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REVIEW

Absorption of chemicals through compromised skin

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Abstract Skin is an important route of entry for many chemicals in the work place. To assess systemic uptake of a chemical in contact with the skin, quantitative information on dermal absorption rates of chemicals is needed. Absorption rates are mainly obtained from studies performed with intact, healthy skin. At the work place, however, a compromised skin barrier, although not necessarily visible is common, e.g. due to physical and chemical damage. As reviewed in this article, there are several lines of evidence that reduced integrity of the skin barrier may increase dermal absorption of chemicals in the occupational setting. An impaired skin barrier might lead not only to enhanced absorption of a specific chemical, but also to entrance of larger molecules such as proteins and nanoparticles which normally are not able to penetrate intact skin. In addition to environmental influences, there is increasing evidence that some individuals have an intrinsically affected skin barrier which will facilitate entrance of chemicals into and through the skin making these persons more susceptible for local as well for systemic toxicity. This review addresses mechanisms of barrier alteration caused by the most common skin-damaging factors in the occupational settings and the consequences for dermal absorption of chemicals. Furthermore, this review emphasizes the importance of maintained barrier properties of the skin.

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Introduction

The principal barrier of the skin is provided by the uppermost layer of the skin, the stratum corneum (SC). The SC comprises of dead keratinocytes embedded in a lipid bilayer matrix, forming a dense and compact structure often described as "brick and mortar" structure (Elias 1983; Elias 2004; Bouwstra and Ponec 2006). The lipid bilayers, "the mortar", are considered to be the rate-controlling barrier for penetration of chemicals across the skin, although, for very lipophilic molecules, partitioning into the more hydrophilic viable tissue may constitute the greater resistance (Elias 1983; Herkenne et al. 2008). At the same time, lipid bilayers are the primary target site for the adverse effects of common skin-damaging factors such as solvents, excessive hydration, and soaps. Other absorption routes comprise diffusion along hair follicles and sweat glands (so-called shunt route) and the transcellular route across cornified cells and lipid bilayers. The latter two routes are believed to play a minor role in dermal absorption, but for slowly diffusing compounds, e.g. highly hydrophilic and large molecules the shunt pathway can be significant (Schaefer and Lademann 2001; Hadgraft and Lane 2005; Moser et al. 2001). The factors which govern the extent of dermal absorption include physico-chemical properties of the penetrant, exposure conditions and the state of the skin. Generally, small molecules (molecular weight < 150 Da) which have good solubility in both water and fat can penetrate the skin better than large, highly hydrophilic or highly lipophilic compounds (McDougal and Boeniger 2002; ECETOC 1993; USEPA 1992). The most commonly used

solubility parameter is the octanol:water partition coefficient (Kow) or its logarithmic form (log Kow). Maximum absorption is often associated with log Kow values between 1 and 2 and decreases significantly when the log Kow value is >3.5 (ECETOC 1993).

Examples of chemicals used in the work place for which dermal absorption plays a significant role in the overall uptake include glycol ethers, phenols, aromatic amines, dimethylformamide, *N*-methyl-2-pyrrolidone, biocides and pesticides (Semple 2004; Grandjean 1990; Bello et al. 2007; Jakasa et al. 2004; Kezic et al. 2001, 1997; Chang et al. 2005; Bader et al. 2008; Wellner et al. 2008).

Whereas physicochemical-related factors have extensively been studied, less is known of the influence of skin barrier condition on dermal absorption rates.

In this article, studies on dermal absorption through impaired skin barrier will be reviewed including field studies, experimental studies in human volunteers (Table 1) and to a less extent in vitro and animal studies. Furthermore, mechanisms of barrier alteration caused by the most common skin-damaging factors in the work place will be addressed and summarized (Table 2). Although the emphasis will be put on industrial chemicals, studies on other chemicals such as drugs will be included. To allow for comparison between compounds of different physicochemical properties, when available, octanol water partition coefficient (Kow) of a compound will be given. The compromised skin has been considered in this review in a broader sense; any change (both temporal and irreversible) in the skin structure and/or skin composition which may alter barrier function has been taken into consideration.

Field studies

Damage to skin, in particular of the hands, is a common and potentially serious problem in many occupational settings. A high prevalence of damaged skin has been reported in high-risk occupations such as health care, metal machining, food preparation, offset printing, hairdressing and cleaning (Diepgen 2003; Lushniak 2003; Chew and Maibach 2003). In a study from Sweden, approximately one-fourth of nurses met the criteria for currently damaged skin on the hands (Larson et al. 1997). The prevalence of the skin lesions, skin scars or skin diseases among Thai and Chinese rayon workers exposed to CS_2 was up to 90% (Chou et al. 2004). In Germany, the point prevalence of impaired skin was close to 70% in the printing industry and approximately 80% among workers in the rubber industry (Korinth et al. 2003, 2005, 2007). These few examples illustrate the magnitude of the problem in high-risk occupations with skin exposure to solvents, water, and detergents. In addition to chemically induced damage, physical and mechanical irritation can occur. Korinth et al. (2005) found unexpectedly high prevalence of erythema and/or scaliness of the hand in dispatch-department workers exposed to physical irritation by paper dust, the point prevalence being 73%.

