

1 **Dermal Uptake of Organic Vapors Commonly Found in Indoor Air**

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12 **Keywords:** Dermal absorption, exposure, percutaneous transport, permeability coefficient,
13 transdermal permeation

14 **Short Title:** Transdermal uptake of indoor organics

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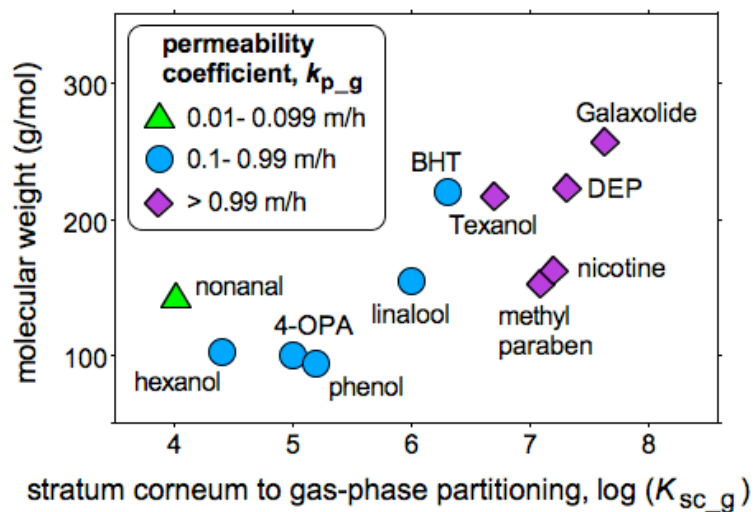
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23 **Table of Contents Art**

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26

27 **Abstract**

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

45 **Introduction**

46 Direct uptake of selected organic compounds from air through skin has been demonstrated
47 in many studies conducted over the past half-century. The primary emphasis in these studies has
48 been on occupational exposures. Experiments include cases in which the whole body of a human
49 subject was exposed and other cases in which only an arm was exposed. Dutkiewicz and
50 Piotrowski [1] reported that, "... a resting, fully relaxed person absorbs through the skin amounts
51 (of aniline) comparable with those absorbed simultaneously through the respiratory tract."
52 Specifically, they estimated that dermal absorption of aniline vapors accounted for 47-64% of a
53 resting person's aggregate aniline intake. Piotrowski [2] more fully described experiments in
54 which both naked and dressed men were exposed to nitrobenzene vapors in a chamber while
55 breathing clean air. He concluded that "about half as much vapour was absorbed through the skin
56 as through the lungs" and that "normal working clothes reduced the absorption by only 20 to
57 30%." Subsequently, Piotrowski [3] conducted similar chamber experiments in which the entire
58 bodies of seven men were exposed to phenol vapors; the dermal absorption rate averaged 70% of
59 the inhalation rate. Kežić et al. [4] exposed only the forearm of five volunteers to vapors of either
60 2-methoxyethanol or 2-ethoxyethanol. Based on the urine concentrations of the metabolites of
61 these glycol ethers, the authors estimated that — for whole body exposure — skin uptake would
62 be approximately 120% of inhalation uptake for 2-methoxyethanol and 70% of inhalation uptake
63 for 2-ethoxyethanol. Altogether, we have identified twenty studies published in peer-reviewed
64 archival journals that have measured direct uptake of various organic vapors by human skin in
65 either whole body or arm/hand experiments [1-20]. Most, but not all, of these studies have been
66 reviewed by Rehal and Maibach [21] and by Rauma et al. [22].

