CHAPTER 10

Estimating the Absorption of Volatile Compounds Applied to Skin

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CONTENTS

INTRODUCTION

Although considerable progress has been made toward estimating the steady-state absorption rates of organic compounds applied to skin as aqueous solutions (Kasting et al., 1992; Potts and Guy, 1992; Wilschut et al., 1995; Johnson et al., 1997), less is known regarding the absorption of chemicals through skin under other conditions.

In particular, the absorption of compounds, either volatile or nonvolatile, applied to skin neat or from volatile solvents is poorly understood. The problem is of great importance in risk assessment for both environmental and occupational chemical hazards, health and personal care products, and chemical warfare agents. This chapter focuses on the skin absorption of volatile chemicals, using fine fragrance ingredients as an example. These materials have been the subject of recent investigations in my laboratory (Kasting and Saiyasombati, 2001, 2003a, 2003b, 2004a, 2004b).

For fine fragrances as well as many other fragranced consumer products, the chief concern in risk assessment is usually the potential for eliciting allergic contact dermatitis, otherwise known as skin sensitization (Robinson et al., 2000; Basketter, 1998; Kimber et al., 1999). The risk is usually assessed using a variety of tools, including structural-alert computer programs (Sanderson and Earnshaw, 1991), animal skin sensitization databases (Basketter et al., 2000), and human repeat insult patch tests (Basketter, 1998). Few, if any, additional animal studies are conducted on cosmetic products or ingredients given the zero animal use guidelines that have been adopted by the cosmetic and personal care industries. Consequently, there is a clear need to make accurate predictions from *in silico* models prior to exposing human subjects via a human repeat insult patch test (HRIPT) or a product introduction onto the market.

A second aspect of risk assessment for fragranced products concerns systemic levels achieved by a combination of dermal absorption and inhalation. The hazards associated with each ingredient are carefully evaluated and controlled by a combination of exposure assessment plus intrinsic toxicity assessment (Gerberick and Robinson, 2000). Because most absorption occurs via the dermal route (caused by high dilution of the vapor into room air), skin absorption provides the link between these two areas. Absorption models should therefore attempt to answer the questions, What fraction of a topically applied dose will be absorbed? and How rapidly will this occur?

For fragrance ingredients, a conservative but widely used approach is to assume 100% absorption (Robinson et al., 2000). There appear to be no widely used guidelines regarding absorption rates.

The method described in this chapter represents a step toward tightening the risk assessment process for volatile compounds. It is simple to use and has been calibrated for fragrance ingredients (Kasting and Saiyasombati, 2001, 2003a, 2003b, 2004a, 2004b). Based on these data and the analysis described below, the method allows the estimation of percentage absorption and absorption rate to within a factor of two for commonly encountered fragrance ingredients. Research is under way to refine the method and extend its range of use to other chemical classes (Bhatt and Kasting, 2003).

METHOD

The simple model depicted in Figure 10.1 is chosen to represent the disposition of a volatile compound, or mixture of compounds, applied to skin. Each ingredient is assumed to dissolve into the lipids of the skin surface and outer stratum corneum

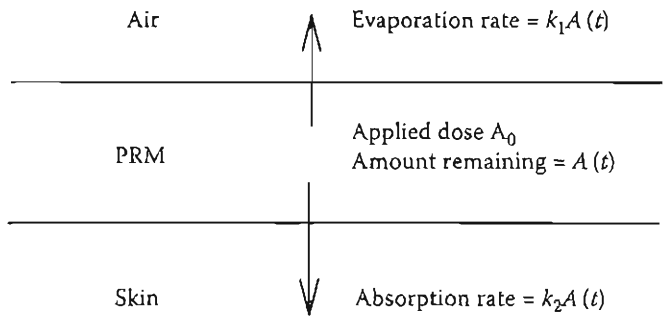

Figure 10.1 Simple model for the disposition of volatile compounds applied to skin. (Adapted from Kasting, G.B. and Saiyasombati, P. *Int. J. Cosmet. Sci.*, 23, 49–58, 2001.)