The skin barrier has frequently been assessed by measuring transepidermal water loss, TEWL. TEWL is the physiological loss of water vapour from the skin in the absence of sweat gland activity. Disruption of the barrier function will lead to increased TEWL (Pinnagoda et al. 1990). Whether increase in TEWL correlates directly with the absorption of chemicals is presently not clear. Human in vivo data suggest that TEWL may be used as a predictor of dermal absorption of hydrophilic and slightly lipophilic compounds (Nilsson 1997). Whether this is true also for highly lipophilic compounds has been questioned and has to wait for more experimental evidence (Levin and Maibach 2005; Chilcott et al. 2002).

The field studies on the influence of skin damage on dermal absorption of chemicals are scarce, partly caused by the complexity in assessment of skin damage and dermal absorption at the work place (Korinth et al. 2003). Skin damage in such studies have been assessed by measuring TEWL, erythema or by visual examination of the skin, whereas skin absorption has been estimated by biological monitoring. Drexler et al. (1995) found higher systemic absorption of carbon disulphide (CS_2) in workers with skin diseases or skin irritation. This is consistent with the results of Chou et al. (2004) who reported that the rayon workers who had hand dermatitis tended to have higher internal exposure to CS_2 than those who had healthy skin. Higher absorption through diseased skin was also reported for dimethyl formamide in workers in synthetic textile production (Wrbitzky and Angerer 1998), although the number of workers with damaged skin (eczema) in this study was rather low. In the rubber industry, a significantly higher internal exposure to aromatic amines was found in workers with erythema as compared to workers with healthy skin (Korinth et al. 2007). Interestingly, in the latter study skin barrier creams seemed to enhance the percutaneous uptake of aromatic amines (Korinth et al. 2007). Enhanced systemic exposure to 2-(2-butoxyethoxy)ethanol was also observed in offset printing workers with skin lesions on hands compared with that for printers without visible skin lesions (Korinth et al. 2003). Systemic exposure in that study which was assessed by biological monitoring correlated better with erythema and scaliness than with TEWL. Hino et al. (2008) used biological monitoring to investigate internal exposure of workers exposed to toluene and xylene during car spray painting. They showed that dermal absorption through areas with hand eczema was the major accelerating factor for systemic absorption of these two organic solvents.

Table 1 Human in vivo penetration studies in compromised skin

Skin damaging factor	Study design/ parameter of absorption	Penetrant	Enhancement factor	References
Solvents				
Acetone	Human volunteers Permeability	Salicylic acid	2	Benfeldt (1999)
1,1,1-Trichlorethane	Human volunteers Permeability	1,1,1-trichlorethane	4	Kezic et al. (2001)
Surfactants				
Sodium lauryl sulphate (SLS)	Human volunteers Permeability	Salicylic acid	46	Benfeldt (1999)
Sodium lauryl sulphate (SLS)	Human volunteers Permeability	Polyethylen glycols MW 150–590	3	Jakasa et al. (2006a)
Sodium lauryl sulphate (SLS)	Human volunteers Permeability	Metronidazole	3	Ortiz et al. (2008)
Hydration/occlusion				
	Human volunteers Permeability	Methyl nicotinate Hexyl nicotinate	2	Zhai et al. (2002)
	Human volunteers Absorption	Lipophilic stereoids	Up to 9	Bucks et al. (1999)
	Human volunteers Permeability	Butoxyethanol vapour	Up to 2	Jones et al. (2003); Johanson and Boman (1991)
	Human volunteers Permeability	Propoxur	4	Meuling et al. (1997)
Mechanical damage				
Tape stripping	Human volunteers Permeability	Hydrocortisone	4	Feldman and Maibach (1965)
Tape stripping	Human volunteers Permeability	Methylprednisolone aceponate	30	Günther et al. (1988)
Tape stripping	Human volunteers Permeability	Salicylic acid	157	Benfeldt (1999)
Tape stripping	Human volunteers Permeability	Aciclovir and peniciclovir	440–1,300	Morgan et al. (2003)
Intrinsically compromised skin barrier				
Skin irritation/disease	Field study/Internal exposure	Carbon disulphide	1.5	Drexler et al. (1995)
Dermatosis	Field study/internal exposure	*N*,*N*-dimethylformamide	3	Wrbitzky and Angerer (1998)
Skin disease	Field study/internal exposure	Carbon disulphide	4	Chou et al. 2004
Skin lesions	Field study; internal exposure	2-(2-Butoxyethoxy)ethanol	Up to 1.7	Korinth et al. (2003)
Skin erythema	Field study Internal exposure	Aromatic amines	Up to 4	Korinth et al. (2007)
Hand eczema	Field study/internal exposure	Toluene Xylene	Up to 5	Hino et al. (2008)
Atopic constitution	Human volunteers Permeability	Sodium lauryl sulphate (SLS)	Approximately 2	de Jongh et al. (2006b)
Atopic dermatitis	AD patients Diffusivity	Sodium lauryl sulphate (SLS)	Approximately 2	Jakasa et al. (2006a)
Atopic dermatitis	AD Patients Diffusivity	Polyethylen glycols MW 150–590	Approximately 2	Jakasa et al. (2007)

