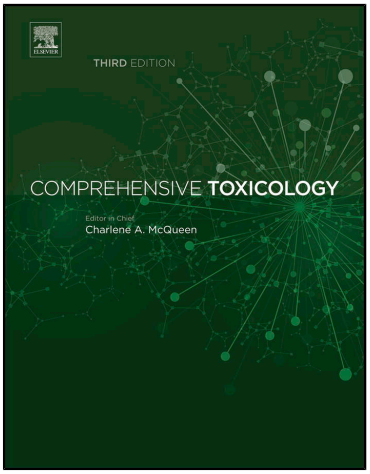

From Kissel, J. C., Bunge, A. L., Frasch, H. F., & Kasting, G. B. (2018) Dermal Exposure and Absorption of Chemicals. In: McQueen, C. A., Comprehensive Toxicology, Third Edition. Vol. 1, pp. 112–127. Oxford: Elsevier Ltd.
ISBN: 9780081006016

Elsevier Science

1.06 Dermal Exposure and Absorption of Chemicals

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

Comprehensive Toxicology, Third Edition, 2018, 112–127

1.06.1 Introduction

Functions of the skin include, but are not limited to, physical protection of internal tissues, bones, and organs; sensing of the external environment; regulation of body temperature; and regulation of water content. Regulation of water transport depends upon the skin functioning as a semipermeable membrane. As such, it can also absorb chemicals other than water from (or emit other chemicals to) the external environment. Evaluation of potential chemical transfer into the skin or into the body via the skin is an essential component of exposure and hazard assessment in the context of risk assessment and is thus a critical element of environmental and occupational health practice. The skin is a potential barrier to systemic absorption, but can also be the target organ. This chapter deals primarily with the former, but the two phenomena cannot be entirely isolated as skin toxicity requires at least partial penetration and skin damage can reduce the barrier property of skin.

1.06.2 Physiology of Skin

Skin is a composite material comprised of layers with varying properties (Fig. 1). A key distinction is drawn between the epidermis and the dermis. The relatively thin epidermis lacks vascularization and is generally considered the primary barrier to uptake of chemicals encountered in the workplace or general environment. The dermis is vascularized and also contains the sweat glands and hair follicles. Transport via those appendages is known to be possible, but is typically neglected in current risk assessment practice in favor of the more studied and better quantified transepidermal pathway. Chemicals that reach the dermis are available for systemic distribution via the general circulation. A subcutaneous fat layer, the hypodermis, lies beneath the dermis, but does not generally play a role in the function of skin as a chemical barrier. The hypodermis does contribute to the body's total storage capacity for poorly metabolized lipophilic chemicals.

In the context of chemical permeation, it is useful to further divide the epidermis into the surface layer, the stratum corneum, and the underlying viable epidermis (Fig. 1). The stratum corneum consists of layers of dead cells (corneocytes) that continuously slough at the skin surface and are replenished by initiation of terminal differentiation at the viable epidermis boundary. The corneocytes are enmeshed in lipids arranged in bilayers. A "brick and mortar" analogy, in which cells are bricks and the lipid bilayers are mortar, is often used to describe the structure of the stratum corneum. The corneocytes are composed of protein (primarily keratin in the interior and a variety of structural proteins in the cornified cell envelope). Chemical transport through the stratum corneum can occur via tortuous path diffusion through lipid bilayers alone or by sequential diffusion through lipid bilayers and intracellular spaces. The lipid bilayers present a substantial barrier to ionized compounds. For nonionic compounds, the stratum corneum is the primary barrier to permeation of hydrophilic and moderately lipophilic compounds (Scheuplein and Blank, 1971). The viable epidermis, which is much more hydrophilic in nature than the stratum corneum, can contribute significantly or predominantly to resistance to permeation of highly lipophilic nonionic compounds (Scheuplein and Blank, 1973). Under normal skin conditions the viable epidermis is fully hydrated (water activity approximately that of normal saline) and a water activity gradient (declining activity from inner to outer layers) is present in the stratum corneum.

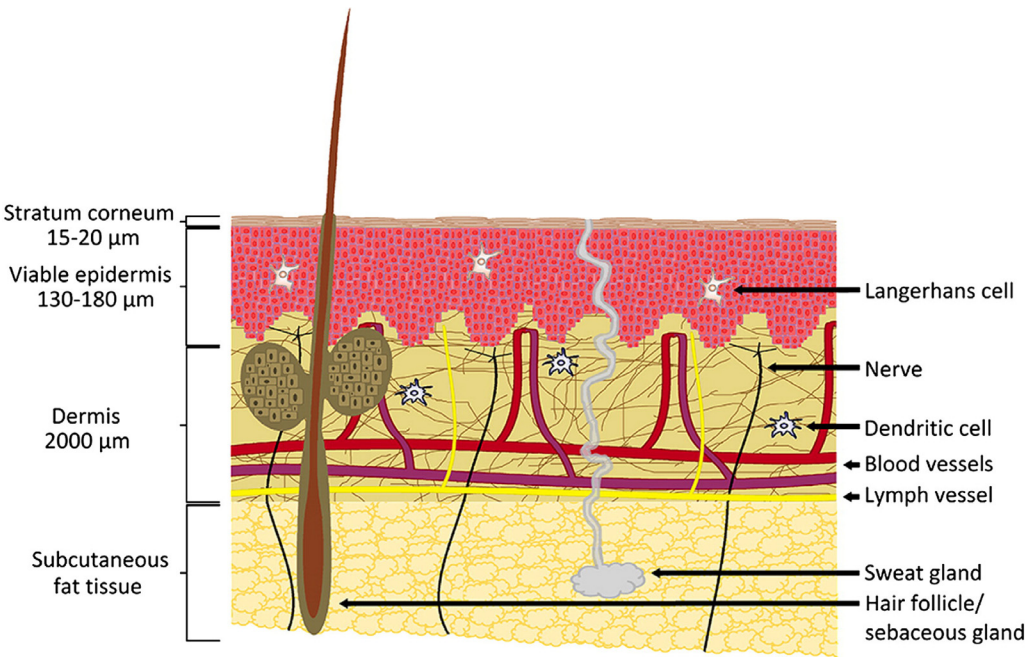

Fig. 1 Cross-sectional view of human skin. Estimated thicknesses shown are from the original. Estimates vary with method and body region (see "Physiology of Skin" section). Reprinted from van der Maaden, K., Jiskoot, W. and Bouwstra, J. (2012). Microneedle technologies for (trans) dermal drug and vaccine delivery. Journal of Controlled Release, 161 (2), 645–655 with permission.

The stratum corneum has long been considered to be roughly 10–20 μm thick, except on the palmar side of hands and on the soles of the feet, where thickness can be much greater (Rushmer et al., 1966). Excluding palmar and plantar skin, the total thickness of the epidermis is generally about 50–100 μm (Sandby-Moller et al., 2003; Robertson and Rees, 2010). Measurement techniques have evolved from gravimetric to microscopic methods, contributing to variability in estimates found in the literature. The underlying dermis is much thicker, typically 500–3000 μm (USEPA, 1992). The nominal (macro) surface area of an adult male human is roughly two square meters (USEPA, 2011). In total, the dermis and the hypodermis can exceed ten percent of human body mass making the skin the largest organ in the body.

