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OCCUPATIONAL DERMATOTOXICOLOGY: SIGNIFICANCE OF SKIN EXPOSURE IN THE WORKPLACE

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INTRODUCTION

In Volume 1, Chapter 6, occupational exposure to toxic chemicals was shown to occur by three possible routes. These include inhalation, cutaneous contact, and ingestion, and each may be significant in the workplace. This chapter will focus on the cutaneous route, with reference to ingestion only when hand to mouth transfer may occur.

Chemicals that contact the skin can interact with it in two ways. First, and most obvious, is when the skin itself is affected and there are pathological changes. The most likely effects include allergic and irritant contact dermatitis. Another way skin contact can affect the worker, but is often much more obscure, is when potentially toxic chemicals are absorbed through the skin, adding to the systemic body burden and toxicity in internal organs.

The preponderance of occupational hygiene measurements have historically been conducted to evaluate inhalation exposures. There are relatively few published studies characterizing skin exposure, and in practice it is rare for occupational hygienists to actually measure skin exposures. This should not be inferred to mean that occupational skin exposures are of little importance as a potential hazard. To the contrary, it has been estimated that 42 percent of the

U.S. workforce is at risk of dermal exposure to hazardous chemicals (NIOSH, 1993). Rather, the lack of attention most likely stems from the sometimes crude and non-validated measurement techniques, a lack of guidance criteria, and lack of government compliance emphasis on skin exposures relative to inhalable exposures. What may have become commonplace is a dangerous philosophy that, if one doesn't look for problems, they won't be found and one will not have to try to figure out how to deal with these exposures as potential problems. The result of this course of inaction is that both employees and employers may suffer the consequences of this ignorance. Fortunately, there seems to be a growing number of professionals in a wide cross-section from government, industry, and labor that believe that more attention to documenting and reducing skin exposures is necessary if we truly intend to protect workers. It is the purpose of this chapter to convince the reader that skin exposures that potentially result in illness are important. Chapter 9 in this volume further demonstrates how dermal exposures are identified and evaluated.

In past years, a subtle process of substituting more volatile chemicals with less volatile ones may have inadvertently shifted what were primarily hazards from inhalation of chemicals, to hazards that primarily contact the skin (see Volume 1, page 295). Rather than having a volatile compound that can easily leave the process or be captured by local ventilation, new non-volatile substitutes persist and may accumulate on surfaces throughout the facility. The choice of low volatility chemicals, combined with a general trend towards lowering occupational air exposure limits, has tended to increase the hazard towards dermal contact. This has created, in some cases, exposure situations that many occupational health and safety staff are not adept at controlling. A case in point has been the substitution of toluene diisocyanate (TDI) with a vapor pressure of 0.05 mm Hg, with methylene diphenyldiisocyanate with a vapor pressure of 5×10^{-6} mm Hg. This substitution apparently has *not* led to a reduction of occupational asthma in recent years, possibly because the dermal route is quite efficient in causing systemic sensitization to chemicals (Kimber, 1996). The number of disability benefit cases due to asthma in the U.K., for instance, has increased since widespread substitution around 1990 of TDI for MDI, with isocyanates being by far the leading chemical class attributed to this disease (Health and Safety Commission, 1997). In Japan, workers exposed to MDI – the low air hazard isocyanate – were found to be far more likely to develop asthma than comparable TDI-exposed workers (Jang et al., 2000).

Actually, about 80% of chemicals for which occupational exposure limit criteria exist are relatively non-volatile (≤5 mm Hg). These compounds might become inhalation hazards if they are heated, sprayed, or aerosolized, but otherwise remain in place for extended periods of time. Over time, low volatility compounds that have become temporarily airborne through heating or physical dispersal can be distributed throughout the workplace. Such compounds may also affect the skin if the aerosolized chemicals impinge upon bare skin. The other principal way low volatility compounds contaminate the skin is when they are physically transferred, which can occur when contacting contaminated surfaces. In one analysis of this issue where a subsample of 176 TLV® compounds were selected, 60% of these were considered non-volatile, of which two-thirds of those compounds could be appreciably absorbed through the skin. For the

volatile compounds, half of those could appreciably be absorbed through the skin (Fiserova-Bergerova, 1990). From an occupational risk perspective, the hygienist may appreciably underestimate the total risk for chemical exposures if only the inhalation route is considered and only air samples are taken. Collecting air sampling results alone could give a false sense of safety if additional non-inhalation routes of exposure exist but are not measured.

Volatilized compounds are less likely to affect the skin in a vapor state because, generally, the mass concentration in contact with the skin is so low. The exception to this is if workers were to enter a highly contaminated environment with respiratory protection but without skin protection (Susten et al., 1990; McDougal et al., 1990; Jacobs and Phanprasit, 1993). A few organic vapors, such as 2-butoxyethanol, can be appreciably absorbed through the skin even at air concentrations that are equivalent to the occupational exposure limit (Johanson and Boman, 1991; Corely et al., 1997). When high solvent vapors are present and only normal work clothes are worn, protection of the skin is insignificant. Therefore, whole body exposure should be assumed in the risk estimation (Piotrowski, 1971).

SKIN AS A TARGET ORGAN

Types of Skin Disease

Occupational skin disease includes any abnormality of the skin induced or aggravated by the work environment. The term dermatitis relates only to skin conditions with an inflammatory component to their pathogenesis, while dermatosis relates to skin disease from any cause and with any pathologic outcome (Tucker and Key, 1992).

Causes of occupational dermatoses include (1) mechanical, caused by friction, pressure, and mechanical disruption, (2) chemical, (3) physical, caused by extremes in temperature and radiation (principally ultraviolet) , and (4) biological, caused by microbiological and parasitic organisms (Tucker and Key, 1992; Harvey and Hogan, 1995). One estimate is that about 75% of occupationally related skin disease seen in the infirmaries of industrial plants was attributed to mechanical trauma. It was noted that while this type of injury is usually relatively minor, it can predispose the skin to more serious dermatoses due to the skin's compromised mechanical barrier (Tucker and Key, 1992).

About 90-95% of all work-related dermatoses, not including those caused by mechanical trauma, are referred to as occupational contact dermatitis (OCD) or eczema (Lushniak, 1995). Occupational contact dermatitis is typically characterized by inflammation and erythema (reddening), itching, or the formation of scales as a result of contact with external chemicals or substances. The occurrence of pustules (small pus-containing superficial lesions) is rare and occurs only with secondary infection. Contact dermatitis can be further divided into two aetiological classes: allergic and irritant.

Allergic contact dermatitis is a delayed-type immunological reaction in response to contact with an allergen in sensitized individuals. This reaction is also referred to as Type 4, or cell-mediated, since there is a procession of cellular events within the body leading up to the inflam-

matory response. Allergenic chemicals penetrate the intact skin as small molecules (usually <400 MW), and they are incompletely allergenic (haptens) until they bind to protein and form a complete allergen (Marzulli and Maibach, 1996). Langerhans cells are specialized cutaneous immune effector cells that direct the allergen to a regional lymph node where interaction with T lymphocytes is followed by replication of sensitized T lymphocytes to complete the induction phase. Sensitization can occur after a single exposure, but requires a lag period of a few days to a couple of weeks for induction to be complete. Once sensitized, it normally takes from 12 to 96 hours for a reaction to occur, but more usually 48 to 72 hours after exposure (Magnusson and Kligman, 1970). Table 3-1 lists some common chemicals known to cause allergic contact dermatitis in industry. Allergic contact dermatitis accounts for about 30 to 50% of the cases of contact dermatitis in the workplace (Holness, 1994).

Induction of allergic contact dermatitis is known to depend on the concentration of the allergen on the skin surface. If a sensitizing dose of the allergen is spread over a larger surface area, the likelihood of sensitization declines appreciably. It is believed that sensitization is dependent on the number of allergen molecules per Langerhans cell, a small number of cells bearing many molecules being more effective than having many cells bearing a few molecules (Upadhye and Maibach, 1992). Table 3-2 shows the effect of varying the concentration of dinitrochlorobenzene, a very potent sensitizer, and surface area, upon sensitization. There appears to be a threshold surface concentration for induction of all sensitizers, and the range of induction concentrations is quite large. Some caution is warranted in strictly interpreting experimental laboratory data, since factors in the workplace which might increase percutaneous absorption of chemicals could theoretically reduce the surface concentration that is necessary to cause sensitization. For instance, repeating small exposures over a period of time seems more effective in inducing sensitization than a single large dose. Genetic disposition plays a prominent role in determining individual susceptibility (Magnusson and Kligman, 1983). Although there appears to be a fairly linear dose-response to sensitizing compounds, once sensitized, there is wide variability in the provocation threshold. The concentration necessary for a response can span at least a 100-fold range (Basketter et al., 1997).

It has been reported that 90% of all occupational allergic contact dermatitis was found on the back of the hands and the forearms (Meneghini and Angelini, 1984). However, contact dermatitis among housewives occurred in almost 50% of cases on the palms, whereas 15% of the time it affected the back of the hands and fingers (Cronin, 1985). In another study of dental laboratory technicians, the fingertips were primarily involved in allergic contact dermatitis (93%), whereas in irritant contact dermatitis, the dorsum of the fingers were affected (80%) (Rustemeyer and Frosch, 1996). Figure 3-1 depicts the locations on the body for occupational diagnosed contact dermatitis based on 879 recent Oregon workmen's compensation cases for the period 1988-1992 (NIOSH, 1997).

Contact urticaria (Type I) is an immediate immunological response in the skin resulting from circulating chemical-specific antibodies coming into contact, most commonly, with exogenous proteinaceous molecules (e.g., animal dander, latex proteins, foodstuffs, industrial enzymes). Its appearance is usually pruritic (i.e., wheal and flare response) and the reaction rarely

Table 3-1
Some chemicals causing allergic dermatitis among workers

Chemical	Occurrence
acrylates	paint plasticizer, plastics
bacampicillin	pharmaceutical
benzocaine	pharmaceutical
chloracetamide	water-base preservative in paints, glues, cosmetics
colophony	electronic solder flux, adhesives
cobalt metal, fume and dust	metal smelting
diglycidyl ether of bisphenol A	epoxy, product fabrication with resin
ethylenediamine	solvent and chemical intermediate
formalin	textiles, embalming
hydrazine	soft solder flux, chemical intermediate, metal cleaning
d-limonene	cleansers, degreasers
mercaptobenzothiazole	rubber, PPC, antimicrobial agent
methacrylate compounds	dental laboratory denture technicians
methylene diisocyanate	rigid polyurethane
neomycin sulfate	pharmaceutical antibacterial
nickel	stainless steel, metal products
p-phenylenediamine	oxidative hair dyes, cosmetology
parabens mixture	preservative in skin medication, cosmetics, cleansers
phenyl glycidyl ether	epoxy resin
picric acid	battery manufacture, colored glass, explosives
poison ivy	outdoor work
potassium dichromate	histology, leather, matches, spackle cpd., photography
substilisins	detergent manufacture
thirams	rubber manufacture, PPC, food disinfectant, lub oils
toluene 2,4-diisocyanate	polyurethane foam manufacture

Table 3-2
DNCB skin sensitizing dose-response with changing concentration on human subjects

Concentration (ug/cm^2)	Application Area (cm^2)	Total DNCB Applied (ug)	Percent Sensitized
8	7.1	62.5	8
16.4	3.5	58.0	54
16.4	7.1	116	50
16.4	14.2	232	73
17.7	7.1	125	62
35.4	1.8	62.5	85
35.4	7.1	250	83
71.0	7.1	500	100

Adapted from Upadhye and Maibach (1992).

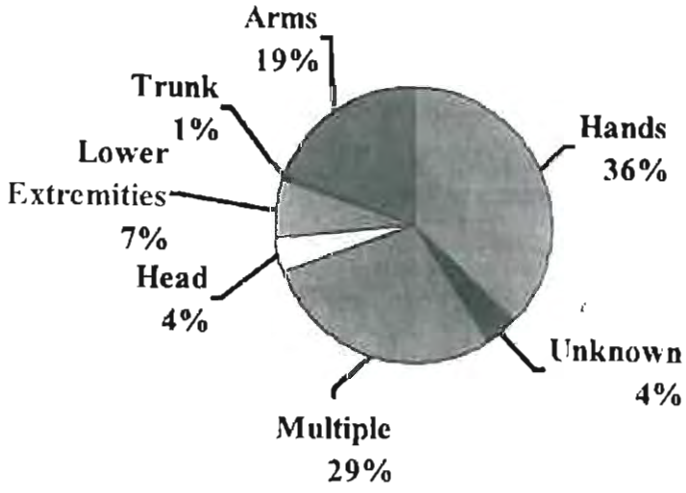

Figure 3-1. Body sites affected by contact dermatitis, as reported on 879 Oregon workmen's compensation cases for the period 1988-1992 (NIOSH SENSOR Dermatitis Program, 1997).

lasts longer than 24 hours. A wheal, or hive, is a firm rounded or flat-topped elevated lesion that results from edema (swelling) of the dermis. Wheals are often pink in color.

In addition to the skin, the respiratory and gastrointestinal tracts, as well as the cardiovascular system, may respond after cutaneous exposure to allergens. Much less frequently, contact urticaria can result from exposure to low molecular weight chemicals forming chemical-protein conjugates (e.g., 2-ethylhexyl acrylate) in the epidermis. Response is mediated by allergen-provoked release of histamine from cutaneous mast cells. In Finland, a recent survey of OCD cases from 1990-1994 found that almost 30% of all occupational immunologically mediated dermatoses were due to contact urticaria, while the remainder were allergic contact dermatitis (Kanerva et al., 1996).

Contact dermatitis from irritants constitutes about 50 to 80% of all OCD cases (Holness, 1994). There are several forms of response common to irritant exposures that are dependent on the chemical substance, the concentration, and the individual exposed. The first type is caused by a single application of a strong compound that results in a toxic, acute reaction. The second type results from repeated exposure that results in erythema, chapping, and fissures in the skin. The third type also results from repeated exposures, but develops into a chronic dermatitis that is characterized by erythema and scaling, with frequent fissuring of the stratum corneum (Weltfriend et al., 1996). A compensatory process of tolerance for irritants (sometimes called "hardening") can occur resulting in lichenified (thickened) skin. A subcategory of irritant dermatitis manifests only after a lag time of 8 to 24 hours or longer, and is thus referred to as being a delayed type (Weltfriend et al., 1996). Some industrial chemicals known to cause delayed effects include epichlorohydrin, ethylene oxide, hydrofluoric acid, some acrylates like hexanediol and butanediol diacrylate, and propane sulfone. In agriculture, the pesticide triphenyl tin hydroxide can cause delayed skin effects. Compounds that cause a delayed irritant reaction characteristically penetrate the stratum corneum slowly, and are cytotoxic to the viable epidermis.

Usually acute irritant response is rapid and begins to subside in 24 to 72 hours (Bjornberg, 1987). However, in experimental studies with sodium lauryl sulfate (SLS), complete functional skin recovery after a single 24 hour exposure had not completely occurred 12 days following exposure (Patil, 1994). The prognosis for complete resolution of both the first and second type of acute irritation is good if exposure is quickly discontinued. The prognosis for chronic irritation of the skin is variable.

Substantial individual range of susceptibility has been found to exist between individuals when exposed in the same way to a model irritant, such as the detergent SLS. The range of threshold concentrations necessary to induce an irritant response to SLS is indicated by the data in Figure 3-2, which cover a range of about 100-fold in concentration. In this study, 110 individuals representing all skin types, ranging from very fair skin (burns easily, never tans) to deep normal pigmentation, were challenged with a 4-hour occluded patch test. There seemed to be little relationship between skin pigmentation type, ability to sunburn, or gender as predictors of skin sensitivity to irritants (McFadden et al., 1998).

The probability of a given concentration to induce irritation is also dependent on the season. This is because of seasonal differences in ambient humidity, and hence skin hydration. In

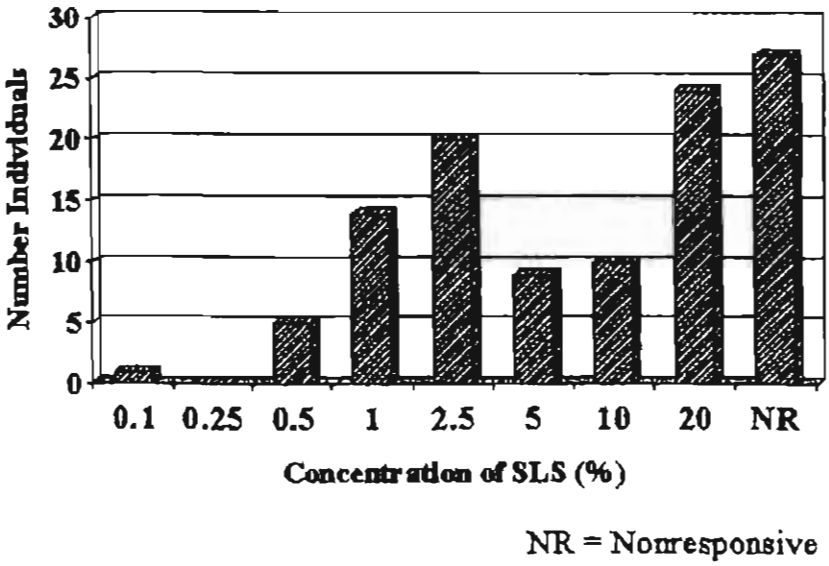

Figure 3-2. Variation in the threshold concentrations necessary for response in "normal" human skin using the irritant sodium lauryl sulfate. Adapted from McFadden et al., 1998.

one test group, 45% reacted to 20% SLS in summer, whereas 91% reacted to this concentration in the winter (Basketter et al., 1996). For other compounds, like alkalies and powders, irritant response seems more likely in the summer (Bjornberg, 1987).