In a recent field study in Latino farm workers, a higher prevalence of green tobacco sickness in relation to self-reported rash, itch and superficial wounds was observed indicating higher dermal uptake of nicotine due to skin abnormalities (Arcury et al. 2008).

Experimental studies

The impact of altered skin barrier condition on dermal absorption has more extensively been studied in experimental settings. In the following section, the enhancing

Table 2 Mechanisms of skin barrier alterations for skin damaging factors

Skin damaging factor	Mechanisms	Examples	References
Solvents	Extraction of SC intercellular lipids Increase in SC lipid fluidity and reduction in diffusional resistance Increase in partitioning into SC Interaction with SC proteins	Acetone, ethanol, aromatic and aliphatic hydrocarbons chlorinated hydrocarbons	Williams and Barry (2004); Rowse and Emmett (2004)
Surfactants	Increase in SC lipid fluidity due to disorganization of the lipid bilayers Reduced cohesion of the SC due to protein interaction Decreased moisture of the SC	Detergents, soaps	Williams and Barry (2004); Trommer and Neubert (2006)
Hydration	Promotes penetrant solubility in the SC Disruption of the SC lipid bilayers leading to reduction in diffusional resistance	Prolonged contact with water, wearing of gloves and protecting clothing	Warner et al. (1999); Warner et al. (2003); Norlén et al. (1997)
Mechanical factors	Reduction of the SC thickness Altered organization of lipid bilayers	SC tape stripping Skin lesions, abrasion, flexing	Rouse et al. (2007); Rosado and Rodrigues (2003a)
Pathological skin conditions	Altered composition, organization and structure of lipid bilayers Reduced hydration of the SC Reduced amount of SC protein filaggrin Reduced cohesion of the SC	Atopic dermatitis, psoriasis, ichthyosis	Pilgram et al. (2001); Proksch et al. (2008)

effect of some skin-damaging factors on dermal absorption will be reviewed. Furthermore, mechanisms responsible for skin barrier perturbation will be addressed.

Organic solvents

Organic solvents are extensively used as degreasers, cleaning agents, solvents for plastics, paints and rubber in many industrial applications. In Britain an estimated 2 million workers have regular contacts with solvents (Semple 2004). Solvents have a profound action on the skin and are responsible for as much as 20% of causes with occupational dermatitis (Kamijima et al. 2007). Skin contact with solvents can lead to local irritant reactions, epidermal necrosis and cytotoxicity associated with oxidative stress (Rowse and Emmett 2004; Costa et al. 2006). The suggested mechanisms by which organic solvents affect skin permeability include extraction and structure alteration of the lipid bilayers. Furthermore, skin contact with some solvents, especially at high concentrations can lead to more drastic effects such as damage of desmosomes and protein-like bridges leading to fissuring of the lipids and splitting of the SC squames (Williams and Barry 2004). This may cause a substantial reduction of the barrier function of the skin. Scheuplein and Ross (1970) graded the defatting potential of solvents based on water permeation as follows: ethanol < acetone < diethyl ether < chloroform < methanol:chloroform mixture. Although skin-damaging effect of solvents is usually associated with contact to liquids, exposure to vapours of volatile organic solvents may equally damage the epidermal barrier (Huss-Marp et al. 2006; Costa et al. 2006).