67 In assessing human exposure to organic pollutants indoors, inhalation and ingestion of dust
68 are routinely included as exposure pathways. The dermal pathway is frequently assumed to be
69 negligible [23, 24]. When considered, the focus has commonly been on dermal uptake following
70 contact transfer to the skin of a pollutant in dust, on particles and from contaminated surfaces
71 [25-32]. Direct transdermal uptake from air is not routinely considered. Yet the studies outlined
72 in the previous paragraph suggest that, for at least some indoor pollutants, direct dermal uptake
73 from air may occur at rates that are comparable to or larger than inhalation intake. We recently
74 published a critical review of the state of knowledge concerning indoor exposures to semivolatile
75 organic compounds (SVOCs) via dermal pathways [33]. That assessment included predictive
76 equations, based on idealized mass-transport considerations, to estimate the steady rate of
77 transdermal uptake of an SVOC from the gas-phase. We concluded that air-to-skin transdermal
78 uptake was potentially comparable to or larger than inhalation uptake for many SVOCs found
79 indoors. The present paper extends that assessment to volatile organic compounds and includes
80 almost eighty organic compounds that are (a) common in indoor environments and (b) found in
81 air primarily in the gas-phase (rather than being associated with airborne particulate matter). A
82 specific aim of this study is to identify those indoor, gas-phase organic pollutants for which
83 dermal absorption via transport directly from air is potentially significant in relation to the more
84 commonly assessed inhalation exposure. A second objective is to make quantitative comparisons
85 between modeled and measured results for those twenty compounds for which the rate of
86 transdermal permeation directly from the air has been measured in human experiments. The
87 paper's third objective is to examine the physical and chemical attributes that most influence the
88 tendency of an airborne organic pollutant to be transported through air adjacent to the skin,
89 across the stratum corneum and viable epidermis, and ultimately to the blood. Overall, the goals

90 of this assessment are to raise awareness of dermal uptake of organic vapors as a route of
91 environmental exposure, to focus research attention on dermal absorption directly from air, and
92 to facilitate inclusion of this pathway in future assessments of total exposure to organic
93 environmental pollutants encountered indoors.

94 **Methods**

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

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

$$111 \quad k_{p_b} = k_{p_w} \times (HRT) \quad (1)$$

112 where R is the gas constant ($0.0821 \text{ atm liter mole}^{-1} \text{ K}^{-1}$) and T is the skin temperature ($305 \text{ K} =$
113 $32 \text{ }^\circ\text{C}$). Finally, k_{p_g} is calculated using a resistor-in-series model:

$$114 \quad 1/k_{p_g} = 1/v_d + 1/k_{p_b} \quad (2)$$

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

$$122 \quad J = C_g \times k_{p_g} \quad (3)$$

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

124 Several assumptions are implicit in this procedure. The Mitragotri model used to calculate
125 k_{p_cw} assumes a simplified one-component lipid system to obtain the required bilayer parameters,
126 avoiding the complexities of the actual multicomponent system (comprising ceramides, fatty
127 acids, cholesterol and various other species) that constitutes the lipid bilayer in the stratum
128 corneum. In comparing predictions made with his model against experimental data, Mitragotri
129 reported a mean error of 5% [35]. The model assumes that the organic permeant moves in a
130 stationary frame of lipid molecules; this assumption breaks down for compounds with MW >
131 400 g/mol. With the exception of chlordane (MW = 410 g/mol), the indoor pollutants considered
132 in this paper have MW's less than 400 g/mol. The model assumes that clearance is fast and that
133 the concentration of the permeant in the blood is close to zero. A distributed clearance model

134 [37] would be a better approximation, but computationally more complicated to a degree that is
135 not justified by the expected improvement in predicted results. Finally, the procedure is based on
136 a fully hydrated stratum corneum, whereas under typical indoor conditions the stratum corneum
137 is only partially hydrated. The consequences of this assumption are examined in the *Limitations*
138 subsection of the *Discussion*.

139 **Dermal uptake and inhalation intake.** Uptake of gas-phase organics via the dermal
140 pathway, D , is estimated as the product of three terms — C_g , k_{p_g} and the total body surface area
141 (BSA):

$$142 \quad D = C_g \times k_{p_g} \times \text{BSA} \quad (4)$$

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

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

$$152 \quad I = C_g \times Q_b \quad (5)$$

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

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

$$157 \quad D/I = k_{p_g} \times \text{BSA}/Q_b \quad (6)$$

158 For the baseline values that we use for a typical adult, i.e. body surface area (BSA ~ 2
 159 m^2) and volumetric breathing rate ($Q_b \sim 0.5 \text{ m}^3 \text{ h}^{-1}$ while at rest), the dermal uptake to inhalation
 160 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
 161 used in this paper can be found in the *Nomenclature* section of the *Supporting Information*.)