1.06.3 Observed Occupational and Environmental Chemical Exposures to Skin of Significance

Exposure of the skin to chemical agents can produce toxicological effects in the skin at the point of entry or systemic effects elsewhere as a consequence of permeation and distribution. Individual chemicals may account for either or both outcomes and are therefore not easily categorized although general distinctions are often drawn between irritants and systemic agents. The greatest threat is posed by chemical exposures that are both corrosive and/or damaging to the skin and toxic. Hydrofluoric acid, for example, is a substantial occupational hazard (Blodgett et al., 2001), capable of causing both chemical burns and systemic fluorosis. Fatal injuries have also occurred as a result of exposure to 2,4-dichlorophenol (2,4-DCP) in industrial scenarios (CDC, 2000). 2,4-DCP is solid at room temperature, but is handled as a high-temperature, pressurized liquid in chemical synthesis processes. Reported fatalities have all been associated with high-pressure leaks leading to 2,4-DCP exposure accompanied by simultaneous scalding injury to substantial skin area. Many chemicals can, however, permeate the skin at sufficient rates to cause fatal systemic effects even in the absence of severe skin damage. **Table 1** presents additional examples of dermal exposures sufficient to cause fatal injuries in both occupational and nonoccupational scenarios. These examples serve as a reminder that dermal exposure hazards can be as severe as the more obvious and intuitive threats presented by ingestion and inhalation of chemicals.

Nonfatal dermal injuries are of course much more common and ultimately more costly when assessed using conventional economic measures. The 2010 National Health Interview Survey Occupational Health Supplement revealed that more than 20% of US workers report frequent occupational contact with chemicals (Calvert et al., 2013). Dermatitis caused by contact irritants or allergens is very common and imposes large economic costs manifest as human discomfort/disability and lost work productivity (Anderson and Meade, 2014; Blanciforti, 2010; Cashman et al., 2012; Kalia and Haiducu, 2012). Dermatitis can be difficult to treat once established (Hogan, 1994). Overall rates of occupational dermatitis appear similar in North America and Europe averaging about 0.8/1000/year (Diepgen, 2003), which translates to a (40 year) working lifetime risk of 3×10^{-2}. High risk populations include hairdressers and food and healthcare workers. The most common contact irritant is water and chronic dermal exposure to water (i.e., "wet work") is a well-established cause of dermatitis. Other important contact irritants include cleansers, acids and bases, and solvents (Cashman et al., 2012). Contact allergens can cause immune system mediated effects both in the skin and, after systemic uptake, in other organs. Dermal exposure to beryllium, for instance, can induce sensitization that ultimately manifests as lung disease (Tinkle et al., 2003). Other important occupational contact allergens and sensitizers include nickel, formaldehyde, some quaternary ammonia compounds, and fragrances (Cashman et al., 2012).

An additional category of skin injury potentially attributable to chemical exposure is induction of skin cancer. Percivall Pott's identification of elevated scrotal cancer risk in chimney sweeps in the eighteenth century (Pott, 1775) is a seminal event in the history of occupational health that ultimately led to the classification of polycyclic aromatic hydrocarbons (PAHs) as carcinogens.

Examples of systemically toxic agents for which the dermal route of exposure is known to be a potentially significant contributor to total exposure include organophosphate pesticides (Baker et al., 1978; Brown et al., 1989) and nerve agents (Munro et al., 1994), nicotine (Arcury et al., 2003), PAHs (van Rooij et al., 1993) and many solvents. Chemicals entering via the skin are not subject to first-pass detoxification in the liver.

1.06.4 Experimental Models of Dermal Absorption

Observation of adverse outcomes associated with dermal exposures has led to scientific investigation of underlying phenomena. Regardless of whether a chemical agent is of concern due to potential skin effects or systemic effects, that agent must at least penetrate through the outer layers of the epidermis to cause an adverse result. Empirical study of penetration phenomena has involved both in vivo and in vitro approaches and use of both human and surrogate species skin. Human skin is the best model for

Table 1 Examples of fatalities attributed to systemic toxicity resulting from short-term dermal exposure to chemicals

Agent	*Scenario*	*References*
Hexachlorophene	Contaminated talcum powder applied to infants	Martin-Bouyer et al. (1982)
Pentachlorophenol	Diapers contaminated in laundering	Armstrong et al. (1969)
Dimethyl mercury	Penetration of latex glove in laboratory setting	Nierenberg et al. (1998)
Paraquat	Occupational Herbicide Application, Lice/Scabies Treatment	Wohlfahrt (1982)

evaluation of human dermal absorption of chemicals, but potential toxicity restricts in vivo human testing to a very limited set of compounds and doses. For a variety of reasons, dermal permeation studies have primarily been conducted either in vitro using human skin, or in vivo in nonhuman species.

1.06.4.1 In Vivo/In Vitro Differences

Verisimilitude between in vitro and in vivo approaches has long been a point of contention (Franz, 1975). Since most human skin permeation testing is done in vitro, relatively little opportunity exists for examination of in vivo/in vitro correspondence using strictly human data. Most in vivo permeation investigations are conducted using rodents whose skin is generally more permeable than human skin. Comparison of in vivo rodent permeation with in vitro human permeation results in confounding of in vivo/in vitro differences by interspecies differences. A relatively limited set of data describing uptake (of mostly pharmaceuticals) in matched pairs of in vivo/in vitro experiments (i.e., same species, chemical, dose, skin region, duration, etc.) has been published by Franz and colleagues (Franz et al., 2009; Lehman et al., 2011; Lehmann et al., 2012) and shows excellent correspondence between in vivo and in vitro outcomes. In vitro approaches are appropriately subject to greater scrutiny when dealing with compounds for which metabolic activity in the skin is of particular concern, but are nevertheless useful for many compounds. Both in vitro and in vivo approaches present significant challenges to experimentalists and results should be interpreted carefully.

1.06.4.2 Interspecies Differences

Much in vivo permeation testing is done in surrogate species. Common surrogates include mice, rats, guinea pigs, pigs, rabbits, and monkeys. Rodent skin is generally thinner, features greater hair follicle density, and is experimentally more permeable than human skin. Pig and primate skin are generally considered superior models for human skin, but present cost disadvantages in comparison to rodent skin. In vivo/in vitro correspondence may also vary with the endpoint being compared (e.g., permeation could be similar even if storage in skin was not).

1.06.4.3 Other Factors

1.06.4.3.1 Skin region

As noted above, skin thickness varies across regions of the body. Generally thinner skin is more permeable, and in humans the scrotum is considered particularly permeable. Other relatively permeable regions include the axilla, forehead, and dorsum of the hand. The palm, thigh, and back are thicker. Abdominal skin is often chosen for in vitro work as it is of intermediate thickness. Thicker skin is not, however, a guarantee of limited permeability. Heel skin, for instance, can be subject to cracking, which can enhance permeation.

1.06.4.3.2 Temperature/blood flow

Increasing dermal absorption of chloroform with increasing bath water temperature has been demonstrated by Gordon et al. (1998) in vivo, in biomarker-based experiments that isolated the dermal pathway. Increased permeability coefficients (a concept discussed in greater detail below) estimated from these experiments (Norman et al., 2008) indicate that increased fluxes were related to increased permeability and not just increased thermodynamic activity of chloroform at higher water temperatures. Increased blood flow to skin is also expected at higher temperatures. This can also increase absorption if absorption is clearance limited at the epidermal boundary.

