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Dermal Uptake of Organic Vapors Commonly Found in Indoor Air

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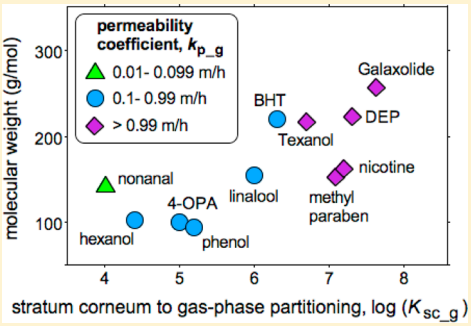
Supporting Information

ABSTRACT: Transdermal uptake directly from air is a potentially important yet largely overlooked pathway for human exposure to organic vapors indoors. We recently reported (*Indoor Air* **2012**, *22*, 356) that transdermal uptake directly from air could be comparable to or larger than intake via inhalation for many semivolatile organic compounds (SVOCs). Here, we extend that analysis to approximately eighty organic compounds that (a) occur commonly indoors and (b) are primarily in the gas-phase rather than being associated with particles. For some compounds, the modeled ratio of dermal-to-inhalation uptake is large. In this group are common parabens, lower molecular weight phthalates, o-phenylphenol, Texanol, ethylene glycol, and α-terpineol. For other compounds, estimated dermal uptakes are small compared to inhalation. Examples include aliphatic hydrocarbons, single ring aromatics, terpenes, chlorinated solvents, formaldehyde, and acrolein. Analysis of published experimental data for human subjects for twenty different organic compounds substantiates these model predictions. However, transdermal uptake rates from air have not been measured for the indoor organics that have the largest modeled ratios of dermal-to-inhalation uptake; for such compounds, the estimates reported here require experimental verification. In accounting for total exposure to indoor organic pollutants and in assessing potential health consequences of such exposures, it is important to consider direct transdermal absorption from air.



INTRODUCTION

Direct uptake of selected organic compounds from air through skin has been demonstrated in many studies conducted over the past half-century. The primary emphasis in these studies has been on occupational exposures. Experiments include cases in which the whole body of a human subject was exposed and other cases in which only an arm was exposed. Dutkiewicz and Piotrowski[1] reported that, "... a resting, fully relaxed person absorbs through the skin amounts (of aniline) comparable with those absorbed simultaneously through the respiratory tract". Specifically, they estimated that dermal absorption of aniline vapors accounted for 47−64% of a resting person's aggregate aniline intake. Piotrowski[2] more fully described experiments in which both naked and dressed men were exposed to nitrobenzene vapors in a chamber while breathing clean air. He concluded that "about half as much vapour was absorbed through the skin as through the lungs" and that "normal working clothes reduced the absorption by only 20 to 30%". Subsequently, Piotrowski[3] 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.[4] exposed only the forearm of five volunteers to vapors of either 2-methoxyethanol or 2-ethoxyethanol. Based on the urine concentrations of the metabolites of these glycol ethers, the authors estimated that — for whole body exposure — skin uptake would be approximately 120% of inhalation uptake for 2-methoxyethanol and 70% of inhalation uptake for 2-ethoxyethanol. Altogether, we have identified twenty studies published in peer-reviewed archival journals that have measured direct uptake of various organic vapors by human skin in either whole body or arm/hand experiments.[1−20] Most, but not all, of these studies have been reviewed by Rehal and Maibach[21] and by Rauma et al.[22]

In assessing human exposure to organic pollutants indoors, inhalation and ingestion of dust are routinely included as exposure pathways. The dermal pathway is frequently assumed to be negligible.[23,24] When considered, the focus has commonly been on dermal uptake following contact transfer to the skin of a pollutant in dust, on particles, and from contaminated surfaces.[25−32] Direct transdermal uptake from air is not routinely considered. Yet the studies outlined in the previous paragraph suggest that, for at least some indoor pollutants, direct dermal uptake from air may occur at rates that are comparable to or larger than inhalation intake. We recently published a critical review of the state of knowledge concerning indoor exposures to semivolatile organic compounds (SVOCs) via dermal pathways.[33] That assessment included predictive equations, based on idealized mass-transport considerations, to estimate the steady rate of transdermal uptake of an SVOC from the gas-phase. We concluded that air-to-skin transdermal

