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Solvents and the skin

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Historically, solvents have caused up to 20% of all cases of occupational dermatitis [1–3]. Occupational skin diseases continue to be one of the most common occupational disorders. Because many cases of occupational skin disease go unreported, these numbers represent the tip of the iceberg. Although the rates of injuries and illnesses are declining, the prevalence rate of occupational skin diseases remains relatively constant at 5% to 20% [4].

The skin

The skin as a barrier: how skin structure affects permeability to solvents

Human skin is a versatile biologic barrier. It protects the individual from a wide variety of noxious stimuli, including chemical, physical (eg, mechanical trauma, UV radiation), and biologic (pathogens, immune stimulants) agents. It also serves complex homeostatic and metabolic functions and is the largest organ in the body. Knowledge of skin ultrastructure and biochemistry is important in understanding how solvents interact with the skin and how the skin barrier functions.

The skin consists of three anatomically distinct layers: the inner subcutis, the dermis, and the outer epidermis (Fig. 1). The subcutis contains lipocytes, fibrocytes, strands of collagen, vascular and lymphatic networks, and nerves. The dermis is a highly vascular connective tissue matrix containing pilosebaceous units, sweat glands, lipocytes, mast cells, and infiltrating macrophages and lymphocytes. Fibroblasts—the dominant cell type—elaborate the extracellular matrix of collagen, elastin, and glycosaminoglycans. The dermis varies in thickness from 0.6 mm on the eyelid to 3 mm on the back, palms, and soles. A basement membrane separates the dermis from the epidermis.

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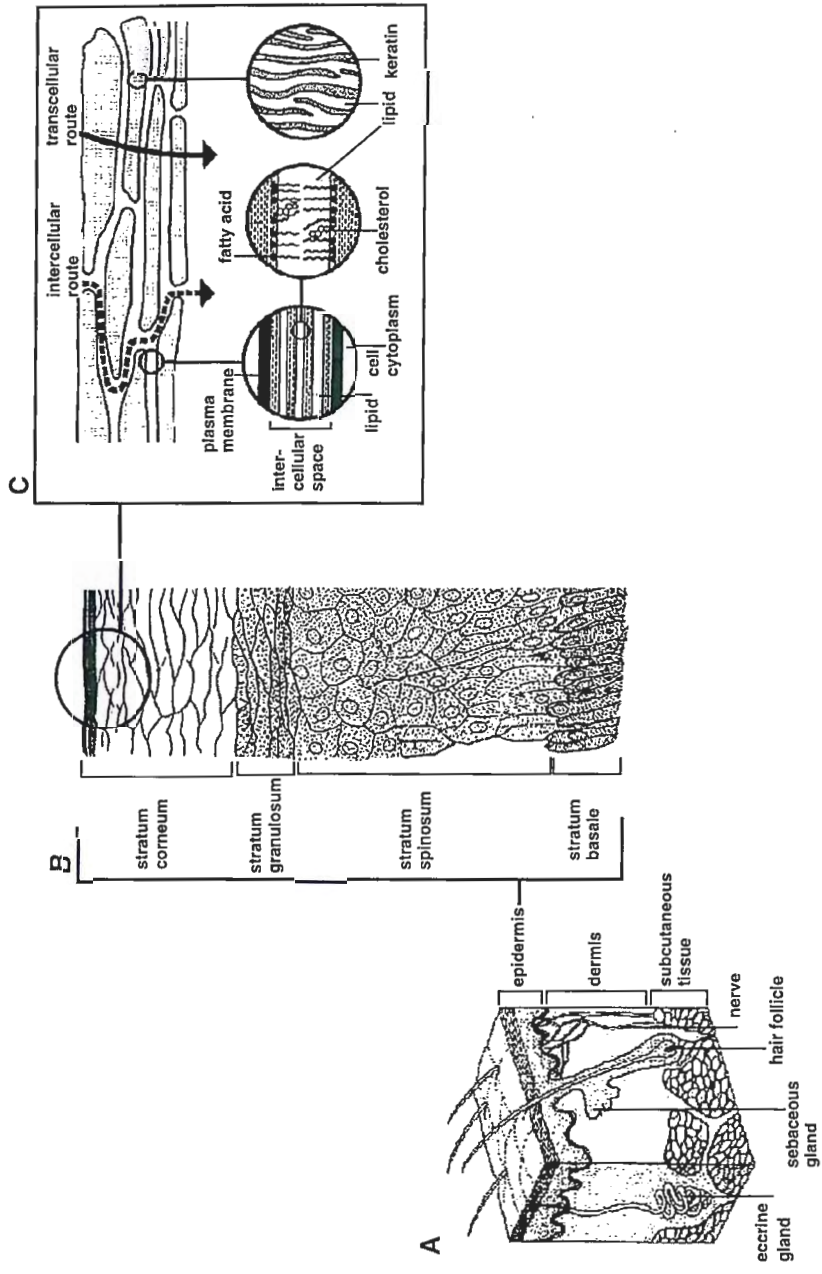
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intercellular route
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plasma membrane
inter-cellular space
cell cytoplasm
lipid
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cholesterol
lipid
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The epidermis (50–100 μm thick) is a dynamic, self-renewing tissue. It is composed of four anatomically and functionally distinct layers: the inner stratum basale, the stratum spinosum, the stratum granulosum, and the outer stratum corneum (SC). Cells differentiate as they migrate from the stratum basale to the stratum corneum, undergoing changes in their structure and composition. Typically it takes 14 days for cells to migrate from the stratum basale to the SC and another 14 days for the SC to be shed. In some skin conditions such as psoriasis, the entire process is accelerated, and cells that are not fully differentiated reach the SC, leading to alterations in the skin's barrier functions.

The stratum basale consists of a single layer of columnar epidermal stem cells 6 to 8 μm in diameter anchored to the basement membrane by hemidesmosomes. Lamellar bodies, responsible for lipid synthesis and elaboration, first appear in the stratum spinosum. In the stratum granulosum, keratin synthesis and lipogenesis increase progressively from lower to upper granulocytes. Lamellar bodies reach their highest density in the upper granulocytes. As keratinocytes begin the transition from granular cell to corneocytes (terminally differentiated keratinocytes), the cellular organelles dissolve, the keratin filaments condense, and the lamellar bodies fuse with the cell membrane, secreting their contents into the intercellular spaces. These lipids undergo enzymatic modification and are stacked into lamellae [5].

Solvents have a formidable and tortuous path to traverse as they cross the SC. Elias [6] described the organization of the SC as "bricks and mortar": the anuclear corneocytes packed with keratin filaments are the bricks and the extracellular lipids are the mortar. Adjacent and overlying corneocytes interdigitate through a series of ridges and undulations in their cell membranes. The desmosomes are like protein "rivets" that mechanically couple the corneocytes together, and with the interdigitations, minimize horizontal distortion, surface roughness [7,8], and penetration of exogenous substances. The individual corneocytes are surrounded by a cell membrane of densely cross-linked proteins and lipid.

The hydrophobic "mortar" is composed of ceramides, cholesterol, and fatty acids in approximately equimolar ratios with small amounts of triglycerides, glycosphingolipids, and cholesterol sulfate [9]. The ceramides play a key role in the lipid organization of the SC barrier [10]. It appears that the long tails of the ceramides form nonpolar layers stabilized by fatty acids and cholesterol, and the smaller ceramide heads form a polar layer. The alternating nonpolar hydrophobic and polar hydrophilic layers of the extracellular lipids are a critical component of

Fig. 1. Skin structure at the (*A*) gross, (*B*) microscopic, and (*C*) subcellular levels. (*Adapted from* www.Snoringcure.ca; Gray, Henry. Anatomy of the human body. Philadelphia: Lea & Febiger; 1918; Patrick Franke. Vitamin D3-Analogon/-Cyclodextrin-Kavitate-Herstellung, Charakterisierung und In-vitro-Liberation aus Dermatika [dissertation]. Berlin: Humboldt-Universität, Mathematisch-Naturwissenschaftliche Fakultät I, Diss., 1998-04-17 [in German]; and Shwarz P. Dermal Systems. Available at: www.acrossbarriers.de; with permission.)

the skin permeability barrier. More detailed discussion of theories on lipid structural organization at the molecular level in SC can be found in papers by Friberg et al [11], Forslind [12], Kitson et al [13], Norlen [14,15], and Bouwstra et al [16].

In the past, the SC was viewed as a dead layer that functioned solely as an impermeable barrier, preventing water loss and protecting the epidermis, dermis, and the individual from noxious agents. We now know that although the SC contains dead cells, it is very much alive [17]. Menon [18] described SC as "a smart material" that is able to respond to environmental changes through the use of a feedback system.

Normal SC is a very efficient barrier, permitting only 2 to 5 g/h/cm^2 of transepidermal water loss (TEWL). In experimental studies, TEWL is often used as an indirect measure of SC water content and therefore a marker of skin barrier function. Increased TEWL is a potent stimulus for repair of the skin barrier [19].

Several mechanisms appear to be involved in the detection of skin barrier disruptions. These include changes in ionic concentration gradients, perhaps induced by TEWL; feedback signaling by modified ceramides and sphingosine; and cytokine signals (tumor necrosis factor α, interleukin-1 α and β, granulocyte-macrophage colony-stimulating factor). These signals upregulate metabolic and cellular responses in the epidermis. SC barrier function is restored by immediate secretion of preformed lamellar body contents and later by de novo synthesis [6,18,21,22]. After the barrier recovers, rates of lipid synthesis return to normal [19]. Studies using TEWL as a measure of barrier function show that 50% recovery occurs by 24 hours, but the process is not complete until 7 days later [23]. Occlusive emollients such as petrolatum can restore damaged skin barrier function by inhibiting TEWL and thereby increasing the water reservoir in the skin [24,25].

The water content of healthy SC varies from 10 to 30% [18,26]. SC is very hygroscopic, absorbing 500% of its dry weight in less than an hour and swelling to 4 to 5 times its thickness [27]. Norlen et al [28] showed that corneocytes in the SC may swell more than 25% vertically, but lateral swelling is limited to 1% to 3%. Lateral swelling appears to be limited by the interdigitations and desmosomes discussed earlier.

Individual and environmental factors that influence skin irritability and permeability

A variety of factors affect skin irritability and permeability, including the anatomic location; individual factors (eg, gender, age, pre-existing skin disease, genetics, skin type, eccrine sweating, repair capacity, hydration of the SC, personal hygiene, skin damage); and environment (temperature, season, humidity). The anatomic location of solvent-exposed skin can have a dramatic effect on skin irritability and permeability. Intact stratum corneum varies from 10 to 20 mm in thickness, depending on the anatomic location [29,30]. Feldmann and Maibach [31] found that SC thickness was one factor that influenced hydrocortisone absorption through the skin. The highest total absorption occurred from the

scrotum, followed by the angle of the jaw, forehead, axilla, scalp, back, forearms, palms, and plantar surfaces in decreasing order. Scheuplein and Blank [32] found highest permeability at the sole of the foot, followed by the scrotum, palm, forehead, and abdomen. These regional differences suggest that skin permeability should dictate the type and composition of protective gear.

There are also regional differences at the ultrastructural and membrane levels. For example, SC of the palm is more susceptible to solvents than SC of the dorsal hand. Although the palmar SC is thicker, it contains five times less lipid between the corneocytes [33–35]. Also, less flexible K6-16 keratin pairs replace the K1-10 pairs found in other areas of skin. These differences help explain how the palms may be chapped, hyperkeratotic, and fissured after chemical exposure, while the skin of the dorsal hand is spared.

Lipid content varies with anatomic location [36–38] and strongly influences percutaneous absorption. Fluhr et al [39] found that the lipid-rich skin of the forehead and back had higher TEWL after acetone treatment than the skin of the abdomen, volar forearm, and lower leg. Acetone extracts both polar and nonpolar SC lipids. Interestingly, in their experiments, skin of the forehead recovered barrier function more rapidly than skin of the abdomen, volar forearm, and lower leg. This may be due to the rapid SC turnover rate of facial skin noted by Baker and Kligman [40]. These findings suggest that the face is an important site for permeation through contact with solvent vapors as well as accidental chemical splashes.

Early studies seemed to suggest that women had stronger irritant reactions than men to detergents and alkalis. However, Bjornberg [41] showed that when subjects are carefully matched and confounding variables controlled, there were no consistent gender differences to 11 different irritants.

Changes in the skin's barrier function occur as an individual ages [42–44]. The skin is damaged more easily and repairs itself more slowly in older individuals [23]. The slowing of epidermal lipid synthesis leads to decreased lamellar body lipid content and less total epidermal lipid [34,45]. These changes decrease skin permeability to and absorption of hydrophobic compounds such as steroids [42,43]. They also lead to skin dryness with increased potential for dermatitis and absorption of hydrophilic solvents. As the average age of the workforce increases, skin protection methods will need to change to accommodate decreased skin barrier function.

Qualitative and quantitative changes in lipid composition and organization that lead to impaired barrier function and increased TEWL may be a common mechanism in skin diseases like atopic dermatitis, psoriasis, essential fatty acid deficiency, and ichthyosis [46–49]. The SC of individuals who have atopic dermatitis contains up to 50% less ceramides than normal skin [45]. This causes changes in the organization of the SC lamellar phase [50], leading to decreased hydration and a higher TEWL [20,45,51]. Atopic dry skin is damaged more severely by chemical exposure and takes longer to restore barrier function than normal skin [52]. Individuals with any of these skin conditions are at increased risk for further skin problems if they work with solvents.

Genetics probably plays a role in skin susceptibility to solvent damage. Individual differences in epidermal lipid composition may contribute to skin irritability and recovery time [51]. Skin phase I and phase II enzymes involved in metabolism of chemicals are genetically determined. The aryl hydrocarbon hydroxylases probably play a role in chemical carcinogenesis. Other epidermal enzyme deficiencies in HMG Co A reductase, serine palmitoyl transferase, fatty acyl cocarboxylase, or β-glucocerebrosidase may be involved in skin diseases characterized by xerosis and desquamation.

Skin type is genetically determined. Reed et al [53] found that the skin barrier in individuals who have skin type II/III (usually burns, tans less than average) is more susceptible to damage and recovers more slowly than skin type V/VI (rarely burns, tans profusely). However, skin type does not predict development of irritant dermatitis [54]. Reed et al [53] also found that gender and race do not influence skin barrier recovery.

Eccrine sweat can serve a protective function by diluting toxic substances and lavaging them from the skin. However, chemical dusts and particles can also become trapped by sweat and cause irritation. If sweating leads to overhydration and maceration (eg, in the presence of occlusion from gloves or protective clothing), increased permeation of the skin may occur through fissures and breaks in the barrier.

Water is an essential component of the SC: it maintains skin pliability, elasticity, and resistance to trauma [24,55]. Water is also essential for the function of enzymes that control the degradation of desmosomes and formation of natural moisturizing factors [24]. The SC contains from 10% to 30% bound water [18] and a concentration gradient of water spans the SC from the fully hydrated portion adjacent to the epidermis to the outermost layer that is exposed to air [56]. Hydration is influenced by corneocyte thickness, number of desmosomes, the way in which keratin filaments are packed, and the rate of filaggrin breakdown [18,24].

When the level of hydration drops below 5 to 10 mg per 100 mg SC dry weight, pliability and elasticity decrease [33,57]. The SC cracks more easily and corneocytes are shed in larger sheets [58,59]. Increasing hydration of the SC causes a progressive decrease in its effectiveness as a barrier [27,60–62].

Once barrier function is disrupted, the skin becomes more vulnerable to penetration by solvents and is therefore more susceptible to irritant contact dermatitis. Allergens have increased access to the deeper layers of the epidermis where they may react with Langerhans' cells, causing skin sensitization or allergic contact dermatitis. Microorganisms adhere to damaged skin more easily, leading to increased potential for infections. "Immersion dermatitis" from wet work or frequent hand washing is a common cause of barrier disruption.