1.06.4.3.3 Skin Hydration

Skin that is either abnormally dry (i.e., chapped or cracked) or abnormally wet can be more permeable than normal skin. However, much of the evidence for increasing permeability with increasing hydration comes from experiments involving extended exposure to water or high humidity environments that may or may not be relevant to short term exposures such as hand washing or showering. For instance, Miller and Kasting (2010) showed a substantial increase in parathion permeation through human skin in vitro for occluded versus nonoccluded samples over 76 h. A starting-point approximation accepted by the authors is that fully hydrated skin is 3–4 times more permeable to most substances than is partially hydrated (i.e. air-exposed) skin (Wang et al., 2006, 2007). However, full hydration may require hours of exposure. Chang and Riviere (1991) showed little effect of skin hydration on absorption of parathion in pig skin with less than two hours exposure to 90% humidity.

1.06.4.3.4 Occlusion

Occlusion generally serves to increase dermal absorption by increasing skin temperature and water content (see preceding sections) and by suppressing volatilization loss. Internal contamination of gloves can, for instance, lead to higher exposure than would occur in the absence of glove use (Rawson et al., 2005). Volatilization loss can be a very important mitigating factor in the case of bare skin exposure to compounds with relatively high vapor pressures.

1.06.4.3.5 Skin damage

Because the intact stratum corneum is the primary barrier to permeation of many compounds, damage or removal of the stratum corneum can enhance permeation. This is especially true of hydrophilic compounds. For highly hydrophobic compounds, damage to the stratum corneum accompanied by swelling of the viable epidermis may actually retard uptake (Boman and Wahlberg, 1989). Estimation of dermal absorption through damaged skin is facilitated by the use of multilayer skin absorption models (see "Automated Computation" section) in which the stratum corneum layer can be mathematically removed and blood flow can be increased to simulate the biological response to injury.

1.06.4.3.6 Skin age

The skin of premature newborns is relatively permeable, but matures to normal barrier properties by approximately the expected full-term delivery date (Kalia et al., 1998; Sekkat et al., 2004). Risk assessments generally do not include adjustments for age of human skin. However, conditions typically encountered within the diapered area of infants (including hydration and skin irritation/damage) may warrant special consideration when evaluating consumer product safety (see, for example, SCCS, 2011).

1.06.4.3.7 Ionization

Ionic species are readily transported through aqueous environments, but there is no continuous aqueous path through skin. Epidermal lipid bilayers represent a significant barrier to ionized species. For ionizable compounds, the relevant concentration for prediction of absorption is the concentration of the unionized form (Swarbrick et al., 1984). The formula for estimation of the nonionized fraction is:

$$f_{\text{nonionized}} = \frac{1}{1 + 10^{g}}$$

where $g = (\text{pH} - \text{p}K_a)$ for acids and $g = (\text{p}K_a - \text{pH})$ for bases (Vecchia and Bunge, 2002a).

1.06.4.3.8 Desquamation

The stratum corneum turns over about once every two weeks in normal human skin (and much faster in the case of skin diseases such as psoriasis). Permeation of highly lipophilic chemicals that diffuse slowly due to sequential sorption/desorption may be partially offset by sloughing of skin cells. The impact of desquamation on absorption has been modeled by Reddy et al. (2000).

1.06.4.3.9 Decontamination

Washing or other forms of decontamination will typically remove surface chemical, but not the chemical that has penetrated beyond surface cell layers but not into systemic circulation (i.e., the "depot"). Fig. 2 shows in vitro permeation data for diethyl phthalate, with and without skin surface washing at 40 min post exposure (Frasch and Barbero, 2008). Total absorption is greatly reduced by washing in those experiments due to removal of the surface reservoir. However, claims can be found in the literature of

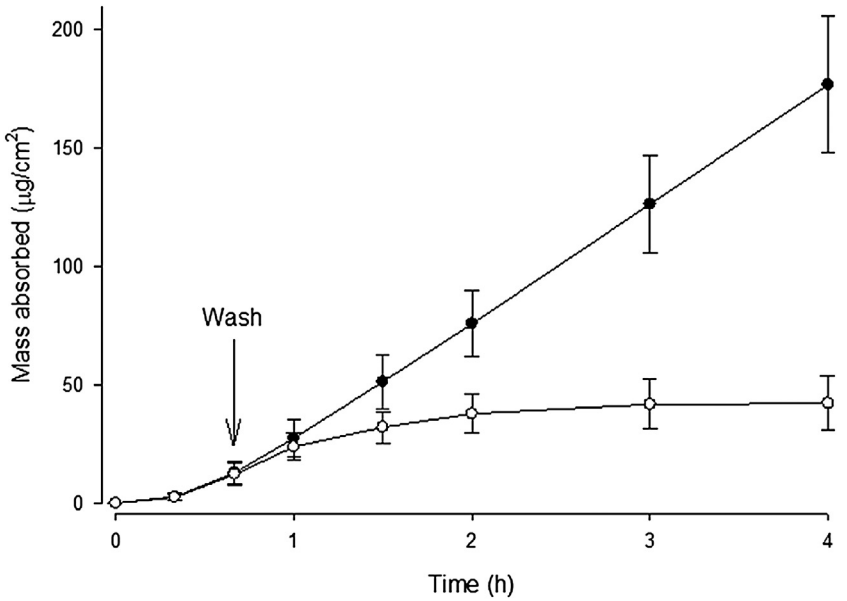

Fig. 2 Absorbed mass of diethyl phthalate with (*open circles*) and without (*closed circles*) skin surface washing at 40 min post exposure. Absorption proceeds transiently following washing as chemical within the skin depot is absorbed. However, washing substantially diminishes total absorption compared with no washing. Data from Frasch, H. F. and Barbero, A. M. (2008). The transient dermal exposure: Theory and experimental examples using skin and silicone membranes. Journal of Pharmaceutical Sciences, 97 (4), 1578–1592.

a "wash-in effect" (Moody and Maibach, 2006), whereby permeant flux is transiently increased following washing, ostensibly because the depot is driven into the systemic circulation. These claims are speculative and based on questionable evidence.

1.06.4.3.10 Appendages

It is well established that initial permeation of skin is sometimes observed before diffusion through the composite lipid/corneocyte matrix of the stratum corneum can reasonably be expected to have occurred (Scheuplein, 1967; Scheuplein and Blank, 1971). Scheuplein (1967, 1976) and later others (Kasting et al., 1992; Peck et al., 1994; Tang et al., 2001; Mitragotri, 2003) have argued that skin appendages including hair follicles and sweat glands were the likely route of rapid permeation through the skin. This argument can readily be shown to hold for small, inorganic ions using electrical methods (Grimnes, 1984; Burnette and Onpipattanukul, 1987; Cullander and Guy, 1991) and staining with charged dyes (Abramson and Gordon, 1940; Scheuplein, 1978). However, this phenomenon is not limited to hydrophilic permeants. Kasting et al. (2005) have observed early permeation with vanillylnonanamide (synthetic capsaicin, log $K_{o/w}=3.74$) and DEET (log $K_{o/w}=2.02$). Intuition suggests that the pathway for hydrophilic compounds might be the sweat ducts and that for lipophilic compounds the sebaceous ducts, but this distinction can be easily challenged. For example, rodent skin, which has many hair follicles but no sweat ducts, has lower electrical resistance than human skin (Davies et al., 2004), implying easier transmission of hydrophilic substances. The overall Importance of appendages in permeation of human skin remains unclear (see "Appendageal Transport" section).