The influence of solvents on skin permeability has been studied in several in vivo studies. The mechanisms of skin barrier alterations and damaging factors found in human studies have been summarised in Table 2. The effect of an organic solvent on skin permeability depends greatly on the physicochemical properties of a solvent, in particular on its ability to react with the lipid bilayers and protein structures of the stratum corneum (Rowse and Emmett 2004; Trommer and Neubert 2006). One of the most investigated groups of solvents are alcohols, in particular ethanol which has frequently been used as a penetration enhancer by topical application of various drugs. Ethanol extracted appreciable amounts of lipids from the stratum corneum, but did not induce lipid disorder (Bommannan et al. 1991). Furthermore, ethanol did not enhance skin permeation of the moderately lipophilic (e.g. log Kow < 3) estradiol (log Kow 2.7) in vivo in humans (Pershing et al. 1990). However, as shown in humans in vivo, longer chain alkanols (C_6–C_{10}) were not only able to reduce the presence of lipids at the skin surface but also to increase the conformational disorder of the intercellular lipids of the SC. Thus, the uptake of alkanols into the upper SC correlated significantly with the lipid disordering observed (Dias et al. 2008). An enhancing effect of low molecular weight alcohols was also found for methanol, which significantly promoted in vivo absorption of the moderately lipophilic toluene (log Kow 2.7) in mice

(Tsuruta 1996). Increased dermal absorption due to solvents has been reported in human volunteers for salicylic acid (log Kow 2.3) after pre-treatment with acetone (Benfeldt 1999). Defatting of the skin of hairless guinea pigs with chloroform/methanol (2:1) mixture increased in vivo absorption of hydrocortisone (log Kow 1.6) and benzoic acid (log Kow 1.9) 5- and 2.7-fold, respectively (Moon et al. 1990). In addition to the enhancement of the absorption of other chemicals, some solvents, especially at high concentrations, may enhance their own absorption, probably by damaging the skin and hence increasing permeability during dermal exposure (Rowse and Emmett 2004). Thus, prolonged contact with xylene (log Kow 3.2) led to its increased absorption in volunteers (Dutkiewicz and Tyras 1968; Engström et al. 1977). This is consistent with the 26-fold enhancement of in vivo dermal uptake of chloroform (log Kow 2.0) in hairless rats after exposure to neat solvent as compared to a saturated aqueous solution (Islam et al. 1999). Furthermore, faster absorption of 1,1,1-trichloroethane (log Kow 2.5) in volunteers showing skin irritation has been described implying alteration of the skin barrier in these persons during dermal exposure (Kezic et al. 2001).

The influence of solvents on skin barrier has more extensively been studied in vitro. Thus, ethanol and acetone vehicles markedly (6–18 times) increased in vitro dermal absorption of paraben esters (log Kow 2.0–3.6) under occlusion which was associated with increased diffusion due to extraction of lipids from the SC. The enhancing effect of ethanol in that study was twice that of acetone (Cross and Roberts, 2000). Moreover, in vitro dermal absorption of *n*-butanol (log Kow 0.88) was significantly increased in the presence of toluene as well as a chloroform:methanol mixture which are both known to be very effective in extracting lipids from the SC (Boman and Maibach 2000). Pre-treatment of hairless mouse skin with acetone enhanced in vitro penetration of hydrophilic polyethylene glycols (log Kow −1.6) of different molecular weight (MW of 300, 600 and 1,000) and the increase was related to the degree of barrier disruption (Tsai et al. 2001a). The latter study suggest also that not only higher amounts but also more varieties of chemicals (i.e. larger molecules) may penetrate skin with a compromised barrier than normal skin, implying a higher risk of intoxication and sensitization by environmental agents through skin with an impaired barrier function.

In contrast to the frequent observation of an enhancing effect of solvents on the absorption of hydrophilic compounds, the effect of solvents on the absorption of lipophilic chemicals is less clear. Pre-treatment of the skin of hairless mice in vivo with acetone enhanced the in vitro permeability to both hydrophilic and amphiphatic compounds (log Kow −3, 7–1.5) but not of more lipophilic compounds (log Kow 2.7 and 3.9) (Tsai et al. 2001a, b). This is in agreement with in vivo study of Rosado and Rodrigues (2003b), who reported a more pronounced effect of solvent pre-treatment on the absorption of a hydrophilic dye in comparison with a lipophilic dye. Consistent with these findings, pre-treatment of human skin with vaporous acetone, styrene, toluene, xylene, and tetrachloroethylene did not enhance permeability of 1,2,4-trimethylbenzene (log Kow 3.4), although an increased TEWL in the pre-treated skin implied a reduced skin barrier (Costa et al. 2006). In contrast to these studies, the pre-exposure to jet fuel consisting of aliphatic and aromatic hydrocarbons caused a 2- to 4-fold increase in absorption of lipophilic compounds such as ethyl benzene (log Kow 3.1), *o*-xylene (log Kow 3.2), naphthalene (log Kow 3.4) trimethylbenzene (log Kow 3.6), dodecane (log Kow 7.2), and tridecane (log Kow 7.6) (Muhammad et al. 2005). Dermal absorption of the moderately lipophilic hydrocortisone (log Kow 1.6) did, however, not change after pre-treatment with 1,1,1-trichloroethane (Bucks et al. 1983), which is in contrast to the reported 5-fold enhancement of hydrocortisone absorption following pre-treatment with a chloroform:methanol mixture (Moon et al. 1990).

