeliest=6, max=10								Tamas et al., 2006; Pandrangi and Morrison, 2008; Weschler and Nazaroff, 2008.
[TSP] ($\mu g/m^3$)	Log-normal, μ_g=37.34, σ_g=2.17, p95=182								Ramalho et al., 2012.
$f_{om\text{-}part}$	Normal, μ=0.35, σ=0.2								Salthammer and Schripp, 2015.
ρ_{part} (g/m^3)	Normal, μ=1.6E+6, σ=0.5E+6								Pitz et al., 2003.
W** (kg)	Log-normal, μlnx=2.68, σlnx=0.17, p95=22.0								Tanguy et al., 2007.
A** (m^2)	Log-normal, μ=-0.28, σ=0.12, p95=0.94								Sabaterie et al., 2013.
T (h/d)	Normal, μ=17.17, σ=0.63								Zeghnoun and Dor, 2010.

A: body surface area; BPA: bisphenol A; C_a: SVOC total concentration in indoor air; C_g: SVOC concentration in the gas phase; diaz: diazinon; DMP: dimethyl phthalate; $f_{om\text{-}part}$: volume fraction of organic matter associated with airborne particles; γ_d: coefficient describing the external transport of a gas phase SVOC from the bulk indoor air to the boundary layer adjacent to the skin; H: Henry's law constant; HHCB: galaxolide; K_{ow}: octanol/water partition coe$_f$ficient; μ: arithmetic mean; μ_g: geometric mean; per: permethrin; phe: phenanthrene; ρ_{part}: density of airborne particles; σ: standard deviation; σ_g: geometric standard deviation; t: daily exposure duration; [TSP]: total suspended particle concentration; W: body weight. Distribution parameters may be different for a same distribution law because of diversity of reporting data in the literature.

*: Measured or estimated at 25°C.

**: Spearman's rank correlation between mass and body surface area is 0.99 for a 4-year-old male child (Sabaterie et al., 2013).

***: Hazardous Substances Data Bank (HSBD), ChemIDplus, Chemspider, Chemicalize and the French toxicological and environmental data sheets from INERIS.

RESULTS AND DISCUSSION

1. Daily dermal intake variation

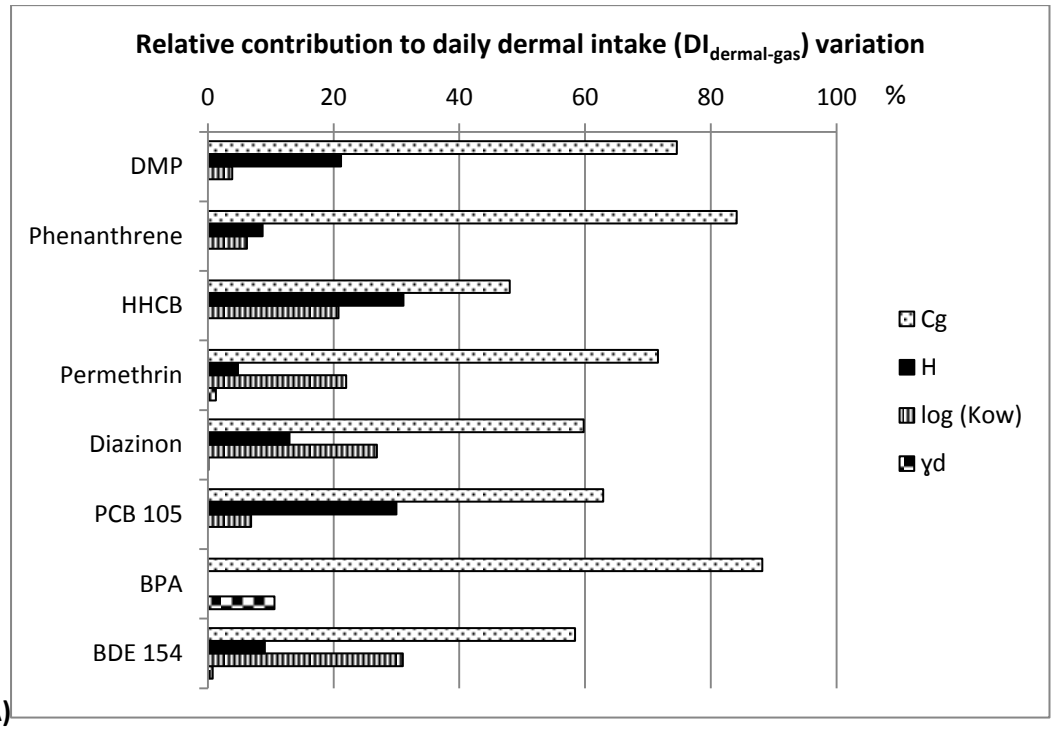
Daily dermal intake variations are presented in Table 2.