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uptake was potentially comparable to or larger than inhalation uptake for many SVOCs found indoors. The present paper extends that assessment to volatile organic compounds and includes almost eighty organic compounds that are (a) common in indoor environments and (b) found in air primarily in the gas-phase (rather than being associated with airborne particulate matter). A specific aim of this study is to identify those indoor, gas-phase organic pollutants for which dermal absorption via transport directly from air is potentially significant in relation to the more commonly assessed inhalation exposure. A second objective is to make quantitative comparisons between modeled and measured results for those twenty compounds for which the rate of transdermal permeation directly from the air has been measured in human experiments. The paper's third objective is to examine the physical and chemical attributes that most influence the tendency of an airborne organic pollutant to be transported through air adjacent to the skin, across the stratum corneum and viable epidermis, and ultimately to the blood. Overall, the goals of this assessment are to raise awareness of dermal uptake of organic vapors as a route of environmental exposure, to focus research attention on dermal absorption directly from air, and to facilitate inclusion of this pathway in future assessments of total exposure to organic environmental pollutants encountered indoors.

METHODS

Transdermal Permeability Coefficient. The indoor air transdermal permeability coefficient, k_{p_g}, is a mass-transfer coefficient that describes the rate of transport of an organic compound from bulk air through the boundary layer adjacent to the skin and then from air at the surface of the skin through the epidermis to the dermal capillaries. In the present paper, k_{p_g} is estimated for numerous gas-phase organic compounds using a procedure that we outlined previously.[33] Wilschut and ten Berge have reported an analogous approach.[34]

The procedure begins with a deterministic model proposed by Mitragotri[35] to calculate the compound's permeability coefficient through the stratum corneum when the vehicle in contact with the skin is water (k_{p_cw}). We then use a relationship developed by Bunge et al.[36] to estimate B, the ratio of k_{p_cw} to the viable epidermis permeability coefficient (k_{p_ew}) for the compound in question (see eq S2). The parameter B is used to estimate the compound's permeability coefficient through the stratum corneum/viable epidermis composite when the vehicle in contact with skin is water (k_{p_w}). The permeability coefficient through the stratum corneum/viable epidermis composite when the vehicle in contact with the skin is air (k_{p_b}) is calculated using Henry's constant (H, expressed in units of (mol/L) atm^{-1}; note that this convention is the inverse of that commonly used in the dermal literature)

$$k_{p\_b} = k_{p\_w} \times (HRT) \tag{1}$$

where R is the gas constant (0.0821 atm liter mole^{-1} K^{-1}) and T is the skin temperature (305 K = 32 °C). Finally, k_{p_g} is calculated using a resistor-in-series model:

$$1/k_{p\_g} = 1/v_d + 1/k_{p\_b} \tag{2}$$

Here, v_d is the mass-transfer coefficient that describes the external transport of a compound from the gas-phase in the core of a room through the boundary layer adjacent to the skin. Throughout the work reported in this paper, we assume that $v_d \sim 6$ m h^{-1}.[33] Further details are provided in section S1 of the Supporting Information. The key parameters in calculating k_{p_g} are the organic compound's molecular weight (MW), octanol–water partition coefficient (K_{ow}), and Henry's constant (H). Once k_{p_g} has been estimated, the transdermal flux of an organic compound, J, can be evaluated:

$$J = C_g \times k_{p\_g} \tag{3}$$

Here, C_g is the compound's gas-phase concentration.

Several assumptions are implicit in this procedure. The Mitragotri model used to calculate k_{p_cw} assumes a simplified one-component lipid system to obtain the required bilayer parameters, avoiding the complexities of the actual multicomponent system (comprising ceramides, fatty acids, cholesterol, and various other species) that constitutes the lipid bilayer in the stratum corneum. In comparing predictions made with his model against experimental data, Mitragotri reported a mean error of 5%.[35] The model assumes that the organic permeant moves in a stationary frame of lipid molecules; this assumption breaks down for compounds with MW > 400 g/mol. With the exception of chlordane (MW = 410 g/mol), the indoor pollutants considered in this paper have MW's less than 400 g/mol. The model assumes that clearance is fast and that the concentration of the permeant in the blood is close to zero. A distributed clearance model[37] would be a better approximation but computationally more complicated to a degree that is not justified by the expected improvement in predicted results. Finally, the procedure is based on a fully hydrated stratum corneum, whereas under typical indoor conditions the stratum corneum is only partially hydrated. The consequences of this assumption are examined in the *Limitations* subsection of the Discussion.

Dermal Uptake and Inhalation Intake. Uptake of gas-phase organics via the dermal pathway, D, is estimated as the product of three terms — C_g, k_{p_g}, and the total body surface area (BSA):

$$D = C_g \times k_{p\_g} \times \mathrm{BSA} \tag{4}$$

Based in part on the findings of Piotrowski,[2] we assume that clothing presents negligible resistance to the transport of organic compounds from air to skin. We further assume that the flux through skin achieves steady state. More precisely, we assume that the time-averaged flux is well modeled as the product of the time-averaged airborne concentration multiplied by a mass-transfer coefficient derived for steady-flux conditions. Because of loss processes that may interfere with transdermal transport, such as desquamation, the dermal uptake from air estimated herein represents an upper limit.