An in vitro study in porcine skin showed that 1,1,1-trichloroethylene pre-treatment almost doubled dermal permeability to triazine, a moderately lipophilic (log Kow 2.2) preservative which is often added to cutting-fluid formulations in the metal-machining industry (Baynes et al. 2005).

Surfactants

Detergents can affect the skin barrier by interacting with epidermal lipid and protein components leading to alteration of the crystalline structure of SC lipid bilayers and reduced cohesion of the SC (Williams and Barry 2004; Trommer and Neubert 2006). Certain anionic surfactants such as sodium lauryl sulphate (SLS) affect not only the epidermal barrier itself but during prolonged exposures also the underlying viable cell layers leading to skin inflammation and possibly further deterioration of the skin barrier (Fartasch 1997; Ting et al. 2004; Gloor et al. 2004; Koopman et al. 2004; de Jongh et al. 2006a, b; de Jongh et al. 2007). Of the detergents, SLS has been the most studied with respect to skin barrier function. SLS is widely used in pharmaceutical vehicles, cosmetics including soaps and cleansers, foaming dentifrices and foods (Walters 1989; Trommer and Neubert 2006). Jakasa et al. (2006a) studied percutaneous penetration of polyethylene glycols (log Kow −1.6) of different molecular weights (MW 200–600) in human volunteers. SLS caused a 3-fold increase in the permeability coefficient for all MWs. A markedly higher 46-fold enhancing effect of SLS was reported by Benfeldt (1999), who investigated percutaneous penetration of salicylic acid (log Kow 2.3) in vivo in human volunteers. In

a recent volunteer study, Ortiz et al. (2008) showed a three-fold increase in the penetration of a topical drug metronidazole (log Kow −0.1) through skin pre-treated with 1% SLS for 24 h. In an in vivo dermal exposure study in hairless guinea pigs, pre-treatment with 2% SLS led to 2- to 4-fold increase in dermal uptake of hydrocortisone (log Kow 1.6) and benzoic acid (log Kow 1.9) (Moon et al. 1990). The effect of SLS on the in vivo percutaneous penetration has been shown to depend on the exposure conditions such as SLS concentration, exposure pattern and the lipophilicity of the penetrant. In an in vivo study in guinea pigs, pre-treatment with SLS caused higher systemic absorption for three moderately lipophilic (log Kow 1.6–3.5) drugs, but not for the most lipophilic one (log Kow 6.0) (Wilhelm et al. 1991). Similar conclusion can be drawn from in vitro studies. SLS did not enhance in vitro absorption of highly lipophilic pentachlorophenol (log Kow 5.1) (Baynes et al. 2002). Nielsen (2005) investigated in vitro percutaneous penetration of a number of pesticides varying in lipophilicity through skin that was pre-treated with 0.1 and 0.3% SLS for 3 h and found that percutaneous penetration of more hydrophilic compounds was affected the most. Penetration of highly lipophilic compounds (log Kow > 3) through the SLS pre-treated skin increased little, whereas for less lipophilic compounds (log Kow of 0.7 and 1.7) the penetration increased twofold. For a more hydrophilic chemical (the pesticide glyphosat; log Kow −1.7) the penetration was increased close to 20-fold following pre-treatment with 0.3% SLS for 3 h (Nielsen et al. 2007). This is in agreement with the study of Borrás-Blasco et al. (1997) who reported that 12-h exposure to 1% SLS increased the in vitro penetration rates of compounds that have values of log Kow < 3 but do not affect penetrants with a log Kow above 3. In addition to enhanced absorption, SLS showed to facilitate penetration of larger molecules. Tsai et al. (2003) investigated the in vitro penetration of polyethylene glycols (PEGs) in hairless mice after SLS pre-treatment. In that study, the penetration of PEGs increased with the degree of barrier disruption as measured by TEWL. Furthermore, the MW at which PEG penetration could not be measured, the cut-off value, was larger for the SLS-damaged skin. Thus, in the control skin, a cut-off value of 414 Da was found, which was increased to 766 Da in the skin compromised by SLS. Higher skin permeability for hydrophilic PEGs due to SLS exposure is in agreement with already cited in vivo study in human volunteers of Jakasa et al. (2006a).