Table 2: Variations in daily dermal intake ($DI_{dermal\text{-}gas}$), expressed as the relative interdecile range, for each SVOC and for each of the two situations regarding gas phase concentration (A: C_g measured, B: C_g modeled).

Situation	SVOC	Relative interdecile range $= \frac{d90 - d10}{d50}$
A	Dimethyl phthalate (DMP)	3.1
	Phenanthrene	1.9
	Galaxolide (HHCB)	6.3
	Permethrin	2.2
	Diazinon	3.1
	PCB 105	2.8
	Bisphenol A (BPA)	1.2
	BDE 154	1.6
B	Dimethyl phthalate (DMP)	6.2
	Phenanthrene	1.4
	Galaxolide (HHCB)	2.8
	Permethrin	3.6
	Diazinon	3.1
	PCB 105	3.7
	Bisphenol A (BPA)	17.8
	BDE 154	7.3

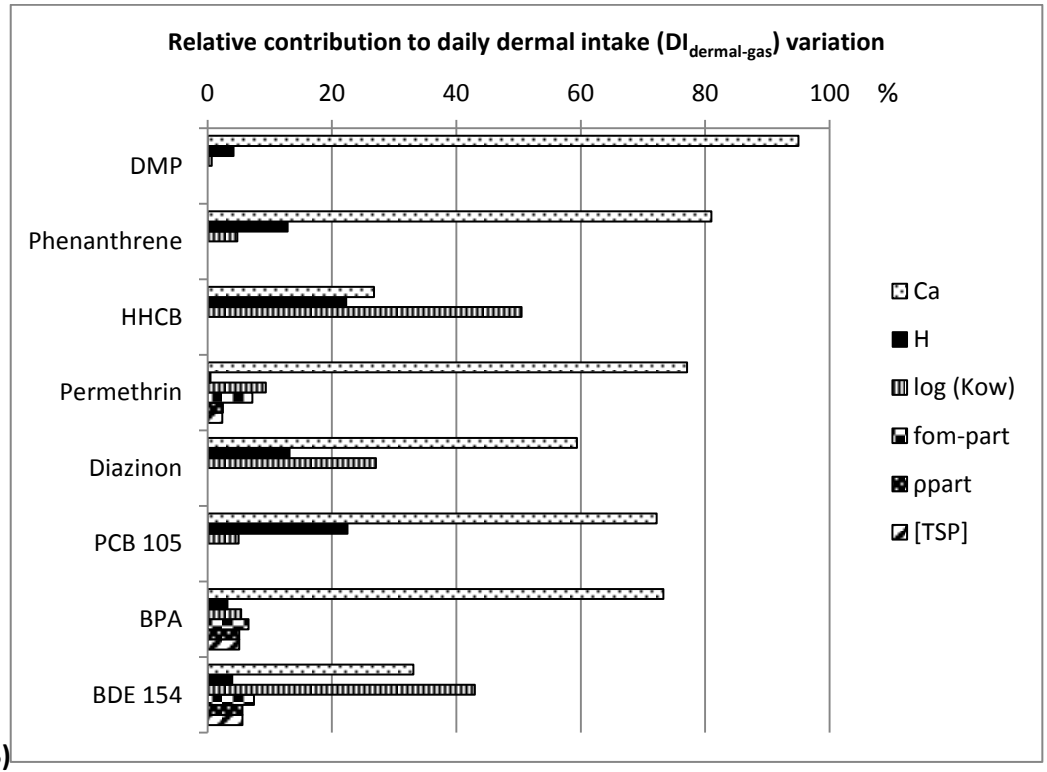
The relative interdecile range of $DI_{dermal\text{-}gas}$, when C_g value is measured (situation A), ranged from 1.2 for BPA to 6.3 for galaxolide (HHCB). When C_g is estimated from C_a (situation B), $DI_{dermal\text{-}gas}$ variation was highest for BPA having a relative interdecile range of 17.8 and lowest for phenanthrene, at 1.4. The following sensitivity analysis results allow us to interpret $DI_{dermal\text{-}gas}$ variation, particularly for compounds having high relative interdecile ranges.