Intake of gas-phase organics via inhalation, I, is estimated as the product of C_g and the volumetric breathing rate, Q_b:

$$I = C_g \times Q_b \tag{5}$$

We assume here that 100% of what is inhaled is absorbed. Hence, the estimated inhalation intake is also an upper bound.

The ratio of dermal uptake to inhalation intake for gas-phase organics (D/I) is then estimated as

$$D/I = k_{p\_g} \times \mathrm{BSA}/Q_b \tag{6}$$

For the baseline values that we use for a typical adult, i.e. body surface area (BSA ~ 2 m^2) and volumetric breathing rate ($Q_b \sim 0.5$ m^3 h^{-1} while at rest), the dermal uptake to inhalation

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intake ratio, D/I, is simply 4 k_{p_g} when k_{p_g} is expressed in units of m/h. (Units for the parameters used in this paper can be found in the *Nomenclature* section of the Supporting Information.)

Because particles diffuse much more slowly than gases, the gas phase is expected to dominate over the particle phase for dermal absorption of airborne organics. Conversely, for inhalation exposure, the volumetric breathing rate is a limiting process for intake: both particle- and gas-phase organics are introduced into the respiratory tract at rates proportional to their respective airborne concentrations. Equation 5 only addresses inhalation intake of gas-phase organics. Hence, the D/I ratios estimated by eq 6 apply only to the gaseous portion of an airborne organic compound. This distinction is unimportant for the indoor pollutants considered in this paper, since they are present primarily in the gas-phase (>97%; see Table S1). However, the reader is cautioned that eq 6 is inappropriate for organic compounds that have a meaningful fraction of their airborne concentration in the particle phase.

Fraction of Indoor Organic in the Gas Phase. The values listed in Table S1 for the fraction of an indoor organic pollutant in the gas-phase, $f_g = C_g/(C_g + C_p)$, were estimated as follows

$$f_g = C_g/(C_g + C_p) = 1/(1 + (\mathrm{TSP} \times K_p)) \quad (7)$$

where C_p is the airborne concentration of organic in the particle phase, TSP is the average mass concentration of airborne particles, and K_p is the particle/gas-phase partition coefficient for the organic of interest.[38] We have estimated K_p based on the assumption that partitioning of organics into particles is governed primarily by absorption into the condensed-phase organic matter:

$$K_p = (f_{om} \times K_{og})/\rho_{part} \quad (8)$$

Here, f_{om} is the fraction of airborne particulate matter that is organic, K_{og} is the octanol/air partition coefficient, and ρ_{part} is the airborne particle density.[39] For typical indoor conditions, we assume a temperature of 25 °C, TSP = 20 μg/m^3, f_{om} = 0.4, and ρ_{part} = 1 × 10^6 g/m^3 (= 1 g/cm^3).

RESULTS

Estimated Transdermal Uptake of Organic Vapors. For thirty-three organic compounds with indoor sources, Table 1 lists relevant physical and chemical parameters and calculated overall transdermal permeability coefficients (k_{p_g}). Table S1 is an expanded version of Table 1, with data for approximately eighty indoor pollutants and additional columns listing the ratio of stratum corneum permeability to viable epidermis permeability (B), estimated ratios of dermal uptake to inhalation intake (D/I), and predicted fractions in the gas-phase (f_g) under typical indoor conditions. Although some of the indoor pollutants in Tables 1 and S1 may be classified as SVOCs, all exist primarily in the gas-phase: gas-phase partitioning is predicted to be greater than 97% in each case for typical indoor conditions. For the first 15 compounds listed in Table 1, k_{p_g} exceeds 2.5 m/h, indicating that direct transdermal absorption of these compounds is anticipated to be an important exposure pathway relative to inhalation intake (the estimated dermal uptake to inhalation intake rate, D/I, exceeds a factor of 10). Noteworthy among these entries are several organic compounds that are frequently found indoors at concentrations larger than 100 ng/m^3.[38−43] These include common parabens, lower molecular weight phthalates, synthetic musks, and o-phenylphenol. For the 18 compounds in the lower portion of Table 1, k_{p_g} is between 0.25 and 2.5 m/h, implying D/I values in the range 1−10. Among the ubiquitous indoor pollutants in this group are nonylphenol, Texanol, α-terpineol, 4-oxopentanal, chlorpyrifos, linalool, and 2-butoxyethanol. Table S1 includes indoor pollutants with k_{p_g} less than 0.25 m/h. For compounds (n = 20) with k_{p_g} values in the range 0.025−0.25 m/h (D/I ratios of 0.1−1), the dermal pathway is marginally important. This group includes PCB28, PCB52, chlordane, and some aliphatic alcohols (e.g., 1-octen-3-ol, butanol, hexanal, and 3-octanol). For compounds (n = 26) in Table S1 with k_{p_g} less than 0.025 m/h, the dermal pathway appears unimportant relative to inhalation. This group includes aliphatic hydrocarbons, single ring aromatics, one- or two-carbon chlorinated solvents, formaldehyde, terpenes, and isoprene.