Skin permeation increases with a rise in temperature [63]. Two potential explanations for this observation are increased blood flow or increased skin hydration [64,65]. In some cases, a higher temperature also increases the irritant potential of a chemical [66]. Exposure to rapid changes in temperature can lead to disturbance of barrier function. For example, going from a cool, dry, air-

conditioned indoor work area to hot, humid outdoor weather in summer or the converse in winter may contribute to barrier disruption [59]. Prolonged exposure to low temperature (20°F) decreases formation and secretion of new lamellar bodies; when the hands are warmed, this can lead to excessive water loss. Repetition of the cycle leads to dry skin [67].

Rogers et al [34] found a 30% reduction in total SC lipids at three different anatomic sites during the winter months. The unsaturated lineoleate esterified to ceramide 1, which plays an important role in membrane fluidity and SC flexibility decreases and is replaced by oleate fatty acid [34]. This is one of the factors in increased dry skin complaints in winter [59] and potentially decreased barrier function.

Low humidity also plays a role in dehydration of the SC and subsequent damage to barrier function in human skin [68]. At a relative humidity of less than 50% (room temperature), the SC water content drops below 10%, leading to a decrease in skin pliability and softness [69,70]. Individuals with atopy and those with fair skin seem to be more susceptible to these changes [71]. All of these environmental factors cause mild, reversible changes in SC barrier function.

Solvent characteristics and skin irritability/permeability

A solvent's physical and chemical characteristics (molecular structure, pH, pKa, hydrophobicity, volatility) determine its ability to irritate or permeate the skin. A low molecular weight hydrophobic solvent permeates better than a high molecular weight or hydrophilic solvent. Generally, ability to irritate the skin and ability to permeate the skin are inversely related. Klauder and Brill [72] found that the skin irritant effect decreases as the boiling point increases. Substances such as kerosene, naphtha and light oils with boiling points below 450°F are better at extracting epidermal lipids and therefore tend to be irritants causing dermatitis. Petroleum distillates such as lubricating, cutting, machine, and transformer oils with boiling points above 600°F are poor epidermal lipid extractants and tend to be more keratogenic, leading to folliculitis, epitheliomas, hyperpigmentation, and keratoses.

In general, poorly absorbed solvents and solvents that extract lipids cause more severe skin damage and fewer systemic symptoms. Solvents with amphiphilic properties (ie, they are lipophilic and easily dissolved in water) pose special dangers because they are readily absorbed and penetrate the skin easily. Glycol ethers and dimethyl formamide are well-known examples. The octanol/water-partitioning ratio (K_{ow}) is a commonly used measure of polarity and hydrophobicity. Solvents that have high partition coefficients (more hydrophobic) pass through the epidermis more easily. The best skin penetrants have a K_{ow} around 100.

Other characteristics that affect penetration include vehicle, solubility, duration of contact, occlusion, concentration/dose. The vehicle containing the chemical plays a critical role: for a given concentration of chemical, permeation may vary 1000-fold depending on the choice of vehicle [73].

Water-soluble molecules penetrate the SC poorly. However, they are able to enter the skin through an alternate pathway: the openings of sweat glands and hair follicles [74]. Sweat glands and hair follicles can effectively shunt chemicals into the bloodstream by avoiding the rate-limiting stratum corneum. This may present a novel pathway for drug delivery [75,76]. Although this pathway represents less than 1% of the total skin surface area, it can be significant for highly toxic molecules or for solvents that come in contact with areas rich in hair follicles or sweat glands.

Occlusion can increase the penetration of topical drugs tenfold, thereby greatly increasing clinical efficacy [77–79]. This desirable pharmacologic phenomenon also occurs in the workplace, but often with highly undesirable results. Clothing, gloves, face masks, jewelry (eg, rings and watches), socks, shoes, and boots can all occlude the skin, increasing solvent penetration. The type and extent of occlusion (eg, tight versus loose clothing, breathable natural fiber versus synthetic, glove material) and anatomic site are important factors in determining solvent permeation. Occlusion drives permeation by maintaining a higher dose at the skin surface, preventing evaporation, and decreasing mechanical removal by friction and exfoliation.

However, occlusion does not increase the penetration of all chemicals, particularly hydrophilic compounds. Bucks et al [60] found that occlusion had a significant impact on the permeation of phenol but did not increase penetration of parasubstituted phenols. They postulated that lipophilicity accounts for the observed differences.

Finally, a solvent's inherent toxicity plays a key role in determining whether skin contact leads to local irritation or systemic toxicity.

Skin permeation, distribution, metabolism, and excretion of solvents

Historically, the SC was seen as a dead layer that functioned solely as an impermeable barrier to prevent water loss and protect the epidermis, dermis, and the individual from noxious agents. This view has changed dramatically over the past few years as our understanding of skin ultrastructure, metabolism, and function has grown. The first step in skin permeation is absorption of the solvent to the surface of the SC. Percutaneous absorption is a temperature-dependent process [80] that is affected by solvent binding to the SC [81], the surface area of skin contact [82], solvent concentration, solvent contact time with the skin, and all of the other factors that affect skin permeability.

The greatest potential for percutaneous absorption occurs when a high concentration of solvent is spread over a large area of the body's surface and occluded for an extended period of time. Walsh et al [83] reported a case in which a 12-year-old boy was trapped under an overturned tractor for 1 hour. His clothing became saturated with spilled gasoline and he developed a 50% body surface area burn, followed by renal failure and death.

Percutaneous absorption can be altered by repeated contact with a chemical [84,85]. Some solvents seem to enhance their own absorption, probably by

damaging the skin and hence increasing permeability during the initial stages of dermal exposure. Other mechanisms may be related to the reservoir capacity of the SC.

Bucks et al [60] envisioned a series of six steps as a chemical traverses the skin:

1. Dissolve or partition into SC lipids
2. Diffuse through lamellar lipid domains
3. Partition into epidermis (more hydrophilic)
4. Traverse epidermis and upper dermis
5. Gain access to cutaneous capillary
6. Enter systemic circulation

This scheme for chemical uptake does not take several factors into account: the time for solvent to enter the skin from the time of application (lag time), the speed with which the solvent is absorbed, the reservoir effect of the SC, metabolism in the SC, and the potential for enzyme induction. Vickers [86] showed that the SC could act as a depot or reservoir, releasing chemicals slowly over an extended period. Slowed absorption and extended release favor metabolism of a solvent, because prolonged time in the skin allows for enzyme induction and increases the potential for contact with and metabolism by enzymes.

Once a solvent reaches the viable epidermis, hydrophilic agents can diffuse into the intercellular water and hydrophobic agents can partition into the cell membrane, improving the chances of entering the circulation. The rate of diffusion in the dermis depends on interstitial fluid movement, interactions with dermal constituents and blood flow that in turn is influenced by body temperature, age, and hormonal status.

The epidermis contains an array of phase I and phase II enzymes including a cytochrome P-450 system, gluconyl transferases, mixed-function oxidases, and esterases. If the surface area of the epidermis is taken into account, skin enzyme activity can rival or even exceed that of the liver (80% to 240%) [87]. This metabolic ability can enhance the skin's barrier function by detoxifying substances or, conversely, can create potent toxins from inert substances. When repeated dermal exposures to a chemical result in enzyme induction, the skin may play an increased role in metabolizing the chemical.

Kinetic models of percutaneous absorption

Percutaneous absorption with neat (undiluted) chemicals was studied in human volunteers until the late 1970s. Observed partition coefficients of industrial solvents are summarized in Hansen and Andersen [88], Wilschut et al [89], Leung and Paustenbach [90], and Paustenbach et al [91].

Several different mathematical models have been proposed to estimate K_p, the skin permeation coefficient [32,92–95]. A discussion of these models can be found in Wilschut et al [89]. Paustenbach et al [91] compared the permeability

coefficients calculated from equations with observed permeability coefficients and found that in most cases the model overestimated dermal penetration.

Dermal absorption is difficult to predict [89,96–100]. A number of factors can affect modeling predictions including the kinetics of uptake, partitioning into skin and body compartments, metabolism, and excretion. Models often use the steady state permeability coefficient (K_p) to estimate absorption. This can lead to underestimation of the amount of solvent absorbed [101,102], because absorption is higher during the early part of skin exposure. Another confounding factor is the potential for solvents to enhance their own absorption by damaging the skin during exposure.

Physiologically based pharmacokinetic (PBPK) models can integrate a variety of data to predict the uptake and distribution of chemicals in humans based on data collected from laboratory animals. PBPK models are especially helpful in assessing dermal exposure under non–steady state conditions and when exposure concentrations change with time (eg, if the solvent is lost through volatilization). PBPK models are finding increasing application in the study of percutaneous solvent absorption [103–107].

Permeation enhancers

A wide array of chemicals including surfactants, fatty acids, amides, polymers, and vesicular carriers (liposomes) can act as permeation enhancers, facilitating transdermal drug delivery [108,109]. Solvents such as alcohols (eg, ethanol, propylene glycol), pyrrolidones, terpenes and their derivatives, dimethyl formamide, and dimethyl sulfoxide are also potent permeation enhancers.

Application of Fick's first law of diffusion shows that skin permeability can be altered by disrupting (ie, fluidizing) the SC's lipid lamellae, thereby increasing the diffusion coefficient, or by shifting the solubility parameter. Simple solvents such as propylene glycol, ethanol, and N-methyl pyrrolidone appear to act by shifting the solubility parameter of the skin in favor of the solvent. Providing that steady state has been achieved, Fick's laws suggest that an effect on diffusion and an effect on solubility are multiplicative rather than additive. This may have important implications for mixtures of solvents that contain a membrane fluidizer and are also supersaturated. The saturation level of the permeant (as distinguished from the concentration) is important; increased concentration does not always increase flux, but saturation can affect flux dramatically. Supersaturation can occur when a cosolvent evaporates on the skin [110].

Patterns of cutaneous injury caused by solvents

Contact dermatitis

Irritant contact dermatitis is an acute, nonimmunologicly mediated reaction that develops within minutes to a few hours after exposure to the irritant and normally heals quickly. Allergic contact dermatitis is a cell-mediated hypersen-

sitivity reaction that occurs approximately 48 hours after sensitized individuals are re-exposed to the sensitizing allergen. Although irritant and allergic contact dermatitis have very different etiologies, they can be similar in clinical appearance, histology, and immunohistology. These similarities reflect the final common pathway of the inflammatory cascade. Nonimmunologic and immunologic reactions cannot be differentiated based on their clinical appearance but are distinguished by the exposure history and patch testing.

Emmett [111] has described the spectrum of irritant dermatitis, which ranges from tissue corrosion to cumulative insult dermatitis. Irritant solvents provoke a local reaction at the site of contact due to their inherent chemical properties. The strongest irritants cause tissue corrosion, often loosely referred to as a "chemical burn," wherein cells die and become necrotic [112]. Unlike thermal burns, in which damage stops when the heat source is removed, tissue corrosion may continue until the solvent is consumed, the tissues are consumed, or the solvent is inactivated.

The depth of tissue corrosion depends on the chemical properties of the solvent, the duration of contact with the skin, and the presence or absence of occlusion. The clinical presentation of tissue corrosion ranges from erythema to bullae to erosions, ulcers, and frank necrosis. In general, irritant reactions occur immediately on contact, although reactions to a few solvents such as phenol may be delayed, appearing several hours after exposure.

Irritants cause injury to most individuals. Irritant reactions have sharply demarcated borders and are characterized by erythema, edema, and vesiculation. A scar may be present after healing with deep corrosion, but hypo- and hyperpigmentation are absent. Repeated irritant reactions at the same site may result in hyperkeratotic skin with a leathery appearance.

At the other end of the spectrum, cumulative insult dermatitis results from chronic exposure to weak irritants and may not appear until after several weeks of exposure. The skin may appear reddened, scaly, fissured, or excoriated. Cumulative insult dermatitis is more common in individuals who have a personal or family history of atopy. It can be very slow to resolve, and improvement is dependent on avoidance of the irritant.

Finally, subjective contact dermatitis is characterized by a burning or stinging sensation after contact with certain chemicals (eg, lactic acid). Although no clinical signs are present, the sensation is reproducible in double-blinded exposure tests.

Contact urticaria

Contact urticaria may present clinically as small, erythematous, pruritic papules (hives); larger, erythematous, pruritic wheals; or angioedema that may be life-threatening if the airway is involved. Immunologic contact urticaria is usually IgE-mediated, although IgG and possibly IgM may be involved. The list of agents that cause immunologic contact urticaria is growing; these agents are especially important causes of occupational hand dermatitis. Some solvents described as causing immunologic contact urticaria include ethyl, butyl, iso-

propyl, and benzyl alcohol; formaldehyde; methyl ethyl ketone; polyethylene glycol; 1,1,1-trichloroethane; and xylene.

Contact urticaria may also occur as the result of contact with chemicals that cause mast cells to release vasoactive substances like histamine, leukotrienes, prostaglandins, or substance P. Some solvents that cause nonimmunologic urticaria include ethyl, butyl, and isopropyl alcohol; chloroform; dimethyl sulfoxide; formaldehyde; Naptha 21/99; and turpentine.

Radioallergosorbent testing or scratch, prick, or patch testing may be helpful in distinguishing immunologic from nonimmunologic contact urticaria. Avoidance of the allergen is the cornerstone of treatment; antihistamines may help to subdue symptoms from a reaction. If there is potential for an anaphylactic reaction, individuals should wear a MedicAlert bracelet and carry an epinephrine auto-injector (eg, an EpiPen, DEY, Napa, CA).

High-pressure injection injuries

High-pressure injection (HPI) injuries were first described as an occupational hazard almost 70 years ago [113,114], yet they are rarely reported in the medical literature [115]. HPI injuries are true surgical emergencies because even with expert treatment, the long-term outcomes range from considerable loss of hand and finger function to amputation in up to 48% of cases [116,117]. The volar aspect of the second or third digit on the nondominant hand is the most common site of injection; the left hand is involved twice as often as the right hand [118]. Other body parts may be affected [119].

A pressure of seven atmospheres will penetrate the skin; pressures in excess of 7000 psi have been associated with a 100% amputation rate [120]. Paint spray guns, compressed air lines, hydraulic pumps, diesel-fuel injectors, presses for injection molding, hydraulic injection systems on equipment, spray and grease guns, and dry-cleaning equipment have all been involved in HPI.

Variables affecting the outcome include time between injury and decompression/operative treatment, pressure, site of injection, volume of injected material, and the nature of the injected material. Water, air, and low-volume vaccines are the least noxious agents. Injection with oil, grease, or latex paints is associated with a better outcome than spirit- or oil-based paints [121–123]. Solvents cause the most tissue damage.

Gutowski et al [124] reported a series of five patients who sustained HPI injuries of dry-cleaning solvents to the fingers. The solvents included "dry cleaning fluid" (two cases), "dry cleaning fluid containing isoparaffin hydrocarbons and dichlorofluoroethane" (one case) and "dry cleaning fluid containing isoparaffin hydrocarbons, dichlorofluoroethane, and methoxypropanol" (two cases). There was no mention of the volume of solvent injected or systemic toxicity. Three cases presented late in their course and had worse outcomes; one of the three required amputation.

HPI injuries may have an innocuous appearance initially. The entrance site may be difficult to see without magnification or may appear to be a pinprick. Pain

is not a reliable indicator of severity because there may be anesthesia from tissue compression when the injury occurs. There is gradual onset of swelling, ischemic changes manifested by blanching or mottling, and increasing pain. Assessment by a hand surgeon as soon as possible is critical. Education is the most effective form of prevention. Workers should not test for leaks with their fingers because high-pressure jets will penetrate all types of gloves, clothing, and even shoes or boots.