(SC) and , consequently, to evaporate and absorb at rates proportional to its fraction of saturation in these lipids (Kasting and Saiyasombati, 2001). The evaporation rate (ER) and absorption rate (AR) are given by

$$\text{ER (\% of dose/h)} = \frac{100k_1}{k_1 + k_2} e^{-(k_1+k_2)t} \tag{10.1}$$

$$\text{AR (\% of dose/h)} = \frac{100k_2}{k_1 + k_2} e^{-(k_1+k_2)t} \tag{10.2}$$

where

$$k_1 = k_1^v \cdot P_{vpr} / (K_{oct} S_w)_r \tag{10.3}$$

$$k_2 = k_2^T \cdot MW_r^{-2.7} \tag{10.4}$$

In Equation 10.3 and Equation 10.4, P_{vp} is vapor pressure in torr, K_{oct} is the octanol–water partition coefficient, S_w is water solubility (g L^{-1}), and MW is molecular weight. All properties are calculated at skin temperature, usually taken to be 30 to 32°C. The subscript r indicates that the property has been divided by a characteristic value; thus, $P_{vpr} = P_{vp}/1$ torr, $(K_{oct} S_w)_r = K_{oct} S_w/(1000 \text{ g } L^{-1})$, and $MW_r = MW/100$ Da. Estimated values for k_1^v and k_2^T are shown in Table 10.2. The integrated forms of Equation 10.1 and Equation 10.2 yield the cumulative amounts evaporated and absorbed at time t hours postdose:

$$\%\ \text{evap}(t) = \frac{100k_1}{k_1 + k_2}\left[1 - e^{-(k_1+k_2)t}\right] \tag{10.5}$$

$$\%\ \text{abs}(t) = \frac{100k_2}{k_1 + k_2}\left[1 - e^{-(k_1+k_2)t}\right] \tag{10.6}$$

After a long time ($t \rightarrow \infty$), Equation 10.5 and Equation 10.6 yield

$$\% \text{ evap}(\infty) = \frac{100x_r}{k + x_r} \tag{10.7}$$

$$\% \text{ abs}(\infty) = \frac{100k}{k + x_r} \tag{10.8}$$

where $k = k_2^T / k_1^v$ and $x_r = P_{vpr} MW_r^{2.7} / (K_{oc1} S_w)_r$. Using the parameters in Table 10.2, Equation 10.7 was shown to correlate the cumulative evaporation data from a controlled human forearm evaporation study involving 11- and 12-component fragrance mixtures (Vuilleumier et al., 1995) with r^2 values of 0.80 and 0.73, respectively (Saiyasombati and Kasting, 2003b). The compounds tested and their physical properties are shown in Table 10.1, and the correlations are shown in Figure 10.2. The corresponding estimated percentage absorption, calculated as % abs(∞) = 100 – % evap(∞), is shown in Figure 10.3.

Based on the results in Figure 10.2 and Figure 10.3, Equation 10.7 and Equation 10.8 tend to overpredict evaporation and underpredict absorption of the highly volatile "top note" ingredients linalool (I), dihydromyrcenol (II), and 10-undecanal (III), for which $x_r \geq 0.5$. This deficiency can be largely corrected by the following empirical modification, which may be proposed for risk assessment purposes:

$$\% \text{ evap}(\infty) = \frac{100x_r - 15x_r^2}{0.165 + x_r} \quad ; \qquad 0 < x_r < 1 \tag{10.9}$$

$$\% \text{ abs}(\infty) = \frac{16.5 + 15x_r^2}{0.165 + x_r} \quad ; \qquad 0 < x_r < 1 \tag{10.10}$$

Smooth curves calculated from Equation 10.9 and Equation 10.10 are shown on Figure 10.2 and Figure 10.3. The root mean square (rms) deviation of Equation 10.10 from the estimated percentage absorption values is 11% for both fragrance vectors. The maximum underprediction of absorption (31% calculated vs. 55% observed) occurs for 10-undecanal (III) when incorporated in the fixed fragrance, Vector B. The maximum overprediction (68% calculated vs. 45% observed) occurs for *cis*-7-*p*-menthanol (VIII) when incorporated in the unfixed fragrance, Vector A. These values support the contention that Equation 10.10 estimates absorption to within a factor of two for fragrance ingredients applied to skin under conditions comparable to those in Vuilleumier et al. (1995). Thus, Equation 10.10 is the central equation in this report.