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

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

$$174 \quad f_g = C_g/(C_g + C_p) = 1/(1 + (\text{TSP} \times K_p)) \quad (7)$$

175 where C_p is the airborne concentration of organic in the particle phase, TSP is the average mass
 176 concentration of airborne particles, and K_p is the particle/gas-phase partition coefficient for the

177 organic of interest [38]. We have estimated K_p based on the assumption that partitioning of
178 organics into particles is governed primarily by absorption into the condensed-phase organic
179 matter:

$$180 \quad K_p = (f_{om} \times K_{og})/\rho_{part} \quad (8)$$

181 Here, f_{om} is the fraction of airborne particulate matter that is organic, K_{og} is the octanol/air
182 partition coefficient and ρ_{part} is the airborne particle density [39]. For typical indoor conditions,
183 we assume a temperature of 25 °C, TSP = 20 $\mu\text{g}/\text{m}^3$, $f_{om} = 0.4$ and $\rho_{part} = 1 \times 10^6 \text{ g}/\text{m}^3 (= 1$
184 $\text{g}/\text{cm}^3)$.

185 **Results**

186 **Estimated transdermal uptake of organic vapors.** For thirty-three organic compounds
187 with indoor sources, Table 1 lists relevant physical and chemical parameters and calculated
188 overall transdermal permeability coefficients (k_{p_g}). Table S1 is an expanded version of Table 1,
189 with data for approximately eighty indoor pollutants and additional columns listing the ratio of
190 stratum corneum permeability to viable epidermis permeability (B), estimated ratios of dermal
191 uptake to inhalation intake (D/I), and predicted fractions in the gas-phase (f_g) under typical
192 indoor conditions. Although some of the indoor pollutants in Tables 1 and S1 may be classified
193 as SVOCs, all exist primarily in the gas-phase: gas-phase partitioning is predicted to be greater
194 than 97% in each case for typical indoor conditions. For the first 15 compounds listed in Table 1,
195 k_{p_g} exceeds 2.5 m/h, indicating that direct transdermal absorption of these compounds is
196 anticipated to be an important exposure pathway relative to inhalation intake (the estimated
197 dermal uptake to inhalation intake rate, D/I , exceeds a factor of 10). Noteworthy among these
198 entries are several organic compounds that are frequently found indoors at concentrations larger

199 than 100 ng/m³ [38-43]. These include common parabens, lower molecular weight phthalates,
200 synthetic musks and o-phenylphenol. For the 18 compounds in the lower portion of Table 1, k_{p_g}
201 is between 0.25 and 2.5 m/h, implying D/I values in the range 1-10. Among the ubiquitous
202 indoor pollutants in this group are nonylphenol, Texanol, α -terpineol, 4-oxopentanal,
203 chlorpyrifos, linalool, and 2-butoxyethanol. Table S1 includes indoor pollutants with k_{p_g} less
204 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
205 of 0.1-1), the dermal pathway is marginally important. This group includes PCB28, PCB52,
206 chlordane, and some aliphatic alcohols (e.g., 1-octen-3-ol, butanol, hexanal and 3-octanol). For
207 compounds ($n = 26$) in Table S1 with k_{p_g} less than 0.025 m/h, the dermal pathway appears
208 unimportant relative to inhalation. This group includes aliphatic hydrocarbons, single ring
209 aromatics, one- or two-carbon chlorinated solvents, formaldehyde, terpenes and isoprene.