The influence of alcohol and other factors on solvent metabolism

Facial flushing, or "degreaser's flush," is a solvent/skin reaction first described in 1974 by Stewart et al [125]. It refers to erythema of the face, neck, or shoulders that develops when even small quantities of trichloroethylene (Tri) are inhaled followed by alcohol consumption within 1 to 2 hours of Tri exposure. The reaction begins with red blotches on the nose and malar eminences that become confluent. The erythema peaks in about an hour and then begins to fade. Sometimes the flushing is accompanied by nausea and vomiting and resembles a disulfiram-like reaction [126].

In 1974, Bauer and Rabens [127] reported four workers who had been exposed to Tri who developed generalized dermatitis and varying degrees of solvent euphoria/intoxication after alcohol consumption. One worker also progressed to toxic hepatitis.

Alcohol competitively inhibits the metabolism of Tri, leading to a two- to threefold increase in Tri levels in the blood [128]. Acetaldehyde causes flushing, hyperventilation, and tachycardia in humans [129]. Elevated acetaldehyde levels are associated with alcohol intolerance in persons of Asian ancestry and in 5% to 20% of the Caucasian population [130]. Tri metabolites may cause "degreaser's flush" by increasing blood aldehyde levels.

In 1991, Sato et al [131] used a physiologic simulation model to analyze the interactions of alcohol consumption and Tri exposure. They predicted that consumption of moderate amounts of alcohol before work or at lunchtime would cause marked increased in blood Tri levels. In their model, alcohol consumption in the evening would have little effect at an exposure level of 50 ppm Tri but considerable effect at 500 ppm Tri.

A similar alcohol intolerance syndrome (disulfiram-like reaction) has been reported for dimethyl formamide (DMF). Symptoms include facial flushing, palpitations, chest tightness, dizziness, sweating, and nausea. These symptoms developed in workers who were exposed to DMF and then consumed alcohol within 24 hours. The exact mechanism is unknown, but DMF appears to have an inhibitory effect on alcohol dehydrogenase [132–134].

Riihimaki et al [135,136] studied xylene–ethanol interactions in four healthy volunteers. They found that consumption of a moderate amount of ethanol (0.8 g/kg) before a 4-hour respiratory exposure to m-xylene led to significant changes in xylene metabolism and excretion. Ethanol increased the blood xylene level 1.5- to 2-fold and decreased urinary excretion of methylhippuric acid by approxi-

mately 50% for several hours after xylene inhalation stopped. Four volunteers had transient increases in blood acetaldehyde levels and some experienced nausea. One out of eight volunteers in another study developed dermal flushing.

Alcohol decreases the clearance of toluene, thereby increasing hepatotoxicity [137,138]. Even low levels of alcohol intake (eg, a single drink) cause a decrease in metabolism [139,140].

Dossing et al [141] exposed four healthy volunteers to 100 ppm toluene, then studied the effects of ethanol, cimetidine, and propranolol on toluene metabolism. They found that ethanol decreased the urinary excretion of two toluene metabolites, o-cresol and hippuric acid, by 50% and increased the mean alveolar concentration by a factor of 1.7. Cimetidine and propranolol did not appear to affect toluene metabolism under these conditions.

Inoue et al [142] noted that Chinese, Japanese, and Turkish workers exposed to solvents under similar working conditions had different patterns of excretion of toluene metabolites. This led the authors to speculate that there may be ethnic differences in toluene metabolism.

Lifestyle and genetic factors can influence workers' reactions to solvents and other chemicals. Concomitant medications, alcohol, tobacco, and recreational drug use may induce or inhibit enzyme systems affecting solvent metabolism. Additional information about medication dose and quantities of substance used, time of consumption in relation to solvent exposure, and use patterns (regular versus intermittent) may be helpful in investigating unusual reactions to solvents.

Effects on mucous membranes

Solvent absorption through mucous membranes is highly efficient because the SC and its skin barrier function are absent. Mucosal surfaces are rich in capillaries, providing rapid transport to the systemic circulation and avoiding first-pass skin and hepatic metabolism.

In the occupational setting it is difficult if not impossible to separate nasal absorption from absorption through other parts of the respiratory tree. There are two additional sites for solvent absorption in nasal mucosa: the olfactory neurons and the cerebrospinal fluid. Although transneuronal absorption tends to be slow [143], it can be an important route for toxic solvents with little odor or where exposure occurs over longer periods.

Solvents and the nail

There is little published information about solvent effects on the nail. Irritant, cumulative insult and allergic contact dermatitis can affect the nails and may lead to onycholysis (detachment of the nail from its bed at the distal end or lateral attachments), onychorrhexis (narrow, parallel, longitudinal furrows), onychoschizia (splitting of the nail at the distal end), subungual hyperkeratosis (epithelial hyperplasia of subungual tissue), paronychia (paraungual inflammation), crumbling of the nail plate, and Beau's lines (transverse depressions) [144].

Workers whose jobs require frequent or persistent immersion of the hands in water are at increased risk for developing paronychia. Schwartz et al [145] listed 36 different occupations at increased risk for paronychia. Common features of these jobs include repeated immersion of the hands in water; contact with solvents, soaps, alkalis, or oils; and trauma or maceration.

In a cross-sectional study, Lubach and Beckers [146] found that wet work increased nail brittleness, onychorrhexis, and onychoschizia in women but not men. Templeton [147] described progressive occupational onycholysis in women who had prolonged immersion of the hands in water and mechanical trauma at a ketchup-bottling plant.

Jia et al [148] observed a variety of nail disorders including onychorrhexis, leuconychia (white nails), onychauxis (overgrowth and thickening of nail), and onychoschizia in 52 Chinese workers. Prolonged contact with formaldehyde solutions can cause brown discoloration of the nails [145]. Turpentine can cause eczema of the periungual tissues and fingers as well as a subungual hyperkeratosis [149].

Koilonychia or "spoon nail" is a dystrophy in which the nail is concave and the edge is everted. Ancona-Alayon [150] described six cabinetmakers who had koilonychia and routinely used a solvent mixture of methanol, toluene, and xylene to clean metal accessories for furniture.

Specific solvents

A solvent is defined as "a substance capable of dissolving another substance (solute) to form a uniformly dispersed mixture (solution) at the molecular or ionic size level" [151]. Aprotic solvents are not able to act as proton donors or acceptors. Solvents have three chief applications: (1) in cleaning and degreasing; (2) as raw materials; and (3) as carrier or dispersion media. Organic solvents are a common cause of contact dermatitis [152].

This section reviews the patterns of cutaneous injury caused by specific solvents and lists processes and industries in which workers may be exposed to these solvents. The spectrum of reactions reported is surveyed, with emphasis on chronic exposures, severe skin reactions, and the attendant potential for systemic toxicity. Table 1 summarizes some of this information. Table 2 summarizes selected regulatory information as of June, 2004.

There are many case reports in the solvent literature. Case reports play an important role in helping to identify potential problems with solvents by showing a temporal association between an exposure and health effects. Multiple case reports lend credence to an association, but only a well-controlled epidemiologic study can demonstrate a relationship between a solvent and a health effect. However, the determination of a causal relationship depends on fulfillment of the Hill criteria [153].

Details in case reports are sometimes sketchy, making accurate interpretation of the report a challenge. Vital information on skin contact with the solvent (amount, area exposed, concentration, length of exposure), purity (grade of

Table 1
Summary of solvents and skin effects

Name and CAS[a] number	Applications	Potential routes of entry	Volatility
Acetamide acetic acid amide; ethanamide; methanecarboxamide **60-35-5**	Solvent; electrochemistry; organic synthesis	Skin	VERY LOW
Acetone 2-propanone; propan-2-one; dimethyl ketone **67-64-1**	Solvent for gums, waxes, resins, fats, greases, oils, inks, dyes, cellulose derivatives	Skin, Resp, GI	HIGH 234 mm Hg
Acetonitrile cyanomethane; ethanenitrile; methyl cyanide **75-05-8**	Solvent; manufacturing plastics, pharmaceuticals, catalyst; refining copper; high performance liquid chromatography (HPLC)	Skin	MEDIUM 90 mm Hg
Acrolein 2-propenal; acrylic aldehyde **107-02-8**	manufacturing resins, pharmaceuticals, perfumes; as a biocide; chemical warfare agent (WWI)	Skin, Resp, GI	
n-Amyl acetate acetic acid, pentyl ester; 1-pentyl acetate; n-pentyl acetate **628-63-7**	Paints, pharmaceuticals, photographic film, nail polish, printing fabrics, artificial leather	Skin, Resp, GI	
Benzene **71-43-2**	Chemical intermediate; component of gasoline	Skin, Resp, GI	MEDIUM 97mm Hg
Benzyl alcohol benzenemethanol; benzenecarbinol **100-51-6**	Solvent; pharmaceuticals, degreasing agent, cleaner, paints, inks, cosmetics, perfumes, textiles, resins; component of color developer C-22	Skin	VERY LOW 1 mm Hg
1-Butanol n-butyl alcohol; propyl carbinol **71-36-3**	Solvent; paints, lacquers, varnishes; pharmaceutical manufacturing	Skin, Resp, GI	LOW-MEDIUM
2-Butanol sec-butyl alcohol; methyl ethyl carbinol **78-92-2**	Coatings, paint remover, foods, resins, adhesives, cleaners, synthesis	Skin, Resp, GI	
tert-Butanol 2-methyl-2-propanol; 1,1-dimethyl ethanol **75-65-0**	Solvent, dehydrating agent	Skin	

Skin absorption	Overall toxicity rating	Type of skin lesion(s)	Other health hazards
Easily absorbed	Extremely toxic		Hepatotoxic. High acute toxicity. Carcinogen in animals.
	Low toxicity	Skin irritant; dryness; erythema	Low acute and chronic toxicity compared with other solvents.
Easily absorbed	Highly toxic	Irritation of mucosal membranes	Metabolized to cyanide by liver; may lead to respiratory paralysis, convulsions, and death.
		Severe skin irritation	Pulmonary edema
		Allergic contact dermatitis; sensitizer	
Very easily absorbed	Extremely toxic	Acute: erythema, blistering. Chronic: drying, defatting, dermatitis; risk of secondary infection if fissuring occurs	Carcinogen: causes aplastic anemia, leukemia, probably other cancers in humans. Hepatotoxic. Adipose tissue is reservoir.
Easily absorbed	GRAS[b]	Mild to moderate irritation; rarely, contact urticaria	
	Low toxicity	Contact dermatitis	Mucous membrane irritant
	Low toxicity		
	Low toxicity		Mild skin irritant

(continued on next page)

Table 1 (*continued*)

Name and CAS[a] number	Applications	Potential routes of entry	Volatility
2-Butoxyethanol butyl glycol ether; ethylene glycol monobutyl ether; butyl cellosolve **111-76-2**	Solvent for resins; cleaners, insecticides, leather treatment, varnish, lacquers, hair dyes, cosmetics	Skin, Resp, GI	
n-Butyl acetateacetic acid n-butyl ester **123-86-4**	Solvent in paints, coatings; leather treatment	Skin, Resp, GI	MEDIUM 13 mm Hg
Carbon disulfide carbon disulphide **75-15-0**	Production of rayon, silk, PVC spinning solutions; resin synthesis, rubber solutions, agriculture, mining, pharmaceuticals	Skin	HIGH 366 mm Hg
Carbon tetrachloride tetrachloromethane **56-23-5**	Chlorofluorocarbon production	Skin, Resp, GI	HIGH 116 mm Hg
Chlorodifluoromethane CFC 22 Freon 22 **75-45-6**		Skin, Resp, GI	gas at room temperature
Chloroform trichloromethane; methane trichloride **67-66-3**	Production of HCFC-22 and fluoropolymers (plastics)	Skin, Resp, GI	HIGH 199 mmHg
Chloromethane methyl chloride **74-87-3**	Manufacture of synthetic rubber, silicones	Skin, Resp	Gas at room temp

Skin absorption	Overall toxicity rating	Type of skin lesion(s)	Other health hazards
		Erythema, drying, formation of fissures; dermal absorption has led to hemato-, nephro-, hepato-toxicity	Hemato-, nephro-, hepato-, and CNS toxin
	Low toxicity	Allergic contact dermatitis	Mucous membrane irritant
Very easily absorbed	Extremely toxic	Defatting causes inflammation, cracking of skin; Extended contact - extreme irritant; 2nd and 3rd degree chemical burns	Causes mental illness, brain disease, nerve damage. Can worsen coronary heart disease, cause arrhythmias. The liquid is a severe irritant of the skin and eyes. Reproductive hazard.
Very easily absorbed	Extremely toxic	Skin erythema. Irritant dermatitis from defatting; cracking, potential secondary infection. Anesthesia.	Animal carcinogen. Nephro- and hepatotoxic. Harmful to ozone layer.
	Low toxicity		Extremely high vapor concentrations can cause palpitations, heart failure on exposure. Weak evidence for carcinogenicity in animals. Harmful to ozone layer.
	Extremely toxic	Brief exposure: little or no irritation. Repeated or prolonged exposure (especially with occlusion) causes skin and mucous membrane irritation and inflammation	Carcinogen in animals. Nephro- and hepatotoxic. Extremely high vapor concentrations can cause heart failure. Reproductive hazard.
	Extremely toxic	Allergic contact dermatitis	Reproductive hazard. Repeated exposure to low concentrations damages CNS. Symptoms can be delayed for several hours after exposure. Nephrotoxin

(continued on next page)

Table 1 (*continued*)

Name and CAS[a] number	Applications	Potential routes of entry	Volatility
Cyclohexane hexamethylene; hexahydrobenzene **110-82-7**	Solvent for cellulose ethers, resins, waxes, fats, oils, bitumen, rubber; nylon synthesis	Skin	MEDIUM 99 mmHg
Cyclohexanone pimelic ketone; cyclohexyl ketone **108-94-1**	Chemical intermediate, solvent, paints	Skin, Resp, GI	LOW 4 mmHg
Dichlorodifluoromethane CFC 12; Freon 12 **75-71-8**	Previously used as a propellant	Skin, Resp	Gas at room temp
Dichlorofluoromethane CFC 21; Freon 21 **75-43-4**		Skin, Resp, GI	
Dichloromethane methylene chloride **75-09-2**	Solvent, paint stripper, cement for plastics, decaffeination of coffee, vapor degreasing, pharmaceutical process solvent	Skin, Resp, GI	HIGH 442 mmHg
1,2-Dichlorotetra-fluoroethane Freon 114 **76-14-2**		Skin, Resp, GI	Gas at room temp
Diethyl ether ethyl ether; diethyl oxide; 1,1-oxybisethane **60-29-7**	Solvent, extracting agent	Skin, Resp, GI	HIGH 538 mmHg
Diethylene glycol dibutyl ether butyl diglyme; bis(2-butoxyethyl)ether **112-73-2**		Skin, Resp, GI	VERY LOW <0.4 mmHg
Diethylene glycol diethyl ether ethyl diglyme; bis(2-ethoxyethyl)ether **112-36-7**		Skin, GI	VERY LOW <0.4 mmHg
Diethylene glycol dimethyl ether diglyme **111-96-6**	Solvent, metals, organo-metallic compounds	Skin, Resp, GI	LOW 2.4 mmHg

Skin absorption	Overall toxicity rating	Type of skin lesion(s)	Other health hazards
	Low toxicity	Prolonged exposure causes skin and mucous membrane irritation	Irritant; anesthetic at high concentrations.
	Slight toxicity	Irritant dermatitis from defatting; contact dermatitis; repeated dermal exposure to vapor can lead to CNS depression	Irritant.
	Low toxicity	Irritant dermatitis; rarely a sensitizer	Extremely high concentrations can cause palpitations, heart failure at time of exposure.
	Highly toxic		Hepatotoxic. Possible hazard to pregnancy at very high exposure levels. Harmful to ozone layer.
		Mild skin irritant - can release small amounts of HCl	Metabolized to carbon monoxide. Can cause arrhythmias in people with underlying cardiac disease. Animal carcinogen.
	Low toxicity		Extremely high concentrations can cause palpitations, heart failure at time of exposure.
	Low toxicity	Defatting, skin drying	Irritant. No longer used as anesthetic gas because risk of death at anesthetic levels, explosive hazard
	Low toxicity	Defatting, skin drying	DEGDBE does not have reproductive toxic hazards of other glycol ethers.
	Highly toxic	Defatting, skin drying	Reproductive toxic hazard.
	Extremely toxic	Defatting, skin drying	Reproductive toxic hazard.