In addition to the primary allergic and irritant types of dermatitis, there are several non-eczematous occupational skin diseases, including fungal and bacterial infections, furuncles (boils), acne, folliculitis, changes in pigmentation, nail diseases, and skin cancer. For information on the potential of various chemical, plant, and biological agents known to cause occupational skin disease, several reference texts are recommended (Adams, 1990; Marks and Vincent, 1992; Lovell, 1993; Hogan, 1994a; Rietchel and Fowler, 1995).

DIAGNOSIS OF OCCUPATIONAL CONTACT DERMATITIS

To the naked eye, irritant and allergic contact dermatitis are virtually indistinguishable. In acute stages the clinical signs of contact dermatitis include erythema, papules, vesicles, and exudation. The affected person may experience itching or a burning sensation. In chronic cases, as a result of hyper-proliferation in the epidermis from chemical injury, fissuring, scaling and lichenification (thickening) develop (Leung et al., 1997).

Patch testing and a thorough history are currently the best tools for distinguishing irritant from allergic causes. Difficulties can arise when the patient does not remember or does not know the composition of a complex product. Compounds that form in-situ after the primary

ingredients are mixed, and are often not identified by material safety data sheets. The MSDS identification of a compound when the concentration is less than 1 percent (10,000 ppm) is not required in the U.S. or Europe. However, there are many sensitizers that will illicit a response at or below this concentration (deGroot, 1994).

The diagnosis of occupational allergic contact dermatitis could be made if there was a history of previous work exposure, and if there was a positive skin patch test result to that compound. Conversely, a diagnosis of irritant contact dermatitis is made in the absence of a patch test response when the test concentration is regarded to be non-irritating at the concentration applied. Complications arise when the chemical being tested is applied at a concentration that is irritating to some individuals. This is most likely to occur when the chemical is a weak or moderate sensitizer and higher concentrations are needed in order to avoid false negative results (Rietschel and Fowler, 1995). An ideal patch test concentration for allergen response will be low enough not to cause irritation, but concentrated enough to illicit a response in truly sensitized persons.

It is very difficult to distinguish between an allergic and irritant response on a skin patch test, although the allergic response typically tends to itch more, and has the general appearance of having raised, palpable, vesicular surfaces with borders that spread beyond the patch test site; the spread is not typically observed with irritation (Rycroft, 1996). Irritant responses have glazed-looking surfaces with sharp borders determined by the patch dimensions. It is important to apply the test concentrations to normal skin, and typically the human back fits this requirement. A reaction to an irritant patch test tends to develop quickly and disappear quickly (within 7 days); whereas allergic patch test reactions often develop after 48 hours and become more intense with time (Tucker and Key, 1992). A practical overview of patch testing and the technical and ethical problems associated with it is covered by Storrs (1996).

Recent research suggests that cytokine profiles might be used to distinguish between irritant and allergic contact dermatitis, but the utility of this approach has not yet been proven. This idea represents a potentially important area for future research (Enk and Katz, 1992; Paludan and Thestrup-Pederson, 1992).

Sometimes both irritants and allergens are involved in the dermatoses, since the damage achieved by irritants to the skin can facilitate the passage of sensitizing compounds through the skin (Angelini et al., 1996). Although irritant contact dermatitis is usually far more prevalent in the workplace, persons with allergic contact dermatitis are more likely to seek medical treatment because the symptoms are generally more severe and more persistent (Meding, 1989; Lantinga, 1984).

Skin testing can also be used to diagnose contact urticaria. The test compound may be applied directly, without covering, usually to dermatitic skin, and the response can be read in 40 to 45 minutes. A comprehensive list of industrial chemicals that have been identified to cause allergic contact urticaria are available in Rietschel and Fowler (1995).

Skin patch testing should only be performed by a qualified dermatologist. The patch test protocol typically consists of applying a number of compounds, at a concentration that is gener-

ally non-irritating, under occlusion, for a period of 48 to 96 hours. After that period, the test patch is removed and visually graded for signs of erythema and vesicles (Rietschel and Fowler, 1995). The test site is read at 48 hours and again at 96 hours after initial application. Usually, the response in allergic contact dermatitis becomes evident 24 to 48 hours after exposure. Distinguishing between allergic and irritant dermatitis, and contact urticaria is important. The diagnosis will influence the degree of exposure avoidance necessary (prevention), the treatment, and long-term prognosis.

PREVALENCE AND INCIDENCE OF WORKPLACE DERMATOSES

In epidemiologic reports of disease cases, the terms prevalence and incidence are often used. These are both expressed as rates. Prevalence is the number of existing cases during a defined time period per number of persons. Incidence indicates the number of new cases per defined time period and number of persons. Because prevalence includes all existing cases, including ones that may have first become apparent years earlier and continue to persist, this number is usually appreciably higher than the incidence rate.

Statistics on the incidence of occupational skin disease in the U.S. are derived from annual surveys conducted by the Bureau of Labor Statistics (BLS). The statistics indicate a general decline from the early 1970s until 1990. However, it has been suggested that this may not be a true decline, but reflects reporting changes where skin disease is treated as first-aid rather than as a lost-time incident (Cooley and Nethercott, 1994). After 1990, the rate of new cases increased slightly, and more recently appears to remain stable (see Figure 3-3).

Dermatoses caused or aggravated by work have been estimated to be under-reported by between 10 and 50-fold (Discher et al.,1975; Mathias, 1985). In the early days of required OSHA reporting of occupational illness, there was evidence of significant under-reporting of dermatitis.

The Discher study, commissioned by NIOSH and completed in 1975, indicated that only 1 out of 13 identified dermatitic conditions due to work were entered into the OSHA-200 log (Discher et al.,1975). Employers were most likely to record when compensation claims had been filed or acute conditions occurred, and claims where a date of onset was known. Among 600 manufacturing industry workers that were examined, occupational dermatitis had affected 8.3%, which increased to 13.3% in those workplaces where only marginal or inadequate controls were in place.

Even with recognized under-reporting, occupational dermatitis has been a major cause of illness and lost work days ever since records first began being collected. Some estimates of the true prevalence of occupational skin disease cases put the figure in the U.S. between 0.5 to 2.9 million cases per year (Lushniak, 1995). The 1988 National Health Interview Survey, Occupational Health Supplement, interviewed 30,074 persons nationwide (Nat. Ctr. Health Stat., 1989; Behrens et al., 1994). A requirement for recording dermatitis was that it occurred for at least three consecutive days during the past year. Dermatitis prevalence was found among 11.2% of

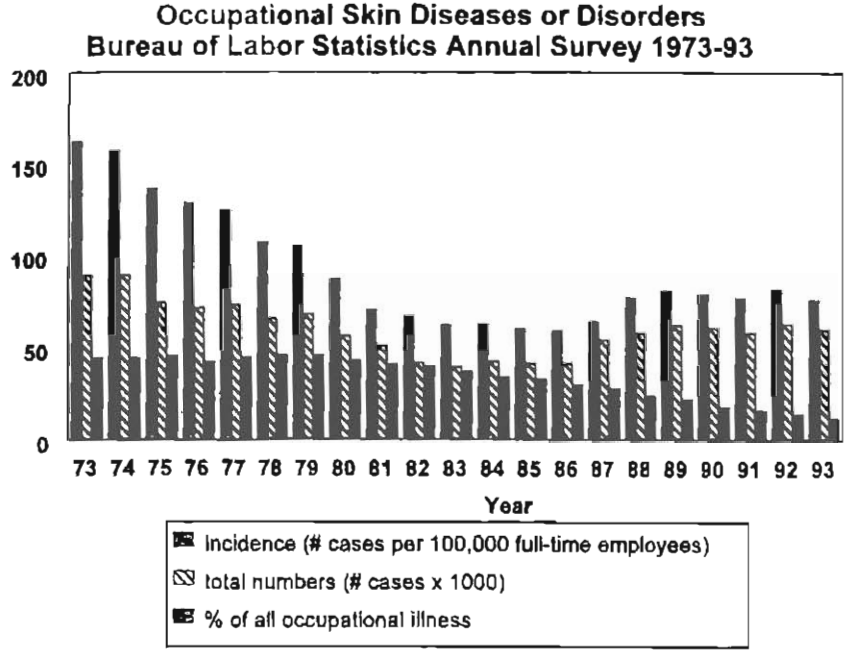

Figure 3-3. Incidence of new reported cases of dermatitis in the United States per year. Data from the U.S. Bureau of Labor Statistics.

the survey, while the prevalence of OCD was indicated in 1.7%, or an estimated 1.87 million cases nationally. This is equivalent to 1700 cases per 100,000 workers. This self-reported prevalence rate is in sharp contrast to the 76/100,000 cases of occupational skin disease or disorders reported to the U.S. Bureau of Labor Statistics in 1993. Interestingly, only 16/100,000 workers' cases were severe enough to result in one or more days away from work (Burnett et al., 1998).

In 1984, the National Labour Inspection Service (NLIS) in Denmark established the Register of Occupational Diseases. In Denmark, all doctors and dentists are required to notify the NLIS of all work-related diseases, even suspected cases. During the period 1979-1989, 17,746 cases of skin disease were reported, which ranked third behind musculoskeletal disorders and hearing damage. This is equivalent to an annual incidence rate of about 85/100,000 workers. Respiratory diseases, by comparison, excluding allergies, contributed 8,107 cases, with an additional 4,600 cases attributed to respiratory allergies (Haklier-Sorensen, 1996a, 1996b).

In Finland, the Act on the Supervision of Labour Protection of 1974 has obligated doctors to report every case of occupational disease. In 1993, 16% of the occupational diseases were attributed to dermatoses, ranking fourth behind musculoskeletal diseases, hearing loss, and diseases caused by asbestos. Eighty-four percent of all occupational skin disease was classified as

contact dermatitis. Irritant dermatitis constituted 50%, allergic contact dermatitis 36%, and contact urticaria 14% of these cases. The most common causes of irritant contact dermatitis were detergents (33%), wet work (10%), oils, greases, cutting fluids, organic solvents, and dirty work (18%), and foods (8%). The most common causes of allergic contact dermatitis were rubber chemicals (26%), synthetic resins, plastics, glues, and paints (19%), and metals (16%). The source of the rubber chemical allergies were most often attributed to protective gloves. On the other hand, no cases of occupational allergic dermatoses were detected in the rubber industry during 1993 (Kanerva et al., 1995).

Some industries exhibit a greater risk of contact dermatitis than others. For instance, the agricultural workforce, which represents 1% of the private sector workforce, had 4% of the cases, while 65% of occupational skin disease cases were found in manufacturing, where 30% of the workforce is employed (Wang, 1978). An incidence of 12.6 % of occupational skin disease was found in one factory using phenol/formaldehyde resins in Sweden (Bruze and Almgren, 1988). Health-screening for occupational skin disease in construction workers indicated a current prevalence of 16%, although only 8% was attributed to occupation (Wahlberg, 1969). A questionnaire survey and follow-up exam of painting trade workers in Sweden indicated that 16.7% currently had skin disease, while 30% reported current or past skin disease. Upon detailed examination, 34% were classified as being from occupational causes, 22% were doubtful, and 44% were not occupationally related (Hogsberg and Wahlberg, 1980). The prevalence of irritant skin changes in third year hairdresser apprentices was 55% in one study in Germany (Wolfgang et al., 1998), while 83% of professional hairdressers in a city in Taiwan had contracted occupational dermatitis (Goh, 1994). Table 3-3 lists the major industries in the U.S. with the highest incidence of occupational dermatitis. More detailed analyses of the occurrence of occupational dermatitis in other countries can be found elsewhere (Smit et al., 1993; Smit et al., 1993a; Smit et al., 1995; Kanerva et al., 1995).

Although there is a reasonable concern that work-related skin conditions are under-diagnosed, there is also danger of possible over-diagnosis. This stems from the fact that only about 65% of all skin disease seen among workers is attributed to occupation (HSE, 1993). One critical study of 250 workers from 14 different industries indicated that only 51% of study participants had skin findings consistent with workplace exposure (Plotnick, 1990). Thus, non-work causes could confound the proper attribution of cause and effect in regard to bona-fide occupational dermatitis.

The prognosis for contact dermatitis in chronic cases is surprisingly poor (Burrows, 1972). This seems true for both allergic or irritant dermatitis, as neither seems to clearly have a better prognosis (Hogan et al., 1990; Fitzgerald and English, 1995; Cooley and Nethercott, 1994). Fregert (1975) reported that only one quarter of the patients with hand eczema were symptom-free two to three years after diagnosis. In another study of chemical workers, recurring symptoms of contact dermatitis varied between 35% and 80%, depending on the severity of the symptoms, the period of follow-up, and the intensity of exposure (Williamson, 1967). Driessen et al. (1982) prospectively studied eczema patients for four to seven years after they had initially seen a dermatologist, and found that 56% of the patients with irritant contact dermatitis

Table 3-3
Occupations in U.S. with occupational skin diseases or disorders, numbers and incidence rates by major industry

Major Industry	Total No. Cases	Incidence (Cases per 100,000 Full-Time Employees)
Agriculture/forestry/fish	3600	345
Manufacturing	31,800	179
Services	12,600	60
Construction	2200	56
Transportation/utilities	2800	53
Mining	200	29
Wholesale/retail trade	4400	23
Finance/insurance/realty	600	10
Total	58,200	77

Data from U.S. DOL, 1993.

were cured, versus 37% of the patients with allergic contact dermatitis. Wall and Gebauer (1991) noted that over one quarter of workers who changed jobs because of occupational dermatitis chose occupations in which the new work environment further added to their occupational skin disease. On the other hand, Rosen and Freeman (1993) reported an improvement in occupational contact dermatitis in patients who were able to change their working pattern, and an even greater improvement in those who left the original industry altogether. Others have not detected such an improvement in outcome (Keczkes et al., 1983). The possible reasons for the poor prognosis of occupational contact dermatitis have been succinctly summarized by Hogan (1994) and Birmingham (1986). These include misdiagnosis, continued exposure, misuse of topical medications, atopy, chronicity of condition, insufficient advice to patients, non-dermatological factors, poor wash facilities, improper cleaning agents, cross-sensitivity, and multifactorial causes.

Irritant contact dermatitis is more prevalent in occupations involving wet work such as cleaning, hairdressing, nursing and health care, and food handling. Water itself is damaging to the skin if it is in contact with the skin for prolonged periods. Furthermore, resistance to chemical irritants and physical damage is reduced. This is probably reflected in the high prevalence

of skin problems in such groups as professional cleaners (Nielsen, 1996), and among those who wash their hands frequently with soap and water, such as food handlers and health care workers (Mathias, 1986; Grunewald et al., 1995).

Individual risk factors that have been determined to be most likely to be associated with contact dermatitis are a history of atopy (especially atopic eczema) and dryness of skin (Smit et al., 1994; Leung, 1995). Atopic individuals have a 13-fold increased susceptibility to irritants, probably because of the poorer integrity of their stratum corneum (Shmunes and Keil, 1983). Surprisingly, and not completely understood, but believed to be related to a T-lymphocyte deficit, is that atopy has a protective effect on the risk of allergic contact dermatitis (Smit and Coenraads, 1993; Rees et al., 1990). However, atopic individuals are more susceptible to immediate, contact urticaria than normal persons due to a significantly higher presentation of IgE on their B-lymphocytes (Ward et al., 1991). Dry skin, probably as a result of overuse of soaps and other exogenous factors, is indicative of mild damage to the skin. Damaged skin is more prone to assault from a number of external agents capable of causing dermatitis.

COST OF OCCUPATIONAL DERMATITIS

Costs associated with any type of occupational illness include lost or reduced productivity, medical diagnoses and treatment, administrative costs, and when the worker is unable to work due to the illness, workmen's compensation for lost wages.

Although allergic dermatitis accounts for about 20% of all occupational contact dermatitis, it is responsible for a disproportionate number of lost time cases. In one study, 37% of patients with allergic dermatitis took sick leave, versus 14% with irritant contact dermatitis (Meding and Swanbeck, 1990). The proportional distribution of the number of days taken as sick leave for dermatitis in one state are shown in the pie diagram in Figure 3-4.