210 **Empirical evidence supporting estimated transdermal uptakes.** What is the basis for
211 confidence that estimates of transdermal uptake parameters reported in Table 1 and Table S1 are
212 approximately correct? For twenty of the listed compounds, published studies [1-20] have
213 measured k_{p_g} or the ratio of dermal uptake to inhalation uptake. Table 2 compares values
214 estimated here with published measurement results. (Note: in the case of D/I , when estimated
215 values are compared to measured values, we are assuming that metabolism is equivalent for the
216 dermal and inhalation pathways once the compound enters the blood.) We have calculated the
217 ratio “modeled-to-measured” for each compound in each study. The median value of this ratio is
218 0.7, i.e. within 30% of unity; the interquartile range is 0.3 to 1.2. With the exception of
219 tetrachloroethylene, the modeled values of k_{p_g} are within a factor of five of the measured values
220 in each case, while modeled values of D/I lie within a factor of seven of measured results. For
221 the 14 compounds with modeled dermal to inhalation ratios (D/I) greater than 0.1, the ratios of

222 “modeled-to-measured” results have a median value of 0.96 and range from 0.17 to 6.7. The
223 “modeled-to-measured” outcomes are not strongly biased relative to the expected value of unity:
224 eight of the values are larger than one and six are smaller. We have plotted log (measured) versus
225 log (modeled) results for both k_{p_g} (Figure S1) and D/I (Figure S2). The relationships are
226 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
227 ($n = 27$; MW = 72-166 g/mol). Given anticipated subject-to-subject variation in the dermal
228 uptake of organic vapors [5, 6] along with substantial uncertainties in the estimated properties of
229 the compounds, these comparisons support a finding that the modeling approach provides
230 reasonable estimates of transdermal uptake rates. An important caveat for interpreting these
231 modeled-to-measured comparisons is that transdermal permeation from the gas-phase has not
232 been experimentally studied for those compounds in Table 1 with the highest modeled k_{p_g}
233 values. Additional experimental studies are warranted to test the model predictions for
234 compounds predicted to have high transdermal permeability coefficients.

235 Although we are aware of no studies that have directly measured uptake of lower molecular
236 weight phthalate vapors via dermal absorption from air, two studies [44,45] have measured
237 transdermal uptake of diethyl phthalate (DEP) and di(n-butyl) phthalate (DnBP) when these
238 compounds were contained in a cream (each at 2% by mass) that was directly applied to human
239 skin at a surface coverage of 2 mg/cm^2 . Based on metabolites measured in blood [44], the
240 reported maximum measured flux was $2000 \text{ } \mu\text{g m}^{-2} \text{ h}^{-1}$ for DEP and $52 \text{ } \mu\text{g m}^{-2} \text{ h}^{-1}$ for DnBP.
241 Based on metabolites measured in urine [45], the maximum measured flux was $1500 \text{ } \mu\text{g m}^{-2} \text{ h}^{-1}$
242 for DEP and $450 \text{ } \mu\text{g m}^{-2} \text{ h}^{-1}$ for DnBP. For air saturated with DEP and DnBP vapors, we
243 calculate that the maximum fluxes for direct dermal absorption are $4600 \text{ } \mu\text{g m}^{-2} \text{ h}^{-1}$ for DEP and
244 $185 \text{ } \mu\text{g m}^{-2} \text{ h}^{-1}$ for DnBP (see *Supporting Information* (S2) for details). A comparison of these

245 modeled fluxes from air with the measured fluxes for absorption from a 2% cream indicates that
246 our estimated values of k_{p_g} for DEP and DnBP are plausible.

247 **Discussion**

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

263 In using the approach presented here to assess the potential importance of the dermal
264 pathway, one must also consider the exposure time necessary for a steady-state transdermal flux
265 model to reasonably approximate reality. The time that an individual spends in a given indoor
266 environment, the frequency of bathing (and its effectiveness in removing skin absorbed organic
267 contaminants), and the time scale for shedding the stratum corneum each pose a constraint on the

268 time available to achieve steady state. In general, for larger values of MW and K_{sc_g} , longer times
269 are required to reach steady state (see *Supporting Information S3* and Table S2). For compounds
270 with MW larger than 225 g/mol and $\log(K_{sc_g})$ larger than 7, an interval longer than a day
271 appears necessary to legitimize the use of a steady-flux, two-resistor model to accurately
272 represent transport from the gas-phase through the skin. For intervals shorter than the time
273 needed to reach steady state, a transient model such as that presented in Gong et al. [46] should
274 yield better estimates of the transdermal permeation of organic vapors. The time required to
275 establish steady flux can be an important consideration for accurately modeling the air-mediated
276 dermal uptake for many SVOCs; however, it is not a limitation for most VOCs.