(continued on next page)

Table 1 (*continued*)

Name and CAS[a] number	Applications	Potential routes of entry	Volatility
Diethylene glycol monobutyl ether 2-(2-butoxyethoxy) ethanol; butyl carbitol; **112-34-5**	Cleaners and paints for hard surfaces	Skin, Resp, GI	VERY LOW <0.2 mmHg
Diethylene glycol monoethyl ether ethyl diglycol ether; dioxitol; carbitol solvent **111-90-0**	Brake fluids, paints, stains; printing industry (printing inks, ballpoint pens, cleaning agent); textile industry	Skin, Resp, GI	VERY LOW 0.13 mmHg
1,2-Dimethoxy-ethane ethylene glycol dimethyl ether **110-71-4**		Skin	
Dimethyl sulfoxide DMSO **67-68-5**	Solvent for acetylene, sulfur dioxide; hydraulic fluid, antifreeze, cleaners, vet medicine; pesticides	Skin, Resp, GI	
N,N-Dimethyl-acetamide acetic acid dimethylamide; DMAc **127-19-5**	Solvent for plastics, resins, polymers; coatings; crystallization, purification; catalyst	Skin, Resp, GI	VERY LOW 0.56 mmHg
N,N-Dimethylformamide DMF **68-12-2**	Pharmaceutical manufacturing; solvent for cleaning printed circuit boards; acrylic fiber spinning (non-US)	Skin, GI	LOW 3 mmHg
1,4-Dioxane diethylene dioxide **123-91-1**	Solvent for cellulose, polymers, resins	Skin, Resp, GI	MEDIUM 37 mmHg
1,3-Dioxolane glycol formal **646-06-6**		Skin	HIGH 110 mmHg
Dipentene limonene **138-86-3**		Skin, GI	
Epichlorohydrin 1-chloro-2,3-epoxypropane **106-89-8**	Solvent for gums, resins, cellulose, paints, lacquers	Skin	
Ethanol ethyl alcohol **64-17-5**	Solvent, diluent, chemical intermediate (drugs, plastics, lacquers, polishes, plasticizers, perfumes, cosmetics)	Skin, Resp, GI	MEDIUM 58 mmHg

Skin absorption	Overall toxicity rating	Type of skin lesion(s)	Other health hazards
	Low toxicity	Defatting, skin drying	Damages blood cells. Not reproductive toxin
		Defatting, skin drying	
		Defatting, skin drying	
Extremely powerful skin penetrant		Dermal irritation; chemical burns; urticaria, anaphylaxis	
	Highly toxic	Chemical burns	Hepatotoxic. Causes birth defects or fetal loss in animals. May damage testicles.
	Highly toxic	Contact dermatitis; disulfiram-like reaction; systemic symptoms	Nephro- and hepatotoxic. Symptoms of over-exposure: vomiting, abd pain. Causes birth defects in animals.
	Extremely toxic	Irritant dermatitis from defatting; allergic contact dermatitis; significant dermal absorption	Carcinogen in animals. Nephro- and hepatotoxic. Mucous membrane irritant.
	Low toxicity		
		Irritant; sensitizer; Contact dermatitis	Hepatotoxic. Carcinogen in rats but probably not humans.
		Strong skin irritant; chemical burns; sensitizer; Allergic contact dermatitis	Hepato- and nephrotoxic. Animal carcinogen.
	Low toxicity	Prolonged exposure to vapors may irritate skin, mucous membranes; dermatitis; contact urticaria; sensitization rare	Vapors are not very toxic, but are irritating. Industrial ethanol is often "denatured" by adding methanol or other toxic substances.

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Table 1 (*continued*)

Name and CAS[a] number	Applications	Potential routes of entry	Volatility
2-Ethoxyethanol glycol monomethyl ether; cellosolve **110-80-5**		Skin, Resp, GI	LOW 5 mmHg
Ethyl acetate acetoxyethane **141-78-6**	Extracting, cleaning; paints, adhesives; leather treatment	Skin, Resp, GI	MEDIUM 95 mmHg
Ethyl benzene **100-41-4**	Production of styrene; paint solvent	Skin	LOW 9.6 mmHg
Ethylene glycol 1,2-ethanediol **107-21-1**	Polyester resin fibers; antifreeze, coolants, heat transfer solutions	Skin, Resp, GI	VERY LOW 0.075 mmHg
Ethylene glycol dibutyl ether 1,2-butoxyethane; dibutyl cellosolve **112-48-1**		Skin, GI	
Ethylene glycol diethyl ether ethyl glyme diethyl cellosolve **629-14-1**		Skin, Resp, GI	LOW-MED 10 mmHg
Formaldehyde formalin **50-00-0**	Chemical intermediate; skin/hair care products, cosmetics, permanent press textiles; pathology labs, funeral homes	Skin	
Formamide methanamide; carbamaldehyde **75-12-7**	Solvent for resins and plasticizers; chemical intermediate	Skin	VERY LOW
Furfural fural; 2-furanaldehyde **98-01-1**	Extractant in refining lubricating oils, diesel fuels and vegetable oils	Skin, Resp, GI	LOW 2.2 mmHg
Gasoline petrol **8006-61-9**	Fuel, rubber cement	Skin	MEDIUM to HIGH 38–300 mmHg
n-Heptane dipropyl methane **142-82-5**		Skin, Resp, GI	MEDIUM 46 mmHg

Skin absorption	Overall toxicity rating	Type of skin lesion(s)	Other health hazards
	Extremely toxic		Damages blood cells and bone marrow. Causes birth defects and testicular damage in animals.
	Low toxicity	Contact dermatitis; sensitizer	Irritant.
Moderate toxicity	Vesicles		Strong irritant. Weak reproductive hazard.
	Low toxicity	Chronic irritant dermatitis from defatting,	Nephrotoxic when ingested. Very high exposures cause birth defects in animals. Vapor exposures usually too low to be harmful.
		Defatting, skin drying	
	Highly toxic	Defatting, skin drying	
		Irritant; Chemical burns; Allergic contact dermatitis; Contact urticaria	Mucous membrane irritant.
	Highly toxic		Birth defects in animals. Hepatotoxic.
	Extremely toxic	Contact urticaria	Hepatotoxic. Some evidence of carcinogenicity in animals.
	Moderately toxic	Irritant. Chronic exposures lead to dermatitis, dryness, fissures. Prolonged acute exposure: chemical burns	CNS effects. Often contains benzene Carcinogen in rats.
	Low toxicity		Good substitute for hexane.

(continued on next page)

Table 1 (*continued*)

Name and CAS[a] number	Applications	Potential routes of entry	Volatility
n-Hexane **110-54-3**	Manufacturing poly-olefins, synthetic rubbers, pharmaceuticals; extracting oil from seeds	Skin, Resp, GI	HIGH 152 mmHg
Isopropyl alcohol 2-propanol **67-63-0**	Solvent (cellulose nitrate), pharmaceuticals, chemical intermediate, cosmetics (hair, skin lotions), catalyst	Skin, Resp, GI	MEDIUM 46 mmHg
Kerosene kerosine; light petroleum; lamp oil **8008-20-6**	Fuel for lamps stoves, heaters; degreaser, cleaner; insecticides	Resp, Skin, GI	
d-Limonene carvene **5989-27-5**	Solvent; cleaning printed circuit boards; fragrance cleansing agent;	Skin, Resp, GI	LOW 1.9 mmHg
Methanol methyl alcohol; carbinol; wood alcohol; wood spirit **67-56-1**	Solvent in paint, explosives industries; extracting agent; antifreeze; chemical intermediate	Skin, Resp, GI	HIGH 128 mmHg
2-Methoxyethanol methyl cellosolve; ethylene glycol monomethyl ether **109-86-4**		Skin, Resp, GI	LOW-MED 9.8 mmHg
Methyl acetate **79-20-9**	Solvent; adhesives, paints; softening agent		HIGH 219 mmHg
Methyl ethyl ketone MEK; 2-butanone; **78-93-3**	Paints	Skin, Resp, GI	MEDIUM 96 mmHg
Methyl isobutyl ketone MIBK; hexone; 4-methyl-2-pentanone **108-10-1**	Paints, pesticides, chemical intermediate	Skin, Resp, GI	MEDIUM 20 mmHg
Methyl n-butyl ketone 2-hexanone; propylacetone **591-78-6**	Paints	Skin, Resp, GI	MEDIUM 12 mmHg
N-Methyl formamide NMF **123-39-7**	Solvent, chemical intermediate		VERY LOW
N-Methyl-pyrrolidone 1-methyl-2-pyrrolidone; NMP **872-50-4**	Extraction of hydrocarbons; synthesis of acetylene; paint strippers	Skin, GI	VERY LOW 0.3 mmHg
Morpholine tetrahydro-1,4-oxazine; diethylene oximide **110-91-8**	Antioxidant in coolants; component of vulcanizing agent	Skin, GI, Resp	LOW-MED 10 mmHg

Skin absorption	Overall toxicity rating	Type of skin lesion(s)	Other health hazards
	Highly toxic	Mildly irritating to mucous membranes; prolonged skin contact leads to irritant dermatitis	CNS depressant, anesthetic; causes peripheral neuropathy.
	Low toxicity	Skin irritation; Dermatitis; Urticaria	Irritant, can cause CNS depression and coma.
		Skin irritation; Dermatitis; Chemical burns with prolonged exposure	CNS depression.
	Moderately toxic	Powerful irritant and sensitizer; Allergic contact dermatitis in many users	
	Moderately toxic	Acute exposure - skin and mucous membrane irritant; Chronic exposure to liquid or vapor: dermatitis	Ingestion or inhalation may lead to blindness and death.
	Extremely toxic		Damages blood cells, bone marrow. Causes birth defects and testicular damage in animals.
Low toxicity	Sensitizer	Irritant. High levels can damage optic nerve	
	Low toxicity	Mild skin defatting; Irritant; Urticaria	Potentiates neurotoxicity of n-hexane and methyl n-butyl ketone.
	Low toxicity	Irritant	
	Extremely toxic	Mucous membrane irritant	Can cause peripheral neuropathy.
	Highly toxic		Hepatotoxic.
	Moderately toxic	Irritant; Acute contact dermatitis	May cause miscarriage if absorbed during pregnancy. Causes birth defects in animals.
	Highly toxic		Strong irritant. High exposures can damage the lungs, liver, and kidney.

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Table 1 (*continued*)

Name and CAS[a] number	Applications	Potential routes of entry	Volatility
Naptha, coal tar rubber solvent **8030-31-7**	Solvent	Skin	LOW <5 mmHg
2-Nitropropane isonitropropane **79-46-9**	Cosolvent in paints, coatings, printing inks, adhesives	Skin	MEDIUM 17 mmHg
Phenol carbolic acid; hydroxybenzene **108-95-2**	Phenolic and epoxy resins, polycarbonates	Skin, GI	VERY LOW 0.4 mmHg
Propylene glycol **57-55-6**	Polyester resins, cosmetics, foods, pharmaceuticals	Skin	VERY LOW 0.2 mmHg
Stoddard Solvent 1,2-propanediol **8052-41-3**	Lacquers, paints, varnishes, printing inks, photocopier toners, insecticides, pesticides, metal degreasers	Skin, Resp	
Styrene phenylethylene; vinyl benzene **100-42-5**	Manufacture of polymers and plastics	Skin, GI, Resp	LOW 6 mmHg
1,1,2,2-Tetrachloroethylene perchloroethylene; Perc **127-18-4**	Solvent in dry cleaning industry, metal cleaning, vapor degreasing; extraction of animal and vegetable fats, oils; previously, CFC manufacturing	Skin, Resp, GI	MEDIUM 18 mmHg
Tetrahydrofuran 1,4-epoxybutane; tetramethylene oxide; **109-99-9**	Solvent in resins, glues, paints, varnishes, inks; cold cleanser, extractant, paint stripper	Skin, Resp, GI	HIGH 164 mmHg
Toluene methylbenzene; toluol **108-88-3**	Solvent; paints, lacquers, coatings; adhesives, inks, pharmaceuticals, gasoline, gas additives	Skin, Resp, GI	MEDIUM 29 mmHg
1,1,1-Trichloroethane methyl chloroform 1,1,1-TCE **71-55-6**	Solvent for inks, coatings, adhesives, aerosols; vapor degreasing, cleaning circuit boards, electrical equipment, motors	Skin, Resp, GI	HIGH 124 mmHg

Skin absorption	Overall toxicity rating	Type of skin lesion(s)	Other health hazards
	Moderately toxic	Erythema, fissuring, exfoliation	Respiratory depression, pulmonary edema.
	Extremely toxic		Nephro- and hepatotoxic. Carcinogen in animals.
	Extremely toxic	Chemical burns. Death or serious illness can occur rapidly after skin absorption with no warning.	For decontamination, wash thoroughly with water; then wash with polyethylene glycol MW 300 (Macrogel 300) for 30 min
	Very low toxicity	Irritation; sensitizer; contact urticaria	Very low toxicity.
	Moderately toxic	Acute exposure: erythema, irritant dermatitis, vesicles; Prolonged contact: chemical burns; Repeated exposure: dryness, fissures	May cause narcosis. Mixture of solvents; may contain benzene.
	Moderately toxic	Skin irritation; Contact allergy; Repeated exposure: Irritant dermatitis from defatting	Suspected animal carcinogen. Nephro- and hepatotoxic.
	Highly toxic	Repeated exposure: Irritant dermatitis from defatting	Local anesthetic, CNS depressant.
	Low toxicity	Skin irritant	Irritant.
	Moderately toxic	Repeated exposure: Irritant dermatitis from defatting; Vapor contact alone can lead to skin drying	Nephro- and hepatotoxic. CNS intoxicant; sniffing is addictive and can be fatal. Sniffing during pregnancy can cause birth defects. Peripheral neuropathy rare.
	Low toxicity	Irritation, blisters, burns, contact urticaria	CNS depression. Peripheral neuropathy (rare). Harmful to ozone layer.