1.06.5 Basic Mathematical Modeling of Dermal Absorption

Given the number of chemicals in commercial production, and cost and time constraints imposed by experimental investigations, mathematical modeling of absorption is necessary to permit assessment of risks in a timely fashion. A basic approach is to model permeation of the skin as diffusion in a homogenous membrane. The mathematics of diffusion (and of the analogous processes of heat and momentum transfer) has been the subject of investigations in the physical sciences and engineering for many decades. The interested reader is referred to Crank (1975) for extensive treatment of this topic.

1.06.5.1 Diffusion in a Homogenous Membrane

Nonsteady transport in a homogenous membrane by diffusion alone can be described as follows:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2}$$

where C is concentration in the membrane, t is time, D is diffusivity, and x is depth in the membrane. Solution of this second-order partial differential equation for the case of skin initially free of the chemical agent and subsequently exposed to that agent at constant external concentration leads to the family of curves plotted, on nondimensionalized (normalized) scales, in Fig. 3. At early times, the concentration profile of the permeant does not reach the inner boundary of the membrane. Breakthrough occurs

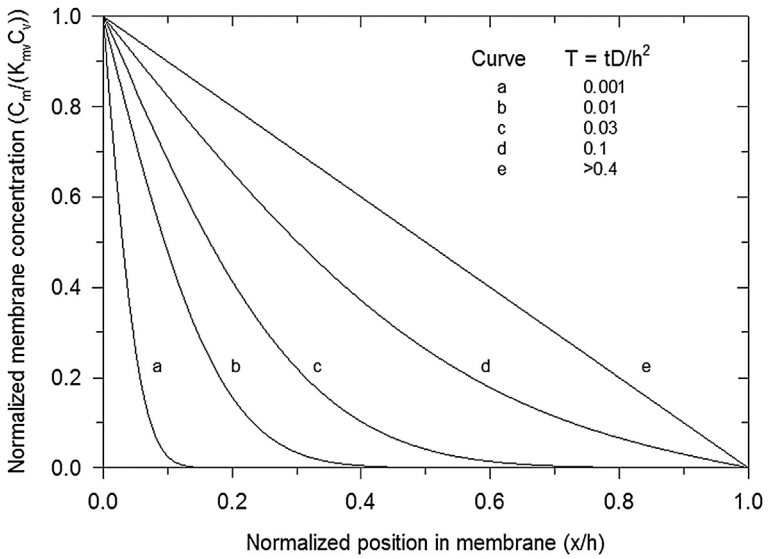

Fig. 3 Plot of nondimensionalized (normalized) time varying concentration profiles (C_m = membrane concentration, C_v = constant concentration in vehicle, K_{mv} = membrane-vehicle partition coefficient) attributable to diffusion in a homogeneous membrane under infinite dose conditions. At steady state (curve *e*), a linear profile is established.

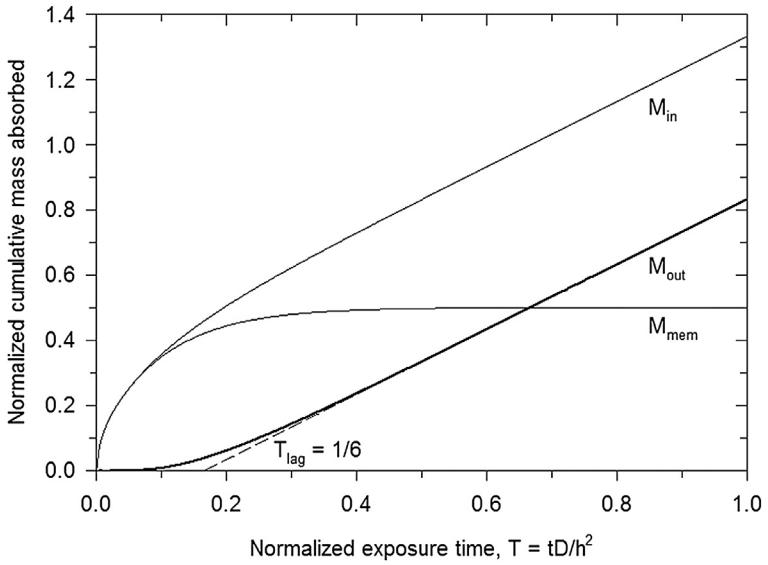

Fig. 4 Plot of cumulative absorption into and through skin in accordance with theoretical description of diffusion in a homogeneous membrane under infinite dose conditions. The upper (M_{in}) curve represents mass absorbed into the skin. The lower (M_{out}) curve represents mass released into subcutaneous circulation. The difference between those two curves represents mass storage in the membrane (M_{mem}). At steady state, the permeability coefficient is conveniently estimated from the slope of the cumulative release curve.

subsequently and eventually, if the dose is sufficient to sustain a nearly constant concentration at the skin surface, the profile reaches steady state (i.e., the linear profile on the right-hand side of the graph).

Fig. 4 provides an alternative perspective on the process described in Fig. 3, displaying predicted mass uptake (left-hand curve) and release (right-hand curve) from the membrane on nondimensionalized scales. The difference between the two curves represents mass storage in the membrane. Initially uptake exceeds outflow and storage increases. Steady state occurs when the slopes of the uptake and release curves are equivalent.

Extrapolation of the release curve to its intercept on the horizontal-axis yields the lag time, t_{lag}, defined (for the case in which resistance is attributed to the stratum corneum alone and that layer is assumed homogenous) as:

$$t_{lag} = \frac{h_{sc}^2}{6 \cdot D_{sc}}$$

where h_{sc} is the thickness [length] of the stratum corneum, and D_{sc} is the diffusivity coefficient [length^2 time^{-1}] in the stratum corneum. In nondimensional form as shown on Fig. 4, lag time is equal to 1/6.

1.06.5.2 Permeability Coefficients and Their Estimation

The steady-state condition is of particular interest as it is conducive to the estimation of the permeability coefficient. At steady state, the left-hand side of the differential equation above is equal to zero and resolution of the right-hand side gives the condition in which flux into the membrane at the outer boundary is equal to flux out of the membrane at the inner boundary. This condition is represented mathematically as

$$J_{ss} = k_p \cdot \Delta C$$

where J_{ss} is steady-state flux [mass/area/time], k_p is the (vehicle and membrane specific) permeability coefficient [length/time], and ΔC is the concentration gradient [mass/volume]. This relationship is commonly referred to as Fick's Law. It permits estimation of the permeability coefficient as the ratio of the flux to the concentration gradient. (Flux is the surface area-normalized slope of the release curve in the dimensional analog to Fig. 4). The concentration gradient must be expressed in consistent units (i.e., if C_{outer} is taken to be $C_{vehicle}$, then C_{inner} must also be expressed as its thermodynamically equivalent concentration in the vehicle) and those units are linked to the permeability coefficient. If removal of the permeant at the inner boundary is rapid, C_{inner} can often be assumed to be approximately zero, simplifying the calculation. Permeability coefficients are routinely estimated from experimental data using Fick's Law. (Readers are cautioned that many individual values of k_p reported in the literature are miscalculated or misreported, i.e., calculated using an incorrectly specified driving force or reported without specification of vehicle and membrane.)