An earlier study, using average lost workday duration and a wage of $8.25, calculated total lost productivity at $11 million annually. However, accounting for the under reporting and indirect costs of skin disease, the estimated total cost of dermatitis might be between $222 million and $1 billion annually (Mathias, 1985). A recent survey estimated that only between 9% and 45% of workers with all types of compensable conditions actually filed claims (Biddle et al., 1998). In 1985-1986, dermatitis in the U.S. ranked sixth for permanent partial disability compensation, following non-chemical injuries such as hearing loss and musculoskeletal damage (Leigh and Miller, 1998).

In Denmark, contact dermatitis accounted for 41% of all recognized cases of occupational disease between 1979-1989. Of the total cases of dermatitis, 64% resulted in compensation for permanent injury and 11% resulted in compensation for loss of earning capacity. Nearly 17% of the total payments for compensation were for skin diseases. Compensation paid by the insurance companies was 32 million Danish Crowns (D.C.) or about $4,726,735, which was followed by respiratory diseases and musculoskeletal disorders. The average payment for com-

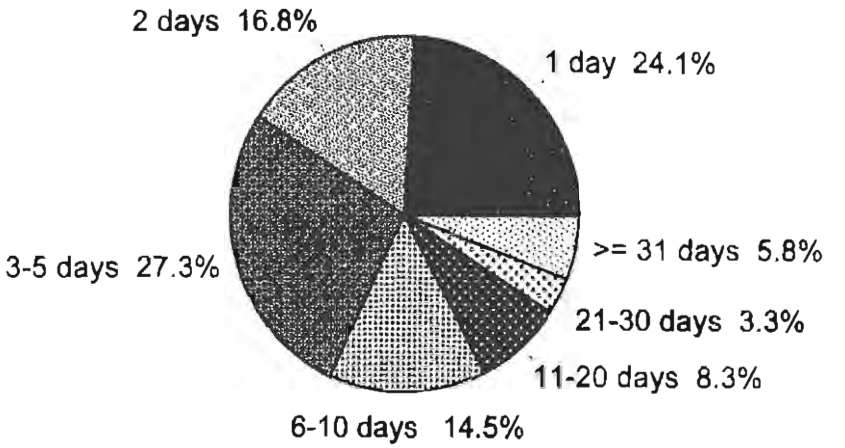

Figure 3-4. Days away from work per case for skin diseases reported to the U.S. Bureau of Labor Statistics, 1993. The total number of cases reported was 12,613.

pensation for permanent injury due to skin disease was 26,000 D.C. ($3,840) and for compensation of loss of earning capacity, 345,000 D.C. ($50,960) (Halkier-Sorensen, 1996a; 1996b).

There seems to be a direct association between higher medical and compensation costs and delayed referral to physicians (Shmunes and Keil, 1983; Gallant, 1986). Not only is the medical prognosis poor, but chronic dermatitis can have severe detrimental social and economic consequences for the affected worker (Breit and Turk, 1976). Each of these reasons points to the importance of early diagnosis and intervention.

Additional costs result when a change of occupation results from disease associated with specific types of work. Data from the former Federal Republic of Germany show that there are workers in many occupations that change professions because of occupational dermatitis (see Figure 3-5). Dermatitis in many occupations far exceeds the number of cases of workers who are forced to change occupations because of respiratory problems (Fed. Rep. Ger., 1990). This change of occupation results in the loss of skilled labor in one profession, and requires time, reduced wages, and training expenses while mastering new skills when new employment is obtained in another occupation.

CAUSES OF ALLERGIC AND IRRITANT DERMATITIS

About 300 potential sensitizers of occupational relevance have been identified and approximately 3,000 chemicals are known to act as possible contact allergens (Menne and Nilesen, 1994). de Groot (1994) provides suggested concentrations for skin patch testing on 3,700 chemicals, although some of these may not be true allergens because they are irritants at low concen-

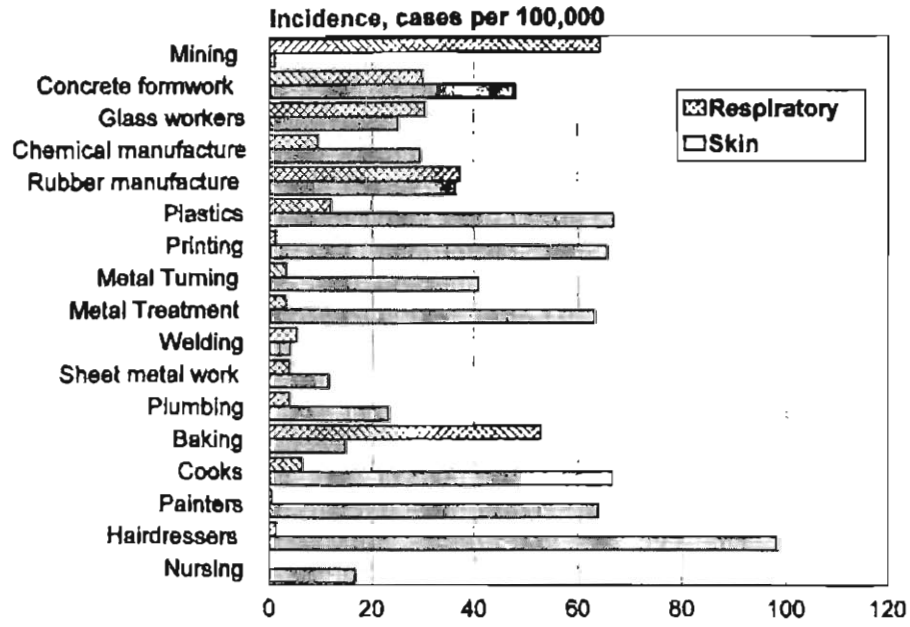

Figure 3-5. Incidence of reported occupational illness in former Federal Republic of Germany requiring change or loss of occupation. Only cases for dermatitis and respiratory disease are reported to compare the relative occurrence of these two classes of disease. Adapted from Berufskankheitenrisiken (Bundesgestaltfur Arbeitsschutzund Arbeitforschung, Federal Republic of Germany (1990)).

trations. The NIOSH Registry of Toxic Effects of Chemical Substances (RTECS) identifies 2,650 chemicals with the potential to irritate the skin (SilverPlatter, 1997).

In Finland, during 1991, the eight most common types of chemicals responsible for allergic contact dermatitis were rubber chemicals, nickel, epoxy resins, formaldehyde, thiuram sulfides, chromate (six valence), isothiazolinones, and colophony. It is likely that the principal contact with rubber chemicals, thiuram sulfides, and isothiazolinones occurred from wearing chemical protective gloves. Sensitization to nickel was reported often for hairdressers who work with stainless-steel scissors, but it is believed that the initial sensitization may occur from wearing inexpensive nickel-plated jewelry. Epoxy resins are encountered in industry, as well as colophony, which constitutes the flux in many solders. Formaldehyde is used as a preservative, and is found in cleaning products and in the textile industry. It is also a principal component in most embalming fluids (Kanerva, et al., 1994).

The most common cause by far of the occupational cases of contact dermatitis, reported in Denmark between 1984 and 1991, was water and detergents (25%). Other significant single causes of contact dermatitis were nickel compounds, hand cleansers (soap), solvents, rubber,

metal (unspecified), cutting oils, gloves, and self-copying (carbonless) paper, accounting for the exposure in over 50% of the reported cases (Halkier-Sorensen et al., 1995). It is interesting that hand cleansers and gloves are near the top of the list when paradoxically the intent of these products is either to protect the skin of the employee, or to protect the health of the recipient of the product or service (e.g., health care) that is provided. Because some workers wash up to 100 or more times per day in some occupations, it is understandable how skin damage might occur (Rustemeyer and Frosch, 1996).

The most common occupations in Finland to experience cutaneous urticaria in 1991 were farmers, bakers, domestic animal husbandry, food preparation, and nurses (Kanerva et al., 1994). In each of these occupations, the allergen is principally proteinaceous. These allergens typically have molecular weights that are in excess of 10 kilodaltons. Currently under investigation is how these HMW proteins penetrate the skin, although if the skin is damaged penetration certainly seems plausible. Natural rubber latex (NRL) protein allergy resulting from glove use has grown significantly among nurses and other health care professionals due to concerns about HIV and hepatitis, and NRL is a significant cause of contact urticaria and systemic sensitization (Turjanmaa, 1996).

INFECTIOUS DISEASES

Occupational activities may potentially expose workers to infectious agents, as might occur in occupations such as solid waste sanitation, livestock rearing, sewage treatment, and the health professions. The skin, especially if damaged by physical or chemical exposure, may be a target site for such infections. In England and Wales, the incidence of new cases of occupational dermatitis associated with infective agents as diagnosed by dermatologists and occupational physicians was 1.6% and 8.4%, respectively (Health and Safety Commission, 1997). In the U.S., approximately 19% of all reported cases of occupational disease were attributed to infections of the skin and subcutaneous tissue (Burnett et al., 1998). One might also predict that damaged skin is more likely to present a portal of entry for systemic infectious disease agents. In general, the literature supports this belief (Abrams and Warr, 1951; Levin and Behrman, 1938; McCulloch, 1962; Watt, 1987; Nield, 1990), and the skin has been suggested as a potential portal of entry for specific infectious agents including viral hepatitis, bacterial infections such as tuberculosis, anthrax, and brucellosis, as well as fungal infections (Gantz, 1995; Veraldi et al., 1992; Meneghini, 1982; Adams, 1990; Ancona, 1990), as examples. Thus, a worker with dermatitis or mechanically damaged skin might be at much greater risk of infection than a worker with healthy, intact skin. Such workers should be adequately protected or removed from such activities.

Management and Prevention of Occupational Dermatitis

The techniques for minimizing occupational dermatitis are very similar to minimizing any other occupational hazard. They include a thorough audit of products and processes in the

workplace that might cause or aggravate existing dermatitis, and an on-going medical surveillance program that can be related directly to job activities in which affected cases are involved. Often a worker afflicted by dermatitis first visits a personal or company medical doctor who might then refer the patient to a dermatologist. It is usually rare for the dermatologist to seek information from or provide information to the hygienist at the workplace. Thus, important information needed to find the cause and solution to the problem are often not shared. If through the medical surveillance program, it appears that there might be a problem with dermatitis, seeking professional, competent assistance may be the most expedient means of finding solutions.

Studies have found direct associations between the duration of dermatitis prior to treatment and a reduction in the favorable long-term prognosis. Because dermatitis is not generally life-threatening, affected workers often tend to "tough it out." In one survey of workers with allergic reactions to epoxy resins, it was found that almost 30% had never consulted a physician about that condition (Nixon and Frowen, 1991). In one chemical manufacturing site where over 1,000 employees worked, additional training in prevention and early reporting of skin conditions resulted in a new dermatitis rate that was only 39% of the former incidence (Heron, 1997). In conclusion, cost savings and a better prognosis of dermatitis might be achieved by encouraging employees to seek early medical consultation, and/or by implementing periodical medical screening that includes dermatological exams (Halbert et al.,1992; Cooley and Nethercott, 1994).

When considering potential new hires for work that might potentially expose them to contaminants that could affect the skin, prior history of dermatitis alone cannot be used as a reason for not hiring. Provisions of the Americans with Disabilities Act of 1990, which came into full effect on July 26, 1992, places a general duty on the employer to allow a prospective worker employment in a job provided he or she can perform the "essential components" of the job without putting other workers at risk or placing him or herself at "material risk of harm." In addition, the law requires that the employer make "reasonable accommodations" in the work tasks and conditions to allow a prospective employee to perform the essential components of the job. This might include provision of simple personal protective equipment. Neither the doctor nor the employer has the right to deny a person a job unless they are able to quantify the risk and establish that the job may result in material harm. Furthermore, an employer is no longer able to require a medical examination of a prospective employee prior to offering employment, with the exception of a drug test. The practical outcome of this would be to strive to provide a safe work environment even for more susceptible workers, or depend on the employee's determination to seek employment elsewhere where it is relatively free of such risks (Nethercott, 1994).

Protecting and restoring the barrier function of the skin are crucial measures in the prevention and management of contact dermatitis. Reducing the causes of contact dermatitis by minimizing contact with offending agents and conditions is the obvious solution. This can be performed through safer chemical substitutions, automation and closed systems, using milder soaps for cleaning the skin, not washing with hot water, keeping the skin as dry as possible, avoiding prolonged skin occlusion (e.g., under gloves), protecting the skin from mechanical and chemi-

cal exposure, and using hypo-allergenic gloves when needed. The prevalence rate of work-related skin rashes was 3.4% among solderers when they typically wore cotton gloves, compared to 15.4% when they did not, demonstrating the efficacy of this simple precaution (Koh, 1994). To date, the efficacy of barrier creams is insufficiently documented (Wahlberg, 1986).

Skin emollients applied to skin may help restore the barrier function of the skin, but studies have detected marked differences in the efficacy of various creams (Halkier-Sorensen, 1996c). Lotions applied to contaminated skin may possibly facilitate percutaneous bioavailability (Davies et al., 1991). A possible deterrent to the use of skin emollients at work is that they must be compatible with the work operations. In the U.S., for instance, food handlers cannot apply skin lotions or creams that are not approved by the Food and Drug Administration. If wearing gloves, some petrolatum or oil-based emollients may help transfer allergens from the gloves to the skin or even degrade the glove (Beezhold et al., 1994; Baur et al., 1998). It is, therefore, important that the efficacy of skin care products is evaluated under conditions of use before being recommended to workers.

Unfortunately, a common mistake made by occupational health management is to over prescribe the use of gloves when intending to protect against skin exposures. As alluded to previously, there is a significant association between the use of gloves as the cause or exacerbation of allergic OCD. Chronic use of gloves can certainly damage the skin through occlusion and by irritation caused by the friction from the glove and glove powders (see Occlusion below and Boeniger, 2002; Taylor, 1994; Wrangsjo et al, 1994; Burke et al., 1995). Use of gloves should be limited when possible to short durations, combined with good work practices and frequent changing.

Self-treatment using topical anesthetics, antibiotics, and antihistamines should be avoided in the treatment of irritant dermatitis, as the skin is more likely to become sensitized to potential allergens in these products. Allergic contact dermatitis to topical corticosteroids and antibiotics, such as neomycin and thiomersal, may occur (Hogan et al., 1990; Wilkinson and English, 1992).

Skin as a Route of Systemic Exposure

The human skin is exquisitely well suited to perform the function that evolutionary demands have required of it. Those main requirements were to help retain internal water, exclude external water soluble compounds, and regulate body temperature through the release of eccrine sweat. Along with the development of our modern industrialized society, the skin is often exposed to a wide variety of chemicals to which it did not evolve to come into contact with.

Molecular diffusion through healthy skin rapidly diminishes for compounds with a molecular weight above 500, but much larger molecules and particles might penetrate the stratum corneum through physical channels (e.g., sebaceous glands, hair follicles). Penetration and diffusion through the appendageal route is also referred to as "shunt" diffusion. Physically or chemically damaged skin might also offer physical pathways of least resistance.

Hair follicles and the associated sebaceous gland (pilosebaceous unit) as well as eccrine sweat pores, generally constitute less than a 0.1% to 0.2% cross-sectional area of the human skin, and for most chemicals that can normally permeate the intact skin, this additional area is insignificant. However, the hair follicle is an invagination of the epidermis extending deep into the dermis, providing a much greater actual area for potential absorption below the skin surface. Penetration through these portals can be considerable for chemicals that do not permeate intact skin, such as larger molecules and even small particles. For instance, 7 μm particles were detected primarily deep within the hair follicles, while 3 μm particles were detected in both the intact stratum corneum and hair follicles (Lauer et al., 1995). Previous studies on particle fate suggest that particles up to 25 μm may penetrate deep into the stratum corneum where they might later dissolve (Schaefer et al., 1982). Most persons consider only liquid chemicals to be available for skin absorption. However, solid materials may become readily mobile by dissolution into the surface sweat and lipids present on the skin, or by transfer from contaminated clothing (Quan, 1994; Wester and Maibach, 1996). Surface dissolution readily occurs, even for dry powders in contact with dry synthetic gloves (Fricker and Hardy, 1994).

Dermal absorption of chemicals can appreciably increase the overall body burden. The cumulative systemic dose will depend on the amount of skin area exposed, duration of exposure, and absorption rate of the chemical exposure. Figure 3-6 shows the relative dermal contribution to systemic dose from limited skin contact with neat chemical in comparison to an 8-hour inhalation exposure at the TLV®. It is clear that even a small area, exposed for intermittent periods, over as little as 15 minutes out of the work day, can equal the systemic dose from a high inhalation concentration.