(continued on next page)

Table 1 (*continued*)

Name and CAS[a] number	Applications	Potential routes of entry	Volatility
1,1,2-Trichloroethane vinyl trichloride **79-00-5**	Solvent for pharmaceutical preparations; manufacture of electronic components	Skin	MEDIUM 24 mmHg
1,1,2-Trichloroethylene trichloroethene; ethylene trichloride; TCE; Tri **79-01-6**	Solvent, extracting agent; vapor degreasing; paint removal products	Skin, Resp, GI	MEDIUM 75 mmHg
Trichlorofluoromethane Freon 11 **75-69-4**		Skin, Resp, GI	Gas at room temp
1,1,2-Trichloro-1,2,2-trifluoroethane CFC 113 Freon 113 **76-13-1**	Solvent, cleaning agent in electronics, metal, drycleaning	Skin, Resp, GI	HIGH 369 mmHg
Turpentine (Steam Distilled) oil of turpentine **8006-64-2**	Solvent, chemical intermediate	Skin, Resp, GI	
Vinylidene chloride 1,1-dichloroethene; 1,1-dichloroethylene **75-35-4**	Solvent; used in production of monoacrylic fibers, copolymers	Skin	HIGH 608 mmHg
VM & P Naphtha varnish marker's naphtha; painters naphtha ligroine **8032-32-4**	Solvent for lacquers, oils, paints, varnishes, rubber cement, degreasing	Skin, Resp, GI	MEDIUM
Xylene dimtheyl benzene methyl toluene **1330-20-7**	Solvent for polyvinyl acetate; synthesis of plasticizers, polyester fibers	Skin, Resp, GI	LOW 6.6-9.6 mmHg

[a] Chemical Abstract Service registry number.
[b] Generally regarded as safe.

solvent), other components (if a solvent mixture), and coexposures may be lacking. Important information about the patient (height; weight; medical, dermatologic, occupational, and exposure history; blood or urine levels of solvent or metabolite; medication use; tobacco use; alcohol consumption; recreational drug use) may not be recorded. All of these factors may influence a worker's

Skin absorption	Overall toxicity rating	Type of skin lesion(s)	Other health hazards
	Highly toxic		Hepato- and nephrotoxic. CNS depressant.
	Highly toxic	Irritant dermatitis from defatting. Prolonged contact can lead to blistering, Stevens-Johnson syndrome. Degreaser's flush	Nephro- and hepatotoxic. Can cause trigeminal neuropathy, (affects facial muscles, possibly sense of taste, smell.)
			Causes kidney, liver cancer in animals.
	Low toxicity		Fibrosing alveolitis. Harmful to ozone layer.
	Low toxicity		CNS depressant. Extremely high vapor concentrations can cause palpitations, heart failure at time of exposure. Harmful to ozone layer.
		Skin irritant, defatting, dryness, fissures. Prolonged contact can lead to blistering. Powerful irritant and sensitizer	CNS depressant.
	Extremely toxic		CNS depressant.
	Low toxicity		Nephro- and hepatotoxic.
	Moderately toxic	Irritant dermatitis from defatting; contact urticaria	May damage kidneys, liver, gastrointestinal tract, and cornea.

biologic capacity to metabolize a solvent and can affect the degree of toxicity. Details about the workplace such as circumstances of the exposure (eg, saturation of clothing, gloves, socks), use of personal protective equipment, and results from workplace monitoring are also helpful in understanding the background leading up to the exposure. The available literature is often weak on these issues.

Table 2
Regulatory information for selected solvents

Name and CAS[a] number	IARC[b] or OSHA carcinogen	ACGIH TWA[c] ppm	ACGIH STEL[d]	ACGIH TLV[e] ppm	Notations[f] and other exposure limits[g]	Montreal protocol
Acetamide **60-35-5**	2B					N
Acetone **67-64-1**	N	500	750 ppm	750	A4; BEI[h] NIOSH 250 ppm OSHA 1000 ppm	N
Acetonitrile **75-05-8**	N	20	60 ppm	40	**SKIN**[i]; A4 NIOSH 20 ppm OSHA 40 ppm	N
Acrolein **107-02-8**	3		ceiling[j] 0.1 ppm	0.1	**SKIN**; A4 NIOSH 0.1 ppm OSHA 0.1 ppm	N
n-Amyl acetate **628-63-7**	N	50	100 ppm	100	NIOSH 100 ppm OSHA 100 ppm	N
Benzene **71-43-2**	1; Z	0.5	2.5 ppm	10	**SKIN**; A1; BEI NIOSH 0.1 ppm OSHA 10 ppm	N
Benzyl alcohol **100-51-6**	N					N
1-Butanol **71-36-3**	N	20		50	NIOSH ceiling 50 ppm OSHA 100 ppm	N
2-Butanol **78-92-2**	N	100		100	NIOSH 100 ppm STEL 150 ppm OSHA 150 ppm	N
tert-Butanol **75-65-0**	N	100		100	A4; NIOSH 100 ppm STEL 150 ppm OSHA 100 ppm	N
2-Butoxyethanol **111-76-2**	N	20		25	NIOSH 5 ppm OSHA 50 ppm	N
n-Butyl acetate **123-86-4**	N	150	200 ppm	150	NIOSH 150 ppm STEL 200 ppm OSHA 150 ppm	N
Carbon disulfide **75-15-0**	N	10		10	**SKIN**; BEI NIOSH 1 ppm, STEL 10 ppm OSHA 20 ppm, ceiling 30 ppm	N
Carbon tetrachloride **56-23-5**	2B	5	10 ppm	5	**SKIN**; A2 NIOSH Ca[l] STEL 2ppm/60 min OSHA 10 ppm	Y
Chlorodifluoro-methane **75-45-6**	3	1000		1000	A4; NIOSH 1000 ppm STEL 1250 ppm OSHA 1000 ppm	Y

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Table 2 (*continued*)

Name and CAS[a] number	IARC[b] or OSHA carcinogen	ACGIH TWA[c] ppm	ACGIH STEL[d]	ACGIH TLV[e] ppm	Notations[f] and other exposure limits[g]	Montreal protocol
Chloroform 67-66-3	2B	10		10	A3; NIOSH Ca STEL 2ppm/ 60 min. OSHA 50 ppm	N
Chloromethane 74-87-3	3	50	100 ppm	50	**SKIN**; A4 NIOSH LFE[l] OSHA 50 ppm	N
Cyclohexane 110-82-7	N	100		300	NIOSH 300 ppm OSHA 300 ppm	N
Cyclohexanone 108-94-1	3	25		25	**SKIN**; A4 NIOSH 25 ppm OSHA 50 ppm	N
Dichlorodifluoro-methane 75-71-8	N	1000		1000	A4; NIOSH 1000ppm OSHA 1000 ppm	Y
Dichlorofluoro-methane 75-43-4	N	10		10	NIOSH 10 ppm OSHA 1000 ppm	Y
Dichloromethane 75-09-2	2B	50		50	A3; BEI NIOSH Ca LFE OSHA 500 ppm	N
1,2-Dichlorotetra-fluoroethane 76-14-2	N	1000		1000	A4; NIOSH 1000ppm OSHA 1000 ppm	Y
Diethyl ether 60-29-7	N	400	500 ppm	400	OSHA 400 ppm	N
Diethylene glycol dibutyl ether 112-73-2	N					N
Diethylene glycol diethyl ether 112-36-7	N					N
Diethylene glycol dimethyl ether 111-96-6	N					N
Diethylene glycol 2-monobutyl ether 112-34-5	N					N
Diethylene glycol monoethyl ether 111-90-0	N					N
1,2-Dimethoxy-ethane 110-71-4	N					N
Dimethyl sulfoxide 67-68-5	N					N

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Table 2 (*continued*)

Name and CAS[a] number	IARC[b] or OSHA carcinogen	ACGIH TWA[c] ppm	ACGIH STEL[d]	ACGIH TLV[e] ppm	Notations[f] and other exposure limits[g]	Montreal protocol
N,N Dimethyl-acetamide 127-19-5	N	10		10	**SKIN**; A4; BEI NIOSH 10 ppm OSHA 10 ppm	N
N,N-Dimethyl-formamide 68-12-2	3	10		10	**SKIN**; A4; BEI NIOSH 10 ppm OSHA 10 ppm	N
1,4-Dioxane 123-91-1	2B	20		20	**SKIN**; A3 NIOSH Ca ceiling 1 ppm/30 min OSHA 100 ppm	N
1,3-Dioxolane 646-06-0	N					N
Dipentene 138-86-3	N					N
Epichlorohydrin 106-89-8	2A	0.5		0.5	**SKIN**; A3 NIOSH Ca LFE OSHA 5 ppm	N
Ethanol 64-17-5	N	1000		1000	A4; NIOSH 1000ppm OSHA 1000 ppm	N
2-Ethoxyethanol 110-80-5	N	5		5	**SKIN**; BEI NIOSH 0.5 ppm OSHA 200 ppm	N
Ethyl acetate 141-78-6	N	400		400	NIOSH 400 ppm OSHA 400 ppm	N
Ethyl benzene 100-41-4	2B	100	125 ppm		A3; BEI NIOSH 100 ppm, STEL 125 ppm OSHA 100 ppm	
Ethylene glycol 107-21-1	N		ceiling 100 mg/m^3	50	A4; OSHA 50 ppm	N
Ethylene glycol dibutyl ether 112-48-1	N					N
Ethylene glycol diethyl ether 629-14-1	N				NIOSH Ca 0.016 ppm ceiling 0.1 ppm/15min	N
Formaldehyde 50-00-0	2A		ceiling 0.3 ppm		**SENSITIZER**[m] A2	
Formamide 75-12-7	N	10		10	**SKIN**; NIOSH 10 ppm	N
Furfural 98-01-1	3	2		2	**SKIN**; A3; BEI NIOSH 15 ppm OSHA 5 ppm	N
Gasoline 8006-61-9	2B	300	500 ppm		A3 NIOSH Ca 15 ppm LOQ	

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Table 2 (*continued*)

Name and CAS[a] number	IARC[b] or OSHA carcinogen	ACGIH TWA[c] ppm	ACGIH STEL[d]	ACGIH TLV[e] ppm	Notations[f] and other exposure limits[g]	Montreal protocol
n-Heptane 142-82-5	N	400	500 ppm	400	NIOSH 85 ppm ceiling 440ppm/ 15min OSHA 500 ppm	N
n-Hexane 110-54-3	N	50		50	**SKIN**; BEI NIOSH 50 ppm OSHA 500 ppm	N
Isopropyl alcohol 67-63-0	3	400	500 ppm	400	A4; NIOSH 400 ppm, STEL 500 ppm OSHA 400 ppm	N
Kerosene 8008-20-6	N			200	NIOSH 100 ppm	N
d-Limonene 5989-27-5	3					N
Methanol 67-56-1	N	200	250 ppm	200	**SKIN**; BEI NIOSH 200 ppm STEL 250 ppm OSHA 200 ppm	N
2-Methoxyethanol 109-86-4	N	5		5	**SKIN**; BEI NIOSH 0.1 ppm OSHA 25 ppm	N
Methyl acetate 79-20-9		200	250 ppm	200	NIOSH 200 ppm STEL 250 ppm OSHA 200 ppm	
Methyl ethyl ketone 78-93-3	N	200	300 ppm	200	BEI; NIOSH 200 ppm STEL 300 OSHA 200 ppm	N
Methyl isobutyl ketone 108-10-1	N	50	75 ppm	50	BEI; NIOSH 50 ppm STEL 75 OSHA 100 ppm	N
Methyl n-butyl ketone 591-78-6	N	5	10 ppm	5	**SKIN**; NIOSH 1 ppm OSHA 100 ppm	N
N-Methyl formamide 123-39-7						
N-Methyl-pyrrolidone 872-50-4	N			100		N
Morpholine 110-91-8	3	20		20	**SKIN**; A4 NIOSH 20 ppm STEL 30 ppm OSHA 20 ppm	N

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Table 2 (*continued*)

Name and CAS[a] number	IARC[b] or OSHA carcinogen	ACGIH TWA[c] ppm	ACGIH STEL[d]	ACGIH TLV[e] ppm	Notations[f] and other exposure limits[g]	Montreal protocol
Naptha, coal tar **8030-31-7**		400		400	NIOSH 100 ppm OSHA 100 ppm	
2-Nitropropane **79-46-9**	2B	10		10	A3; NIOSH Ca LFE OSHA 25 ppm	N
Phenol **108-95-2**	3	5		5	**SKIN**; A4; BEI NIOSH 5 ppm ceiling 15.6 ppm/ 15 min OSHA 5 ppm	N
Propylene glycol **57-55-6**						
Stoddard Solvent **8052-41-3**		100		100	NIOSH 350 ppm ceiling 1800 mg/ m^3/15 min OSHA 200–500 ppm (varies by industry)	N
Styrene **100-42-5**	2B	20	40	20	A4; BEI NIOSH 50 ppm STEL 100 ppm OSHA 100 ppm	N
1,1,2,2-Tetrachloro-ethylene **127-18-4**	2A, 2B	25	100 ppm	25	A3; BEI NIOSH Ca LFE OSHA 100 ppm	N
Tetrahydrofuran **109-99-9**	N	200	250	200	BEI NIOSH 200 ppm STEL 250 ppm OSHA 200 ppm	N
Toluene **108-88-3**	3	50		50	**SKIN**; A4; BEI NIOSH 100 ppm STEL 150 ppm OSHA 200 ppm	N
1,1,1-Trichloro-ethane **71-55-6**	3	350	450	350	A4; BEI NIOSH ceiling 350 ppm/15 min OSHA 350 ppm	
1,1,2-Trichloro-ethane **79-00-5**	3	10		10	**SKIN**; A3 NIOSH Ca 10 ppm OSHA 10 ppm	
1,1,2-Trichloro-ethylene **79-01-6**	2A	50	100ppm	50	A5; BEI NIOSH 25 ppm ceiling 2ppm/1 hr OSHA 100 ppm	N
Trichlorofluoro-methane **75-69-4**	N		ceiling 1000 ppm		A4 OSHA 1000 ppm	Y

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Table 2 (*continued*)

Name and CAS[a] number	IARC[b] or OSHA carcinogen	ACGIH TWA[c] ppm	ACGIH STEL[d]	ACGIH TLV[e] ppm	Notations[f] and other exposure limits[g]	Montreal protocol
1,1,2-Trichloro-1,2,2-trifluoro-ethane 76-13-1	N	1000	1250 ppm	1000	A4; NIOSH 1000ppm STEL 1250 ppm OSHA 1000 ppm	Y
Turpentine (Steam Distilled) 8006-64-2	N	100		100	**SENSITIZER** NIOSH 100 ppm OSHA 100 ppm	N
Vinylidene chloride 75-35-4	3	5		5	A4 NIOSH Ca LFE	N
VM & P Naphtha 8032-32-4		300		300	A3 NIOSH 350 ppm/m^3 ceiling 1800 mg/m^3/ 15 min OSHA 300 ppm	N
Xylene 1330-20-7	3	100	150 ppm	100	A4 NIOSH 100 ppm STEL 150 ppm OSHA 100 ppm	N

[a] CAS, Chemical Abstract Service registry number.

[b] IARC, International Agency for Research on Cancer. IARC Carcinogen classification:
Group 1: Known human carcinogen
Group 2A: Probable human carcinogen
Group 2B: Possible human carcinogen
Group 3: Not classifiable for human carcinogenicity
Group 4: Probably not carcinogenic to humans

[c] ACGIH, American Conference of Governmental Industrial Hygienists; TWA, time weighted average.

[d] STEL, short term exposure limit.

[e] TLV, threshold limit value.

[f] ACGIH carcinogenicity categories:
A1: confirmed human carcinogen
A2: suspected human carcinogen
A3: carcinogen with unknown relevance to humans
A4: not classifiable as a human carcinogen
A5: not suspected as a human carcinogen

[g] OSHA PEL, permissible exposure limit, 8 hr TWA except as noted; NIOSH REL, recommended exposure limit, 10 hr TWA except as noted.

[h] BEI, biological exposure index.

[i] Skin: skin, mucous membranes, and eyes are important potential routes of exposure.

[j] A ceiling limit is the concentration that should not be exceeded during any part of the working exposure.

[k] NIOSH Ca, NIOSH carcinogen.

[l] LFE, lowest feasible exposure.

[m] Potential for sensitization.

In vitro measurement of permeation rates is usually performed with excised skin in diffusion cells. Methods for these studies are reviewed in Bronaugh and Maibach [154,155] and Salem and Katz [156]. In vitro and in vivo rates correlate fairly well for some hydrophilic compounds but not as well for very hydrophilic or lipophilic compounds.

There is very little scientific data on human in vivo percutaneous absorption of solvents. In vitro and in vivo information is presented in each section for the solvents that have been studied. Permeation rates in vivo have been measured in several different ways, including the disappearance of solvents from solution after dermal application; uptake of radioactively labeled compounds; and presence of solvent or metabolite in blood, urine, or exhaled air. Each method has its advantages and disadvantages; unfortunately, the lack of standardization in techniques does not permit direct comparison of studies. Many studies were done with a very small number of volunteers or at different skin sites and show considerable interindividual variability.

Water

Any discussion of solvents should begin with the most common, most overlooked solvent: water. Adequate hydration is essential for optimal skin functioning but in excess, it can have deleterious effects. Water does not extract lipids like chloroform or methanol. It does not cause chemical corrosion like phenol or irritation like ethylbenzene. Instead, water exerts its powerful effects indirectly by altering the structure of the SC.