Table 1. For Selected Organics That Are Found Indoors and Exist Primarily in the Gas Phase, Relevant Physical and Chemical Properties (MW, K_{ow}, H, K_{sc_g}) and Overall Permeability Coefficients (k_{p_g}), with Compounds Rank Ordered According to k_{p_g}

compound	MW g/mol	log (K_{ow})[a] [—]	log (H)[a] (mol/L) atm^{-1}	log (K_{sc_g})[a] [—]	k_{p_g} m/h
diethanolamine	105	−2.5	8.68	8.2	6.0
2,4-D[b]	221	2.9	5.16	8.7	5.8
butyl paraben	194	3.4	4.10	8.0	5.4
propyl paraben	180	2.8	4.22	7.7	5.2
ethyl paraben	166	2.2	4.39	7.4	4.9
di(n-butyl) phthalate	278	4.6	3.61	8.4	4.8
methyl paraben	152	1.5	4.61	7.1	4.7
o-phenylphenol	170	3.5	3.42	7.4	4.6
di(isobutyl) phthalate	278	4.2	3.76	8.3	4.6
nicotine[b]	162	2.0	4.31	7.2	4.4
diethyl phthalate	222	2.6	4.06	7.3	3.4
diazinon	304	4.9	3.10	8.1	3.3
dimethyl phthalate	194	1.5	4.45	6.9	2.9
Galaxolide (HHCB)	258	4.6	2.85	7.6	2.8
Tonalide (AHTN)	258	5.0	2.58	7.7	2.6
monoethanolamine	61	−1.8	5.32	5.4	2.5
nonylphenol	220	6.2	2.00	8.0	2.3
Phantolide	244	4.8	2.35	7.3	1.8
pentachlorophenol[b]	266	4.9	2.30	7.3	1.6
Texanol	216	2.4	3.46	6.7	1.4
ethylene glycol	62	−1.4	4.62	5.0	1.2
hexyl cinnamal	216	5.0	1.86	6.9	1.2
n-methyl-2-pyrrolidone	99	0.063	3.97	5.4	1.2
α-terpineol	154	2.5	2.72	6.0	0.98
phenol	94	1.5	2.62	5.2	0.70
eugenol	164	3.2	2.12	5.9	0.60
4-oxopentanal	100	0.10	3.57	5.0	0.56
chlorpyrifos	351	6.4	1.39	7.5	0.41
linalool	154	3.2	1.85	5.6	0.40
BHT	220	4.7	1.44	6.3	0.38
2-butoxyethanol	118	1.1	2.78	5.0	0.33
dimethylacetamide	87	−0.18	3.37	4.6	0.32
p-tert-bucinal	204	4.0	1.52	5.9	0.26

[a]Computed for T = 32 °C. [b]Compound assumed nonionized. Abbreviations: 2,4-D − 2,4-dichlorophenoxyacetic acid; BHT − butylated hydroxy toluene.

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Table 2. Comparisons between Modeled and Measured Values for either the Transdermal Permeability Coefficient (k_{p_g}) or the Ratio of Dermal to Inhalation Intake (D/I)