Some significant attempts have been made to provide methods for estimation of permeability coefficients that are more broadly applicable. Flynn (1990) assembled a data set describing (largely in vitro) permeation of human skin by 94 compounds with molecular weights (MW) ranging from 18 to 765 and base 10 log octanol/water partition coefficients (log $K_{o/w}$) ranging from −3 to 6. The

data all represent exposure via aqueous solution. Potts and Guy (1992) regressed permeability coefficients calculable from the Flynn data set against MW (a surrogate for molecular size) and log $K_{o/w}$, producing the following commonly cited result:

$$\log k_p = -2.72 + 0.71 \log K_{o/w} - 0.0061 \text{ MW}$$

The Potts-Guy regression is dimensional and produces estimates of k_p (from water vehicle) with units of cm h^{-1}. Many alternatives have been proposed. Readers are directed to reviews by Wilschut et al. (1995), Bunge and McDougal (1998), Vecchia and Bunge (2002a,b) and Brown et al. (2016).

For the single layer membrane case, permeability coefficients can also be estimated from component quantities. For instance, for uptake of a compound from water limited by resistance in the stratum corneum alone, the relevant membrane and vehicle specific permeability coefficient could be estimated as:

$$k_{p,sc,w} = \frac{D_{sc} \cdot K_{sc/w}}{h_{sc}}$$

where $K_{sc/w}$ is the stratum corneum/water equilibrium partition coefficient, and h_{sc} is the thickness of the stratum corneum. The corresponding driving force would then be the concentration gradient expressed as concentration in water.

A particular result that serves as an alternative means of characterizing the dermal absorption potential of a given compound is the theoretical maximum steady-state flux calculated as:

$$J_{ss,max} = k_{p,sc,w} \cdot S_w$$

where S_w is the solubility of the compound of interest in water. An online calculator for $J_{ss,max}$ can be found at the following location: http://www.cdc.gov/niosh/topics/skin/skinpermcalc.html.

1.06.6 Load Effects

Despite the long-standing availability of the theoretically well-grounded mathematics described in the preceding section, regulatory schemes aimed at control of dermal hazards are largely dependent on use of estimates of dermal bioavailability expressed as a fixed fraction of initial mass load. This number is treated as if it is a physical property of a given compound. Because these dermal availabilities are typically small (i.e., less than 10%), the dermal pathway is often dismissed on the grounds that the compound is "not well absorbed." This line of reasoning is not well considered as it can easily be deduced from basic mathematics of the type shown above that fraction absorbed should vary with loading conditions (Kissel, 2011; Frasch et al., 2014). Experimental evidence that fraction absorbed is not constant for a given compound can be found in reviews of rat data submitted to regulatory agencies to support pesticide registration (Thongsinthusak et al., 1999; Zendzian, 2000) and in a broader review of the literature published by Buist et al. (2009).

Kissel (2011) proposed that loading conditions be evaluated by calculation of a characteristic dimensionless quantity termed the dermal number and defined as:

$$N_{derm} = \frac{\text{experimental load}}{\text{maximum loss rate} \times \text{duration}} = \frac{\left[\frac{\text{mass}}{\text{area}}\right]}{\left[\frac{\text{mass}}{\text{area} \times \text{time}}\right] \cdot [\text{time}]}$$

N_{derm} represents the ratio of supply to loss. At low values of N_{derm}, the system is supply limited and steady-state uptake will not be achieved. At high values of N_{derm}, the system is limited by rate of uptake (or other loss mechanism). If losses occur by absorption alone an inverse linear relationship between load and fraction availability would be expected. Failure to observe strict adherence to this inverse linear relationship in experimental data reflects the effects of volatilization losses and maldistribution of load under actual experimental conditions.

Fig. 5 displays in vitro permeation data (percent absorbed or mass absorbed) for vanillylnonanamide (Kasting, 2001) as a function of N_{derm} (i.e., as a function of load). Percent absorbed declines with increasing N_{derm} over most of the experimental range. The ramifications of this observation are discussed further under "Nonoccupational Risk from Dermal Exposure" below.

1.06.7 Matrix/Vehicle Effects

Chemical exposures may occur to neat compound, to contaminated environmental media (e.g., air, water, soil), to mixtures formulated as commercial products, cosmetics or personal care products, to contaminated or deliberately impregnated fabrics, or to pharmaceuticals delivered from topical formulations (e.g., lotions, creams, ointments), or transdermal patches. External phases can affect chemical exposure via damage or occlusion of the skin, alteration of the thermodynamic activity of the agent of interest, or imposition of additional mass transfer limitation.

1.06.7.1 Neat Compound/Solvent Deposition

Chemicals are generally not encountered in neat form although there are exceptions such as solvents (e.g., acetone, ethanol, toluene) that are commercially available at nearly 100% purity. In pure or high strength form, chemicals may be corrosive or

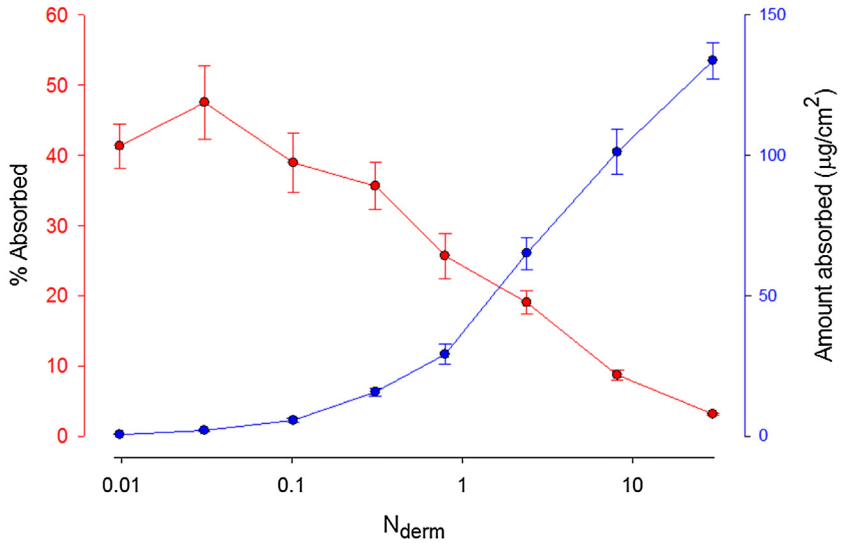

Fig. 5 Variation of percent absorbed (*red symbols*, left axis) and mass absorbed per unit area (*blue symbols*, right axis) of vanillylnonanamide with the nondimensional dermal number, N_{derm}. As N_{derm} declines, fraction absorbed increases until coverage becomes too sparse to maintain absorption. Modified from Frasch, H. F., Dotson, G. S., Bunge, A. L., Chen, C. P., Cherrie, J. W., Kasting, G. B., Kissel, J. C., Sahmel, J., Semple, S. and Wilkinson, S. (2014). Analysis of finite dose dermal absorption data: Implications for dermal exposure assessment. Journal of Exposure Science and Environmental Epidemiology, 24 (1), 65–73; data from Kasting, G. B. (2001). Kinetics of finite dose absorption through skin 1. Vanillylnonanamide. Journal of Pharmaceutical Sciences, 90 (2), 202–212.