Table 10.1 Fragrance Raw Materials Studied in Vuilleumier et al. (1995)

ID	Compound	MW (Da)	P^a_{vp}(torr)	log K^a_{oct}	S^a_w(g/L)	x_r Eq. 4	f^b_{evap} Vector A	f^b_{evap} Vector B
I	Linalool	154	0.13	2.55	2.3	0.52	0.681 ± 0.004	0.575 ± 0.015
II	Dihydromyrcenol	156	0.19	3.03	0.76	0.79	0.735 ± 0.016	0.658 ± 0.022
III	10-Undecanal	170	0.093	4.05	0.072	0.48	0.594 ± 0.004	0.452 ± 0.061
IV	Citronellol	156	0.028	3.25	0.46	0.11	0.500 ± 0.004	0.412 ± 0.007
V	2-Phenyl-1-ethanol	122	0.039	1.36	35	0.08	0.260 ± 0.003	0.186 ± 0.020
VI	(E)-Cinnamic alcohol	134	0.0050	1.95	8.5	0.01	0.039 ± 0.004	0.037 ± 0.006
VII	α-Damascone	192	0.032	3.62	0.19[c]	0.28	0.712 ± 0.007	0.570 ± 0.028
VIII	*cis*-7-*p*-Menthanol	156	0.019	3.33	0.38	0.08	0.545 ± 0.014	0.469 ± 0.054
IX	2,2,2-Trichloro-1-phenylethylacetate	268	0.0029	4.05	0.072[c]	0.08	0.422 ± 0.004	0.405 ± 0.032
X	MPCC[d]	192	0.010	3.87	0.11	0.07	0.330 ± 0.005	0.237 ± 0.022
XI	(E)-2-Benzylideneoctanal	216	0.00088	4.85	0.011[c]	0.01	0.069 ± 0.007[e]	0.043 ± 0.007[e]
XII	15-Pentadecanolide	240	0.00010	5.35	0.0034[c]	0.001	NA[f]	0.066 ± 0.010[e]

[a] For sources of physical properties, see Kasting and Saiyasombati (2001).
[b] Experimental fraction of dose evaporated extrapolated to $t \rightarrow \infty$ (except for XI and XII) (Kasting and Saiyasombati, 2001).
[c] Estimated value, corrected as in Kasting and Saiyasombati (2001).
[d] 3-(4-Methyl-3-pentenyl)-3-cyclohexene-1-carbaldehyde + 4-(4-methyl-3-pentenyl)-3-cyclohexene-1-carbaldehyde.
[e] 0 to 7.25 h only.
[f] This ingredient (a musk fixative) was included in Vector B, but not in Vector A.

Source: Adapted from Saiyasombati, P. and Kasting, G.B., *Int. J. Cosmet. Sci.*, 25, 235–243, 2003.

Table 10.2 Regression Parameters (Mean ± SD, 20 Determinations per Vector) for Fit of Equation 10.3 to Equation 10.6 to Fragrance Evaporation Data in Vuilleumier et al. (1995)

Parameter	Units	Vector A	Vector B
k_1^v	h^{-1}	14.5 ± 10.5	9.1 ± 8.9
k_2^I	h^{-1}	1.9 ± 0.6	1.5 ± 0.5
Regression statistics (Cumulative fits)			
n		143	132
s		0.13	0.16
r^2		0.7960	0.7333

Source: Adapted from Saiyasombati, P. and Kasting, G.B., *Int. J. Cosmet. Sci.*, 25, 235–243, 2003.

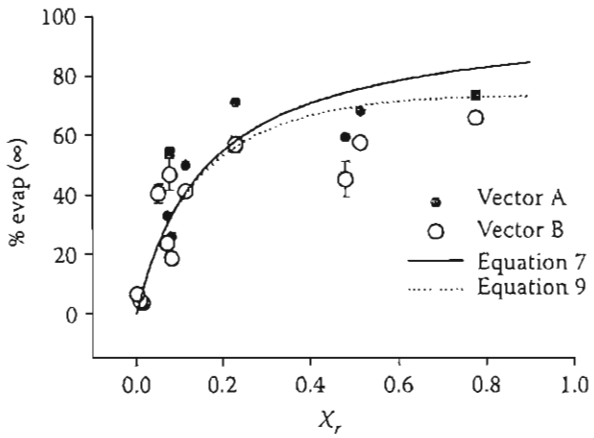

Figure 10.2 Cumulative evaporation of fragrance ingredients described from a human volar forearm (Vuilleumier et al., 1995), extrapolated to infinite time (Kasting and Saiyasombati, 2001). The value of k in Equation 10.7 was calculated as k = 1.5/9.1 = 0.165 (Table 1, Vector B).