In addition to enhancement of dermal absorption of organic chemicals, SLS increases percutaneous penetration of metals such as nickel, lead and cobalt (Lindberg et al. 1989; Emilson et al. 1993; Frankild et al. 1995; Larese et al. 2006). Furthermore, exposure to detergents facilitated in vitro penetration of metal nano particles through human skin (Baroli et al. 2007).

There are many substances which enhance dermal absorption in a similar manner as detergents. Quaternary ammonium chloride, a common used biocide, increased in vitro absorption of the pesticide propoxur (log Kow 1.5) up to 6-fold (Buist et al. 2005). This effect was probably due to structural changes linked to an amphipathic, soap-like character. Many biocidal substances are classified as corrosives or skin irritants. Since these substances are used on a daily basis, their effect on the barrier function deserves more attention in the risk assessment practice (Buist et al. 2005).

Skin hydration

Adequate hydration is essential for optimal skin functioning, but in excess, increased hydration of the SC can lead to reduced barrier function (Warner et al. 2003; Tsai and Maibach 1999). While short exposures to water (1 h or less), even with repetitive application during a day or over many days, appears to have no effect, prolonged exposure to water leads to disruption of lipid bilayers and reduced cohesiveness of the SC in a way similar to surfactants (Warner et al. 1999, 2003; Norlén et al. 1997; Suhonen et al. 1999). Increased hydration of the skin may occur following prolonged or frequent skin contact with water, but also after skin occlusion when normal water evaporation is prevented, e.g. by wearing of gloves or protective clothing. Health care personnel, cleaners, hairdressers all engage in wet work. These occupations are historically all associated with a high prevalence of contact dermatitis, which has often been associated with enhanced penetration of skin irritants through hydrated skin.

The water content of SC is typically 15–20% of the tissue dry weight, dependent on the air humidity (Williams and Barry 2004). After just 4 h of water exposure the SC is dramatically expanded to three times its normal thickness primarily caused by absorption of water by the corneocytes (Warner et al. 2003). The mechanisms by which water alters skin permeability are not fully understood. Clearly, higher content of water in the SC will improve partitioning of hydrophilic compounds and hence increase dermal absorption. Elias et al. (2002) consider the presence of an aqueous pore pathway in the hydrated skin which might enhance permeation of water soluble chemicals. Furthermore, it has been shown in vivo in human skin that hydration induces large pools of water in the intercellular space and cause a disruption of SC lipid organization which might, at least partly, explain enhanced absorption of lipophilic chemicals (Warner et al. 2003).

Increased hydration of the skin causing enhanced dermal absorption of chemicals of different physico-chemical properties has been demonstrated in several human in vivo studies. Thus, increased permeation of hydrophilic methyl nicotinate (log Kow 0.7) as well as of lipophilic hexyl

nicotinate (log Kow 3.1) was demonstrated through hydrated human skin even after 10 min of exposure to water (Zhai et al. 2002). Bucks et al. (1999) showed that occlusion enhanced the penetration of the more lipophilic steroids progesterone (log Kow 3.9), testosterone (log Kow 3.3) and estradiol (log Kow 2.5) but did not change the penetration of the more hydrophilic hydrocortisone (log Kow 1.6). Increased in vitro diffusivity due to occlusion has also been reported for paraben esters (log Kow 2.0–3.6) (Cross and Roberts 2000). The magnitude of enhancement in that study was dependent on the solvent vehicle in which paraben esters were applied. Hikima and Maibach (2006) studied the effect of hydration on in vitro skin flux of 12 model chemicals having a different molecular weight (MW 270–392) and log Kow (1.5–4.1). The skin fluxes increased up to 3.6-fold in hydrated skin, but there was no clear relationship between enhancement ratio and MW and log Kow. Occlusion does, however, not necessarily increase the penetration of all chemicals. Thus, Bucks and Maibach (1999) who investigated the effect of occlusion on the in vivo absorption of nine phenols (Kow 0.04–3.51) reported the least enhancement in absorption for the two phenols with the lowest Kow (Kow 0.04 and 0.32, respectively). Also increased environmental humidity can lead to increased hydration of the skin. Dermal absorption of vaporous 2-butoxyethanol (log Kow 0.83) in human volunteers was enhanced significantly when air humidity increased (Jones et al. 2003; Johanson and Boman 1991). Meuling et al. (1997) investigated dermal absorption of the pesticide propoxur (log Kow 1.5) at different levels of relative humidity varying between 50, 70 and 90%. The percentage body burden attributable to dermal absorption increased from 13% (at 50% relative humidity) to 63% (at 90% RH), indicating that skin moisture is important in dermal absorption of propoxur.