277 **Sensitivity to key parameters.** The accuracy of the estimates for k_{p_g} reported in Tables 1
278 and S1 depends not only on the fidelity of the transdermal permeation model but also on the
279 accuracy of key input parameters, i.e., the octanol-water partition coefficient, K_{ow} , and Henry's
280 constant, H . In addition to limitations in model accuracy [35], determinations of these
281 thermodynamic parameters may be prone to large errors. In the present study, these parameters
282 have been calculated using the chemical property estimation software SPARC (v4.6). Using
283 other software (e.g., EPA's EpiSuite), the calculated values of K_{ow} and H for certain compounds
284 differ from the SPARC values by an order of magnitude or more [47]. We have assessed the
285 sensitivity of k_{p_g} to an order-of-magnitude change in either direction in these key parameters.
286 For the full complement of compounds addressed in this study (Table S1), the results are plotted
287 in Figures S4 and S5, respectively showing sensitivity to K_{ow} and H . In the case of K_{ow} ,
288 substituting values that are an order of magnitude smaller or larger than the baseline value
289 results, on average, in a factor of 0.3 or 3.7 change in k_{p_g} . The permeability coefficient is more
290 sensitive to H . Substituting values for H that are an order of magnitude smaller or larger than the

291 baseline value results, on average, in a factor of 6.5 or 0.2 change in k_{p_g} . Nevertheless, it is
292 reassuring that for the organic compounds in Table 2, with the exception of tetrachloroethylene,
293 the ratio of modeled-to-measured values of k_{p_g} spans a much narrower range, from 0.2 to 3.7, as
294 compared to the measured k_{p_g} values, which span a factor of 3600. Furthermore, there is
295 reasonable agreement between the estimates in Tables 1 and S1 and estimates for a subset of the
296 same compounds ($n = 36$) as predicted with ten Berge's *SkinPermMultiScen v1.1* model [48], for
297 which the thermodynamic parameters were calculated using EpiSuite rather than SPARC (see
298 *Supporting Information (S4)*).

299 **Limitations.** The basis for the analysis used in this paper is a model proposed by Mitragotri
300 [35] to calculate an organic compound's permeability coefficient through the stratum corneum
301 when the vehicle in contact with skin is water. This model is most applicable to a fully hydrated
302 stratum corneum. However, in the case of dermal absorption from indoor air, we anticipate that
303 the stratum corneum will be only partially hydrated. There are procedures for calculating
304 permeability coefficients when the stratum corneum is partially hydrated (e.g., Table 4 in [49]),
305 but the calculations are more complicated than the relatively simple equation derived in
306 Mitragotri's model. For eighteen of the indoor pollutants considered in this paper, most with
307 relatively large values of k_{p_g} , Table S3 compares k_{p_g} values calculated using the procedure in
308 the *Methods* section for fully hydrated stratum corneum with values calculated using the
309 procedure outlined in Wang et al. [49] for partially hydrated stratum corneum. On average, the
310 values calculated assuming a partially hydrated stratum corneum are about two thirds those
311 calculated assuming a fully hydrated stratum corneum. This factor of 2/3 should be considered in
312 the context of the more than five-order-of-magnitude range for k_{p_g} revealed in Table S1 – i.e.,
313 from 0.00001 to 6 m/h. For initial estimates of the relative contribution of dermal uptake of

314 organic pollutants from air compared to uptake via other exposure pathways, the procedure
315 outlined in this paper should be adequate. However, the reader is cautioned that the procedure
316 used in this paper to estimate dermal uptake from air is likely less accurate than estimates
317 obtained by treating the stratum corneum as only partially hydrated.