2. Sensitivity to model parameters



253 **A)**

254



255 **B)**

256

257 **Figure 1:** Relative contribution (%) to total variation of gaseous SVOC daily dermal intakes
258 (µg/kg-bw/d) according to key parameters: C_g, C_a, log (K_{ow}), H, $ɣ_{d,}$ $f_{om\text{-}part}$, $ρ_{part}$, and [TSP] for
259 both situations: A) C_g is measured and B) C_g is estimated from C_a.

Results of the sensitivity analysis are presented in Figure 1 as tornado charts, showing relative contributions to total variation of gas phase SVOC daily dermal intakes (µg/kg-bw/d) according to key parameters. Parameters having a relative contribution that is always lower than 5% are not shown in Figure 1, that is, each of the human parameters: W, A and t (situation A and B) and γ_d (only for situation B).

The sensitivity analysis of $DI_{dermal\text{-}gas}$ calculation, when C_g is measured (situation A), reveals that for the studied compounds the most influential parameters are: C_g, H and log (K_{ow}). $DI_{dermal\text{-}gas}$ estimation is mainly driven by variability in C_g.

When C_g is estimated from C_a (situation B), $DI_{dermal\text{-}gas}$ variation is dominated by variability in C_a, with the exception of HHCB and BDE 154 for which it is mainly driven by uncertainty in log (K_{ow}). For permethrin and BDE 154, uncertainties in $f_{om\text{-}part}$, ρ_{part} and [TSP] are also significant, though less influential in $DI_{dermal\text{-}gas}$ calculation.

For a given age group in both situations, the following parameters make a marginal or null contribution to $DI_{dermal\text{-}gas}$ variation for all of the studied SVOCs: t, W, A, and γ_d - with the exception of BPA in situation A, for which γ_d makes a significant contribution.

3. Variability and uncertainty in C_g and C_a measurements

Indoor air SVOCs concentrations can be variable and/or uncertain. Variabilities in indoor air concentrations (C_g and C_a) are high due to several conditions, such as differences in occupant habits, variety of sources, and dwelling characteristics. For example, Clausen et al. (2012) found that indoor temperature has a significant influence on DEHP air concentrations: this increases by a factor of about 10 with an increase of 12°C in indoor temperature. Furthermore, these concentrations may vary considerably from one country to another

283 depending, for example, on national regulations regarding the use of specific SVOCs
284 (Weschler and Nazaroff, 2008). In this sensitivity analysis, C_g and C_a were retrieved from
285 studies (Fromme et al., 2004; Fromme et al., 2009; Rudel et al., 2010 and Blanchard et al.,
286 2014) having measured these concentrations at various indoor temperatures and in different
287 countries. But C_g and C_a are also uncertain, especially when all or most values are below the
288 LOQ. When C_g and C_a values were below the LOQ (permethrin, diazinon, PCB 105, BPA and
289 BDE 154), the applied distribution shape (custom, triangular and uniform) also brings
290 uncertainty to these unknown values. In order to assess the impact of the distribution on C_g
291 and C_a uncertainty, triangular distributions (between 0, LOQ/2 and LOQ) were also tested in
292 place of uniform distributions (data not shown). The same results were found, providing
293 evidence that distribution shape does not influence the relative contribution of C_g and C_a
294 uncertainty in $DI_{dermal\text{-}gas}$ result variation.

295 Moreover, some LOQs used as maxima in uniform distribution regarding C_g (permethrin,
296 BPA and BDE 154) are open to discussion because they are high in comparison with other
297 studies in which fewer compounds were measured at the same time. This uncertainty can lead
298 to discrepancy between the two situations regarding the distribution we used, especially for
299 BDE 154 concentrations in indoor air (see Table 1) where C_g maximum value (0.6=LOQ) is
300 larger than C_a maximum (0.01). This unrealistic situation is the only one in our study - but it is
301 important to bear in mind that the objective here is a sensitivity analysis linked to information
302 availability, rather than an exposure assessment.

303 4. Uncertainty in physical-chemical parameter values

304 Physical-chemical parameters can either be measured experimentally or calculated using other
305 chemical properties. Depending on which of these methods is used, it follows that values vary
306 by one order of magnitude or more (Finizio et al., 1997) - and these uncertainties will be

propagated in the calculation of $k_{p\text{-}g}$, C_g and $DI_{dermal\text{-}gas}$. On this topic, Weschler and Nazaroff (2008) warned that H, K_{ow} and K_{oa} values, calculated using the SPARC Online Calculator v4.0 (Hilal et al., 2003, 2004), sometimes vary substantially from experimentally derived values. For the same parameters, Schossler et al. (2011) demonstrated that values vary by one order of magnitude or more between the results obtained using software tools such as EPI Suite (US EPA, 2013) or the SPARC Online Calculator v4.6. In this study, log (K_{ow}) and H values were collected from several databases, online calculators and literature sources at 25°C, and for each SVOC (see Table 1). The wide intervals obtained for certain compounds - such as H for HHCB - corroborate the relatively high level of uncertainty for these parameters.