The SC is highly hygroscopic, attracting 500% of its dry weight in less than 1 hour and swelling to 5 times its original thickness [27]. As this transformation takes place, individual corneocytes swell and the interstices expand, leading to inter- and intracellular edema. As the corneocytes detach from each other, premature desquamation begins. All cells of the epidermis—including the keratinocytes, melanocytes, and Langerhans cells—begin to show striking cytotoxic changes [27]. They develop vacuoles and degenerative changes in the mitochondria. These changes may precipitate the release of cytokines provoking further inflammation and subdermal edema. Lacunae, previously hidden, open and provide new avenues for hydrophilic and hydrophobic substances to penetrate the skin.

These ultrastructural changes explain how the chronic dermatitis of "wet work" develops. Many occupations require frequent or persistent immersion of the hands in water. Dishwashers, housekeepers, homemakers, cleaners, window washers, machinists, cannery workers, fishermen and fish processors, bartenders, chefs, confectionery workers, and hairdressers all engage in wet work. Immersion of the hands in water makes the skin more permeable to solvents, soaps, detergents, chemicals, allergens, and other noxious substances [157–159]. This increased permeability also sets the stage for development of cumulative insult dermatitis from very low concentrations of substances that would normally not be injurious [160]. Wet workers are also more susceptible to paronychia as well as dermatophtye infections.

The alternate swelling and drying out of the SC that occurs during frequent handwashing (eg, in health care personnel) can be especially damaging to skin and nails. Frequent immersion may facilitate colonization by undesirable bacteria.

The foot is also susceptible to the same process. Immersion foot described in soldiers during the Viet Nam war is a dramatic example of hydration dermatitis [161–163]. A similar situation can develop in workers whose feet perspire heavily and who wear poorly absorbent socks and synthetic footwear. Sweat, pressure, trauma from abrasive particles, chemical spills, and occlusion can lead to a troublesome chronic dermatitis.

Immersion is not the only route by which water alters skin properties; occlusion is also highly effective. The pharmaceutical industry uses this principle in skin patches that deliver drugs for everything from smoking cessation to birth control. Transdermal occlusion can also occur in workers who wear gloves to "protect" their hands. Perspiration may hydrate the SC sufficiently to aid penetration of chemicals and allergens from gloves. Absorbent cotton gloves worn under an outer glove may help alleviate this situation. However, cotton gloves may also serve as a wick, drawing solvent through punctures in the outer gloves and increasing the surface area where solvent is in direct contact with skin. The outer glove layer provides occlusion, increasing the potential for significant skin absorption and systemic toxicity.

Alcohols

In general, alcohols are well tolerated and have few effects on the skin other than drying. The potential to cause skin irritation seems to decrease as the molecular weight of the alcohol increases. Cumulative skin exposure may lead to irritant contact dermatitis and, in a few rare cases, acute irritant dermatitis [164].

Butanols

The butanols are a family of alcohols that have limited skin irritant potential and a variety of uses. N-butanol is a solvent for lacquers and is used in the manufacture of cements and plastics. 1-Butanol is used in the extraction of perfumes and vegetable oils and in food and beverages. 2-Butanol is an intermediate in the manufacture of methyl ethyl ketone and finds limited use as a solvent for enamels, gums, lacquers, resins, vegetable oils. Tert-butanol, a mild skin irritant, is a widely used as a wax remover, solvent and dehydrating agent. Isobutanol is used in paint and varnish removers, general solvents and perfumes. Scheuplein and Blank [32] calculated an in vitro absorption rate of 0.02 mg/ cm/h for human skin.

Ethylene glycol

Ethylene glycol is used as a solvent and in adhesives, inks, polishes, pesticides and antifreeze. It is metabolized to the toxic glycolic, glyoxylic, and oxalic acids. Sensitivity to ethylene glycol has been reported in two workers who were

exposed during the cutting of glass lenses [165,166]. One patient showed cross-sensitization to propylene glycol [165].

Laitinen et al [167] studied 11 automotive mechanics and concluded that dermal absorption was a significant route of exposure. Driver et al [168] confirmed that ethylene glycol was absorbed through cadaveric human thigh skin using in vitro flow through diffusion cells (flux of 0.25 mg/cm^2/h). A polyethylene glycol–based burn cream was implicated in the fatal intoxication of three patients. All three had elevated blood levels of ethylene glycol, increased anion and osmolal gaps, increased serum calcium, and decreased ionized calcium. The patients developed acute renal failure and subsequently died [169].

Ethanol

Ethanol is an excellent general solvent, diluent, and extracting agent. It is used extensively in the chemical and pharmaceutical industries and in the manufacture of adhesives, cosmetics, inks, perfumes, as well as fuel and antifreeze. Ethanol is a skin irritant and, occasionally, a sensitizer. The identity of the sensitizing agent is not always clear and may be ethanol itself, an aldehyde metabolite, or an impurity. Ethanol is absorbed through human skin; Scheuplein and Blank [170] calculated a K_p of 8×10^{-4}cm/h.

There are a few reports of allergic contact dermatitis to ethanol [171–174]. Urticaria has also been reported [175–177]. Ophaswongse and Maibach [178] reviewed case reports of allergic contact dermatitis from alcohol. They also reported eight cases of allergic skin reactions after consumption of alcoholic beverages. Kelso et al [179] and McCormick and Young [180] described anaphylactoid reactions to ethanol. Cross reactions between primary and secondary or tertiary alcohols are uncommon, but several investigators have reported cross reactions between ethanol and primary alcohols.

Isopropyl alcohol

Isopropyl alcohol is a general solvent for gums, oils, and resins and is used in cements, cleaners, coatings, cosmetics, disinfectants, dyes, fuels, inks, paints, paint thinner, paint remover, and perfumes. It is also used in the production of acetone, esters, ethers and plasticizers. It is a mild skin irritant, and there are rare reports of allergic sensitivity [181]. Isopropyl alcohol is readily absorbed through the skin. Most cases of percutaneous absorption relating to toxicity have been reported in children wherein alcohol sponge baths were used to reduce fever [182–184]. Illness from percutaneous absorption has also occurred in adults with intact skin [185,186].

Methanol

Methanol is used as a solvent for paints, cellulose nitrate, colophony, shellacs, varnishes, and paint removers. It is also used in antifreeze and in the manufacture of formaldehyde and formaldehyde resins, shoes, and linoleum. It is a skin

irritant, and repeated exposure may lead to loss of skin lipids and severe dermatitis. Methanol is metabolized to formic acid and formaldehyde.

Aufderheide et al [187] reported two firefighters who had combined percutaneous and inhalational methanol toxicity. The only complaint both firefighters had on presentation to the emergency department was mild headache. Their physical examinations and anion gaps were normal; however, their peak methanol levels were 23 and 16 mg/dL.

There are reports of central nervous system toxicity and fatalities in children from skin absorption under occlusion [188,189]. A painter whose clothes and shoes were soaked with methanol developed central nervous system toxicity and blindness several days after exposure [190]. Downie et al [191] described a case of methanol poisoning from dermal exposure in Saudi Arabia. A consultant wore a positive-pressure breathing apparatus while supervising the interior cleaning of a tank that had contained methanol. He did not wear protective clothing and his clothes became soaked with methanol during 2 to 3 hours of work in the closed space. Later he worked on deck and the clothing dried out. Eight hours after exposure, he developed visual symptoms consistent with methanol poisoning and was successfully treated with ethanol.

Fiserova-Bergerova and Pierce [192] calculated a dermal penetration rate of 2 mg/cm^2/h based on methanol's physicochemical properties. Scheuplein and Blank [170] found an in vitro K_p of 0.0005 cm/h (absorption rate of 0.4 mg/cm^2/h) for 0.1 M aqueous methanol in human abdominal skin. This compares with an in vitro K_p of 0.0016 cm/h (absorption rate of 1.27 mg/cm^2/h) for human abdominal stratum corneum that Southwell et al [193] reported for neat methanol. They noted a very wide coefficient of variation (71%) in the eight specimens used in their study; the variation for other compounds was less but still high (34%–48%).

Dutkiewicz et al [190] measured disappearance of methanol from the skin of three volunteers whose forearms were exposed for 15 to 60 minutes. They found an average absorption rate of 11.5 mg/cm^2/h. Immersion of a subject's hand in methanol for 2 minutes could lead to absorption equivalent to the inhalation of 50 mg/m^3 methanol over 8 hours.

Batterman and Franzblau [194] measured methanol levels in the blood stream of human volunteers after immersion of one hand in neat methanol for 2 to 16 minutes. They calculated an average derived absorption rate of 8.1 ± 3.7 mg/cm^2/h. The 16-minute immersion yielded blood concentrations of 11.5 mg (SD 2.3 mg) of methanol. The authors concluded that a 20-minute skin exposure would lead to blood levels comparable to the urine biological exposure index of 15 mg/L. Normally, threshold limit value–time weighted average (TLV-TWA) is reached after 8 hours of respiratory exposure to 200 ppm methanol/m^3 air [195]. These results correlate well with those of Dutkiewicz et al [190] despite the differences in site (hand versus forearm) and method (methanol levels in blood versus disappearance of methanol from skin surface).

Nakaaki et al [196] measured urinary methanol levels after dermal exposure to 15 mL of methanol under occlusion. They found that levels were similar to those

after a 4-hour respiratory exposure to 200 ppm in air. These observations show that methanol penetrates the skin readily and brief dermal contact can lead to significant levels of exposure.

Propylene glycol

Propylene glycol is a solvent for fats, oils, waxes, and resins. It is used in flavoring extracts, perfumes, and colors; as an antifreeze; in the manufacture of resins; and as an emulsifier in food. It is a relatively common cause of contact urticaria [197,198]. Coma and fatalities have been associated with absorption of propylene glycol from dressings in burn patients [199,200].

Aldehydes

Formaldehyde

Formaldehyde is a component of skin and hair care products, cosmetics, and permanent press textiles. It is also used in a wide variety of products and may be released from preservatives such as dizaolidinyl urea, imidazolidinyl urea, Quaternium-15, DMDM hydantoin, and Bronopol. Formalin is used as a fixative in pathology laboratories and for embalming.

Formaldehyde solutions of 2% are skin irritants; more concentrated solutions cause chemical burns. Torresani et al [201] reported a case of contact urticaria to formaldehyde. The potential for skin sensitization has been estimated at 5% of the general population [202].

Erythema multiforme was reported in four men who worked in a Canadian circuit board manufacturing plant. Two of the four men had positive patch tests to formaldehyde, and liver involvement was documented in three of the cases [203]. Patch testing to trichloroethylene was not performed. All four men had co-exposures to palladium chloride, copper sulfate, epoxy fiberglass, lead, trichloroethylene, and ammonium persulfate.

Furfural

Furfural is used in refining oil, resins and as a chemical intermediate. In liquid form it is irritating to the skin. Tupasela and Kanerva [204] reported a single case of contact urticaria from furfural exposure. In general, cases of contact urticaria from low molecular weight chemicals are rare; these authors described just 12 cases of contact urticaria from low molecular weight chemicals over a 4-year period.

Flek and Sedivec [205] estimated a percutaneous absorption rate of 0.2 mg/cm^2/h for furfural. They calculated that a 15-minute exposure of one hand could lead to levels similar to those resulting from the inhalation of 10 mg/m^3 furfural in air for 8 hours.

Aliphatic and alicyclic hydrocarbons

Aliphatic and alicyclic hydrocarbons with low boiling points have a higher potential to defat skin and cause dermatitis than those with high boiling points.

Typical skin reactions to this group of solvents include inflammation, hyperpigmentation, and dermatitis. Aromatic hydrocarbon solvents with benzene rings tend to be more irritating to the skin than aliphatic hydrocarbons.

Gasoline

Gasoline is a skin irritant; repeated skin exposure may occur from using gas as a solvent to clean the hands. Jia et al [148] found that repeated dermal exposures to gasoline led to significant decreases in skin lipids (ceramide, fatty acid, and cholesterol), causing dryness, dermatitis, and fissures. These investigators also noted a variety of nail disorders including onychorrhexis, leuconychia, onychauxis, and schizonychia.

Extended contact with gasoline may lead to partial or full thickness tissue burns [206,207]. As mentioned earlier, Walsh et al [83] reported a case in which a 12-year-old boy was trapped under an overturned tractor for 1 hour. His clothing became soaked with gasoline and he developed a 50% body surface area burn, followed by renal failure and death on the twelfth day of hospitalization.

Hexane

Hexane is widely used as a solvent in adhesives, rubber cements, glues, inks, and varnishes. It causes erythema and is a skin irritant. Both N-hexane and methyl butyl ketone are metabolized to a common intermediate 2,5-hexanedione that is neurotoxic. N-hexane exposure levels can be monitored by following urine levels of 2,5-hexanedione.

Hansen and Andersen [88] studied the solubility of several solvents in human psoriasis scales. They found that hexane had limited solubility and concluded that dermal uptake was slow. This novel approach to dermal permeation assumes that psoriatic corneocytes have the same properties as normal corneocytes. Any conclusions from their studies are limited to the outer layers of the SC and would not apply to the deeper layers of the epidermis or the dermis.

Cardona et al [208] estimated that skin absorption can account for as much as 50% of the total absorbed dose of hexane. Perbellini et al [209] have calculated a half-life of 64 hours for hexane in adipose tissue. In their model, which simulates daily exposure to N-hexane, solvent accumulates in fat.

Kerosene

Kerosene is used as a solvent for pesticide sprays and as a fuel. It can also be a skin irritant. Barnes and Wilkinson [210] reported a case of "irritant pseudotoxic epidermal necrolysis" in a boy due to prolonged exposure from contamination of clothing.

There are several forms of naptha. Three of the most common are: (1) a petroleum distillate containing a mixture of hydrocarbons C5-C13; (2) coal tar naptha; and (3) varnish makers' and painters' (VMP) naptha. Petroleum naptha is a solvent for degreasing, dry cleaning, oils, paints, rubber cement, and varnishes. Coal tar naptha is used in asphalt paving and VMP naptha is used primarily as a diluent. Napthas can cause dermatitis, erythema, edema, and fissures [211].

Goodfield and Saihan [212] reported nonimmunologic contact urticaria in four out of eight factory workers who were exposed to Naptha 21/99. Two other workers had hand dermatitis. Naptha 21/99 is a mixture of propyl benzene mesitylene (1,3,5-trimethylbenzene), xylene, and toluene.

Stoddard solvent

Stoddard solvent is a mixture of hydrocarbons C7-C12; its exact composition depends on the production process. It is used in lacquers, paints, paint thinners, varnishes, inks, photocopier toner, adhesives, degreasers, dry cleaning, waterproofing agents, and pesticides. White spirit is similar to Stoddard solvent but contains a mixture of hydrocarbons C7-C11. It is used primarily in the paint industry as a solvent or diluent.

Stoddard solvent can cause irritant dermatitis and erythema. Prolonged or repeated exposure may cause fissures, vesicles, ulceration, and chemical corrosion [213]. Nethercott et al [214] reported several cases of erythema and ulceration on the genitals and buttocks from prolonged skin contact. Stoddard solvent had been used as a dry cleaning agent on the workers' coveralls, and the coveralls were worn without adequate drying. In the more severe cases, the absence of undergarments facilitated dermal absorption.

Amides

Dimethyl formamide

Dimethyl formamide (DMF) is a cleaning solvent for printed circuit boards, a solvent for vinyl-based and polar polymers, and is used in the manufacture of films, coatings (polyurethane lacquers for textiles), pesticides, and pharmaceuticals as a permeation enhancer. DMF penetrates the skin easily and most exposures occur by percutaneous absorption. Dermal symptoms from DMF exposure include skin irritation, delipidization, pruritus, and desquamation. Contact dermatitis with vesiculation and eczema has also been reported [215].

Lauwerys et al [216] described cases of acute DMF intoxication and elevated levels of metabolite excretion in workers in an acrylic fiber factory. Skin protection eliminated their symptoms and reduced urine metabolite excretion.