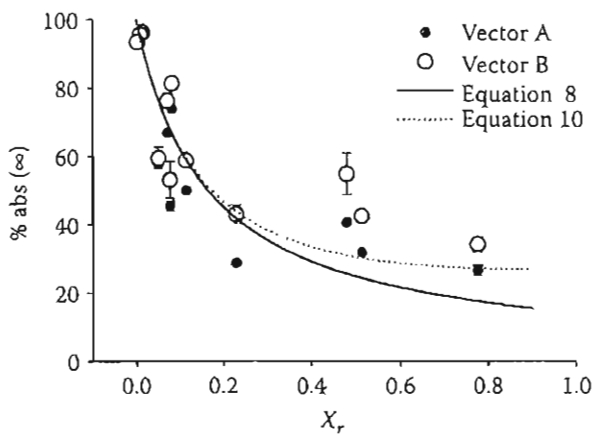

Figure 10.3 Calculated cumulative absorption of fragrance ingredients from a human volar forearm (Vuilleumier et al., 1995), extrapolated to infinite time. The results were calculated from the data in Figure 10.2 by assuming %abs(∞) = 100 – %evap(∞).

MODEL ASSUMPTIONS AND RATIONALE

The model represented by Equation 10.1 to Equation 10.10 is a highly simplified representation of the disposition of volatile chemicals on skin, yet it captures the major features of the data in Vuilleumier et al. (1995) and several related investigations (Kasting and Saiyasombati, 2001, 2003a, 2004a, 2004b). The distinguishing feature of this model versus other kinetic models that can readily correlate rate profiles (see, for example, Guy et al., 1982; Guy and Hadgraft, 1983) is the physical properties dependence contained in Equation 10.3 and Equation 10.4. This section reviews the rationale behind these choices and the assumptions made in the derivation of Equation 10.1 to Equation 10.4. The latter are as follows:

1. The total chemical dose to the skin falls within the small dose limit in which nearly first-order absorption is often observed (Kasting and Saiyasombati, 2001; Kasting, 2001). An upper limit to this range may be taken as 100 μg cm^{-2} (Kasting, 2001), although it may be higher for highly volatile solvents such as ethanol.
2. Compounds evaporate and absorb independently of one another and do not bind irreversibly to skin.
3. The absorptive flux J_{skin} is a fraction of the maximum flux J_{max}. The latter is directly proportional to lipid solubility and inversely related to molecular weight (Kasting et al., 1992). Thus,

$$\begin{aligned} J_{\text{skin}} &= \frac{c_{lip}(t)}{S_{lip}} J_{\max} \\ &= \frac{c_{lip}(t)}{S_{lip}} \cdot \left[\text{const.} \cdot S_{lip} \cdot MW^{-b} \right] \\ &= \text{const.} \cdot c_{lip}(t) \cdot MW^{-b} \end{aligned} \tag{10.11}$$

In Equation 10.11, $c_{lip}(t)$ is the concentration of the compound in the SC lipid phase at time t, S_{lip} is its solubility in these lipids (taken to be the product of water solubility S_w and octanol–water partition coefficient K_{oct}), and b is a positive exponent with a value of about 2.7 (Kasting and Saiyasombati, 2001). The value of b was estimated based on an analysis of the Flynn skin permeability database (Johnson et al., 1997), which represents steady-state permeabilities obtained with hydrated human skin *in vitro*. It is possible that a somewhat higher value of b may apply for volatile disposition on air-dried skin if it is more size selective than hydrated skin. Such a refinement has not been attempted here.

4. The evaporative flux J_{evap} is given by a Henry's law like expression, with the SC lipids as the relevant solvent. Thus,

$$J_{\text{evap}} = \text{const.} \cdot f(v) \cdot c_{lip}(t) \cdot P_{vp} \,/\, S_{lip} \tag{10.12}$$

5. where $f(v)$ is an airflow function, P_{vp} is vapor pressure, and S_{lip} is estimated as $K_{oct} \cdot S_w$. An analogous expression has been used to estimate the evaporation rates of pesticides from soil (Lyman et al., 1982), in which the relevant solvent is the soil organic fraction.

Temperature Dependence

Skin permeability, as well as evaporation rate, are strong functions of temperature. Equation 10.3 and Equation 10.4 are written with this in mind. The values of k_2^T in Table 10.1 apply to skin at a temperature of 30°C; an Arrhenius correction to these values for other temperatures is suggested in Kasting and Saiyasombati (2001). The temperature dependence of evaporation rate, on the other hand, occurs through the variation of P_{vp} with temperature, a dependence that is easily approximated and factored into Equation 10.3. Thus, the model calculations can readily be extended to exposure scenarios involving a range of skin temperatures.