otherwise damaging to the skin. Uptake into damaged skin is not well quantified, although it can generally be presumed to be more rapid than through undamaged skin. Under laboratory or clinical conditions, agents of interest are often delivered in a volatile solvent that evaporates relatively rapidly rather than truly as neat compound (e.g., Scheuplein and Ross, 1974). This is especially common in studies of chemicals with melting points above skin temperature or of chemicals applied at low surface loads. Some potential for damage to the skin (often ascribed to delipidization) or facilitated penetration due to vehicle uptake is presented by solvents (Scheuplein and Ross, 1970; Scheuplein and Blank, 1973) and assessment of data obtained via solvent deposition should include recognition of possible deviance from results that would have been obtained without use of a solvent vehicle.

1.06.7.2 Aqueous Solution

Water is a commonly encountered matrix, both in occupational and nonoccupational environments and in laboratory data. A relatively large database of experiments describing chemical penetration from aqueous solution, dubbed the Flynn database (Flynn, 1990), provides the basis for commonly utilized estimators of skin permeability coefficients (e.g., the Potts-Guy regressions discussed above). Extended contact with aqueous solution is known to alter (generally degrade) the barrier function of skin. Experiments involving hours of water/skin contact should not be considered indicative of permeation expected in exposure scenarios involving short term (minutes or seconds) of contact.

1.06.7.3 Soil

Limited data from experiments describing dermal uptake of chemicals from soil can be found in the literature. The resulting data are both less common and reflective of greater experimental heterogeneity than are data from water. The uptake-from-soil literature has been reviewed by Spalt et al. (2009). Some common limitations include failure to consider loading effects and soil solubility limits. Soils typically have some capacity for sorption of chemicals, especially for moderately to highly lipophilic chemicals. However, consideration of $K_{o/w}$ alone can be misleading. High values of $K_{o/w}$ can result from very low solubility in water. Soil is generally an inferior sorbent for lipophiles compared to octanol. A high soil-water partition coefficient can result from low solubility in water even if solubility in soil is also relatively low.

Reduced thermodynamic activity in soil and the physical barrier to mass transfer represented by the depth of the soil layer would typically be expected to reduce chemical flux into skin. However, in the case of volatile compounds, soil may, under some circumstances, actually enhance cumulative uptake by retarding evaporative loss (and thus extending the exposure period).

1.06.7.4 Air

Dermal absorption from the vapor state has traditionally been ignored in the regulatory arena, as inhalation is presumed the dominant exposure pathway to volatile compounds. However experimental data confirm that dermal absorption from vapor can be

nonnegligible in comparison to inhalation exposure for select compounds (Piotrowski, 1967, 1971; Johanson and Bomar, 1991; Bader et al., 2008; Weschler et al., 2015). Weschler and Nazaroff (2012, 2013) have provided a theoretical framework for evaluation of this phenomenon.

1.06.7.5 Fabric

Clothing or other textiles are commonly in close contact with skin. Contaminated work clothing can be an ongoing source of chemical exposure (Clifford and Nies, 1989), providing both a reservoir of chemical and occlusive conditions (reduced evaporation, increased humidity and temperature) that are conducive to dermal penetration. In some cases, fabric is deliberately treated with a chemical agent, such as an insect repellent, that is not immobilized and will penetrate the skin. Rossbach et al. (2010, 2014) have provided quantitative biomarker-based evidence of uptake of permethrin from impregnated clothing worn by soldiers and foresters. Prediction of uptake from fabric is currently impeded by a general dearth of fabric:skin partition coefficients in the literature.

1.06.7.6 Mixtures

Pesticides, cosmetics and personal care products, and topical dermatological medicines are routinely encountered as formulations (i.e., as chemical mixtures). The chemical of concern may either be the active ingredient, the primary carrier, or another component that contributes to product performance. These mixtures are routinely proprietary, which hinders assessment of the potential for dermal uptake. As in the case of other matrices/vehicles discussed above, chemical formulations can either enhance or retard uptake. Evaluation of absorption from mixtures can be greatly complicated if solutions behave nonideally or if one or more components alter the structure of skin. Apparently anomalous decreased uptake of 2-butoxyethanol (2-BE) with decreasing aqueous dilution (increasing purity), for instance, can be explained by a combination of nonideality at moderate concentrations and dehydration of the skin layer at high concentrations of 2-BE (Bunge et al., 2012). Another factor that complicates prediction of uptake from mixtures is that absorption or evaporative loss of mixture components can alter the chemical activity of the target agent in the external phase.

1.06.7.7 Transdermal Patches

Transdermal patches are deliberately designed to deliver predictable and pharmaceutically significant doses of selected drugs. In the context of this chapter they are primarily of interest in that they illustrate some properties of compounds that are conducive to dermal absorption. Only a limited subset of pharmaceuticals can be practicably delivered via transdermal patches. The first consideration is whether the drug is sufficiently potent that a relatively small dose can be efficacious. In addition, transdermal delivery is only feasible if the compound is lipophilic enough to dissolve in the stratum corneum, but not so lipophilic as to be unable to penetrate the viable epidermis. Some common examples are listed in **Table 2** with relevant physical chemical properties.

1.06.8 Advanced Mathematical Modeling of Dermal Absorption

Many of the factors described above that potentially affect dermal absorption are amenable to modeling. For instance, resistance may not be solely attributable to the stratum corneum, rendering the single homogeneous membrane assumption invalid for some compounds. Other potential issues of interest include transient conditions (arising from finite periods of exposure or from finite doses), transport in more than one dimension, simultaneous transport of more than one solute, hydration or vehicle effects on permeability, inclusion of capillary clearance limitation for readily permeable compounds, inclusion of metabolism and transport of metabolites with altered physical chemical properties, and inclusion of additional structural features revealed by microscopy such as potential follicular shunts. These and other topics are the subject of active investigations. A useful review of models of dermal penetration was presented by Mitragotri et al. (2011). Limited discussion of selected issues is provided here.

Table 2 Some pharmaceuticals commonly delivered by transdermal patch

Compound	*CAS No.*	*MW*	*Log $K_{o/w}$*	*mp (C)*
Estradiol	58-28-2	272.38	4.01	178.5
Fentanyl	437-38-7	336.47	4.05	c. 83
Lidocaine	137-58-6	234.34	2.26	68
Nicotine	54-11-5	162.23	1.17	−79
Nitroglycerine	55-63-0	227.09	1.62	13.5
Scopolamine	138-12-5	303.35	0.98	59
Testosterone	58-22-0	288.42	3.32	155

Properties obtained from https://pubchem.ncbi.nlm.nih.gov/, May, 2016.