compound	modeled k_{p_g} m/h	measured k_{p_g} m/h	modeled/measured k_{p_g} [—]	modeled D/I [—]	measured D/I [—]	modeled/measured D/I [—]	ref [a]
aniline	0.21			0.84	0.9−1.8	0.70[b]	1
2-butoxyethanol	0.33			1.3	2.4−3.8	0.42[b]	7
2-butoxyethanol	0.33			1.3	0.18−0.37	4.7[b]	8
dimethylacetamide	0.32			1.3	0.43	3.0	9
dimethylacetamide	0.32			1.3	0.68[c]	1.9	5
dimethylformamide	0.081			0.33	0.16−0.64	0.83[b]	9
dimethylformamide	0.081			0.33	0.20	1.65	10
dimethylformamide	0.081			0.33	0.68[d]	0.49	6
2-ethoxyethanol	0.19	0.19	1.0	0.74	0.72	1.0	4
furfural	0.14			0.56	0.2−0.3	2.2[b]	11
hexane	0.000029	0.00013	0.22	0.00012			12
1-methoxy-2-propanol	0.13			0.54	0.044−0.11[e]	7.0[b]	13
2-methoxyethanol	0.14	0.36	0.39	0.56	1.2	0.47	4
2-methoxyethanol	0.14	0.14−0.18	0.88[b]	0.56			14
methyl ethyl ketone	0.0075			0.030	0.032−0.040[e]	0.83[b]	13
n-methyl-2-pyrroli done	1.2			4.8	0.72	6.7	15
nitrobenzene	0.033			0.13	0.50	0.26	2
phenol	0.70	0.19	3.7	2.8	0.70	4.0	3
styrene	0.0025	0.0037	0.68	0.010	0.019	0.53	16
styrene	0.0025	0.012	0.21	0.010	0.052	0.19	17
tetrachloroethylene	0.00008	0.0017	0.05	0.0003	0.011	0.03	16
tetrachloroethylene	0.00008	0.00054	0.15	0.0003			12
tetrahydrofuran	0.0056			0.022	0.016−0.050[e]	0.67[b]	13
toluene	0.0010	0.0019	0.53	0.0038	0.009	0.42	16
toluene	0.0010			0.0038	0.018	0.21	13
toluene	0.0010	0.0014	0.71	0.0038			12
1,1,1-trichloroethane	0.00016	0.0001	1.6	0.00065	0.0008	0.81	16
1,1,1-trichloroethane	0.00016			0.00065	0.001	2.6	18
1,1,1-trichloroethane	0.00016	0.00021	0.76	0.00065			12
trichloroethylene	0.00009	0.00049	0.18	0.00036			12
m-xylene	0.0014	0.0026	0.54	0.0056	0.013−0.014	0.47[b]	16
xylene[f]	0.0014			0.0056	0.013−0.026[e]	0.32[b]	13
m-xylene	0.0014			0.0056	0.018	0.35	19
m-xylene	0.0014	0.0012	1.2	0.0056			12
m-xylene	0.0014	0.00062	2.3	0.0056			20

[a]Cited studies exposed whole body or arm of humans to vapors of the listed chemicals. [b]Midpoints of the measured values are used to compute the ratio. [c]Ten subjects; range: 0.15−2.7; see Figure 2 of Nomiyama et al., 2000.[5] [d]Thirteen subjects; range: 0.28−3.7; see Figure 2 of Nomiyama et al., 2001.[6] [e]Uptake assessed by monitoring compound or metabolite in blood, breath, and urine following exposure. Tabulated ranges are mean values for blood assessment, breath assessment, and urine assessment. [f]Unspecified isomer(s).

Empirical Evidence Supporting Estimated Transdermal Uptakes. What is the basis for confidence that estimates of transdermal uptake parameters reported in Table 1 and Table S1 are approximately correct? For twenty of the listed compounds, published studies[1−20] have measured k_{p_g} or the ratio of dermal uptake to inhalation uptake. Table 2 compares values estimated here with published measurement results. (Note: in the case of D/I, when estimated values are compared to measured values, we are assuming that metabolism is equivalent for the dermal and inhalation pathways once the compound enters the blood.) We have calculated the ratio "modeled-to-measured" for each compound in each study. The median value of this ratio is 0.7, i.e. within 30% of unity; the interquartile range is 0.3 to 1.2. With the exception of tetrachloroethylene, the modeled values of k_{p_g} are within a factor of 5 of the measured values in each case, while modeled values of D/I lie within a factor of 7 of measured results. For the 14 compounds with modeled dermal to inhalation ratios (D/I) greater than 0.1, the ratios of "modeled-to-measured" results have a median value of 0.96 and range from 0.17 to 6.7. The "modeled-to-measured" outcomes are not strongly biased relative to the expected value of unity: eight of the values are larger than one and six are smaller. We have plotted log (measured) versus log (modeled) results for both k_{p_g} (Figure S1) and D/I (Figure S2). The relationships are approximately linear, with R^2 = 0.88 for k_{p_g} (n = 17; MW = 76−166 g/mol), and R^2 = 0.84 for D/I (n = 27; MW = 72−166 g/mol). Given anticipated subject-to-subject variation in the dermal uptake of organic vapors[5,6] along with substantial uncertainties in the estimated properties of the compounds, these comparisons support a finding that the modeling approach provides reasonable estimates of transdermal uptake rates. An important caveat for interpreting these modeled-to-measured comparisons is that transdermal permeation from the gas-phase has not been experimentally studied for those compounds in Table 1 with the highest modeled k_{p_g} values.