Systemic absorption of organic chemicals can contribute to a wide variety of adverse health effects. The literature is replete with recorded instances of acute episodes of poisoning from dermal exposures. Table 3-4 lists some agents responsible for acute poisonings with references for further reading. In addition to workplace exposures, acute and subacute toxicity resulting from the topical application of pharmaceutical and cosmetic products have been documented (Freeman and Maibach, 1992). Not reported as frequently are illnesses and functional impairment resulting from chronic exposure by topical contact. A few examples are listed in Table 3-5. Such exposures may be more common than acute episodes, but cause and effect is often far less certain. For example, skin exposure to solvents is often likely, but its contribution to chronic diseases, such as neurological and neuropsychiatric disorders, are unknown (Bos et al., 1991; Hogstedt, 1994; O'Donaghue, 1985; Hanninen et al., 1976; Spencer et al., 1987). Several compounds have been associated with reproductive injury, such as acrylamide, carbon disulfide, dibromochloropropane, glycol ethers, and inorganic mercury. For these compounds, percutaneous absorption is believed to be the principal means of exposure (Tyl et al., 1993).

Metallic compounds in aqueous solutions are less well absorbed, due principally to ionization, which tends to make chemicals less skin permeable than organic compounds (see Volume 1, page 141). Two generalizations appear to be correct: the metal must be water soluble to be ionized, and cations seem more permeable than anions. The mean absorption is less than 1% in five hours when metal compounds such as cobalt chloride, zinc chloride, and silver nitrate

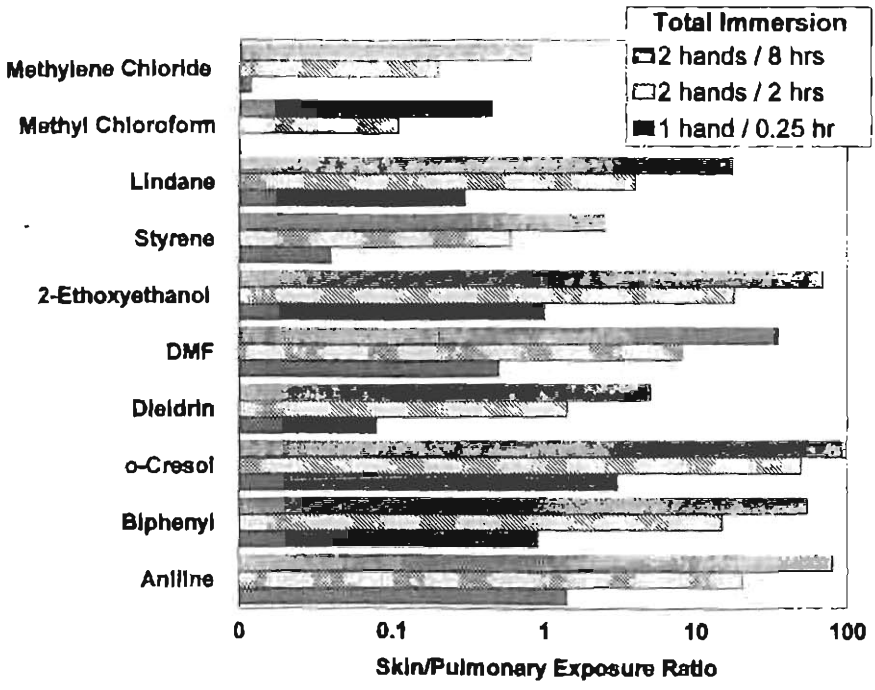

Figure 3-6. Relative absorption of some chemicals from exposure to the hands or by inhalation to TLV® air concentration for 8 hours. Legend indicates relative proportion compared to how much skin area and time the skin would be in contact. Data adapted from Droz-PO, et al., 1990.

are applied to the skin. For mercuric chloride, potassium mercuric iodide, and methyl mercury dicyanidiamide, the absorption increases with higher concentrations between 3.2% and 4.5% in five hours (Subcommittee on the Toxicology of Metals, 1971). Matrix effects appear important. Whether the metallic salt is applied in water or in soil appears to dramatically affect absorption. In *in vitro* experiments with mouse skin, 62% of sodium arsenate was absorbed from water, while <0.3% of the applied dose was absorbed when applied in soil (Rahman et al., 1994). Thus, soil binding appears substantial for some metallic compounds.

Covalently bound organo-metallic compounds are far more permeable since they do not ionize (Siegers and Sullivan, 1992). They also have profound detrimental effects on the central nervous system. The tragic death in 1997 of a Dartmouth College professor conducting environmental toxicity testing was believed to be the result of a single drop, perhaps two, of dimethyl mercury on her permeable latex glove (Lewis, 1997). This is a dramatic example of the potency of some organo-metallic compounds. Organo-metallic compounds, and inorganic metallic cations, which are water soluble or readily dissociate in water, are usually good permeants. Lead acetate and lead nitrate are examples of good permeants (Lilley, S.G. et al., 1988; Stauber

Table 3-4
Some examples of acute and subacute poisoning from transcutaneous exposure

Compound	Industry	Severity	Reference
acrylamide	chemical manufacturing	fatigue, peripheral neuropathy, muscle weakness	He et al., 1989
arsenic trichloride	chemical manufacturing	death	Delepine, 1923
2,4-dichlorophenol	manufacturing	death	Kintz et al., 1992
dinitrocresol	agricultural spraying	death	Herman et al., 1956
ethylene glycol monomethyl ether	textile printing	encephlopathy, bone marrow damage	Ohi and Wegman, 1978
ethylene chlorhydrin	industr. cleanup	death	Middleton, 1930
hydrofluoric acid	petrochemical refinery	ventricular fibrillation, pulmonary edema, death	Tepperman, 1980
hydrocyanic acid	chemical manufacturing	dizziness, weakness throbbing pulse	Drinker, 1932 Potter, 1950
methanol	equipment cleaning	vision impairment dizziness, dyspepsia	Downie, 1992
4,4'-methylene-dianiline	epoxy resin manufacturing	hepatitis	McGill and Motto, 1974
nicotine	tobacco harvesting	nausea, vomiting, dizziness, headache	Ghosh et al., 1991
paraquat	manufacturing and agriculture	pulmonary failure death	Smith, 1988
phenol	disposal of industrial waste	central nervous system toxicity, death	Soares and Tift, 1982
phenol-formaldehyde	manufacturing	hypertension respiratory distress renal impairment	Cohen et al., 1989
thallium	rodenticide	sensory changes	Glamme and Sjostrom, 1955
	manufacturing	parathesia, hair loss, neurological pain	
trichloroethylene	manufacturing	death after 11 mo.	Lockey, 1987

Table 3-5
Some examples of chronic poisoning from skin exposure

Compound	Occupation	Severity	Reference
nitroglycerin	explosives manufacturing	ischemic heart disease	Hogstedt and Axelson, 1977 Hodstedt and Stahl, 1980
triarylphosphate	mechanic, hydraulic fluid	polyneuropathy	Jarvholm et al., 1986
monomethyl ether	eyeglass frame factory	reversible hematological	Larese et al., 1992
methymethacrylate	dental technicians	neurotoxic	Rajaniemi, 1986 Rajaniemi et al., 1989 Sappalainen and Rajaniemi, 1984
polychlorinated	electrical utility	cancer	Loomis et al., 1997

et al., 1994). On the other hand, inorganic lead oxide, which does not dissociate, does not appear to traverse the skin according to Bress and Bidanset (1991), even after prolonged occlusion, although Florence et al. (1988) and Stauber et al. (1994) suggested that there is rapid absorption of both lead oxide and lead metal through the skin. Still, transcutaneous absorption of strontium chloride, with only 0.26% absorbed through intact skin in six hours, increased to 57.4% (200-fold increase) when the skin was abraded (Ilyin, 1975). Similar findings were reported for cobalt chloride, cerium chloride and cesium chloride radionucleotides (Inaba et al., 1979). Thus, the skin can play an important role as a route of exposure for almost any compound if the necessary conditions exist that will facilitate uptake.

Skin as a Contributor to Oral Ingestion

Not only can chemical contaminants be transferred to the skin, but skin contamination can be subsequently transferred to the mouth. It is generally well accepted that smoking and eating in the workplace should not be allowed because workers who have "dirty" hands might transfer

this contamination to their cigarettes or food. How much contamination is of concern is a matter of the toxicity of the compound. For the purposes of illustration, lead is a good example.

Lead is a particularly dense compound. A drop of lead weighs about 570,000 μg (1/20th mL × 11.34 grams per mL × 1 million μg/gram). If only 1/1000th of a drop of lead were dispersed over the surface of two hands, this would be equivalent to about 570 μg.

The OSHA PEL for lead is 50 $\mu g/m^3$ in air. If a worker performing light work activity inhales 10 cubic meters of air during the work shift, 500 μg of lead would be inhaled. Hand wipe samples of battery manufacturing plant workers indicate lead contamination levels of up to 20,000 μg per pair of hands. After washing with soap and water, these levels may be reduced to an average 530 μg (Esswein et al., 1996). Even though these workers washed and apparently had clean hands, the amount of lead on the hands was equivalent to the full work shift inhalation exposure at the PEL. Hand contamination could be effectively transferred to food that is prepared or eaten by hand. Furthermore, surface contamination of the eating facility, that is invisible to the eye, could be transferred to recently washed hands and be a significant source of oral ingestion (Esswein et al., 1996).

For simplicity, this theoretical example did not take into account retention and bioavailability in the respiratory and oral routes. An analysis of this would suggest that this oversight may not be very significant. The penetration and retention of airborne particles into the respiratory tract is generally less than 20%, whereas the absorption of inhaled lead into the blood for the average adult was estimated to be only 40%, or about 8% total absorption (Drill et al., 1979). On the other hand, absorption of lead in the gut is between 8% and 10% (Tola et al., 1973; WHO, 1977). The net absorbed lead by either route are approximately the same.

Several workplace studies support the above calculation that personal hygiene can be important to the total contribution of workplace exposures. These studies have focused on exposures to toxic metals such as lead, cadmium, chromium, and arsenic, and also measured the internal biological levels of these contaminants. Using multiple regression analysis and observational or questionnaire data and personal hand contamination measurements, investigators have found that personal hygienic factors and working methods explain biological levels at least as well as do air monitoring data. In one instance, the correlation between exposure and internal dose at least doubled when information on the oral route was included (Lumens et al., 1994).

Eating and smoking with contaminated hands are viewed as poor work practices that might lead to ingestion of the contaminants. Studies on the amount of transfer of contaminants from hands to food is not available, but Wolfe et al. devised a protocol to determine the amount of contaminants transferred to cigarettes (Wolfe et al., 1975). In that study, parathion transferred from hands to cigarettes was calculated to be a potentially significant contributor to exposure. However, several assumptions were made that might over-estimate the amount inhaled, including that all volatilized compound was inhaled, none was thermally decomposed, and none would be trapped in the butt end or filter of the cigarette. If any of these assumptions were not true,

less exposure would occur. Although extensive data are lacking, the reasoning for prohibiting eating and smoking with contaminated hands seems valid.

In one study, the average worker's hand contamination with cadmium was up to 1,200 μg/hand during the workday, and up to 300 μg/hand before lunch or before leaving the factory (e.g., after washing). These samples were collected simply by rinsing (no scrubbing) the hand with 500 mL of NaOH 0.1N, thus, this represents readily transferable material (Roels et al., 1982). In another study, the mean hand lead increased 33-fold from the pre-shift levels on Monday morning (33.5 μg/500 mL) to 1121 μg/500 mL on Thursday afternoon. Mouth lead contents were measured by rinsing the inside of the mouth with deionized water. Over the same period of time, these concentrations increased 16-fold (Far et al., 1993). These studies, and others, support stressing the impact of hygienic behavior and work practices as important to decreasing the uptake of toxic agents in the workplace. Furthermore, the potential contribution of this route of exposure can be evaluated by measuring the amount of contaminants on the skin (Askin and Volkmann, 1997; Ulenbelt et al., 1990).

A good rule of thumb is that if the occupational air concentration exposure criteria specify less than 10 mg/m^3 of air, the compound is fairly toxic, and the potential for biologically significant amounts of material to be present on the hands for transfer to the mouth exists. At that air concentration, and assuming that 100 mg/day is inhaled during light work, this mass would have a volume of roughly 100 μL. This volume is equivalent to about two drops of water, a mass that could easily be present on unwashed hands (Kissel, 1996). The amount of contaminant present on washed skin is dependent on many variables, and is best determined by objective measurements. However, in one experimental study it was concluded that the average adult (non-working) ingests 10 mg of soil and dust per day from non-food sources (Stanek et al., 1997). This estimate agrees with other experimental measurements of the amount of fine soil transferred from fingers (three fingers above the first knuckle) to the mouth during mouthing. It was found that the geometric mean amount was 11.6 mg, representing 16% of the amount originally on the skin surface (Kissel et al., 1998). Based on the above information, it would seem plausible that substantial amounts of material could be transferred to the mouth from contaminated hands, especially while eating.

Skin Route Contributing to Respiratory Sensitization

In experimental immunotoxicology, an efficient means of sensitizing animals is by topical or intradermal injection (Magnusson and Kligman, 1970). Intradermal injection is most effective for compounds that do not permeate the skin well, but *penetration* of topically applied compounds through damaged skin, as may occur in the workplace, is a real possibility. Egg albumen, for example, when injected intradermally, is very effective as a means of creating systemic humoral sensitization (Arakawa et al., 1995). It is not known to what extent, if any, dermal contact with egg protein has in contributing to the high prevalence of occupational asthma often seen in the egg breaking industry, which has not been studied (Smith et al., 1990).

Compounds that can permeate the skin may cause systemic sensitization as well. Isocyanates are a case in point.

Isocyanate compounds are clearly capable of causing dermal sensitization when applied topically to various animal species. Most of the major isocyanate compounds have been shown to possess this capability, including 2,4- and 2,6-toluene diisocyanate (TDI) (Duprat et al., 1956;) 4,4'-diphenylmethane diisocyanate (MDI) (Tanaka, 1987), isophorone diisocyanate (IPDI) (Stern, 1989), and dicyclohexylmethane-4,4'-diisocyanate (HMDI) (Stadler and Karol, 1985). Dermal sensitization to these compounds in animals parallels reported cases of human dermal sensitization to HMDI (Emmett, 1976; Malten, 1977), TDI (Pham, 1978; Huang, 1991), MDI (Linden, 1980), and 1,6-hexamethylene diisocyanate (HDI) (Wilkinson, 1991).

It would seem illogical to believe that individual organs could be isolated from interaction, and that effecting chemical sensitization in one organ would have no effect on another. In fact, there is increasing evidence that compounds that enter the skin as allergens may be *more* likely to induce respiratory sensitization than compounds entering only through the respiratory system (Kimber, 1996).

Isocyanates are a good example of chemicals possessing the potential for topical exposure to cause respiratory sensitization. There are at least four instances where this has been shown in animal species (Karol et al.,1981; Erjefalt and Persson, 1992; Rattray et al., 1994 Bickis, 1994). One of the most dramatic of these studies is summarized below.

Rattray et al. (1994) tested the influence of the route of exposure on the development of respiratory sensitization in guinea pigs. The test animals received either an epicutaneous, intradermal, or inhalation exposure to MDI, and were challenged with various airborne concentrations of MDI 21 days post exposure. The epicutaneous exposure consisted of a single topical application of either 10%, 30%, or 100% MDI solutions to the shaved scapular region of the guinea pigs. The application sites were occluded for 6 hours. Twenty-five percent of the animals exposed to the 10% MDI solution (2 of 8) and 30% MDI solution (2 of 8) displayed respiratory sensitization upon inhalation challenge; this effect was also observed in 3 of 7 animals in the 100% MDI solution exposure group. IgG_1 anti-hapten antibodies were detected in 5 of 8 and 7 of 8 guinea pigs dermally exposed to the 30% and 100% MDI solutions, respectively. The investigators were unable to sensitize animals to MDI via the inhalation exposure route. In addition, an epicutaneous MDI challenge exposure 22 days following the initial MDI treatment induced dermatologic reactions (redness and swelling) in 71% (17 of 24) of the animals in the 10%, 30%, and 100% exposure groups. These data suggest that dermal exposures are important in MDI-induced respiratory sensitization, and that these exposures may be more effective than inhalation exposures in inducing sensitization.

To date, the only evidence of respiratory sensitization following skin contact in humans consist of anecdotal cases of skin splashes followed by respiratory sensitization, known skin contact with possibly incompletely cured polyurethane products, and workplace studies where respiratory symptoms are prevalent without existence of measurable air concentrations (NIOSH, 1994; NIOSH, 1996; DOW, 1996; Nemert and Lenaerts, 1993; Petsonk et al., 2000). Recently

the ACGIH® TLV® Committee began assigning unique notations for sensitization to compounds, including chemicals capable of causing sensitization by skin or inhalation exposures (ACGIH®, 1999). Historically, the ACGIH® criteria applying to the skin notation purposely excluded such compounds, limiting it only to chemicals capable of causing systemic toxicity. Also, in Germany, compounds that are known to sensitize either the skin or respiratory tract are provided unique notations (MAK and BAT Values, 1997).