When assessing gas/particle SVOC distribution (see Equation 8 in the supplementary material for the detailed calculation), Salthammer and Schripp (2015) assumed normal distributions for H and log (K_{ow}). Due to the lack of data (as discussed above) the authors calculated mean and standard deviation, in order to build normal distribution using just two values for certain compounds. In our study, where at least 15 values for these parameters were retrieved from literature, log-normal distributions were fitted - otherwise we used triangular, minimum extreme or logistic distributions (see Table 1). However, in order to assess the impact of distribution, other distributions, such as uniform, were also tested and the same parameters were found to be most sensitive regarding $DI_{dermal\text{-}gas}$ variability, providing evidence that choice of distribution shape does not influence the relative contribution made by H and log (K_{ow}) in $DI_{dermal\text{-}gas}$ result variation.

In each situation (A and B), H and log (K_{ow}) have a significant influence on $DI_{dermal\text{-}gas}$ variability, depending on the range of H and log (K_{ow}) values. For example, H values for HHCB range from [7.66E-2 to 13.4], which logically leads to this parameter having a greater influence on $DI_{dermal\text{-}gas}$ variability (see Figure 1). These results are consistent with previous

studies: Weschler and Nazaroff (2014) assessed $k_{p\text{-}g}$ sensitivity (see Equation 2) to the same key parameters and also found that the permeability coefficient was more sensitive to H. In the same way, Salthammer and Schripp (2015) assessed the sensitivity of K_p (see Equations 8 and 9 in the supplementary material for the detailed calculation) and found that the error margin in K_p calculation was dominated by H uncertainty. Because log (K_{ow}) and H are two of the most influential parameters on $DI_{dermal\text{-}gas}$ variation for every SVOC and in both situations, reducing their uncertainties could significantly reduce variation on $DI_{dermal\text{-}gas}$ and uncertainty in exposure analysis.

5. Uncertainty in exposure media properties

In earlier studies, default values were used for $f_{om\text{-}part}$, ρ_{part}, [TSP] and γ_d. Regarding the volume fraction of organic matter associated with airborne particles, $f_{om\text{-}part}$, we assumed the same normal distribution parameters as Salthammer and Schripp (2015). Regarding particle density, ρ_{part}, several values are found in the literature and 1.10^6 g/m^3 is often assumed, as a default value (Turpin and Lim, 2001). In order to assess $DI_{dermal\text{-}gas}$ sensitivity to this parameter, normal distribution was used rather than a single value (Pitz et al., 2003). Regarding total suspended particle concentration, [TSP], a default value of 20µg/m^3 was assumed by Weschler and Nazaroff (2008). More recently, Salthammer and Schripp (2015) found that [TSP] strongly influenced gas/particle partitioning, and we decided to build a log-normal distribution for this parameter using data on indoor PM_{10} concentrations (Ramalho et al., 2012). These data are weekly-averaged, and cover different climate zones and seasons. Regarding γ_d, a value of 6m/h is assumed for the coefficient describing the external transport of a gas phase SVOC from bulk indoor air to the boundary layer adjacent to the skin (Weschler and Nazaroff, 2012). The authors have previously estimated this parameter to range between 5 and 10 m/h (Weschler and Nazaroff, 2008). In this study, triangular distribution was built between these three values. This parameter variation's influence on

357 $DI_{dermal\text{-}gas}$ variation was insignificant, with the exception of BPA in situation A (see Figure 1,
358 A). Nevertheless, Weschler and Nazaroff (2008) also proposed an estimate of 3 m/h for the
359 mass-transfer coefficient. In order to provide a comprehensive sensitivity analysis we
360 assessed different distribution shapes: triangular with a minimum of 3, a likeliest value of 6
361 and a maximum of 10 and uniform between 3 and 10. The results (not shown) were identical
362 and γ_d did not become an influential parameter.

363 While exposure media properties such as $f_{om\text{-}part}$, ρ_{part}, [TSP] and γ_d have a slight influence
364 (less than 10%, see Figure 1) for some compounds (permethrin, BPA and BDE 154), they
365 make a marginal or null contribution (less than 5%) to the variance of dermal intake for a
366 given age group, for the other SVOCs and in both situations.