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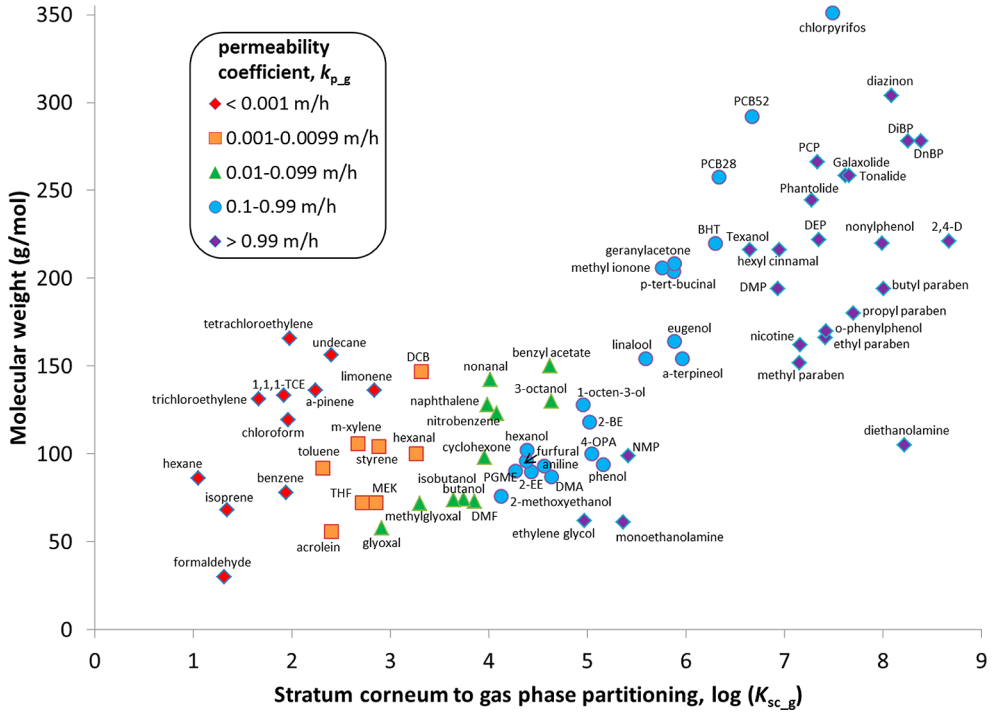

Figure 1. Dependence of indoor air transdermal permeability coefficient, k_{p_g} on molecular weight (MW) and stratum corneum to gas-phase partitioning coefficient (K_{sc_g}) for numerous organic compounds commonly found in indoor air. Different symbols denote magnitude of k_{p_g} on a decade-by-decade scale (see legend). Abbreviations: 1,1,1-TCE − 1,1,1-trichloroethane; 2-BE − 2-butoxyethanol; 2-EE − 2-ethoxyethanol; 2,4-D − 2,4-dichlorophenoxyacetic acid; 4-OPA − 4-oxopentanal; BHT − butylated hydroxy toluene; DCB − dichlorobenzene; DEP − diethylphthalate; DiBP − di(isobutyl)phthalate; DMA − dimethylacetamide; DMF −dimethylformamide; DMP − dimethylphthalate; DnBP − di(n-butyl)phthalate; MEK − methyl ethyl ketone; NMP − n-methyl-2-pyrrolidone; PCB28 − 2,4,4′-trichlorobiphenyl; PCB52 − 2,2′,5,5′-tetrachlorobiphenyl; PCP − pentachlorophenol; PGME − 1-methoxypropan-2-ol; THF − tetrahydrofuran.

Additional experimental studies are warranted to test the model predictions for compounds predicted to have high transdermal permeability coefficients.

Although we are aware of no studies that have directly measured uptake of lower molecular weight phthalate vapors via dermal absorption from air, two studies[44,45] have measured transdermal uptake of diethyl phthalate (DEP) and di(n-butyl) phthalate (DnBP) when these compounds were contained in a cream (each at 2% by mass) that was directly applied to human skin at a surface coverage of 2 mg/cm^2. Based on metabolites measured in blood,[44] the reported maximum measured flux was 2000 μg m^{-2} h^{-1} for DEP and 52 μg m^{-2} h^{-1} for DnBP. Based on metabolites measured in urine,[45] the maximum measured flux was 1500 μg m^{-2} h^{-1} for DEP and 450 μg m^{-2} h^{-1} for DnBP. For air saturated with DEP and DnBP vapors, we calculate that the maximum fluxes for direct dermal absorption are 4600 μg m^{-2} h^{-1} for DEP and 185 μg m^{-2} h^{-1} for DnBP (see Supporting Information (S2) for details). A comparison of these modeled fluxes from air with the measured fluxes for absorption from a 2% cream indicates that our estimated values of k_{p_g} for DEP and DnBP are plausible.