SKIN ANATOMY AND PHYSIOLOGY

In Volume 1, page 138, a basic description of the skin anatomy and physiology is presented. For review, the stratum corneum is the uppermost layer exposed to the outside world. It is composed of flattened denucleated cells called corneocytes, which contain mainly highly cross-linked fibrous keratin proteins. The corneocytes are non-respiring cells that are tightly connected, forming a physically rugged membrane. Each corneocyte is typically 30-40 μm (micrometers) in diameter and only 0.2 to 0.5 μm thick. These are randomly stacked 15 to 25-layers thick over most human skin surfaces (Flynn and Stewart, 1988).

The thickness of the stratum corneum varies by anatomical location on the human body. Table 3-6 shows the average skin thickness for several locations. Overall, the stratum corneum is surprisingly thin. Most of the body surface stratum corneum is only 10 to 16 μm thick, with limited areas of increased thickening related to the need for abrasion resistance, such as on the hands and feet. To help put the thickness of the stratum corneum in perspective, the average human hair has a diameter of about 50 to 70 μm. Polyester adhesive tape (e.g., 3M Scotch Tape®) is about 25 μm thick. The thinnest synthetic glove is about 7 μm thick.

The intercellular space between the corneocytes consists of well organized lipophilic and hydrophilic domains that represent channels of least resistance to diffusion of either water insoluble (lipophilic) or water soluble (hydrophilic) compounds, respectively (Elias et al., 1977; Swartzendruber et al., 1989; Forslind, 1994). About 10% of the stratum corneum mass consists of lipids. The lipid domain constitutes an important, but tortuous pathway for molecular transport through the stratum corneum. A simplified schematic of the stratum corneum construction has been referred to as a brick and mortar model (Michaels et al., 1975). The surface of the skin also naturally accumulates some of these intercellular lipids, as well as sebaceous gland oils, making the stratum corneum generally water resistant.

It is clear that the stratum corneum provides the main barrier protection to the skin. Because chemicals permeating the skin must traverse the intercellular spaces between the flattened corneocytes, the permeability will be reduced by about 1,000 times relative to a pure lipid phase (Michaels et al., 1975). As such, the apparent effective thickness of the stratum corneum has been calculated to be about 500 to 750 μm (Potts and Francoeur, 1991; Potts and Guy, 1992). Another way to look at this is that it would require a homogeneous film at least 500 μm thick, impregnated with the same lipids as the skin, to provide equivalent protection from chemical permeation. Table 3-7 shows how physically removing the thin stratum corneum by cellophane

Table 3-6
Human stratum corneum thickness by anatomical site[1]

Skin Area	Stratum Corneum Thickness, mm
Abdomen	15
Volar Forearm	16
Back	10.5
Forehead	13
Scrotum	5
Back of Hand	49
Palm	400
Sole	600

[1]Adopted from Scheuplein and Blank, 1971

tape stripping increases the permeation of methanol and phenol through mouse skin (Behl et al.,1983).

The viable epidermis is beneath the stratum corneum. This tissue is considerably different physically from the stratum corneum, in that it is primarily aqueous. The germinal stratum granulosum, where new corneocytes are formed, is located within this layer. A complete replacement of the skin corneocytes that make up the stratum corneum occurs every 14 to 28 days in humans (Treherne, 1965). The epidermis provides an important and rather unique immune capability by providing both specific and nonspecific protection against pathogenic microorganisms and environmental antigens. The major cellular constituents are keratinocytes, Langerhan's cells, skin-infiltrating T-lymphocytes, and post-capillary venule endothelial cells. Regional lymph nodes link the skin with the systemic immune system (Leung et al., 1997). The viable epidermis is about 50 to 100 μm in thickness, depending on location.

The thickest layer of the skin is the dermis. It is a richly vascularized area. The appendageal structures, like the hair follicles, eccrine and sebaceous glands, originate in this layer. Within a cubic centimeter of human skin are 11 to 100 philosebacious glands with hair follicles and 100 to 400 eccrine glands. The total cross-sectional area of the appendages is probably 0.1% to 1% of the surface area of the skin, and the total volume available for percutaneous absorption

Table 3-7
Permeation as a function of tape stripping mouse skin, in vitro at 37°C

Number of Tape Strippings	Permeation Coefficient, cm/h	
	Methanol	Phenol
0	3	22
5	48	120
10	260	277
25	291	275
Dermis	395	301

Adapted from Behl, 1983

(excluding hair diameter) is only about one-tenth of that (Blank and Scheuplein, 1969). Although these appendageal structures represent less than 1/100th of the skin surface area, they may represent an important shunt through the stratum corneum for large hydrophobic compounds and particles (Lauer et al., 1995).

Physicochemical Characteristics Favoring Permeability

It has long been recognized that certain chemicals permeate the skin much more readily than others. Knowing the extent of dermal uptake can be used to predict the relative potential of absorption of chemicals in the workplace. This, coupled with the toxicity of the chemical once absorbed, can be used to estimate the potential hazard of exposure if appropriate steps of control are not taken. It is, therefore, desirable to have accurate skin permeation data.

It has been determined from extensive study of the experimental permeation data for humans that the two principal factors that determine a chemical's likelihood to permeate are its solubility and molecular size. Solubility is typically expressed as water solubility or as the octanol-water partition coefficient, the latter being a representation of the chemical's solubility in a non-polar phase versus a polar phase (Surber et al., 1990; Mannhold and Dross, 1996). The log of the P_{ow} is usually reported because of the wide numerical range of octanol-water, or P_{ow} values. Chemicals with a log P_{ow} between -0.5 and 3 usually permeate best, because the intercellular channels contain bipolar moieties. Chemicals that are very lipophilic will rapidly enter the lipophilic stratum corneum but not readily diffuse through the hydrophilic viable epidermis. Such compounds often remain in the stratum corneum for a considerable amount of time, even-

tually permeating through the viable epidermis or being sloughed off by normal cell desquamation. Similarly, very hydrophilic compounds are also typically poor penetrants of the lipophilic stratum corneum, possibly residing within the upper stratum corneum for a week (Bucks, 1993). In addition, some compounds appear to have a strong affinity for proteins, reversibly interacting with specific chemical sites, and P_{ow} is a strong predictor of protein binding affinity. Taken together, protein binding affinity and P_{ow} favor long residence. Some compounds have low solubility in both water and oil, which further preclude transcutaneous penetration. Finally, ionization of weak acids that have a pKa within the physiological pH range of the stratum corneum also favors retention (Miselnicky et al., 1988; Artuc et al., 1980). Prolonged residence in the stratum corneum is referred to as substantivity.

The second chemical-specific property of importance to percutaneous penetration is the molecular size of the compound. Above a molecular weight of 500, flux through the intact skin is usually negligible for most chemicals. Within this range, however, are a large number of chemicals of commercial and toxicological importance.

Although large compounds may not permeate the skin rapidly, they apparently can penetrate by some (at present poorly understood) physical means. For example, contact urticaria results from cutaneous contact with high molecular weight (HMW) protein allergens, usually exceeding 10,000 MW (>10 kilodalton). Contact urticaria is a common problem among workers that are exposed to animal products, enzymes, and food proteins (Kanerva et al., 1996). It is not known how these proteins traverse the stratum corneum to first induce sensitization, and then later to allow absorption sufficient for elicitation of a response, but there is increasing evidence that such large compounds can cross the intact stratum corneum. Those professions experiencing high contact urticaria prevalence may also experience physical damage to the skin from cuts and abrasions, and penetration of the protein may be enhanced because of this. However, mice have been sensitized through topical application on intact skin by ovalbumin (Wang et al., 1996). The molecular weight of ovalbumin (OVA) is 45 kilodalton. In the experiment, OVA was left on the intact skin under occluded patches for seven continuous days, and occlusion could affect the barrier integrity of the stratum corneum. This resulted in statistically significant elevations in OVA-IgE specific antibody in the dosed group. It was also determined that the concentration required to induce sensitization decreased with repeated epicutaneous exposures. In addition, natural rubber latex proteins were determined to penetrate intact human skin in small amounts, and exposing the proteins to damaged skin resulted in significantly increased penetration (Hayes et al., 2000). As with OVA, mice have been sensitized to natural latex protein allergens by topical exposure, and show respiratory response upon later inhalation exposure (Woolhiser et al., 2000). Additional studies are presently under way at various laboratories to better understand the mechanisms by which HMW proteins and particles reach the viable epidermis and induce an antibody response.

Mathematical Modeling of Permeation

Once solubilization of low molecular weight compounds occurs in the surface of the stratum corneum, transit by molecular diffusion takes over. In solution, percutaneous diffusion of compounds through the skin is predicted by Fick's First Law, which simply states that the flux (J_s) of the compound through the skin is a function of the concentration gradient and the permeation rate constant (cm/hr) so that:

$$J_s = C_s \times K_p \qquad \text{[Equation 3-1]}$$

where C_s is the concentration of the compound (mg/cm^3) and K_p is the permeation constant (cm/hr). Thus, flux is expressed in units something like mg/cm^2/hr. By reorganizing the equation so that K_p equals J_s/C_s, it can be realized that K_p can be experimentally determined by dividing the equilibrium mass absorbed by the concentration at the exposed surface. Ideally, this is performed at several concentrations, and the relationship should be linear if saturation of the skin has not occurred. Thus, K_p is theoretically concentration independent up to saturation and linearly related to concentration differences across a membrane at steady-state. Skin saturation is an important limitation in that Fick's Law applies only to dilute solutions where the capacity of the chemical to solubilize into the limited permeation pathways within the stratum corneum is not exceeded. Often, the concentration range in which K_p is constant is quite narrow, above which the flux rate proportionally diminishes with increasing concentration. Once saturation occurs, as when high substantivity of the chemical in the stratum corneum forms a concentrated skin depot, the concentration gradient across the stratum corneum membrane will diminish. As a result, the flux rate for pure compounds is often no greater than for saturated aqueous solutions, unless chemical damage of the stratum corneum occurs (e.g., methanol, carbon tetrachloride).

In a bit more complex modeling of skin flux, it is realized that the chemical's diffusivity (Dskin) through the skin, as well as partitioning of the chemical in the vehicle in which a chemical exists and in the skin ($R_{skin/veh}$), which are due to respective solubilities, and the thickness of the skin (l_{skin}) are inherent components of K_p. Thus,

$$J = K_p C_{veh} \cong \frac{D_{skin} R_{skin/veh}}{l_{skin}} C_{veh} \qquad \text{[Equation 3-2]}$$

It helps to understand the above components of K_p, and in some instances K_p can be calculated from experimentally measuring these components, however, the latter is rare. It must be realized that vehicle effects can be very influential with regard to $R_{skin/veh}$, and if the compound is in a solvent other than water, the K_p must be empirically determined for the compound in that matrix. It is not appropriate to use a K_p for water to estimate flux from another solvent (Flynn, 1990).

When experimental K_p is not available, mathematical approaches might be used to predict this. One approach is to use statistical algorithms based on best fit of equations to empirical data. One example is the Potts and Guy (1992) equation, which incorporates solubility as measured by P_{ow} and molecular weight such that:

$$\log K_p = -2.72 + 0.71 \log P_{ow} - 0.0061\,MW \qquad \text{[Equation 3-3]}$$

This equation has an r^2 of 0.67 based on the empirical data set of approximately 100 compounds compiled by Flynn (1990). There are many other correlation models determined by other researchers that have attempted to predict K_p from physico-chemical data. In fact, Vecchia and Bunge (2001) have recently compiled 22 different skin permeation correlation models taken from the literature.

Among the more advanced models for predicting K_p are that of Cleek and Bunge (1993) and Wilschut et al. (1995), which attempt to take into account the two phase differences between the lipid-rich horny stratum corneum and aqueous viable epidermis or the theoretical existence of polar and lipophilic pathways, respectively. This approach has increased the prediction accuracy for the more hydrophilic compounds compared to other models. Researchers have considered multiple physical-chemical descriptors in addition to $\log P_{ow}$ and molecular weight, including topological indices, hydrogen bonding, solvation free energy, and molecular orbital descriptors, in an attempt to create better quantitative structure-activity relationship (QSAR) models (Sitkoff et al., 1994; Barratt, 1995; Roberts et al., 1995; Cronin et al., 1999). To date these attempts have been limited by small data sets.

Once a permeation coefficient is obtained, it can be used to calculate the approximate amount of compound absorbed through a given skin exposed area, and duration of exposure for a saturated aqueous concentration. Adopting the Fick's Law equation to include exposed skin area and duration of exposure, one can estimate the internally absorbed mass (M) by:

$$M = K_p \times C_{veh} \times A \times t \qquad \text{[Equation 3-4]}$$

where A = area (cm^2) and t = time.

Since flux is the product of the permeation coefficient and the concentration in aqueous solution, it is intuitive that the maximum flux ($MaxJ_s$) of a compound in an aqueous solution can be estimated by

$$MaxJ_s\,(mg/cm^2/hour) = K_p \times WS\,(S_w) \qquad \text{[Equation 3-5]}$$

where S_w = maximum solubility of the compound in water (in mg/cm^3 or in $moles/cm^3$).

Using the aqueous saturation concentration to calculate the maximum flux is a rough approximation of a compound's maximum flux rate, because it only considers the physical limitation of aqueous saturation in computing $MaxJ_s$, and does not necessarily consider skin saturation aspects.

Note that in aqueous solution, the maximum flux *decreases* with increasing octanol-water partition coefficient, while the permeation coefficient *increases*. They are *inversely* related because in an aqueous solution, the concentration needed to saturate the solution by lipophilic compounds decreases with increasing lipophilicity, and the flux decreases since flux is dependent on concentration. However, if you compared two chemicals in an aqueous solution that were of equal concentration, the one with the higher K_p would permeate faster.

The modeling approach selected by Wilschut et al. (1995) sufficiently estimates K_p, at least for some compounds. For example, the calculated K_p for aqueous phenol is 0.0066, whereas experimentally determined K_p was 0.0082 (Roberts et al., 1977). The calculated maximum flux using equation 5 is 0.0383 mg/cm²/hr, whereas the experimentally determined flux for aqueous phenol was 0.008 to 0.02. However, for pure phenol the experimental flux is only 0.004 mg/cm²/hr. As the aqueous dilutions have higher empirical fluxes than neat phenol, this probably exemplifies the importance of the strong partitioning effect of water in this instance (see discussion under Factors in next section on variables affecting percutaneous absorption). Although these models are useful for initial risk assessments concerning skin exposures, they are far from infallible. Calculated K_p values can differ from experimental K_p values by up to three orders of magnitude (Vecchia and Bunge, 2001). The underlying question is which data, be it empirically determined or mathematically computed, is more accurate for estimating human absorption. Obtaining large amounts of empirical skin permeation data using a standard laboratory protocol and a wide range of log P_{ow} and molecular weights, is critical to improving these models.

Substance P_{ow} values are available from a number of sources, including the Hazardous Substance DataBank through Medlars Database System (National Library of Medicine, Bethesda, MD), the Silver Platter "Chembank" CD-ROM, or on the internet by contacting mjollnir@daylight.com, subject: help (the last printed version of this database was in Hansch, 1979). Many P_{ow} values for chemical compounds, along with calculated or experimental flux rates, are provided in a report from the U.S. EPA (1992).

Permeation models for chemicals through the skin that are based on Fick's Law assume that the permeant be, strictly speaking, in a dilute aqueous solution. These models predict fairly well for compounds of moderate lipophilicity. For the extremes in aqueous solubility (very hydrophilic or lipophilic compounds), the partitioning effect due to the presence of water plays an increasingly important role. For instance, hydrophilic compounds prefer remaining in water rather than the lipophilic stratum corneum, thus less chemical tends to be absorbed from the aqueous solution compared to the pure compound (Bunge et al., 1995).

For neat highly water soluble or lipophilic compounds, the permeation rate cannot be easily estimated, and direct experimental determination is required, as the flux may be higher or

lower than the flux for saturated aqueous solutions. The pure chemical may also directly damage the stratum corneum, which will dramatically increase absorption, e.g., methanol.

Several cautions must be kept in mind regarding all such model equations and the inherent limitations of the empirical data from which they are derived. The models do not take into account various abnormal physiological and pathological conditions, and physico-chemical factors that could greatly influence the dermal penetration rate (Barber et al., 1992; Vecchia and Bunge, 2001).

- General models may predict empirical results better for certain classes of compounds than others that may be scarcely represented in the empirical data set. Typically, compiled empirical data sets have not included many highly hydrophilic or highly lipophilic compounds. *In vitro* experimental permeation systems are especially prone to errors with highly lipophilic compounds, because the compounds may not be as readily removed from the viable epidermis due to lack of a functioning microcapillary blood perfusion.
- The models have been developed from experiments using normal skin. As will be discussed below, physically damaged skin, or skin previously exposed to chemicals, will likely allow much more penetration of chemicals than healthy, intact skin. Further, empirical data from aqueous solutions may not account for possible damaging effects that higher concentrations of chemicals might have on the skin and its barrier function.
- The empirical data using aqueous solutions do not reflect non-aqueous matrix effects of the vehicle, including whether the compound is in soil.
- Some of the compounds in the empirical databases are prone to ionization, which is pH and concentration dependent, and a factor that can affect skin penetration rate by one to two orders of magnitude.
- The empirical data is often performed at temperatures ranging from room temperature (i.e., ~25°C) up to body temperature (i.e., ~37°C). Permeability coefficients roughly double with a temperature increase of 5° – 7°C (Vecchia and Bunge, 2001).