367 6. Variability in human parameters

368 Human parameters such as body weight (W), body surface area (A) and daily exposure (t)
369 make a marginal or null contribution (less than 5%) to the variance of dermal intake for a
370 given age group, for each SVOC and in each situation. However, one has to bear in mind that
371 we ran the model for a given age group and that these parameters would have a larger impact
372 when applied on a more diverse population. Regarding the role of clothing in dermal
373 exposure, Piotrovski (1971) assessed the exposed body surface area (A) and found little
374 difference in dermal absorption between clothed and naked people exposed to phenol vapor.
375 More recently Morrison et al. (2016) assessed the influence of clothing on the dermal uptake
376 of two phthalates (DEP and DnBP). The authors found that clean clothes were protective
377 against air pollutants; whereas worn clothes, because they have adsorbed air pollutants,
378 increased dermal intake. Because only clean clothes could be considered protective, we
379 decided to not take into account the role of clothing in this sensitivity analysis, and to assume
380 total body surface area exposed to indoor air when calculating $DI_{dermal\text{-}gas}$. However, the fact

that we found A to make a marginal or null contribution (less than 5%) to the variance of dermal intake, does not mean that clothing should not, when possible, be taken into account in assessing dermal exposure. In this case the proportion of exposed body surface area has to be taken into account.

In addition to the important role of clothing, other parameters not included in this model are suspected of influencing or playing a role in dermal exposure were not taken into account in this sensitivity analysis: skin temperature, metabolic processes on (e.g. ionization) or in the skin, the effects of bathing on SVOC levels in skin-surface lipids, etc.

Furthermore, it is important to bear in mind that we did not assess model uncertainty - only parametric uncertainty when using this model. A first source of uncertainty is model boundaries. Indeed our model relies partly on equation of Mitragotri (2002) that may lead to greater uncertainty when MW is higher than 400, which is the case for BDE 154. In addition, more sophisticated, and recent, models exist taking into account the dynamics of aerosols and/or the clothing effect. Regarding the dynamics of aerosols, Shi and Zao (2015) showed that, in their model, air exchange rate and surfaces cleaning frequency were influential parameters, while density of settled dust and its organic fraction were important media properties. Also, the transient model proposed by Gong et al. (2014), addresses the rapidly changing conditions and concentrations and considers a convective mass transfer resistance in the boundary air layer adjacent to the skin, and leads to lower estimates of dermal uptake. Morrison et al. (2016) improved this model taking clothing effect modeling, and showed that bathing frequency and change of clothes frequency were influential. Also, the introduction of a skin surface lipid film in the models and its interactions with clothing may affect the results, so do the corresponding additional parameters, such as for instance the thickness of this lipidic film.

CONCLUSION

When assessing dermal absorption of gas phase SVOCs, variation of dermal intake estimation is driven firstly by variability and uncertainty in indoor air concentration (C_g or C_a), and secondly by uncertainty in SVOC physical-chemical parameters: log (K_{ow}) and H. While exposure media properties such as volume fraction of organic matter in the particle phase ($f_{om\text{-}part}$), particle density (ρ_{part}), concentration ([TSP]) and transport coefficient (γ_d) do have a slight influence (less than 10%) for some compounds, human parameters such as body weight (W), body surface area (A) and daily exposure (t) make a marginal or null contribution (less than 5%) to the variance of dermal intake for a given age group.

Considering that $DI_{dermal\text{-}gas}$ variation can be high for some compounds, exposure assessors aiming to assess SVOC $DI_{dermal\text{-}gas}$ using the $k_{p\text{-}g}$, or to estimate C_g from C_a, must pay particular attention to the determination, estimation, and selection of the following SVOC-specific parameters: concentration in gas phase (C_g) or indoor air (C_a), K_{ow} and H.

It is however important to remain aware, when analyzing these results, that exposure to an SVOC is strongly dependent on its partition between gas phase and particulate phase. When an SVOC is more abundant in the gas phase, dermal absorption will be greater than dust ingestion, and conversely, when a SVOC is more present in the particulate phase, dust ingestion is likely to be greater than dermal absorption (Weschler and Nazaroff, 2012). Therefore, less volatile SVOCs ($P_s < 10^{-6}$ Pa), which are more present in the particulate phase and have a low predicted dermal absorption, do not require the same caution in estimation of dermal intake in order to assess their total exposure to indoor SVOC.

In general, inclusion of an uncertainty analysis in exposure assessment appears to be essential. In view of these sensitivity analysis results, reducing log (K_{ow}) and H uncertainties could significantly reduce uncertainties in $DI_{dermal\text{-}gas}$ assessment.

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