Systemic symptoms from an acute DMF exposure due to skin absorption include dizziness, nausea, vomiting, and abdominal pain. After acute intoxication, hepatotoxic effects can be delayed while the liver metabolizes DMF to N-hydroxymethylformamide. Potter [217] described a worker who had a 20% body surface area exposure who developed dermal irritation and erythema shortly after exposure. Sixty-two hours after dermal contact, the patient developed abdominal pain, nausea, and hypertension. His symptoms resolved over the course of 7 days. Generally, elevated liver function tests (LFTs) from acute exposure return to normal in 2 to 3 weeks.

Chronic exposure is often associated with eye irritation, headache, anorexia, abdominal pain, and toxic hepatitis with elevated LFTs. The ratio of alanine aminotransferase to aspartate aminotransferase in DMF hepatotoxicity is usually

greater than 1; levels may remain elevated for 5 months or longer after cessation of exposure. Asymptomatic workers with chronic exposure may have elevated LFTs even when personal exposure limits (PELs) have been strictly observed [218].

An alcohol intolerance syndrome (disulfiram-like reaction) with facial flushing, palpitations, chest tightness, dizziness, sweating and nausea has been reported. Symptoms developed in workers who were exposed to DMF and then consumed alcohol within 24 hours. The exact mechanism is unknown, but DMF appears to have an inhibitory effect on alcohol dehydrogenase [132–134].

In a study that monitored the urinary excretion of DMF metabolites, Maxfield et al [219] found that percutaneous absorption ranged from 13% to 39% of the amount absorbed from the respiratory tract. Mraz and Nohova [220] studied the dermal penetration of liquid DMF in four human volunteers and found a permeation rate of 9.4 mg/cm^2/h (SD ± 4.0 mg/cm/h; range 6.5–16.3). Subjects immersed one hand in 100% liquid DMF for 15 minutes; subsequently, DMF metabolites in their urine were monitored for 5 days. Subjects excreted the same amount of metabolite after a 10-minute immersion of one hand in DMF as they did after an 8-hour inhalation exposure to DMF vapor at 60 mg/m^3 (twice the TLV). The excreted metabolite N-hydroxymethyl-N-methylformamide peaked at 4 to 8 hours after exposure, while N-hydroxymethylformamide peaked between 10 and 14 hours postexposure. DMF vapor was readily absorbed by the skin and absorption was enhanced by higher temperature and higher relative humidity. These data suggest that DMF accumulates in the skin and is eliminated slowly.

Dimethyl acetamide

Dimethyl acetamide (DMAC) is used as a solvent for resins and polymers, in crystallization and purification, and as a reaction catalyst. DMAC penetrates the skin easily and can cause nausea, headache and weakness. Marino et al [221] reported a case of dermal and respiratory exposure to DMAC and ethylenediamine that resulted in chemical burns, conjunctivitis, esophagitis, rhabdomyolysis, hepatitis, and hallucinations with delirium.

Nomiyama et al [222] exposed human volunteers twice to 6 ppm DMAC for 4 hours; the exposures were separated by intervals of at least 96 hours. They estimated that the mean dermal absorption accounted for approximately 40% of the total uptake.

Because DMAC is a potential hepatic and renal toxin, biologic monitoring should be performed if there is potential for skin contact or inhalation. N-methylacetamide [79-16-3] is measured in urine specimens collected at the end of the shift; levels should be less than 40 ppm for individuals and 20 ppm metabolite average for workers on the job.

Amines

N-methyl pyrrolidone

N-methyl pyrrolidone (NMP) is an aprotic solvent that is increasingly used as a less toxic substitute for dichloromethane, trichloroethane, trichloroethylene, and

glycol ethers [152]. It is used in the electronics (semiconductor) industry, in coatings, cleaning agents, in agriculture as a solvent carrier for pesticides, and in graffiti removal. It is also used in topical pharmaceutical preparations to enhance skin penetration [223–225].

Leira et al [152] reported that 10 out of 12 Norwegian workers in a circuit board manufacturing plant experienced acute contact dermatitis of the hands after contact with NMP. The workers were exposed over a 2-day period and used latex gloves intermittently. The hand dermatitis resolved with the use of cotton liner gloves inside the latex gloves. However, the authors recommend the use of butyl rubber gloves for better skin protection.

A Swedish study of 38 graffiti cleaners found that urinary levels of a metabolite 5-hydroxy-N-methyl pyrrolidone (5-HNMP) ranged from 0.03 to 18.3 mmol/mol creatinine [226]. The authors suggested that skin permeation was an important route of exposure.

Akrill et al [227] studied the uptake of 5% to 25% solutions of NMP for 15 minutes. Excretion of 5-HNMP peaked at 10 hours and continued for 48 hours. A 15-minute dermal exposure to 15% NMP was equivalent to an 8-hour respiratory exposure to 10 mg/m^3 [228].

Aromatic hydrocarbons

Benzene

Benzene is used as an intermediate in the production of ethylbenzene; in the manufacture of synthetic rubbers, agricultural chemicals, dyes, glues, lubricants, paints, pharmaceutical agents; and as a component of gasoline. Occupational exposures occur in all phases of the petroleum industry from refining to gasoline storage and service stations, in the rubber industry, and in chemical and shoe manufacturing. Benzene causes erythema, drying, dermatitis, vesiculation, and chemical burns with prolonged skin contact.

Franz [229] used [^{14}C] benzene to study percutaneous absorption in human skin in vivo and in vitro. In vitro absorption was 0.7% and in vivo absorption was 0.2%. [^{14}C] Benzene penetrated the skin rapidly but also volatilized quickly. Franz concluded that contact time with the skin determined the rate of absorption. In other studies, Franz applied neat benzene briefly (10 to 20 seconds) to the palms and forearms of human volunteers. He found that absorption on the palm averaged 0.003 mL/cm^2 and 0.002 mL/cm^2 on the forearm.

Experimentally, the permeability constant for benzene varies depending on the vehicle used to apply it to the skin. Blank and McAuliffe [230] calculated permeability constants ($\times 10^{-3}$ cm/h) of 111 (water), 3.7 (isooctane), 2.4 (hexane), 1.4 (gasoline), and 0.94 (hexadecone). Fiserova-Bergerova and Pierce [192] calculated that a skin exposure of 360 cm^2 could lead to dermal absorption of 30 times the respiratory absorption at the TLV for a comparable period of time.

Nakai et al [231] studied the in vitro permeation of [^{14}C] benzene through human skin in an aluminum dermal absorption block [232] modified for volatile substances. Nakai et al [231]found a two- to threefold variation in benzene

permeability coefficients with changes in temperature. The permeability coefficient was 0.10 cm/h at 15°C, 0.14 cm/h at 26°C, and 0.26 cm/h at 50°C.

Ethylbenzene

Ethylbenzene is a starting material for the manufacture of styrene. It is also used on a limited basis as a general solvent in paints and lacquers, paint thinners, and in degreasing. It can be a skin vesicant. Dutkiewicz and Tyras [233] found maximal urine concentrations of mandelic acid in human volunteers 2 hours after dermal exposure. The percutaneous absorption rate was estimated at 28 mg/ cm^2/h in direct studies and 2 mg/cm^2/h in urine metabolite studies. Ethylbenzene vapors do not appear to be absorbed through the skin significantly [234].

Styrene

Styrene is a solvent for synthetic rubber and resins, and in the past, was used in the manufacture of plastics, polymers, and in boat-building. Today, it is seldom used as a solvent. It is a mild skin irritant, and repeated exposure leads to drying and irritation. There are case reports of blisters [235] and chemical burns [236] from skin exposure to styrene. Sjoborg et al [237] described a case of contact allergy to styrene with cross-reaction to vinyltoluene. Exposure can be monitored by following urine mandelic acid or phenylglyoxylic acid levels.

Dutkiewicz and Tyras [238] estimated that liquid styrene was absorbed through the skin at a rate of 9 to 15 mg/cm^2/h. Engstrom et al [239] estimated an absorption rate of 0.06 mg/cm^2/h on the hand. Berode et al [240] calculated an absorption rate of 0.06 mg/cm^2/h based on excreted and exhaled metabolites, which is significantly lower than respiratory absorption. Thus if one hand (500 cm^2) were immersed in liquid styrene for 30 minutes, approximately 15 mg of styrene would be absorbed. The biologic exposure index for styrene in blood is 0.55 mg/L at the end of the shift. Dermal absorption of styrene vapors is probably minimal [241].

Toluene

Toluene is widely used as a solvent and in adhesives, paints, paint thinners, cellulose nitrate lacquers, fingernail polish, inks, and gasoline. Skin contact for 30 minutes may cause a burning sensation and slight erythema [242]. Vapor contact alone can lead to skin drying. Toluene is lipophilic and distributes to vascular and lipid-containing tissues including the central nervous system, bone marrow, liver, kidneys, and nervous system [243]. Urine hippuric acid levels can be monitored as a biologic marker of exposure.

Shibita et al [244] described a 22-year-old man who sustained a 71% body surface area exposure to a toluene-based paint. Initially the skin damage seemed mild; however, the patient developed extensive blistering and necrosis followed by acute renal failure, disseminated intravascular coagulation, and death. The

authors stressed the importance of immediate and vigorous irrigation of exposed skin.

Several studies have investigated the percutaneous absorption of toluene in human volunteers. In an early study, Dutkiewicz and Tyras [238] estimated percutaneous absorption by measuring the loss of toluene from a solution applied to the skin of nine volunteers. They estimated that liquid toluene was absorbed through the skin at a rate of 14 to 23 mg/cm^2/h. Based on their data, the Environmental Protection Agency estimated a K_p of 1 cm/h for aqueous toluene. However, the method Dutkiewicz and Tyras used may lead to overestimation of the flux into the skin, and it is not clear that steady state conditions were reached in their study.

Aitio et al [245] had three human volunteers immerse one hand in neat toluene for 5 minutes, then measured blood levels of toluene drawn from the same arm and the contralateral arm. They found in 0.2 to 0.5 mg/L toluene in the ipsilateral arm and noted that the difference persisted for up to 3 hours. These levels were comparable to inhalation of 100 ppm toluene at rest. This is similar to the results of Sato and Nakajima [242], who found blood levels of 0.2 mg/L after human volunteers immersed one hand in neat toluene for 30 minutes; however, they found higher levels of blood toluene than Aitio et al after their volunteers inhaled 100 ppm toluene vapor for 4 hours.

Monster et al [246] estimated that washing both hands with toluene for just 5 minutes could lead to skin permeation equivalent to 3% of the total uptake from an exposure to 100 ppm toluene over 8 hours. Kezic et al [247] used linear system dynamics to calculate permeation rates from exhaled air after respiratory and dermal exposure to toluene. Volunteers were exposed to toluene for 3 minutes on a 27-cm^2 area of the volar forearm. Maximal permeation was reached within a few minutes of exposure. Dermal flux into the skin of neat toluene was 223 ± 81 nmol/cm^2/min.

Thrall et al [248] used real-time breath analysis and PBBK to study the dermal absorption of aqueous toluene in human volunteers. A PBBK model takes non–steady state conditions into account and allows changes in exposure concentration with time to be incorporated into the model. They found an average K_p of 0.012 cm/h (range: 0.003–0.02) in six volunteers.

Xylene

Xylene is a starting material for the production of ethylbenzene and is an important solvent in the paint industry. It is also used in dyes, glues, inks, varnishes, pesticides, coatings, fabrics, perfumes, and in medical technology. Prolonged skin contact can lead to a burning sensation, erythema, delipidization, and dermatitis [249].

Altman [250] described a case of allergic contact urticaria that presented as facial dermatitis. Patch testing showed an immediate 25-mm urticarial patch to 100% xylene and a 15-mm patch to 1% xylene at 15 minutes. The patient had no reaction to the other patch tests. Three control subjects had negative tests to the 1% and 100% xylene. Palmer and Rycroft [251] reported a case of airborne

contact urticaria in a cytology technician who experienced repeated episodes of widespread urticaria. She had minimal direct skin contact with xylene. The patient developed severe erythema and wheals on patch testing, leading the authors to conclude that the reaction was immunologically mediated.

Dutkiewicz and Tyras [238] reported that the dermal absorption rate of liquid xylene varied from 4.5 to 9.6 mg/cm^2/h in 10 human volunteers. In their studies, absorption increased with prolonged contact and if the volunteer's skin was damaged.

Lauwerys et al [252] measured excretion levels of metabolites after a 30-minute dermal exposure. They reported a flux ranging from 42 to 260 mg/ cm^2/h in 13 human volunteers. The different values obtained in these two studies may be due to the methods and whether steady state conditions were achieved. In a study described in more detail in the previous section on toluene, Kezic et al [247] measured a flux for neat xylene of 46 ± 17 nmol/cm^2/min in human skin in vivo.

Engstrom et al [253] studied percutaneous absorption while human subjects immersed both hands in neat xylene for 15 minutes. They found an average absorption rate of 120 mg/cm^2/h or about 35 mg total. This was equivalent to the amount absorbed systemically from a 15-minute respiratory exposure to 100 ppm xylene vapor. Absorption increased with prolonged contact and continued for up to 5 hours after skin contact ceased. Low et al [254] have shown that xylene distributes to subcutaneous fat and has an estimated half-life for elimination of 50 hours. This raises concerns about accumulation in fat over time.

Two studies have reported apparent increases in xylene absorption in people with atopic dermatitis [253,255]. Very little is known about the effects of skin diseases like atopic dermatitis, eczema, and psoriasis on skin permeability. It is logical that any disturbance in the SC would decrease its protective function and increase the vulnerability of the epidermis and dermis.

Chlorinated hydrocarbons

Most of the chlorinated hydrocarbons were discovered in the 1800s. Their narcotic properties have been known since the time of their discovery, and many were used as anesthetics until their often lethal side effects were described.

Carbon tetrachloride (tetrachloromethane)

Carbon tetrachloride (tetrachloromethane) is a solvent for fats, oils, resins, waxes. In the past, carbon tetrachloride was used as a metal degreaser and grain fumigant; as a chemical intermediate in the manufacture of chlorofluorocarbons; and in fire extinguishers. Skin contact leads to erythema, skin whitening, defatting, and dermatitis. When heated, carbon tetrachloride decomposes to phosgene, hydrogen chloride, and chlorine. Stewart and Dodd [256] found that immersion of a volunteer's thumb in neat carbon tetrachloride for 30 minutes led to a peak alveolar air concentration close to 1 ppm. They concluded that the immersion of both hands could lead to absorption of toxic levels of carbon tetrachloride.

Chloroform (trichloromethane)

Due to its powerful narcotic effect, chloroform (trichloromethane) finds limited use as a solvent, cleaning agent, and chemical intermediate in the production of chlorofluorocarbon, rubber adhesives, and in rubber vulcanization. Nakai et al [257] calculated a K_p of 0.14 cm/h for permeation of dilute aqueous [^{14}C] chloroform through 0.2 cm^2 samples of Caucasian breast or abdominal skin in vitro. Skin samples were used within 2 hours of surgery and were dermatomed to 0.2 to 0.4 mm thick. Similar results were obtained for trichloroethylene (0.12 cm/h); however, the K_p for tetrachloroethylene was an order of magnitude less (0.018 cm/h).

Methylene chloride (dichloromethane)

Methylene chloride (dichloromethane) is used in the production of cellulose acetate and cellulose butyrate films; as a degreasing agent; and as a solvent extractant for caffeine (coffee), hops, castor oil, cocoa butter, and drugs. Methylene chloride is being replaced as a paint/varnish remover by water-based systems. It is a skin irritant, and evidence suggests that dermal absorption occurs [256]. Two different pathways for methylene chloride metabolism have been described: (1) oxidation in the liver by a cytochrome P450-dependent system produces carbon monoxide and (2) conjugation with glutathione leads to formaldehyde production.