These are all potentially important limitations of the present models in prediction chemical penetration during workplace exposures.

Table 3-8 provides some examples of the flux through human and animal skin for some compounds in saturated aqueous solution and neat concentrations. The experimental flux from an air concentration at the TLV® for some of the compounds is also shown for comparison, when available. It should be noted that experimental fluxes often differ when reported by different experimenters. Since experimental K_p can be imprecise due to many experimental variables, the calculated fluxes may provide a practical alternative when sound experimental data are not available.

Table 3-8
Absorption flux of neat compounds, aqueous saturated solutions, and some vapors through human and animal skin

Compound	Neat Compound, In Vivo ($mg/cm^2/hr$)[1]	Saturated Aqueous Calc. Flux from Experimental K_p ($mg/cm^2/hr$)	Saturated Aqueous Calc. Flux from Calculated K_p[5]	Vapor Uptake, In Vivo at TLV® ($mg/cm^2/hr$)
Aniline	0.2 - 0.7	0.75	0.11	1.5×10^{-4} [6]
Benzene	0.24 - 0.4; 0.22 [3]	0.2	0.04	3.2×10^{-4} [6]
2-butoxyethanol	0.05 - 0.68 [2]; 0.9 [3]		1.6	2.4×10^{-4} [7,8]
n-butanol	0.53 [4]	0.31	0.40	
dimethylformamide	9.4		0.34	
ethylbenzene	22- 33		0.009	
2-ethyoxyethanol	0.8	0.23	0.43	
methanol	11.5 [2]	1.3	1.25	
2-methoxyethanol	2.8		1.27	
methyl ethyl ketone	5.3 [2]; 5.8 [2]		0.53	
styrene	9 - 15; 0.06 [2, 9]	0.01	0.01	2.6×10^{-4} [6] 0.04 [8] 0.016; 0.05
toluene	14 - 23; 0.32 [3, 10] 0.08 [2, 11]		0.02	0.014 [6]
m-xylene	0.12 - 0.15; 0.06 [9]		0.009	0.011 [6]

[1] See Leung and Pastenbach (1994) for references
[2] Recent data. [3] Used Pig skin, generally 2-3 times greater flux than human;
[4] DiVincenzo & Hamilton (1978) dog in vivo
[5] Used Robinson Model, see Wilschut et al. (1995); [6] Riihimaki & Pfaffli (1978); [7] Corley et al.(1997)
[8] Calculated from experimental K_p; [9] Tsuruta, rat skin (1982); [10] Jacobs & Phanprasit (1993)
[11] Ursin et al. (1995)

Factors Affecting Dermal Absorption and Effects on the Skin

ANATOMICAL DIFFERENCES

Permeation of chemicals through the stratum corneum occurs through the intercellular bipolar lipid channels. However, it has been determined that there are regional variations in skin permeability that correspond to the differing amounts of intercellular lipids. Table 3-9 shows the relative difference in permeation of three compounds and water through various regions of the human body. Parathion is the least water soluble, while hydrocortisone is the most. The increase in hydrocortisone permeation in some regions of the body appears to correspond to eccrine sweat production. Note how the palm, even though about 27 times thicker than the forearm (refer to Table 3-6), is almost equivalent in its barrier function. The planar stratum corneum (palms and soles of the feet), although thicker and able to resist physical abrasion better, has less extracellular lipid and poor diffusion barriers to chemicals, especially those that are more hydrophilic. The percentage weight of lipids in the soles, for instance, is 1.3%, whereas lipids account for 7.2% by weight in the forehead (Elias et al., 1981). Comparison of the water

Table 3-9
Comparative relative permeability of human skin to topical ^{14}C Hydrocortisone, Parathion, Malathion, and Water

Regional Variation	Parathion[1]	Malathion[1]	Hydrocortisone[1]	Water[2]
Forearm (ventral)	1	1	1	1
Palm	1.3	0.9	0.8	3.7
Ball of foot	1.6	1	—	12.6
Abdomen	2.1	1.4	—	1.1
Back of hand	2.4	1.8	—	1.8
Scalp	3.7	—	3.5	—
Angle of jaw	3.9	—	13	—
Forehead	4.2	3.4	6	2.7
Axilla	7.4	4.2	3.6	—
Scrotum	11.8	—	42	5.5

[1]data from Maibach et al., 1971
[2]data from Schueplein and Blank, 1971

loss through each site (20 - 40 g/m²/hr., versus 4-7 g/m²/hr., respectively) correlates with the difference in extracellular lipid (Lotte, 1987).

The greater permeability of some body regions can be important if that is the location of contact with chemicals. For instance, the head region, notably the jaw angle and behind the ear, are particularly permeable. Aerosol deposition of chemicals to these typically exposed areas, or transfer of chemicals through direct contact with contaminated hands or safety equipment (e.g., eye glasses, respirators), is certainly possible. Workplace studies have produced evidence that indicates that, not only surface contact concentration, but also the anatomical site, along with its unique skin permeability, should be taken into account when interpreting skin deposition data. A study of pesticide exposure found that patch data from some select locations, such as the neck and ankles, correlate better with biological monitoring results than whole body measurements (de Cock, 1995). In a study of skin permeability to polyaromatic hydrocarbons, average absorption rate constants at different skin sites were found to range from 0.036/hr to 0.135/hr (Van Rooij et al., 1993). Thus, the amount absorbed per skin site from equivalent skin concentrations will vary.

Just as there are regional differences in skin permeability, there are also differences in susceptibility to skin irritants. Permeability and irritant response are probably partially related, although biological mediators of response also play a role (Harvell and Maibach, 1994). Cua et al., 1990, found the thigh to be the most sensitive to the irritant sodium lauryl sulfate, while the palm and ankle were least responsive to this chemical.

INDIVIDUAL DIFFERENCES

Inter-individual differences in persons with apparently healthy skin appear common and can be appreciable. According to Feldman and Maibach (1974), the standard deviation expected is one-third to one-half the mean value. Assuming a normal distribution, one person in 10 will absorb twice the mean value, while one in 20 will absorb three times this amount (Maibach et al.). Up to 10-fold differences in interpersonal skin absorption rate have been seen within small groups exposed to such compounds as hydrocortisone and parathion (Feldmann and Maibach, 1965; Maibach, 1976; Dary, 1994). The apparent transdermal absorption rate of nitroglycerin in healthy volunteers, using the same site, but three different topical delivery systems, resulted in variations from 21% to 78% with six subjects (Wester and Maibach, 1987). Individual variation in alveolar air concentrations following a 30-minute skin exposure to five different chlorinated solvents is shown in Table 3-10. A wide range in the apparent uptake was seen, assuming minor confounding from differences in *in vivo* metabolism of the absorbed compound (Stewart and Dodd, 1964). Similar large inter-individual differences were seen by Lauwerys et al. (1978) when 11 male volunteers were asked to immerse both hands into pure m-xylene for 20 minutes. The skin of all volunteers was free of lesions. The total amount of m-xylene absorbed ranged from 16 to 110 mg. Same person differences tested twice over at least a one week period were two-fold or less. The range of skin permeability seen in healthy

Table 3-10
Individual range in alveolar air concentration following a 30-minute dermal exposure

Solvent	Subjects	End of Exposure	30-min. Post-exposure
carbon tetrachloride	3	0.11– 0.83	0.45 – 0.79
trichloroethylene	3	0.033 – 0.76	0.10 – 0.40
tetrachloroethylene	5	0.17 – 0.17	0.26 – 0.35
methylene chloride	3	2.3 – 3.6	1.1 – 6.6
1,1,1- trichloroethane	6	0.19 – 1.02	0.54 – 0.77

Adapted from Stewart and Dodd (1964)

individuals may also account for the wide range of susceptibilities of response to irritants (Judge et al., 1996; McFadden et al., 1998).

Gender and race, as these relate to the skin, have only been marginally studied to date. However, significant gender-related differences have not been found after repeated, daily application of an irritant (Lammintausta et al., 1987; Goh and Chia, 1988). Black skin was found to respond to irritation more than white skin, using objective techniques such as transepidermal water loss and increased cutaneous blood flow. However, no differences in erythema or in diagnosed cases of dermatitis have been noted (Basketter et al., 1996; Anonymous, 1973; Behrens et al., 1994). Age decreases the thickness, lipid content, and transepidermal water loss, but responsivencss to both irritants and allergens appears to decline with age (Cua et al., 1990; Harvell et al., 1994).

In occupational situations, where the skin is regarded as the principal route of exposure, individual variation in skin absorption may contribute to the differences often seen in biolcgical monitoring results when the extent of exposure appears comparable. Controlling for these differences in skin absorption, probably due to differences in skin integrity, would be an advance in skin exposure monitoring. It may be possible, in the future, to use the various noninvasive instrumental techniques that are presently available to check individual skin characteristics, however, these have not yet been utilized in studies simultaneously measuring internal dose. Skin measurement techniques have been used mainly in laboratory settings, but are increasingly being used to study individual differences in skin integrity in the workplace, which may be indirectly related to susceptibility to irritants, allergens, and systemically absorbed chemicals.

PHYSICAL DAMAGE

The barrier properties of the stratum corneum, given its thinness, are quite unique. The important practical aspect of this knowledge is the realization that when the stratum corneum is

healthy, it can perform an outstanding job of resisting chemical insults. However, if this thin barrier is physically damaged, or the intercellular lipids are altered, the stratum corneum becomes much less of a barrier. Table 3-11 presents some examples of damage by abrasion and ultraviolet light irradiation to the stratum corneum, and the effect that different types of damage might have on absorption.

Abrasions and cuts are probably the most common insults to workers' skin. As shown in Table 3-11, a non-intact stratum corneum offers little protection against permeation. There have been numerous documented cases where exposure to chemicals, not normally absorbed through the skin in sufficient amounts to cause even mild effects, have actually resulted in death when a few scratches were present. In one case, a woman pruning orchard trees that had been sprayed earlier with paraquat, developed scratches on her unprotected arms and hands during her work. Normally, paraquat is not a dermal exposure hazard due to its poor permeation through healthy skin. In this case, death ensued from respiratory failure a few days later (Newhouse, 1978). Experimentally removing the stratum corneum by tape stripping resulted in 2.6 to 8.5-fold increases in absorption of seven different pesticides (Maibach and Feldman, 1974). Some dangerous radionuclides, like cobalt-chloride (which are poorly absorbed through intact skin (<0.1%)) will rapidly penetrate abraded skin (52%) after 60 minutes (Kusama et al., 1986).

Table 3-11
Effect of type of physical damage on skin absorption of nicotinic acid human skin

Condition of Skin	% Absorbed In Vivo	% Absorbed In Vitro
Normal	7	5
Abraded	47	51
Tape Stripped		58
UV Irradiated[1]		
1.5 minutes	22	7
6 minutes	51	13

[1] application was made 3 days after irradiation
Adapted from Bronaugh and Stewart, 1985a

Workplace risk assessments should consider skin condition. In one study of chlorophenol exposed workers in a timber mill, the urine concentrations exceeded what was predicted based on skin contact measurements by 70%. It was subsequently determined that the workers' forearms typically became abraded from unprotected contact with the wood, probably allowing more percutaneous absorption than would occur through intact skin (Fenske et al., 1987).

Ultraviolet irradiation from natural sunlight has been shown to increase the permeability of chemicals through the skin. Studies in both animals and humans have shown increases of two- to three-fold after acute UV irradiation for compounds such as hydrocortisone, nicotinic acid, and ethanol (Solomon and Lowe, 1979; Bronaugh and Stewart, 1985; McAuliffe et al., 1991). However, after prolonged exposure to UV irradiation, the skin seems to become more resistant to permeation. This is presumably due to an increased amount of stratum corneum lipids in irradiated skin (Lehmann et al., 1992). More research is needed to determine if skin permeation is affected in workers chronically exposed to sunlight.

Cold-induced damage to the skin has been studied and found to disrupt the percutaneous penetration of model compounds, and to inhibit the repair of the barrier. This type of damage could help to explain the high prevalence of occupational dermatitis in some jobs like fish processing (Halkier-Sorensen et al., 1995).

In addition to physical causes of damage to the stratum corneum, chemical exposures can alter the skin as well. In the presence of organic solvents or surfactants, the surface as well as the intercellular lipids can be removed or disorganized, changing the partitioning and permeation of chemicals into the skin (Surber et al., 1990). After acute to subacute exposures, normal barrier function may be restored fairly quickly (~2 days) or take two to three weeks for recovery, depending on the type of solvent or surfactant and the chronicity of exposure (Grove, 1985; Patil et al., 1994; Malten, 1968; Effendy et al., 1995; Wilhelm et. al., 1994; Lamaud et al., 1984).

DERMATOSES

Dermatoses constitute a broad range of skin conditions that can result from a variety of chemical and physical traumas to the skin, and, as pointed out before, damaged skin presents a less effective barrier. Dermatitis is a form of damage, especially when the dermatitic skin is in the acute stage of response. For instance, percutaneous absorption of the pesticide lindane in patients with severe scabies was 10 to 40-fold greater than in persons without scabies (Lange et al., 1981). In other studies, measurable differences were seen in metabolite excretion of carbon disulfide exposed workers and in dimethylformamide exposed workers who had skin irritation or skin disease (Drexler et al., 1995; Wrbitzky and Angerer, 1998). Percutaneous absorption of xylene vapor appeared to be about three times greater in a volunteer with atopic dermatitis (Riihimaki and Pfaffli, 1978). Finally, a higher blood concentration of a pesticide was seen in a formulator when compared to his co-workers, which was attributed to the presence of scleroderma in the worker with high blood levels (Starr and Clifford, 1971). Hyperproliferation of the stratum corneum, as in psoriasis, exfoliative dermatitis, or ichtyosis, also results in increased

permeability of the skin (Solomon and Lowe, 1979; Scheuplein and Bronaugh, 1983). Rapidly generated stratum corneum, while thicker, is a poorer barrier.

Irritation of the skin can also result in increased percutaneous absorption. The data in Table 3-12 show an enhancement in percutaneous absorption that is related to the water solubility of four model compounds (Wilhelm et al., 1991). These compounds were applied to the upper back of hairless guinea pigs after 0.5% sodium lauryl sulfate in water was applied in an occlusive chamber for 24 hours. Because the diffusional resistance of the stratum corneum is greater to polar compounds than to non-polar compounds, any disruption of the barrier should enhance penetration of hydrophilic compounds to a greater extent than would occur for lipophilic compounds. The data support this in that enhancement was 260% for the most hydrophilic compound but only 130% for the most lipophilic.

In another experiment with sodium lauryl sulfate, which induces irritation, response to nickel salts in sensitized persons, as well as animals, was appreciably increased with the addition of the irritant (Samitz, 1958). Irritation, as well as several other factors, which can influence sensitization, is reviewed elsewhere (Kligman,1966).

OCCLUSION

Occlusion is one of the most effective means of increasing chemical permeation through the skin. Covering the skin with a moisture impenetrable barrier not only prohibits evaporative loss of any chemical that may have contaminated the surface of the skin, but rapid skin hydration and increased temperature increases the permeation rate of the contaminant. This effect has long been known, as demonstrated by Burckhardt (1939), who successfully used occlusion to promote sensitization to turpentine. With occlusion, nearly all animals were sensitized; with-

Table 3-12
Effect of chemical irritation on percutaneous penetration

Compound	Log Partition Coefficient	Percent Enhancement
HC	1.6	260
IM	3.1	160
IB	3.5	190
AC	6	140

Adapted from Wilhelm et al., 1991

out it none were sensitized. In this experiment, the site of exposure was occluded for eight to 12 hours.

The stratum corneum normally contains between 5% and 15% water, but this can be increased to as much as 50% by external factors (Bird, 1981). Occlusion is an effective way to hyper-hydrate the skin. The mechanisms by which hydration can influence percutaneous absorption include altering the partitioning between the surface chemical and the skin due to the increasing presence of water, swelling the corneocytes and possibly altering the intercellular lipid phase organization, increasing the skin surface temperature, and increasing the blood flow. It has been postulated that with hyper-hydration of the stratum corneum, the effective partition coefficient of the penetrant between the stratum corneum and viable epidermis is reduced, because the two tissue phases now appear more similar (Bucks et al., 1991).