Airflow Dependence

Intuitively, one expects that evaporative loss from the skin will be directly related to the wind velocity or airflow over the skin surface. That this is so has been demonstrated in my laboratory (Saiyasombati and Kasting, 2003a, 2004a) using methods similar to those employed in Vuilleumier et al. (1995). A picture of the test apparatus employed in Saiyasombati and Kasting (2004a) is shown in Figure 10.4, and a plot of the airflow dependence obtained for evaporation of a model fragrance ingredient, benzyl alcohol, is shown in Figure 10.5 (open circles). In this section, we relate these laboratory results to those in Vuilleumier et al. (1995) and establish a basis for the use of Equation 10.10 as a plausible absorption estimate for unoccluded skin sites on broad body surfaces (torso, arm, leg) exposed to relatively still air indoors. Adjustments for more permeable skin sites (face, postauricular, underarm) are discussed in the next section.

The data in Figure 10.2 and Figure 10.3 (on which the present model was calibrated) were generated on human volar forearm using a dose cell similar to that shown in Figure 10.4 and an airflow of 5 L h^{-1} or 83 ml min^{-1} (Vuilleumier et al., 1995). These conditions may be equated to those in Saiyasombati and Kasting (2004a) (Figure 10.5, open circles) at comparable airflows on the basis of a similar cell design and experimental method. From the physical properties of benzyl alcohol at 30°C reported in Saiyasombati and Kasting (2003a) (P_{vp} = 0.0847 torr, MW = 108.1 Da, log K_{oct} = 1.1, S_w = 44.7 g L^{-1}), a value of k_1^v = (10.5 ± 2.2) h^{-1} at v = 83 ml min^{-1} may be calculated for the *in vivo* benzyl alcohol evaporation data in Figure 10.5, which is comparable to the range k_1^v = 9.1 to 14.5 h^{-1} found in Table 10.1.

Additional studies with benzyl alcohol applied to cadaver skin *in vitro* demonstrated a similar airflow dependence to that shown *in vivo* Saiyasombati and Kasting (2003a). The results are shown as solid circles in Figure 10.5. The evaporation rates *in vitro* and *in vivo* were found to vary in direct proportion to the airflow and inversely with the volume of the dose cell, which was about eightfold higher *in vivo* (Saiyasombati and Kasting, 2004a); thus, the *in vitro* airflow corresponding to 83 ml^{-1} *in vivo* was about 10 to 15 ml min^{-1}. This may be seen by comparing the evaporation profiles in Figure 10.5.

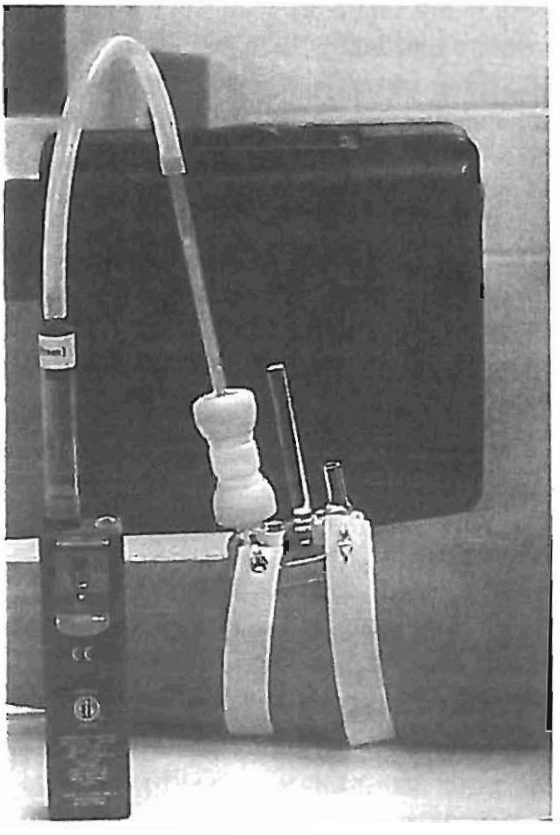

Figure 10.4 Apparatus for trapping volatiles from a human forearm *in vivo* (Saiyasombati and Kasting, 2004a).