Mechanical damage

Mechanical damage caused by scrubbing, skin friction or abrasion will result in partial or complete removal of the SC which is the principal barrier of the skin. The impact of mechanical damage is usually studied by removal of the SC using adhesive tape, the so-called tape stripping. The reported effect of skin stripping is merely dependent on the extent of SC removal. Furthermore, available data suggest that skin stripping has more impact on the penetration of hydrophilic compounds as compared to highly lipophilic compounds (Schäfer-Korting et al. 2007).

Using cutaneous microdialysis, Morgan et al. (2003) investigated the effect of the barrier damage induced by tape stripping of the SC on the penetration of water-soluble drugs in human volunteers. They found a strong correlation between the degree of damage as assessed by TEWL and penetration of hydrophilic penciclovir (log Kow −2.1) and acyclovir (log Kow −1.8). Complete removal of the SC increased dermal absorption of these two compounds 400- to 1,300-fold compared to intact skin. In a volunteer study using microdialysis, the absorption of salicylic acid (log Kow 2.3) was highly enhanced (150 times) in a tape-stripped skin (Benfeldt 1999). Feldman and Maibach (1965) showed a 4-fold increase in dermal absorption of hydrocortisone (log Kow 1.6) following skin stripping. Likewise, Günther et al. (1988) found almost 100-fold increased systemic uptake of methylprednisolone aceponate (log Kow 4.0) after removal of SC by tape stripping.

Damaging the skin of hairless guinea pigs with cellophane tape leads to 3- and 2-fold increases in the dermal uptake of hydrocortisone (log Kow 1.6) and benzoic acid (log Kow 1.9), respectively (Moon et al. 1990).

Similar effect of SC removal on percutaneous penetration has also been reported from in vitro studies. Thus, skin abrasion by a rotating brush had the greatest penetration enhancement (2- to 100-fold) in vitro for hydrophilic caffeine (log Kow −0.07) and acyclovir (log Kow −1.6) in comparison with more lipophilic methyl paraben (log Kow 1.9) and butyl paraben (log Kow 3.6) (Akomeah et al. 2007). Likewise, Hayes et al. (2000) showed a 23-fold higher penetration of latex proteins through abraded skin in vitro. Using a tritiated water permeation assay to evaluate epidermal barrier integrity, the amount of latex protein penetration was found to positively correlate with degree of dermabrasion. That the entrance of macromolecules is facilitated in mechanically damaged skin was shown also for hydrophilic dextranes (4–10 Da), for which penetration in hairless mice skin was increased 300-fold in tape-stripped skin when compared to uncompromised skin (Ogiso et al. 1994).

Recently, mechanical stimulation occuring during repetitive flexing has been demonstrated to potentially alter the structural organization of skin and lead to increased penetration of nanoparticles by compromising the permeability barrier of the epidermis (Tinkle et al. 2003). This is in agreement with a study of Rouse et al. (2007) who reported that a repetitive flexing motion increases the rate at which nano particles can penetrate intact skin. This might explain the high prevalence of podoconiosis in the African rift valleys due to exposure of unprotected feet to soils with high concentrations of nano-size particles zirconium and beryllium (Rouse et al. 2007). This supports the view that damaged skin not only increases the absorption rate but also allows penetration of larger compounds which normally would not be able to penetrate across intact skin.

Intrinsically compromised skin barrier

There are several pathological conditions characterized by an inherent skin barrier defect. Patients suffering from atopic dermatitis (AD) have reduced ceramide content,

whereas in the SC of lamellar ichthyosis the amount of free fatty acids is decreased and the ceramide profile is altered (Di Nardo et al. 1998; Imokawa 2001; Leung et al. 2003). The altered composition of the SC lipids results in aberrant lipid organization in the SC of patients with atopic dermatitis and lamellar ichthyosis (Pilgram et al. 2001). In addition to the defects in the lipid bilayers of the SC, it has recently been reported that about 10% of people of European ethnicity are carriers of loss-of-function mutations in the filaggrin gene (Irvine and McLean 2006; Palmer et al. 2006). Filaggrin is a key protein of the SC that facilitates terminal differentiation of the epidermis and formation of the skin barrier. Haploinsufficiency for filaggrin in mutation carriers, or complete loss in homozygotes or compound heterozygotes, leads to impaired barrier formation, which manifests as varying degrees of dry skin, ichthyosis, and/or AD (Kezic et al. 2008; O'Regan and Irvine 2008). Furthermore, as a precursor of amino acids and derivatives that act as "natural moisturizing factor" (NMF) filaggrin is largely responsible for the ability of SC to keep the skin hydrated (Rawlings and Harding 2004). Recently it has been shown that carriers of filaggrin null mutations have reduced content of NMF in their SC and increased epidermal water loss, which together might at least partly explain dry skin conditions in atopics (Kezic et al. 2008). The significant increase in the occurrence of AD over the past decades with up to 20% incidence in the current infant population (Cork et al. 2006; Vasilopoulos et al. 2004) is therefore a major point of concern. As a consequence of alterations in barrier function, it has been suggested that larger compounds such as allergens may cross the skin leading to systemic atopic response (O'Regan and Irvine 2008). This is supported by a recent study demonstrating an association between the prevalence of sensitization to aeroallergens and the skin barrier function assessed by TEWL (Boralevi et al. 2008). A history of AD is an important risk factor for development of occupational contact dermatitis (Coenraads and Diepgen 1998; Diepgen 2003; Dickel et al. 2003; Meding et al. 2005). Only recently, de Jongh et al. (2008) reported increased risk for irritant contact dermatitis in the carriers of filaggrin gene mutations.