DISCUSSION

Attributes of Organics Likely To Be Dermally Absorbed Rapidly from Air. The transdermal permeation coefficient, k_{p_g}, for an organic compound depends primarily on its molecular weight, MW, and its stratum corneum/air partition coefficient, K_{sc_g}.[33] Where a compound lies in a plot of MW versus log (K_{sc_g}) can provide a rapid visual indication of the potential importance of direct dermal uptake from air. Figure 1 summarizes such information for all of the compounds in Table S1 with MWs less than 350 g/mol. Different symbols indicate the magnitude of k_{p_g} on a decadal scale. For compounds with k_{p_g} larger than 0.99 m/h (as denoted by purple diamonds), the dermal intake may exceed inhalation intake by a factor of 4 or more. For compounds with k_{p_g} between 0.1 and 0.99 m/h (blue circles), the ratio of dermal to inhalation intake is estimated to be between 0.4 and 4. For compounds with k_{p_g} between 0.01 and 0.099 m/h (green triangles), the dermal to inhalation intake ratio is estimated to lie in the range 0.04 and 0.4. For other compounds (orange squares and red diamonds), dermal intake can normally be neglected when estimating indoor exposures. In summary, transdermal uptake directly from air is progressively more significant, relative to inhalation, for organic compounds with larger values of K_{sc_g} and — among compounds with similar K_{sc_g} values — for those with smaller molecular weights.

In using the approach presented here to assess the potential importance of the dermal pathway, one must also consider the exposure time necessary for a steady-state transdermal flux model to reasonably approximate reality. The time that an individual spends in a given indoor environment, the frequency of bathing (and its effectiveness in removing skin absorbed organic contaminants), and the time scale for shedding the stratum corneum each pose a constraint on the time available to achieve steady state. In general, for larger values of MW and K_{sc_g}, longer times are required to reach steady state (see Supporting Information S3 and Table S2). For compounds with MW larger than 225 g/mol and log (K_{sc_g}) larger than 7, an interval longer than a day appears necessary to legitimize the use of a steady-flux, two-resistor model to accurately represent

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transport from the gas-phase through the skin. For intervals shorter than the time needed to reach steady state, a transient model such as that presented in Gong et al.[46] should yield better estimates of the transdermal permeation of organic vapors. The time required to establish steady flux can be an important consideration for accurately modeling the air-mediated dermal uptake for many SVOCs; however, it is not a limitation for most VOCs.

Sensitivity to Key Parameters. The accuracy of the estimates for k_{p_g} reported in Tables 1 and S1 depends not only on the fidelity of the transdermal permeation model but also on the accuracy of key input parameters, i.e., the octanol−water partition coefficient, K_{ow}, and Henry's constant, H. In addition to limitations in model accuracy,[35] determinations of these thermodynamic parameters may be prone to large errors. In the present study, these parameters have been calculated using the chemical property estimation software SPARC (v4.6). Using other software (e.g., EPA's EpiSuite), the calculated values of K_{ow} and H for certain compounds differ from the SPARC values by an order of magnitude or more.[47] We have assessed the sensitivity of k_{p_g} to an order-of-magnitude change in either direction in these key parameters. For the full complement of compounds addressed in this study (Table S1), the results are plotted in Figures S4 and S5, respectively, showing sensitivity to K_{ow} and H. In the case of K_{ow}, substituting values that are an order of magnitude smaller or larger than the baseline value results, on average, in a factor of 0.3 or 3.7 change in k_{p_g}. The permeability coefficient is more sensitive to H. Substituting values for H that are an order of magnitude smaller or larger than the baseline value results, on average, in a factor of 6.5 or 0.2 change in k_{p_g}. Nevertheless, it is reassuring that for the organic compounds in Table 2, with the exception of tetrachloroethylene, the ratio of modeled-to-measured values of k_{p_g} spans a much narrower range, from 0.2 to 3.7, as compared to the measured k_{p_g} values, which span a factor of 3600. Furthermore, there is reasonable agreement between the estimates in Tables 1 and S1 and estimates for a subset of the same compounds (n = 36) as predicted with ten Berge's *SkinPermMultiScen v1.1* model,[48] for which the thermodynamic parameters were calculated using EpiSuite rather than SPARC (see Supporting Information (S4)).