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

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

334 **Implications.** The compounds in Figure 1 have been identified in indoor air and settled dust
335 [38-43] and most of them, or their metabolites, have been identified in human blood or urine
336 [52]. When investigators attempt to connect the levels of an indoor pollutant measured in various

337 indoor media with the levels of that pollutant (or its metabolites) measured in blood or urine, the
338 focus has been on inhalation and dust ingestion. If the dermal pathway is considered, the
339 pollutant is commonly assumed to have reached the skin surface via contact with dust or
340 contaminated surfaces [25-32], rather than being transported to skin directly via the air. Yet for
341 roughly a third of the compounds in Figure 1 — including parabens, lower molecular weight
342 phthalate esters, terpene alcohols and Texanol — direct dermal uptake from air appears to occur
343 at rates that are comparable to or larger than inhalation intake. A primary intent in reporting this
344 work is to raise awareness, to promote further measurements, and to facilitate inclusion of
345 transdermal uptake directly from air when researchers and practitioners assess an individual's
346 total exposure to organic pollutants in indoor environments.

347 **Acknowledgements**

348 We thank John Kissel and Wil ten Berge for useful comments during a workshop on dermal
349 absorption at the 2012 meeting of the International Society of Exposure Science. WWN's efforts
350 on this research were funded in part by the Republic of Singapore's National Research
351 Foundation through a grant to the Berkeley Education Alliance for Research in Singapore
352 (BEARS) for the Singapore-Berkeley Building Efficiency and Sustainability in the Tropics
353 (SinBerBEST) Program. BEARS has been established by the University of California, Berkeley
354 as a center for intellectual excellence in research and education in Singapore.

355 **Supporting Information**

356 S1 – Calculating transdermal permeability coefficients; S2 – Calculating maximum flux for DEP
357 and DnBP vapors; S3 – Time scale to achieve steady state; S4 – Comparison with *SkinPerm*
358 model predictions; S5 – Nomenclature (for primary paper and for supporting information); Table

359 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 –
360 For selected indoor pollutants, MW , K_{og} , k_{p_b} and τ_s ; Table S3 – Comparison of k_{p_g} calculated
361 for fully and partially hydrated stratum corneum; Figure S1 – Measured versus modeled values
362 for k_{p_g} ; Figure S2 – Measured versus modeled values for D/I ; Figure S3 – For selected indoor
363 pollutants, $\log(K_{sc_g})$ versus $\log(K_{og})$; Figure S4 – Sensitivity of k_{p_g} to an order of magnitude
364 change in K_{ow} ; Figure S5 – Sensitivity of k_{p_g} to an order of magnitude change in H ; Figure S6 –
365 Comparisons between k_{p_g} estimated using the approach presented in the present paper and that
366 presented by ten Berge (SkinPermMultiScen v1.1).

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509

510 **Figure Caption**

511 **Figure 1.** Dependence of indoor air transdermal permeability coefficient, k_{p_g} on molecular
512 weight (MW) and stratum corneum to gas-phase partitioning coefficient (K_{sc_g}) for numerous
513 organic compounds commonly found in indoor air. Different symbols denote magnitude of k_{p_g}
514 on a decade-by-decade scale (see legend). Abbreviations: 1,1,1-TCE – 1,1,1-trichloroethane; 2-
515 BE – 2-butoxyethanol; 2-EE – 2-ethoxyethanol; 2,4-D – 2,4-dichlorophenoxyacetic acid; 4-OPA
516 – 4-oxopentanal; BHT – butylated hydroxy toluene; DCB – dichlorobenzene; DEP –
517 diethylphthalate; DiBP – di(isobutyl)phthalate; DMA – dimethylacetamide; DMF –
518 dimethylformamide; DMP – dimethylphthalate; DnBP – di(n-butyl)phthalate; MEK – methyl
519 ethyl ketone; NMP – n-methyl-2-pyrrolidone; PCB28 – 2,4,4'-trichlorobiphenyl; PCB52 –
520 2,2',5,5'-tetrachlorobiphenyl; PCP – pentachlorophenol; PGME – 1-methoxypropan-2-ol; THF –
521 tetrahydrofuran.

522

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/liter) 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

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-pyrrolidone	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).