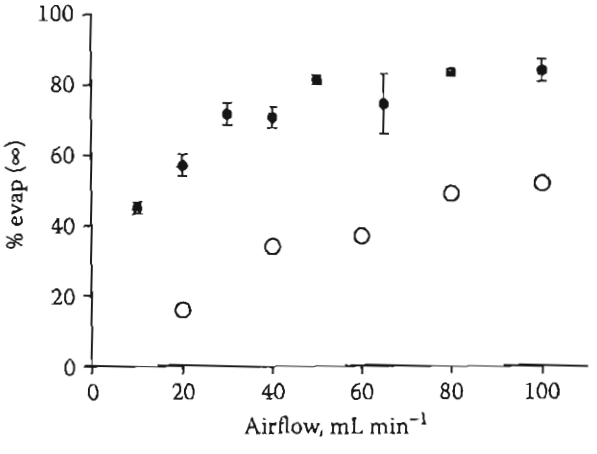

Figure 10.5 Cumulative percentage of benzyl alcohol evaporated from human skin as a function of airflow in the collection cell. •, *in vitro*, 2.25 h postdose (Saiyasombati and Kasting, 2003a); *in vivo*, 2 h postdose (Saiyasombati and Kasting, 2004a).

Finally, recent work in my laboratory with another test permeant, (*N,N*)-diethyl-*m*-toluamide (the mosquito repellant DEET), has established a relationship between DEET disposition on skin *in vitro* (Bhatt and Kasting, 2003) and in several human *in vivo* studies (Feldmann and Maibach, 1970; Spencer et al., 1979; Selim et al., 1995). The best comparison to the *in vitro* results is a clinical study in which ^{14}C-DEET was applied to the forearm of test subjects, and the dose site was subsequently covered with a perforated aluminum dome (Selim et al., 1995). The dose was removed after 8 h, and urinary excretion of radioactivity was determined over 128 h. This comparison suggests that the *in vitro* airflow corresponding to the perforated dome exposure *in vivo* is about 20 ml min^{-1} (G.B. Kasting and V. Bhatt, 2004, unpublished data). The combination of this result with the earlier finding that the data in Vuilleumier et al. (1995) correspond to approximately 10 ml min^{-1} *in vitro* forms the basis for proposing the use of Equation 10.9 and Equation 10.10 for risk assessment. The perforated dome study (Selim et al., 1995) conservatively approximated still room air, and an additional small safety margin is provided by the fact that the conditions in Selim et al. (1995) evidently correspond to a higher *in vitro* airflow than do those in Vuilleumier et al. (1995).

Influence of Skin Site and Occlusion

To maintain consistent safety factors, it is both reasonable and appropriate to modify Equation 10.9 and Equation 10.10 for exposures involving highly permeable skin sites or high degrees of occlusion. The following modifications are suggested based on literature data (Feldmann and Maibach, 1967; Maibach et al., 1971; Scheuplein and Blank, 1971; Wester et al., 1984; Rougier et al., 1988; Schwindt et al., 1998; Guy and Maibach, 1984) on site-to-site variations in skin permeability.

Skin Site

Postauricular and facial skin have been found to be two- to sixfold more permeable than broad body surfaces, including forearm (Feldmann and Maibach, 1967; Maibach et al., 1971; Scheuplein and Blank, 1971; Rougier et al., 1988; Guy and Maibach, 1984). Underarm, genitalia, and other mucosal surfaces are even more permeable (Feldmann and Maibach, 1967; Maibach et al., 1971; Guy and Maibach, 1984). For the last sites, it is recommended that Equation 10.9 and Equation 10.10 be replaced with a 100% absorption estimate in the absence of additional data. This conservative estimate is made in light not only of increased skin permeability, but also of the relatively high occlusion of these sites under clothing. For postauricular and facial skin, a substitute for Equation 10.10 based on a threefold higher value of the absorption rate constant k_2^T may be suggested:

$$\%\ \text{abs}(\infty) = \frac{49.5 + 15x_r^2}{0.495 + x_r} \quad ; \quad 0 < x_r < 1 \tag{10.13}$$

Occlusion

Fully occluded sites do not allow evaporation and furthermore lead to hydrated skin and higher skin temperatures. A 100% absorption estimate must be applied for long-term occluded exposures to skin-permeable compounds such as fragrance ingredients, pesticides, and volatile organic solvents. Rates of absorption may be estimated using available methods for nonvolatile compounds (Kasting et al., 1992; Potts and Guy, 1992; Wilschut et al., 1995; Johnson et al., 1997). For example, the Potts-Guy equation (Potts and Guy, 1992) has been shown to satisfactorily describe the absorption of fragrance ingredients from aqueous solution (Hostynek, 1997).