Occlusion does not appear to influence the percutaneous absorption of all compounds equally. Rather, the impact of occlusion is influenced by the polarity of the chemical. It most increases the absorption of moderately lipophilic molecules, but is less effective on the absorption rate of highly lipophilic or highly hydrophilic compounds. Figure 3-7 illustrates this process for four steroids with and without occlusion. There may be some chemical-specific factor that also affects occlusive penetration, since the same degree of enhancement at each value of

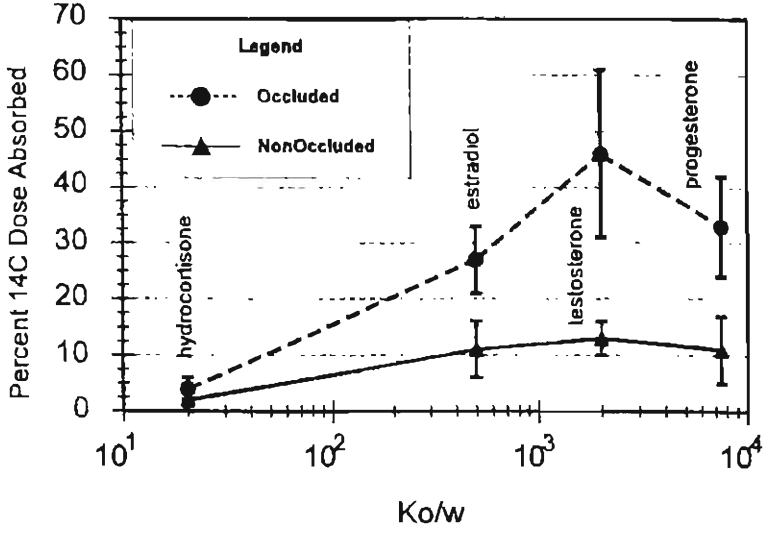

Figure 3-7. Effect of occlusion on four steroids as a function of different water solubilities. The results are from a single topical application of 4µg/cm² to the ventral forearm of human volunteers. Occlusion was continuous for 24 hours, after which the skin site was washed. Adapted from Bucks et al., 1991.

K_{ow} is not always seen with all compounds (Makki et al., 1996; Behl, 1980). Nevertheless, occlusion appears to enhance percutaneous absorption to some extent for all compounds tested.

Just as the permeability of human skin was shown to vary from location to location, it seems that there are anatomical differences in the extent of enhancement of percutaneous absorption due to occlusion (see Figure 3-8). In an experiment by Qiao et al. (1993) using weanling pigs, occlusion greatly increased parathion absorption in most sites tested, but to a lesser degree in the skin of the shoulder region. In terms of human relevance, the pig abdominal skin absorption value matches the absorption value for human forearm skin in non-occluded tests with parathion. This data also underscores the importance of skin site selection when conducting animal experimentation and comparing results between laboratories.

It should be realized that skin permeation effects of occlusion in the workplace scenario are likely to occur when the contaminant gets underneath personal protective clothing. Gloves or a rubber respirator provide excellent occlusive coverings. There have been reports where increased personal clothing protection has increased exposure because the clothing became contaminated on the inside (Kusters et al, 1992).

The above studies demonstrate the increase in permeation due to a one-time occlusion of contaminants on normal skin. In addition, prolonged occlusion has been found to produce chronic impairment of the barrier function of the skin. Figure 3-9 shows the results of an

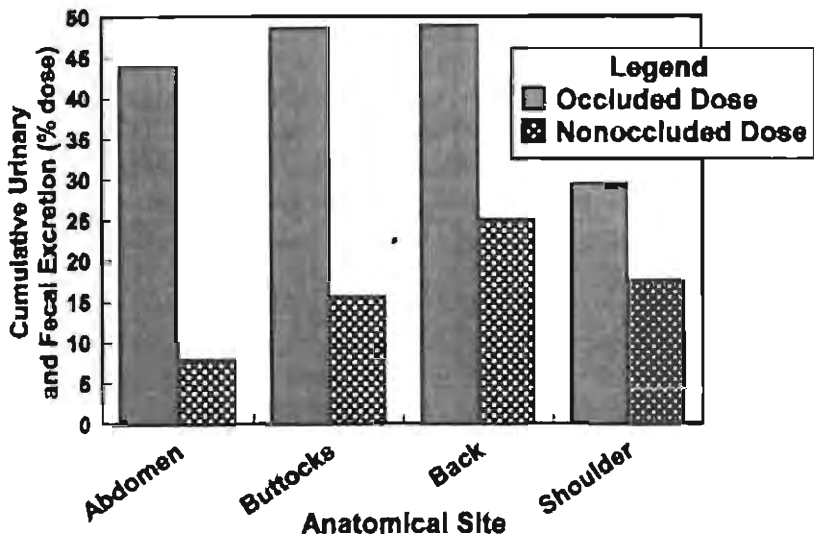

Figure 3-8. Effects of anatomical site and occlusion on the percutaneous absorption and excretion of 2,6-parathion in vivo in pigs. Skin sites were occluded and urine and feces were collected for 168 hours. Maximal excretion occurred for the occluded and nonoccluded groups in 24-36 and 36-48 hours, respectively. While occlusion significantly increased absorption for all sites, regional differences by skin site were found.

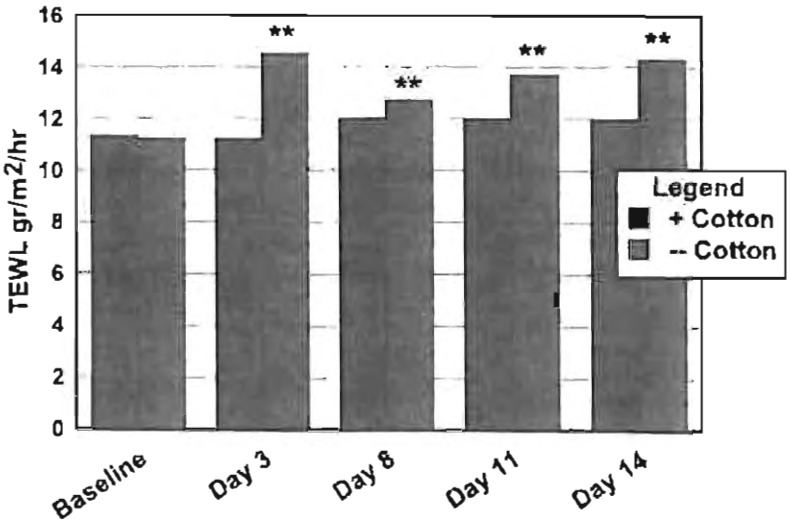

Figure 3-9. Effect of long term experimental occlusion on human skin. Wearing of occlusive glove for 6 hours per day for 14 days had a significant detrimental effect on skin barrier function, as measured by transepidermal water loss measurements. When a cotton glove was worn underneath, the effect was not detected. It was concluded that gloves may be a substantial factor in the pathogenesis of cumulative irritant contact dermatitis, but that with proper use the risk might be minimized. Adapted from Ramsing and Agner, 1996.

experiment to determine the long-term effect on barrier function by prolonged use of an occlusive glove (Ramsing and Agner, 1996). The protocol involved 18 volunteers who wore non-latex hypo-allergenic gloves for a minimum of six hours while sleeping at night. During sleep, the skin temperature and friction were reduced (a best case situation). Half of the volunteers wore cotton gloves underneath the occlusive glove. The results indicated increased trans-epidermal water loss for each of the measurement days up to day 14 for the skin with the occlusive glove only. However, use of the cotton glove prevented this damage. The authors concluded that prolonged occlusion can damage the barrier function of the skin, and might enhance susceptibility to irritants and sensitizing agents. Minimizing the use of gloves and using a cotton glove underneath are two ways to reduce the occlusive effects on the skin.

Susceptibility to irritants was demonstrated by Graves et al. (1995) after the skin was occluded. In their experiment, the skin was occluded for four hours or eight hours. After the covering was removed, skin permeability was evaluated by measuring the time to onset of hyperthermia due to topical application of the irritant hexyl nicotinate. After four hours of occlusion, the time to onset was reduced to 59% of its pre-occlusion value. After eight hours of occlusion, this was further reduced to 38% of the pre-occlusion value.

Within two days of occlusion, marked cytotoxic damage to Langerhans cells, melanocytes, and keratinocytes occurred (Klingman, 1996). Intercellular edema and marked swelling

of corneocytes was also prominent. The damaging effects of prolonged hydration can quickly lead to dermatitis.

Interesting questions asked by Graves et al. (1995) were: (1) At what duration of wearing a glove continuously would there be a significant impairment of the stratum corneum barrier function? (2) How frequent and how long should non-occluded periods be to prevent a cumulative effect? (3) Is the impairment of barrier function seen in these experiments sufficient to increase the incidence of irritant contact dermatitis? and (4) Does this impairment correspond to an increased susceptibility to mechanical trauma? These are all relevant and practical questions, and further research will be needed to provide answers.

TEMPERATURE AND RELATIVE HUMIDITY

Molecular diffusion and solution will increase within matrices as the temperature increases. It should be no surprise that as temperature increases, the permeation of chemicals through membranes such as the skin will also increase. Normally, the skin surface temperature is between 32° and 35° C, but this can increase or decrease with heightened or lowered ambient temperature, or if the temperature of a liquid contacting the skin is different.

Figure 3-10 illustrates how the ambient temperature affected the excretion of p-nitrophenol in the urine of human volunteers after 5 grams of 2% parathion dust had been applied topically

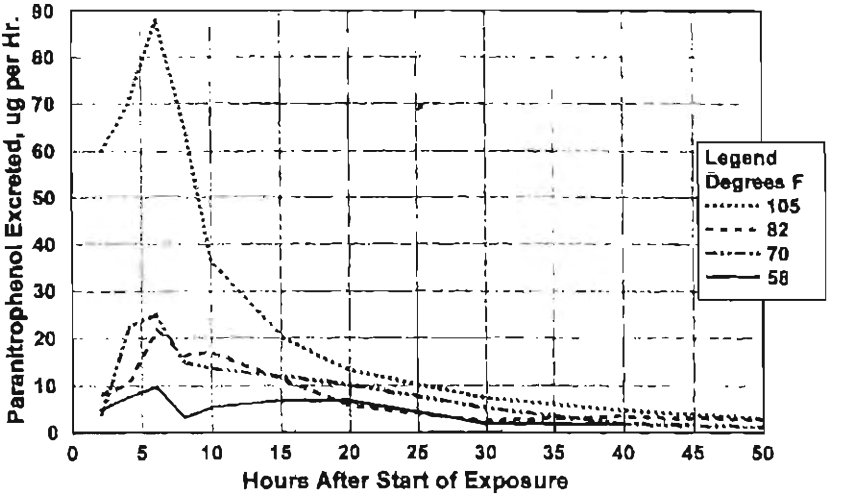

Figure 3-10. Para-nitrophenol excreted by human volunteers following dermal exposure to 2% parathion dust at different ambient temperatures. There were two replicate tests at 58°F, one at 70°F, three at 82°F and nine at 105°F. Adapted from Funckes, et al., 1963.

for two hours. Only one hand and forearm were exposed and placed into a temperature-controlled chamber. Following the two hour exposure, the skin surface area was decontaminated by scrubbing with soap and water for five minutes, followed by two washes with ethyl alcohol. The average excretion rate increased from 4.9 µg/hr. at 58° F (14° C) to 19.6 µg/hr. at 105° F (40° C) over 41 hours (Funckes et al., 1963). Chemical vapor penetration has also been empirically determined to increase with ambient temperature. Percutaneous absorption of aniline vapor, for example, increases about 20% for each 5° C increase in air temperature (Dutkiewicz, 1960). Percutaneous uptake was also significantly increased for 2-butoxyethanol vapor when the air temperature (but also humidity) was increased from 23° C to 33° C (Johanson and Boman, 1991).

Increasing relative humidity has been shown to increase percutaneous absorption. Chang and Reviere (1991) found that the percutaneous absorption of parathion increased by two- to four-fold when the humidity was increased from 20% to 90%, while the temperature remained the same.

DURATION AND FREQUENCY OF SKIN CONTACT

In the workplace, contact with chemicals may be intermittent and sporadic. A key characteristic of the chemical that will determine the residence time of a single contact is the volatility of the chemical. For uncovered skin, highly volatile chemicals will evaporate before appreciable percutaneous absorption occurs (Riefenrath, 1989). Volatility inversely correlates with the persistence of a chemical on the skin surface and the amount of chemical ultimately absorbed systemically. Figure 3-11 presents the results of continuous dermal exposure to n-butanol (vapor pressure [v.p.] = 6 mm Hg) and 1-minute exposure every 30 minutes. The periodic exposure results in a blood concentration that is lower than for continuous exposure. For more volatile compounds, such as toluene (v.p. = 21 mm Hg) and 1,1,1-trichloroethane (v.p. = 100 mm Hg), no such cumulative effect occurs (Boman et al., 1995). The absorbed dose of highly volatile compounds from repeated short exposures is appreciably less when compared to continuous immersion (Stewart and Dodd, 1964). Presumably, the systemic absorption of compounds less volatile than n-butanol would eventually approach continuous contact conditions as evaporative loss decreases further.

Typically, experimental percutaneous absorption studies test naive skin where the chemical agent is applied only once. Is this indicative of repeated exposures that are more likely to occur in the workplace? Some studies have attempted to answer this. Briefly, no cumulative effect of repeated exposures has been observed concerning the permeability of the skin, *unless* the skin is damaged by the chemical exposure (Bucks et al., 1990). Increased absorption was observed in skin damaged by chemical exposure when salicylic acid or hydrocortisone were repeatedly applied to the skin (Roberts and Horlock, 1978; Wester et al., 1977). Both chemicals are known to affect the integrity of the stratum corneum. With other compounds, such as malathion and benzoyl peroxide, no difference in absorption was seen after repeated exposures (Wester et al., 1983; Courtheoux et al., 1986). Washing with soap and water between dose

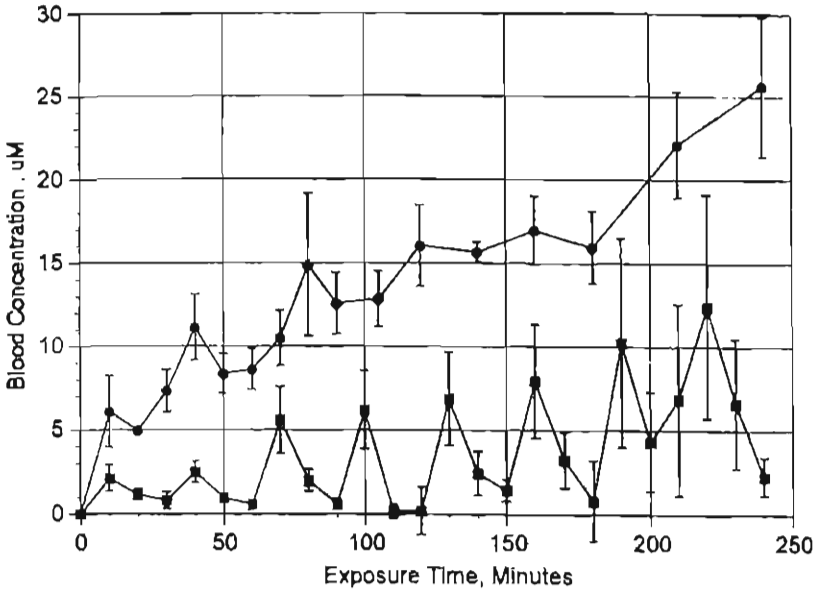

Figure 3-11. Concentration of n-butanol in blood in guinea pigs during continuous and intermittent skin exposure. There is generally an increasing blood concentration with repeated exposures over time. Compounds that are more volatile do not exhibit this trend, and it is rational to expect the converse, that compounds that are less volatile will remain on the skin longer and better mimic continuous exposure. Adapted from Boman et al., 1995.

applications contributed to increased absorption of most compounds, but this has only been demonstrated with animals. Human skin may be more resistant to damage from soaps, but this question will require further study (Bucks et al., 1989a).

VEHICLE

A vehicle in this context is commonly a liquid in which another contaminant, which may be more toxic, is contained. Vehicles are important to percutaneous absorption because they may enhance the absorption rate by either disrupting the stratum corneum barrier function, or encouraging partitioning towards the skin, or a combination of these processes. As will be shown in the next examples, vehicles, or the co-components of a mixture, can have significant effects on how much of a toxic chemical enters the skin. Thus, the rate of uptake can differ appreciably from neat (pure) chemical absorption.