The alteration of the skin barrier in AD patients is shown by increased TEWL not only in the inflammatory zone but also in the skin with a clinically normal appearance (Seidenari and Giusti 1995; Gupta et al. 2008; Kim et al. 2006). Jakasa et al. (2006b, 2007) showed higher diffusion of SLS and polyethylene glycol of different molecular size through clinically not affected skin of AD patients. Higher permeability for SLS was shown also in the individuals with atopic diathesis without manifestation of atopic dermatitis (Jongh de et al. 2006a). Aalto-Korte and Turpeinen (1993) found a highly significant correlation between degree of skin damage assessed by TEWL and percutaneous absorption of hydrocortisone (log Kow 1.6) in atopic dermatitis patients. Indirect proof for impaired skin of AD patients comes also from the clinical observation of patients presenting contact urticaria to proteins and patients suffering from AD with positive tests to allergenic proteins (Berard et al. 2003; Wakelin 2001). In addition to AD, Lavrijsen et al. (1993) reported that the penetration of hexyl nicotinate (log Kow 3.1) on the volar forearm was accelerated in patients with various keratinization disorders including autosomal dominant ichthyosis vulgaris, X-linked recessive ichthyosis and autosomal recessive congenital ichthyosis. Reduced epidermal barrier, assessed by TEWL has also been found in psoriatic skin. Psoriasis is a very common skin disease that affects 2–3% of the western population (Lowes et al. 2003). In active psoriasis TEWL was increased up to 20 times, and high TEWL values have also been found in 'uninvolved' skin of psoriatic patients (Motta et al. 1994; Goon et al. 2004).

Conclusion

The available literature convincingly demonstrates that damaged skin in workers in high-risk occupations is common. In addition to skin damage caused by exposure to environmental factors, some individuals have an intrinsically compromised skin barrier. The most striking example is atopic diathesis which is a known risk factor for occupational contact dermatitis. Once barrier function is compromised, the skin becomes more permeable for chemicals leading to a higher risk for systemic toxicity. Furthermore, a less effective barrier will facilitate absorption of irritating chemicals and allergens leading to further deterioration of the barrier.

The magnitude of enhancing effect will depend on the type of damage and physicochemical properties of a penetrating chemical. Most chemicals exert their skin-damaging effect by altering the composition and the structure of the lipid bilayers in the stratum corneum, thus acting upon both the chemical's partitioning and diffusion through the skin. Since hydrophilic viable epidermis acts as an additional barrier for lipophilic compounds, the overall enhancing effect due to altered lipid bilayers of the stratum corneum will be lower for highly lipophilic compounds.

A compromised skin barrier will not only increase the absorption, but will also allow for penetration of larger compounds which normally would not be able to penetrate intact skin. Examples are proteins and nano particles.

This review emphasizes the need for maintaining an intact skin barrier. Generally, education and training to raise awareness of dermal penetration and the importance of an uncompromised skin barrier will be important preventive tasks. Further, the misconception that certain occupations

carry skin lesions as integral parts of the job need to be addressed by regulators as well as occupational hygienists. For the more susceptible parts of the population, specific information may be needed, and screening to enable protection could be considered (Dickel et al. 2004; Flyvholm and Lindberg 2006; John et al. 2006; Kütting and Drexler 2008; de Jongh et al. 2008). On the regulatory level, agencies issuing guidelines and performing risk assessments should consider that penetration through compromised skin may be significantly higher than through healthy skin. Thus, hazard indicators on chemicals and products related to local effects (corrosion, irritancy, or allergy) as well as systemic effects such as skin notations may need revisions (Sartorelli et al. 2007).

To conclude, enhanced dermal absorption through compromised skin should be considered in risk assessment as well as risk management related to dermal exposures.

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