Limitations. The basis for the analysis used in this paper is a model proposed by Mitragotri[35] to calculate an organic compound's permeability coefficient through the stratum corneum when the vehicle in contact with skin is water. This model is most applicable to a fully hydrated stratum corneum. However, in the case of dermal absorption from indoor air, we anticipate that the stratum corneum will be only partially hydrated. There are procedures for calculating permeability coefficients when the stratum corneum is partially hydrated (e.g., Table 4 in ref 49), but the calculations are more complicated than the relatively simple equation derived in Mitragotri's model. For eighteen of the indoor pollutants considered in this paper, most with relatively large values of k_{p_g}, Table S3 compares k_{p_g} values calculated using the procedure in the *Methods* section for fully hydrated stratum corneum with values calculated using the procedure outlined in Wang et al.[49] for partially hydrated stratum corneum. On average, the values calculated assuming a partially hydrated stratum corneum are about two-thirds those calculated assuming a fully hydrated stratum corneum. This factor of 2/3 should be considered in the context of the more than five-order-of-magnitude range for k_{p_g} revealed in Table S1 − i.e., from 0.00001 to 6 m/h. For initial estimates of the relative contribution of dermal uptake of organic pollutants from air compared to uptake via other exposure pathways, the procedure outlined in this paper should be adequate. However, the reader is cautioned that the procedure used in this paper to estimate dermal uptake from air is likely less accurate than estimates obtained by treating the stratum corneum as only partially hydrated.

The estimates for dermal uptake presented here do not account for the presence of enzymes in the skin that metabolize certain compounds. For example, di(n-butyl) phthalate is partially hydrolyzed by esterases during penetration through human skin.[50] The reader is cautioned to be mindful of the potential for pollutant metabolism in the skin; inclusion of this process is beyond the scope of the present assessment.

Still another factor to consider is ionization of absorbed organics.[33] Compounds that are acidic or basic (e.g., 2,4-D, pentachlorophenol and nicotine) can exist in both neutral and ionized forms in skin-surface films. Only the neutral form is expected to permeate skin rapidly. For relevant species, acidic or basic ionizing reactions can substantially increase the number of molecules that must be transported from the gas-phase to skin-surface films to achieve a steady balance between the neutral species at the skin surface and its gas-phase counterpart. A consequence of this larger capacity of skin-surface films is a correspondingly longer time to reach steady state for such compounds. Skin pH tends to be the range of 5 to 6;[51] however, the extent to which small organic molecules ionize in skin-surface films is not well-known. Given the potential importance of transdermal permeation as an exposure pathway for certain acidic or basic organic gases, the topic of species ionization in skin surface films warrants further study.

Implications. The compounds in Figure 1 have been identified in indoor air and settled dust,[38−43] and most of them, or their metabolites, have been identified in human blood or urine.[52] When investigators attempt to connect the levels of an indoor pollutant measured in various indoor media with the levels of that pollutant (or its metabolites) measured in blood or urine, the focus has been on inhalation and dust ingestion. If the dermal pathway is considered, the pollutant is commonly assumed to have reached the skin surface via contact with dust or contaminated surfaces,[25−32] rather than being transported to skin directly via the air. Yet for roughly a third of the compounds in Figure 1 — including parabens, lower molecular weight phthalate esters, terpene alcohols, and Texanol — direct dermal uptake from air appears to occur at rates that are comparable to or larger than inhalation intake. A primary intent in reporting this work is to raise awareness, to promote further measurements, and to facilitate inclusion of transdermal uptake directly from air when researchers and practitioners assess an individual's total exposure to organic pollutants in indoor environments.

■ ASSOCIATED CONTENT

Supporting Information

S1 − Calculating transdermal permeability coefficients; S2 − Calculating maximum flux for DEP and DnBP vapors; S3 − Time scale to achieve steady state; S4 − Comparison with *SkinPerm* model predictions; S5 − Nomenclature (for primary paper and for Supporting Information); Table S1 − For selected indoor pollutants, MW, K_{sc_g}, K_{ow}, K_{og}, H, B, k_{p_b}, k_{p_g}, D/I, and f_g; Table S2 − For selected indoor pollutants, MW, K_{og}, k_{p_b}, and τ_s; Table S3 − Comparison of k_{p_g} calculated for

fully and partially hydrated stratum corneum; Figure S1 − Measured versus modeled values for k_{p_g}; Figure S2 − Measured versus modeled values for D/I; Figure S3 − For selected indoor pollutants, log (K_{sc_g}) versus log (K_{og}); Figure S4 − Sensitivity of k_{p_g} to an order of magnitude change in K_{ow}; Figure S5 − Sensitivity of k_{p_g} to an order of magnitude change in H; Figure S6 − Comparisons between k_{p_g} estimated using the approach presented in the present paper and that presented by ten Berge (SkinPermMultiScen v1.1). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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