A dramatic example of how the vehicle can influence the uptake of contaminants in a solution is depicted in Figure 3-12. Three dilutions of alachlor in the water soluble commercial formulation were tested for permeation using *in vitro* human skin (Bucks et al., 1989b). One

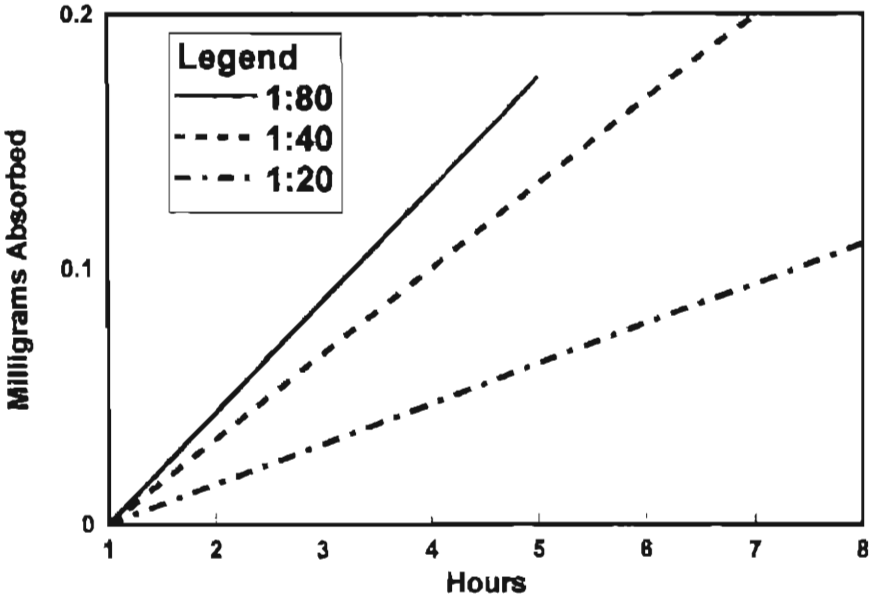

Figure 3-12. Effect of formulation dilution on the in vitro percutaneous absorption of alachlor. Increasing the dilution of the alachlor formulation resulted in significant enhancement ($p<0.01$) in the rate and extent of alachlor penetration. The reason for this might be due to a favorable shifting of the partition coefficient with dilution in water. Adapted form Bucks et al. (1989).

might assume increasing absorption with more concentrated dilutions would occur because diffusional mass going into the stratum corneum is dependent on the concentration of the chemical on the surface. However, the opposite was seen in these experiments. The 1:80 dilution led to twice the absorption as the 1:20 dilution. The authors hypothesized that, in this experiment, the more concentrated dilution contained more of the non-aqueous solubilizing material, which is able to "hold" the alachlor in the solution. When the concentration is decreased in the most dilute mix, most of the solution is aqueous and the highly hydrophobic alachlor preferentially migrates towards the skin. The skin:vehicle interface concentration may, therefore, be greater in the 1:80 dilution than in the more concentrated dilutions.

Another example of vehicle effects on percutaneous absorption, particularly where the vehicle is a mixture of solvents, is demonstrated in the data in Table 3-13. In this experiment, xylene absorption as measured by methylhippuric acid excretion, was compared to exposures of pure xylene, 1:1 mixture of xylene plus isobutanol, or 10:10:1.5 mixture of xylene, isobutanol, and water to saturation (Riihimaki, 1979). In each case, volunteers immersed both hands up to the wrists in the solvents for 15 minutes at room temperature. Interestingly, the addition of a small amount of water to the mix dramatically increased the xylene permeation rate so that it was almost three times greater than the xylene-isobutanol mix, and slightly more than pure xylene alone. With only xylene and isobutanol, there appeared to be a conspicuous dehydration

Table 3-13
Percutaneous absorption of m-xylene and mixed solvent effects in *in vivo* human skin

Solvent	Symptoms	Methylhippuric Acid Excretion
Pure Xylene	Erythema No "tightness"	1.0
1:1 Xylene + Isobutanol	Erythema No "tightness"	0.4
10:10:1.5	Mild wrinkling; skin dry and oily	1.1

Adapted from Riihimaki, 1979

of the skin by isobutanol and a delay in the absorption of xylene evident in the methylhippuric acid excretion (data not shown). The result seen by adding a small amount of water might be due to the increased hydration of the stratum corneum provided by the addition of water, or increasing the partitioning of xylene out of the saturated aqueous mixture towards the skin.

More typically, the effect of the vehicle is compared among different pure solvents. The rule of thumb that "likes dissolve likes" applies to permeation in that hydrophilic solutes will tend not to partition to the skin if in a hydrophilic solvent, and lipophilic solutes will tend not to partition as well into the skin if present in a lipophilic solvent. The importance of the lipophilicity of the vehicle on maximum permeability for a wide range of compounds was studied by Lien and Gao (1995), who found that the ideal lipophilicity of the permeants in a lipophobic vehicle was between log P_{ow} 2.5 to 6, but in a lipophilic vehicle the ideal lipophilicity of the permeants was shifted to 0.4 – 0.6. This principle is exemplified by the 10-fold difference in the skin flux rate of benzocaine when in a water (lipophobic) vehicle or in polyethylene glycol (PEG) 400 (lipophilic). The solubility of benzocaine in water is 1.26 g/L whereas the solubility is 435 g/L in PEG 400. The skin flux rates were 0.1 mg/cm2/hr and 0.01 mg/cm2/hr, respectively (CTFA, 1983).

A summary of many of the above-mentioned factors that can affect skin permeation rate are included in the results shown in Figure 3-13. These experiments assessed the impact of adding water to saturation, to a variety of alcohols with carbon numbers 1 through 10 (Scheuplein and Blank, 1973). By adding carbon length to a simple alcohol reduces its polarity (increases lipophilicity). These experiments with aqueous and neat alcohol solutions demonstrate the importance of the aqueous contribution, its effect on key physical parameters, and the interaction of these measurement parameters with percutaneous flux (J_s) through the epidermis. The partitioning (K_m) effect from the aqueous solution is strong, but the concentration reduction of the alcohols with increasing carbon number causes the flux to decrease since flux is dependent on concentration. Notice how the permeation rate (K_p) increases in the aqueous solution as the carbon number increases. The opposite is seen for the pure alcohol exposures. This is because the stratum corneum/chemical partition coefficient is low for pure lipophilic compounds. To illustrate this point, liquid hexanol (concentration 8.2 moles) is approximately 150 times more concentrated than saturated aqueous hexanol (0.55 moles), yet the K_p of aqueous hexanol is almost twice as great. The large measured flux for the pure alcohols with low carbon number (especially methanol) is attributed to the damaging effects on the stratum corneum. This damaging effect increases the theoretical flux about 10,000 times.

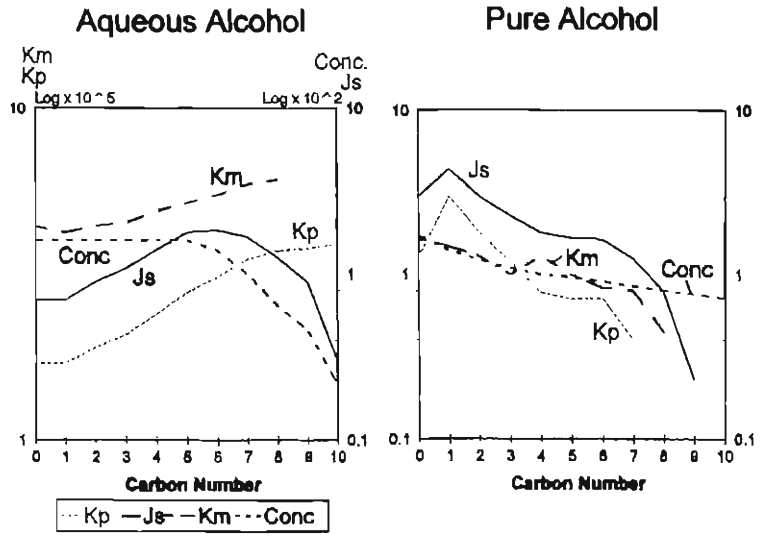

Figure 3-13. Effect of adding water to alcohols with 1 - 10 carbon numbers. Refer to text for complete explanation.

Key: K_p = permeability constant
J_s = flux of solute
K_m = tissue: solvent partition coefficient
Conc. = solute concentration (moles/liter)

Adapted from Scheuplein et al., 1973.

MATRIX

Often workplace exposures to chemicals occur through a particle matrix. Thus, toxic compounds may adhere to soil particles, dust, or other "dirt-like" matrix and come into contact with the skin. Unfortunately, a limited amount of research has been published on this subject.

The absorption of eight compounds *in vivo* in rhesus monkeys over a 24-hour period, when the compound was applied in either soil or one of three solvent vehicles, is shown in Figure 3-14. The application sites were covered with a non-occlusive patch during exposure to prevent loss of particles from the skin surface. Although soil reduced the overall absorption of these compounds to about 60% of absorption compared to when applied in solvent, there were some compounds for which the absorption was similar regardless of matrix (Wester and Maibach, 1996).

In the same study, an *in vivo* percutaneous absorption study of the pesticide 2,4-D was performed with rhesus monkeys with the objective of comparing the kinetic rate of absorption (Wester and Maibach, 1996). The pesticide was applied to the skin in either acetone (and left to quickly evaporate) or soil (1 mg/cm^2). The mean percentage absorbed at 8 hours was 3.2 ± 1.0 when applied in acetone, but only 0.05 ± 0.04 when applied in soil (see Figure 3-15). Absorption increased for the soil vehicle at 16 hours to 2.2 ± 1.2, and at 24 hours 9.8 ± 4.0 percent had been absorbed. The increase of absorption when applied in acetone appeared linear over time and at 24 hours peaked at 8.6 ± 2.1%. Thus, over a long period (24 hours), absorption from either vehicle appeared about equal for 2,4-D, regardless of whether it was in a soil matrix or applied in acetone. However, a marked delay in absorption presumably indicates the time it must take for 2,4-D to get from the soil into and through the skin.

Different findings were reported in a prior study. Shu et al. (1988) found that the dermal penetration of TCDD in soil after just 4 hours of contact with *in vivo* rat skin was approximately 60% of the amount absorbed following 24 hours of contact. The skin absorption kinetics appeared faster for TCDD than the findings described above for 2,4-D. Despite the rapid initial flux, at 24 hours, only approximately 1% of the TCDD was absorbed. As in the study of 2,4-D, the soil was kept in place while on the skin with a non-occlusive covering. Other variables, like TCDD concentration in soil (10 vs 100 ppb), and the presence of used crankcase oil (0, 0.5, 2.0%) had no significant influence on dermal bioavailability.

Turkall et al. (1994) performed a study on pure and soil-absorbed naphthalene in dermally exposed male rats. Within 12 hours after application, it was found that approximately 50% of the naphthalene dose was excreted in the urine and was equivalent when applied in the pure form or as the clay soil-absorbed mix. The corresponding result was 33% for sandy soil-bound TCDD. The study protocol directed that the administered doses be sealed in a vapor tight chamber attached to the skin.

On the other hand, Yang (1989) compared the percutaneous absorption of benzo[a]pyrene (B[a]P) from petroleum crude or fortified soil, using rats as the experimental animal, and found

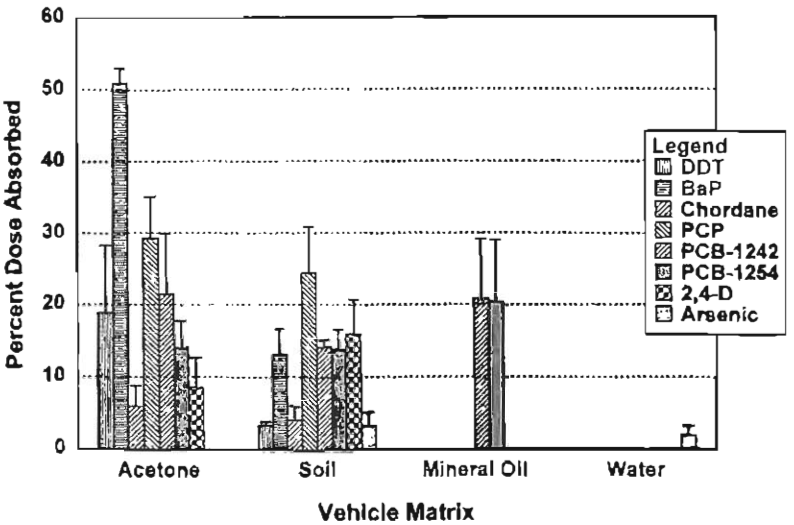

Figure 3-14. Percutaneous in vivo absorption from solvent vehicle or soil. Compounds were applied to the skin of rhesus monkeys at equal concentrations in soil or a liquid vehicle such as acetone, mineral oil or water and urine and feces collected for 24 hours. Adapted from Wester and Maibach, 1996.

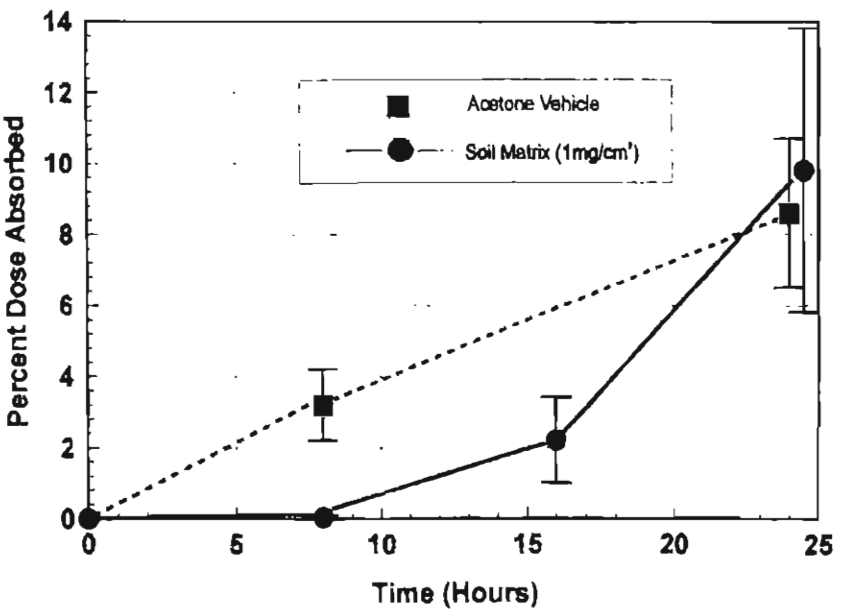

Figure 3-15. Kinetics of percutaneous absorption of 2,4-D in rhesus monkeys when applied in acetone (and left to evaporate) or in a soil matrix (adapted from Wester and Maibach, 1996).

that the percentage of the dose absorbed from the crude was 4 to 5 times greater than when an equivalent amount of B[a]P in crude oil was applied in soil.

Thus, different results concerning the effect of soil on percutaneous absorption have been found in these studies using various compounds and experimental protocols. Partitioning factors, duration of exposure, deposition rate and other unknown factors may be important for explaining these discrepancies. A theoretical and mathematical treatment of the physical chemistry involved in chemical-soil interactions with the skin has been presented in a series of articles (McKone, 1990, 1991; McKone and Howd, 1992). The ability to predict uptake accurately will likely improve as empirical data are collected in appropriately designed experiments.

Percutaneous absorption studies of volatile solvents in soil matrixes have been conducted using benzene, toluene and xylene (Skowronski et al., 1988, 1989, 1990). The solvents were either applied pure or mixed with soil and contained under a covered cap to prevent evaporation. When benzene was tested, clay soil decreased the dermal penetration, while the same soil had little effect on toluene absorption. In the xylene experiment, pure compound produced a slightly higher peak plasma concentration than for soil-absorbed xylene, but there was no delay in the time it took to reach maximum plasma concentration (1 to 2 hours). In the clay soil, the amount of xylene absorbed was equivalent to the pure xylene exposure.

A possible flaw with some of these studies is that they may have applied a soil loading upon the skin that is normally unlikely to adhere to people. Field studies involving a range of outdoor activities indicate that, at most, about 1 mg/cm^2 dry to slightly moist soil will adhere to skin (Kissel 1996a). Recent sampling of manual row crop harvesters found 1 to 1.6 mg/cm^2 as an average soil loading over both hands, although much of the contamination is on the palms (Boeniger, unpublished data). The loading does increase with moisture content, and other factors could affect this as well (Kissel et al., 1996).

The U.S. EPA and others have speculated that there is a finite thickness of soil upon the skin that a substance can diffuse through and result in absorption into the skin (U.S. EPA, 1992). This surface loading amount has been termed the "monolayer" thickness. Based on available data and expert judgment, the U.S. EPA estimated the monolayer thickness to be equivalent to about 5 mg/cm^2, which would have a 5 millimeters thickness if the soil had a density of one (U.S. EPA, 1992). More recent evidence indicates the monolayer occurs at a surface loading of only 2 mg/cm^2 for soil with a particle size less than 150 μm (Duff and Kissel, 1996). Experimental proof that soil loading affects cutaneous absorption was provided by Touraille et al., (1997). They found that the relative percent absorption of cyanophenol from contaminated soil at 7 hours was inversely proportional to soil loading. When the soil loadings were 5, 11, 40, or 140 mg/cm^2, the percent absorbed was 16, 10.9, 2.4, and 0.84, respectively. This indicates saturation of the process of chemical absorption from soil. The finding that a topical corticosteroid halcinonide cream that was applied at loadings above 5 mg/cm^2 did not appear to increase the rate of permeation corroborated this (Walker et al., 1991). Thus, the percutaneous absorption results from soil-bound chemical permeation studies performed in labo-

MODERN INDUSTRIAL HYGIENE

Volume 2

Biological Aspects

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ACGIH®
American Conference of Governmental Industrial Hygienists, Inc.
Cincinnati, Ohio, U.S.A.

ISBN: 1-882417-48-8

Printed in the United States of America

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