LIMITATIONS OF MODEL

The method described in this chapter represents a first attempt to quantitatively relate the skin disposition of volatile chemicals to their physical properties and to environmental conditions, including variable temperature and airflow over the skin surface. The relationships were developed for fragrance ingredients; however, it is likely they can be extended to include other important classes of compounds such as noncorrosive industrial solvents, pesticides, herbicides, and (noncorrosive) chemical warfare agents. Drawing the comparison to steady-state skin permeability models in which much more is known, it is evident that considerable experience must be gained with the use of such models before widespread acceptance may be expected. Areas for further attention are outlined next.

Dose Dependence

Equation 10.1 to Equation 10.10 were developed within the low-dose limit in which the applied compound(s) dissolve rapidly into the SC lipids. If the lipid volume is taken to be V_{lip}, then $c_{lip}(0) = \text{Dose}/V_{lip}$. Substitution of this relationship into Equation 10.11 and Equation 10.12 leads directly to Equation 10.1 to Equation 10.4. However, the SC lipid volume is small (100 to 150 $\mu g\ cm^{-2}$), and only a fraction of this volume can be immediately accessed by a topically applied permeant. Appropriate incorporation of a solubility limit, such that $c_{lip}(0) \leq S_{lip}$, would provide upper bounds to both the evaporation rate (Equation 10.1) and absorption rate (Equation 10.2) without changing their relative values. The key is establishing the accessible lipid volume and confirming or improving on the octanol solubility model. This problem has been discussed elsewhere (Kasting, 2001).

Ingredient Interactions

The present model assumes that ingredients diffuse and evaporate independently, whereas thermodynamic and mass transport considerations dictate that interactions must occur in concentrated mixtures (Cussler, 1997). Careful analysis of the evaporation rates in Vuilleumier et al. (1995) shows this to be the case: The musk ingredient, compound XII in Table 10.2, depressed the initial evaporation rates of

the fragrance top notes in a complex mixture (Saiyasombati and Kasting, 2003b). My group attempted to account for these interactions using activity coefficients calculated from a (universal quasichemical functional activity coefficient) UNIFAC/UNIQUAC approach (Reid et al., 1987) but were unable to obtain any improvements to a unit activity assumption in the context of one- and two-compartment kinetic models (Saiyasombati and Kasting, 2003b). The subject is worth revisiting in a true diffusion–evaporation model.

Kinetic Profiles

Equation 10.1 and Equation 10.2 lead to simple, exponential decays without time lags for both evaporation and absorption rates. There is experimental evidence to support more protracted decay curves and, of course, a diffusive time lag for absorption (Saiyasombati and Kasting, 2003a, 2003b). These features can be accommodated using two-compartment kinetic models that explicitly consider a vehicle layer (Saiyasombati and Kasting, 2003a, 2003b). However, the impact of this refinement on cumulative evaporation and absorption calculations is minimal, and the parameter assignments are not unique. A more promising direction is to use a diffusion model for the SC rather than a well-stirred compartment. This approach can account for both absorption time lag and curvature in semilogarithmic plots of absorption and evaporation rates using fewer undetermined parameters (G.B. Kasting and V. Bhatt, 2004, unpublished observations). It is the direction of the current research in our laboratory.

Physical Properties Dependence

Whether compartmental or diffusion models are employed, relationships analogous to Equation 10.3 and Equation 10.4 must be developed and confirmed to have predictive capabilities. Equation 10.3 stems directly from steady-state skin permeability relationships (cf. Equation 10.12), whereas Equation 10.4 is derived from Henry's law using octanol to represent the SC lipids (cf. Equation 10.11). Both of these relationships have room for improvement. An empirical modification, Equation 10.9 and Equation 10.10, to the physical properties relationship implied by Equation 10.3 and Equation 10.4 was suggested in this report to better correlate the data in Vuilleumier et al. (1995). Physically based modifications are needed.

CONCLUSION

A simple kinetic model for the disposition of volatile chemicals applied to skin has been developed and calibrated for fragrance ingredients and mixtures. The model allows the estimation of the percentage of each ingredient evaporated and absorbed as a function of time to within a factor of two. Suggestions for extension and refinement of the approach are provided.

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