1.06.8.1 Automated Computation

Prediction of dermal penetration and permeation using mathematics of the type described above (see "Basic Mathematical Modeling of Dermal Absorption") requires estimation of multiple parameters such as permeability coefficients. Hand calculation can rapidly become burdensome. Embedding quantitative structure activity relationships useful for parameter estimation into programs that perform the basic calculations presents obvious advantages. One such example, available as IH SkinPerm™, has been published by Tibaldi et al (2014). The model assumes all resistance to permeation resides in the stratum corneum, so it is a one layer model. It does permit estimation of absorption from both liquids and vapors and is oriented toward use by industrial hygienists.

1.06.8.2 Transient Exposures

Per Fig. 4, the skin can provide storage capacity for chemicals that have penetrated into outer layers, but not yet permeated into systemic circulation. When exposure ceases or is interrupted by washing, mass in the skin (referred to as the "depot") is still available for transport into circulation. Competition between further uptake and potential loss mechanisms, such as migration out of the skin by evaporation, is of interest. Frasch and Bunge (2015) have modeled this situation. Because short-term storage capacity in the skin for lipophilic compounds is primarily found in the stratum corneum, a single layer model is sufficient. Continued uptake after washing evident in Fig. 2 is consistent with expectation based on this modeling.

1.06.8.3 Multilayer Membranes

Given that the stratum corneum and viable epidermis are structurally dissimilar in important ways that impact the relative resistance each represents to permeation, an obvious potential improvement to modeling of skin as a homogeneous membrane is therefore to model skin as a heterogeneous membrane. The simplest case is two homogeneous layers in sequence, allowing alternative properties in the stratum corneum (sc) and viable epidermis (ve).

Bunge and coworkers (Cleek and Bunge, 1993; Bunge and Cleek, 1995; Bunge et al., 1995) have investigated this topic in some depth and provided analytical solutions for limiting cases, including nonsteady state. One consequence of the two-layer conceptualization of skin is an overall permeability coefficient that permits both layers to contribute to mass transfer resistance:

$$k_{\mathrm{p,overall}} = \frac{1}{\frac{1}{k_{\mathrm{p,sc}}} + \frac{1}{k_{\mathrm{p,ve}}}}$$

1.06.8.4 Heterogeneous Skin Architecture

Kasting and coworkers (Kretsos et al., 2004, 2008; Nitsche et al., 2006; Wang et al., 2006, 2007; Kasting et al, 2008; Ibrahim et al., 2012; Dancik et al, 2013; Kapoor et al., 2016) have published multiple works aimed at producing mathematically tractable models of finite dose conditions that incorporate microscopic skin features and component-specific properties and loss by volatilization. An Excel©-based model implementing these calculations is available from those authors. A Java applet implementing the Dancik et al. (2013) version of the model can be accessed online at the following web link: http://www.cdc.gov/niosh/topics/skin/finiteskinpermcalc.html.

One common variation is so-called "brick and mortar" models. Examples have been presented by Wang et al. (2006, 2007) and Chen et al. (2008, 2013). These models explicitly describe the stratum corneum as discontinuous corneocyte layers separated by lipids and allow both transcelluar and tortuous path diffusion.

1.06.8.5 Multisolute Absorption

The overwhelming focus of dermal absorption modeling to data has been on single compound exposure scenarios despite the fact that chemicals of interest are routinely encountered as formulations or mixtures. A model permitting simultaneous evaluation of transport of multiple solutes has been developed by Miller and Kasting (2015). An Excel-based model implementing this calculation is available from those authors.

1.06.8.6 Appendageal Transport

Quantification of the contributions of appendageal pathways remains elusive. Several proposals have been advanced (Kasting et al., 1992; Mitragotri, 2003; Wilschut et al., 1995), yet none has been demonstrated to be reliably predictive. The afore-mentioned models do not suggest size-selectivity beyond that associated with aqueous diffusion, despite considerable evidence to the contrary (Peck et al., 1994; Lai and Roberts, 1999; Baswan et al., 2016). It is notable that a recent review of follicular drug delivery discusses many qualitative observations, but contains not a single equation or quantitative statement of possible use in risk assessment (Patzelt and Lademann, 2013). That review focuses on particle delivery, yet the authors concede that mounting evidence supports that particles greater than 100 nm in diameter do not penetrate the skin. There is, in fact, considerable interest in targeted delivery to

the hair follicle for the purposes of hair growth (Tsai et al., 1994a,b) or dandruff control (Schwartz et al., 2011). But the role of follicular delivery in systemic drug therapy, or the need to include it in systemic risk assessments, is not established. The model proposed by Mitragotri (2003) provides a possible current option for estimation of steady-state absorption of hydrophilic permeants.

1.06.9 Management of Risk of Dermal Exposure to Chemicals

1.06.9.1 Occupational Risk From Dermal Exposure

Human exposures to chemicals in the occupational environment are typically much greater than in the nonoccupational environment, so regulatory approaches initially developed here. Occupational health standards for chemicals are based primarily on inhalation risk in both the US and Europe and most commonly take the form of air concentrations deemed to not present unacceptable risk over some specified time interval (e.g., a time-weighted eight-hour average). If such a standard is derived from human epidemiology, as is occasionally the case, the standard may also (unintentionally) incorporate the contribution of dermal absorption from air or airborne particulates, as exposure via that pathway would likely not have been prevented in the episode(s) from which the human data were obtained. If the presence of the compound in question in the vapor phase (as opposed to the suspended particulate phase) is nonnegligible, the contribution of dermal absorption from vapor can sometimes rival the contribution from direct inhalation (Piotrowski, 1967, 1971; Johanson and Bomar, 1991; Bader et al., 2008; Weschler et al., 2015). If air standards are based on rodent or other surrogate species studies that did not involve whole body exposure, then those air standards cannot be assumed protective with respect to potential uptake of vapor via skin. Air standards are also irrelevant to skin contact with liquids or solids.

1.06.9.1.1 Skin notation

The most common deliberate approach to mitigation of occupational dermal exposures to chemicals is addition of a skin notation to tables of recommended or mandated air-concentration based occupational limits. These notations are qualitative statements of potential hazard via dermal exposure. There is no universal standard for assignment of a skin notation. Depending upon the jurisdiction, roughly 30% of chemicals for which an occupational air standard exists also have a skin notation (Nielsen and Grandjean, 2004).

Skin notations were first issued in Germany in 1958 (Nielsen and Grandjean, 2004). In the US, skin notations were first published by the American Conference of Governmental Industrial Hygienists (ACGIH) and the National Institute of Occupational Safety and Health (NIOSH). Neither is a regulatory agency, so these skin designations do not have the force of law. However, the Occupational Safety and Health Administration (OSHA) does have regulatory authority and has issued skin notations based on the ACGIH and NIOSH recommendations. Employers are legally required by OSHA to prevent material impairment of health, but methods for doing so are not strictly prescribed and may include personal protective equipment (PPE).

NIOSH has recently updated their strategy for assigning skin notations and has devised a hazard-based system that addresses systemic toxicity, direct effects including irritation and corrosivity, and immune-mediated effects (NIOSH, 2009). Skin notation may be assigned for one or more of the criteria and are coded accordingly. Skin notation profiles for over 50 chemicals, including supporting literature reviews, have been posted on the NIOSH website: http://www.cdc.gov/niosh/topics/skin/skin-notation_profiles.html.

1.06.9.1.2 Quantitative estimation of occupational dermal risk

In some sectors, dermal hazards are addressed through formal, although typically simplified, risk assessments in a manner analogous to that used to set air standards. Formal dermal occupational exposure limits, expressed, for instance, as chemical load per unit area of skin, have been proposed (Bos et al., 1998; Brouwer et al., 1998), but generally not adopted due to inherent difficulties associated with sampling given the temporal and spatial heterogeneity in skin load (relative to air sampling). Limitation of dermal exposure is typically approached alternatively by specification of protocols for estimation of exposure that are a prerequisite for product registration (i.e., approval to market). This is most evident in regulation of biocides, where dermal exposures have long been recognized to potentially and substantially exceed inhalation exposures (e.g., Durham and Wolfe, 1962). Exposure estimates generated via these protocols are typically compared to doses assumed to not cause adverse effects using a margin of safety approach. Specification of PPE or reentry interval (delay required to permit agent dissipation prior to admission of laborers to the treated area) may result if acceptable margins cannot be otherwise achieved. Inclusion of these requirements on packaging labels is then mandated for legal sale.

In the US, registration of biocides falls primarily on the USEPA and an extensive record of exposure protocol development and regulatory decisions is available to both potential registrants and the broader public. Data required of potential registrants includes basic chemical properties, specified toxicity tests (including dermal challenges), and exposure data. USEPA disfavors direct toxicity testing in humans, but will accept results of exposure trials conducted in vivo in humans if trial designs conform to federal standards for human studies. Registrant data of varying types may be formally designated confidential business information (CBI) and subject to restricted access. Because biocides are produced primarily by multinational corporations that operate in multiple jurisdictions and those corporations benefit from uniformity of regulation, similar approaches to occupational pesticide regulation have evolved in the US and in Europe. In other sectors, where recognition of dermal hazards has been slower to develop, regulatory strategies are

Table 3 Ratios of loads applied in absorption experiments from which availability estimates were drawn to loads predicted in risk assessments

Compound[a]	*Risk study*	*Scenario*	*Predicted load* ($\mu g/cm^2$)	*Absorb study*	*Experimental load* ($\mu g/cm^2$)	*% abs*	*Ratio Ex/Pr*[b]
PFO	Washburn et al. (2005)	Spot cleaner	2×10^{-3}	Fasano et al. (2005)	30,000	0.048	2×10^{7}
PFO	Washburn et al. (2005)	Medical garments	2×10^{-5}	Fasano et al. (2005)	30,000	0.048	2×10^{9}
DEHP	Wormuth et al. (2006)	PCP[c] use male adult	c. 10^{-2}	Elsisi et al. (1989)	6,500	0.11	$>10^{5}$
BDE	Trudel et al. (2011)	Child	c. 10^{-5}	Roper et al. (2006)	10,000	3.1	$1\cdot10^{9}$
PFOS	Egeghy and Lorber (2011)	Child dust	3×10^{-4}	Fasano et al. (2005)	30,000	0.048	1×10^{8}
PFOA	Lorber (2011)	Child dust	6×10^{-6}	Fasano et al. (2005)	30,000	0.048	5×10^{9}

[a]*PFO*, perfluorooctanoate; *DEHP*, bis(2-ethylhexyl) phthalate; *BDE*, brominated diphenyl ether; *PFOS*, perfluorooctane sulfonate; *PFOA*, perfluorooctanoic acid.
[b]Ratio of experimental skin load used to determine fractional availability to predicted load in exposure scenario (unitless).
[c]PCB, personal care product.

less advanced. While the largest risks are to the occupationally exposed, the biocide registration requirements also include residential user protocols, so some overlap between occupational and nonoccupational regulation exists.

A second arena in which risk-based regulation of dermal hazards has been developed in the US involves cleanup of hazardous waste sites. USEPA's Risk Assessment Guidance for Superfund (RAGS) (USEPA, 2004) provides guidance for estimation of dermal exposure to contaminants in two matrices, water and soil. The water protocol is notable for the fact that permeation is estimated using a physics-based approach (i.e., using a permeability coefficient and a thermodynamic driving force) based on approaches developed by Bunge and coworkers (Cleek and Bunge, 1993; Bunge and Cleek, 1995; Bunge et al., 1995). In contrast, the soil protocol utilizes assumed fixed values of fractional availability that have limitations as discussed above (see "Load Effects"). These protocols are applicable to both occupational (cleanup worker) and nonoccupational (residential) populations.

Recently USEPA (2014a,b) proposed a first-of-its-kind dermal carcinogenic slope factor (DSF) for benzo[a]pyrene (B[a]P). Evaluation of the predictive ability of the proposed DSF is complicated by exposure to solar radiation among worker populations subject to dermal PAH exposure, such as roofers and asphalt pavers. Although USEPA decided in early 2017 not to finalize the proposed DSF, it remains a topic of investigation, and is noteworthy because the endpoint of concern is cancer at the portal of entry. USEPA does not have jurisdiction over many of the occupations in which PAHs are a common hazard. Nevertheless, if a DSF is ultimately adopted, it will impact management of hazards to workers at cleanup sites and influence risk management decisions in other sectors.

1.06.9.2 Nonoccupational Risk From Dermal Exposure

Increasing attention is being given in the first world to the overall flow of materials in industrial societies and to life cycle assessment of consumer goods. The latter requires estimation of aggregate exposure to consumer chemicals. This trend is particularly evident in Europe, where REACH (Registration, Evaluation, Authorization, and restriction of CHemicals) legislation (European Union, 2007) has effectively mandated application of approaches formerly focused on occupational health practice to a much wider range of consumer products. REACH has spawned development of multiple platforms for estimation of aggregate exposures to consumer product chemicals. This activity has focused substantial effort on prediction of chemical contact rates for a variety of scenarios previously ignored or subject to only very crude approximation. However, assumption of fixed fractional dermal absorption is still the standard paradigm (i.e., once chemical contact rates are estimated, the absorbed dose is assumed to be a fixed fraction of the material encountered, regardless of load conditions). This practice presents the traditional flaws described above. **Table 3** displays some recent risk assessments that utilized fractional absorption rates obtained from published experiments conducted at relatively high skin loads and then applied those results directly to exposure scenarios in which predicted loads were much lower. These types of analyses typically lead to dismissal of dermal exposure risk, which may or may not actually be justified. In the US, there is currently no comprehensive consumer product regulation comparable to REACH, but discussion of the need for more rapid and comprehensive screening of consumer chemicals is occurring in the context of modification of the Toxic Substances Control Act (TSCA).

1.06.10 Conclusions

Readily absorbed chemicals, such as solvents, can permeate human skin at rates exceeding 1 mg cm^{-2} h^{-1}. Many pesticides can be absorbed at μg cm^{-2} h^{-1} rates, while very lipophilic compounds such as some flame retardants may only be absorbed at the ng or pg cm^{-2} h^{-1} level. Evaluation of area and duration of skin contact permits screening level assessment of potential exposure. Risk is ultimately dependent upon both exposure and toxicity, and low-level absorption over extended periods and skin area can lead to adverse outcomes. Methods applied to assess dermal absorption of chemicals in the context of regulatory policy in the US and Europe remain relatively unsophisticated.

See also: 9.18. Ocular and Dermal Local Tissue Tolerance Studies.

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