Perchloroethylene (tetrachloroethylene)

Perchloroethylene (tetrachloroethylene) has a relatively low toxicity and therefore has largely replaced trichloroethylene as a dry cleaning and a degreasing agent in the tanning of pelts and leather. It is a solvent for greases, fats, waxes, bitumen, and tar. It is also used in the leather, metal, rubber, adhesives and plastics industries. Like many of the chlorinated hydrocarbons, perchloroethylene is being replaced by other systems for environmental reasons. Two separate studies have suggested an increased risk of melanoma in workers exposed to perchloroethylene [258,259].

Aitio et al [245] found that immersion of a subject's hand for 5 minutes led to a solvent blood concentration in that arm of 1.5 mg/mL. This was 130 times higher than a blood sample drawn from the contralateral arm. However, based on a calculated a skin penetration rate of 0.11 mg/cm/h [192] and a calculated K_p of 0.018 cm/h [257], the risk of toxic dermal absorption of tetrachloroethylene is extremely low.

1,1,1-Trichloroethane

1,1,1-Trichloroethane dissolves fats, oils, resins, waxes, bitumen, and asphalt. It is also used as a cleaning solvent, in textile spotting, inks, paint, adhesives, and drain cleaners. 1,1,1-Trichloroethane it is an excellent degreasing agent. In cold cleansing, it is vaporized and a cold part is suspended in the vapor stream. The

trichloroethane condenses on the part and dissolves dirt and grease, flushing it from the surface; then the solvent evaporates.

Fiserova-Bergerova and Pierce [192] calculated a skin penetration rate of 1.64 mg/cm^2/h. Stewart and Dodd [256] found that immersion of a subject's hand for 30 minutes led to a peak alveolar concentration of 22 ppm; similar results were obtained for trichloroethylene, perchloroethylene, and methylene chloride.

Nakaaki et al [196] applied 15 mL of 1,1,1-trichloroethane to a 12.5 cm^2 area of skin for 2 hours under occlusion and measured solvent concentrations of 3 to 5 ppm in the exhaled air of two volunteers. This was similar to levels seen after a 2-hour respiratory exposure to 10 to 20 ppm/m^3 1,1,1-trichloroethane in air.

Aitio et al [245] simulated hand washing by having volunteers immerse one hand in neat 1,1,1-trichloroethane for 5 minutes. Blood drawn from the ipsilateral side had a 1,1,1-trichloroethane concentration of 0.5 mg/mL— 35 times higher than the contralateral side. The difference between the two arms disappeared after 5 hours.

In a study described in the previous section on toluene, Kezic et al [247] found two distinct rates for skin permeation of 1,1,1-trichloroethane. Three volunteers reached maximal permeation rates after a few minutes; the measured flux in this group was 90 ± 92 nmol/cm^2/min in human skin in vivo. The other group of three volunteers reached maximal permeation rates after 20 to 25 minutes; the measured flux in this group was 22 ± 11 nmol/cm^2/min. Faster permeation may be correlated with a greater degree of skin irritation on contact.

1,1,2-Trichloroethylene

1,1,2-Trichloroethylene (Tri) dissolves fats, waxes, and rubber. It is a solvent for metals, oils, sulfur, and many resins; an extractant; and is used in typewriter correction fluid and as a degreasing agent. Like many of the chlorinated hydrocarbons, Tri is being replaced by other systems for environmental reasons. 1,1,2-Trichloroethylene can cause the full spectrum of skin disease ranging from erythema/edema [260] to generalized exfoliative dermatitis [261] and fatal Stevens-Johnson syndrome [262].

Conde-Salazar et al [263] described a subcorneal pustular eruption in a patient after exposure to trichloroethylene. Goh and Ng [264] reported a patient who had recurrent erythematous xerotic plaques with fissuring localized to the arms and trunk. Skin biopsy revealed epidermal parakeratosis with a superficial perivascular lymphohistiocytic infiltrate.

Nakayama et al [265] described a 21-year-old printer who developed generalized erythema with a maculopapular rash that progressed to erythroderma and exfoliative dermatitis with mucous membrane involvement and severe liver dysfunction after a 2-week exposure to Tri. Patch tests were positive for Tri and trichloroethanol (TCE), a Tri metabolite. The authors concluded that the patient's dermatitis was mediated by a delayed-type hypersensitivity mechanism. The patient continued to experience generalized dermatitis after his exposure stopped, perhaps because of slow, ongoing release of Tri from stores in fatty

tissues. Davidson and Beliles [266] have estimated the half-life of Tri in adipose tissue at 3.5 to 5 hours.

Occlusion with gloves or solvent-soaked clothing has led to dermatitis with severe blistering [267] and bullous eruptions [268]. Phoon et al [262] described a series of five electronics workers who cleaned electronic parts, as well as their hands and forearms, with TCE. The duration of exposure ranged from 2 to 5 weeks. All five workers had abrupt onset of fever, generalized erythema, exfoliative dermatitis (Stevens-Johnson syndrome), and liver dysfunction. One patient died from septicemia and fatal toxic hepatitis. The authors considered the possibility of a hypersensitivity reaction to Tri in these cases.

Goon et al [269] described a 36-year-old Chinese man with fever, a generalized erythematous maculopapular rash, mucous membrane erosions, and elevated LFTs. Purpuric bullae developed on the soles of his feet on the seventh day of hospitalization. Subsequently, his skin exfoliated and he died on the fourteenth day of hospitalization. The patient had worked in an air-conditioned room on a factory assembly line for 1 month and stopped work when he became ill. Two automated degreasing machines with Tri were located 5 m from his work station, but he had no direct contact with Tri while at this job. Air levels of Tri were always less than 25 ppm (TLV 50 ppm, Singapore) and workers' annual urinary trichloroacetic acid (TCA) levels were less than 100 mg/L (biologic TLV, Singapore). After the patient's death, air TCE levels at the degreasing machines measured 24% to 53% of the TLV. Two out of three coworkers at nearby work stations had elevated levels of urinary TCA (148.2, 122.0, and 80.1 mg/L), but no one had any skin rashes or other complaints. The authors concluded that this case represented a hypersensitivity reaction to Tri.

Yoshida et al [270] reported chemical burns, pneumonia, and coma in a 58-year-old man who fell headfirst into a Tri reservoir bath. Eight hours after the immersion, serum concentrations of Tri and its metabolites were: 31.4 mg/mL (Tri), 16.5 mg/mL (TCE), and 79.5 mg/mL (TCA). The authors reported a biphasic elimination of TCE and TCA from the serum with estimated half-lives of 52.6 h (TCE) and 50.4 h (TCA) in the initial fast phase and 268.3 (TCE) and 277.2 h (TCA) in a subsequent slow phase, respectively.

These results are in sharp contrast to the half-life of Tri in blood of 21.7 hours that Kostrzewski [271] observed in three men who had acute inhalational poisoning. The differences underscore the importance of both the dose and routes of exposure.

Sato and Nakajima [242] compared the concentration of Tri in exhaled breath, blood, and urine of human volunteers after dermal or respiratory exposure. Subjects immersed 1 hand in neat Tri for 30 minutes or inhaled vapor with 100 ppm Tri for 4 hours. The inhaled uptake of Tri was three times as high as the uptake through the skin, but Tri concentrations in end-tidal air were twice as high for dermal exposure as respiratory exposure.

Fiserova-Bergerova and Pierce [192] calculated a skin penetration rate of 0.27 mg/cm/h. Nakai et al [257] calculated a K_p of 0.12 cm/h for partial thickness human skin in vitro.

1,1,2-trichloro-1,2,2-trifluoroethane

1,1,2-trichloro-1,2,2-trifluoroethane is used as a solvent in electronics, dry cleaning, cold degreasing operations, and as a chemical intermediate. It can cause narcosis and arrhythmias at moderate concentrations. Prolonged or repeated skin contact may cause dermatitis.

Esters

Amyl acetate, a solvent for lacquers and paint, is also used in the manufacture of polishes and photographic film. N-butyl acetate is a solvent for polyurethane paints, nitrocellulose lacquer, perfumes, photographic film, and nail polish. Ethyl acetate is used as a solvent for quick-drying paints, adhesives, polishes, lacquer, perfume ingredients, polyacrylates, and polystyrene. Methyl acetate is a solvent for fats, nitrocellulose, and oils and is also used in plastics, perfumes, and lacquers.

Ethers

Dioxane

Dioxane is a solvent for dyes, fats, greases, oils, organic compounds, resins, and waxes; it is also found in lacquers, plastics, paints, and varnishes. It is a defatting agent and can cause dermatitis. Fregert [272] reported a case of hand eczema in a worker who used dioxane as a degreaser for metal parts. A fatal case of dioxane intoxication occurred in a worker who used the solvent to keep his skin free of glue over a 1-week period [273].

Ethyl ether

Ethyl ether is a solvent for oils, resin, cellulose nitrate, and waxes. It is widely used as a solvent and extractant and is used in the manufacture of photographic film and in the perfume industry. In the past, ethyl ether was used as an anesthetic agent; however, because of its explosive properties, other gases have replaced it.

Tetrahydrofuran (diethylene oxide)

Tetrahydrofuran (diethylene oxide) is a solvent for glues, polyvinyl chloride (PVC)-based printing inks, paints, varnishes, and resins. It is used as a cold cleanser; in coating solutions for films, textiles, and video/computer/recording tapes; and for bonding/solutions welding PVC. It is a minor skin irritant. Brooke et al [274] studied the dermal uptake of tetrahydrofuran vapor and found it similar to xylene and toluene vapors. They estimated that dermal uptake of these three vapors contributes approximately 1% to 2% of the total body burden.

Glycol ethers

In general, glycol ethers are important in paints and coatings; they keep other components in solution, and improve penetration and bonding. They also act as coalescents by promoting flow and the development of a film, evaporating

afterwards. Glycol ethers are used in cleaning agents, spot removers, carburetor cleaners, metal cleaners, glass cleaners, and in the semiconductor industry. Both ethoxyethanol and 2-methoxyethanol are teratogenic and have been replaced by other solvents in the paint industry. Many of the monoethylene glycol ethers are being replaced by their less toxic monopropylene glycol ethers as well as other solvents. Monoethylene glycol ethers penetrate skin more rapidly than their diethylene glycol ether equivalents. The skin penetration rate decreases with increasing molecular size [275,276]. Other glycol ethers have been implicated in bone marrow injury in lithographers (multicolor offset and UV-cured printing processes), but the role of percutaneous absorption versus inhalation is unclear [277].

Diethylene glycol methyl ether

Preliminary studies on dermal absorption and jet fuels suggest that diethylene glycol methyl ether, a de-icer added to jet fuel, may enhance skin penetration of other jet fuel components [278].

2-Butoxyethanol (ethylene glycol butyl ether)

2-butoxyethanol (2-BE) is a solvent used in floor polishes and waxes, resins, varnishes, and cleaning agents (upholstery, leather, glass). It is also used to decrease viscosity in hair products and cosmetics. Skin contact leads to drying, the formation of fissures, and erythema; there is no evidence for skin sensitization [279]. Greenspan et al [280] patched tested human volunteers to 10% 2-BE under occlusion for 24 hours and found mild skin irritation. Skin absorption can lead to hematologic, hepatotoxic, and renal toxic effects.

Dugard et al [275] calculated a percutaneous absorption rate of 0.2 mg/cm^2/h for 2-BE, while Walter and Scott [281] found a lower rate of 0.03 mg/cm^2/h. Johanson et al [282] exposed volunteers to 50 ppm butoxyethanol and found that dermal uptake can account for up to 75% of total uptake when whole body is exposed to vapor.

2-Ethoxyethanol (ethylene glycol monoethyl ether)

2-Ethoxyethanol (2-EE) is the most widely produced ethylene glycol ether. It is used as a solvent for nitrocellulose, colophony, shellac, resins, lacquers, varnish removers, coatings, printing ink formulations, and in cleaning. Wilkinson and Williams [283] determined the permeation of 2-EE, 2-BE, and 1-methoxy-2- propanol through excised full thickness or dermatomed human breast tissue using flow-through diffusion cells. They found steady state fluxes of 143 ± 19 nmol/ cm^2/h (2-EE), 544 ± 64 nmol/cm^2/h (2-BE), and 48 ± 6 nmol/cm^2/h (1-methoxy-2- propanol). Flux was dependent on dose volume, concentration, and skin thickness.

Lockley et al [284] studied the percutaneous absorption of 2-EE in split human skin obtained from breast reduction surgeries. The skin was dermatomed to 300 mm and placed in an in vitro flow-through diffusion system. They found a flux of 265 nmol/cm^2/h for undiluted 2-EE. Previous studies had reported a per-

cutaneous absorption rate of 0.8 mg/cm^2/h [275] and 0.13 mg/cm^2/h [281] for 2-EE in human volunteers.

2-Methoxyethanol (ethylene glycol monomethyl ether)

2-Methoxyethanol (2-ME), or ethylene glycol monomethyl ether (EGME), is a solvent for cellulose esters, dyes, inks, paints, lacquers, resins, stains, varnishes, and surface coatings. It also is used as an anti-icing additive in hydraulic fluids and jet fuel; a perfume fixative; and in silk-screen printing, photographic and photolithographic processes, textile and leather finishing, the production of food-contact plastics, and the semiconductor industry. Skin contact with liquid or vapors is an important route of exposure. Dermal absorption of 2-ME vapors can exceed the respiratory absorption from the same concentration of vapors [285,286].

Ohi and Wegman [287] described two employees in a textile printing plant who used 2-ME as a substitute cleaning agent for acetone. Both workers developed encephalopathy and bone marrow injury, and one had pancytopenia. Air samples from their work area were below the TLV, and both cases of EGME poisoning were attributed to dermal exposure. Skin exposure contributed significantly to development of systemic toxicity in two other cases [288,289].

Three young women who used a 70% acetone:30% EGME mixture to glue cellulose acetate frames together developed leucocytosis, lymphocytosis, macrocytosis, and borderline low hemoglobin levels. Their workplace was well ventilated, so exposure probably occurred from insufficient skin protection. All hematologic parameters returned to normal when exposure stopped [290].

Nakaaki et al [196] found that 15 mL of 2-ME under occlusion was rapidly absorbed through the skin of volunteers. Blood levels reached 200 mg/mL after 2 hours of skin exposure. This was faster than absorption of methanol, acetone, and methyl acetate. The authors noted that skin irritation developed at the site of exposure to 2-ME.

Dugard et al [275] reported a percutaneous absorption rate of 2.82 mg/cm^2/h for 2-ME, while Walter and Scott [281] found a lower rate of 1.66 mg/cm^2/h. Leber et al [276] calculated a rate of 2.2 mg/cm^2/h that is between the rates of Dugard et al and Walter et al.

Ketones

Acetone

Acetone is a powerful solvent for cellulose derivatives, dyes, fats, greases, oils, waxes, and inks. It is used in adhesives; as an extracting agent and detergent; and in cleaners and thinners. It is also used in the production of methyl methacrylate, bisphenol A, acetate silk, and cellulose acetate films. It has low skin irritant potential, but upon repeated contact it acts as a defatting agent. Acetone is easily absorbed by the skin, which can lead to significant blood and urine levels. Tosti et al [291] reported a case of contact dermatitis to acetone during treatment for alopecia areata.

Harris and Jackson [292] described a case of acetone intoxication in a patient whose cast was set with acetone-containing liquid. Although there was respiratory uptake, the authors suggested a role for dermal absorption because of the long lag time.

Nakaaki et al [196] found that 15 mL of acetone under occlusion was rapidly absorbed through the skin of volunteers and led to blood concentrations of 4 to 12 mg/mL. This was equivalent to 2 hours of respiratory exposure to 50 to 150 ppm in air.

Cyclohexanone

Cyclohexanone is a solvent for nitrocellulose, cellulose, and acetate resins; natural resins; crude rubber; shellac; and PVC. It is also used as a degreaser, in floor paints, and to enhance adhesive properties. Sanmartin and De La Cuadra [293] described a case of contact dermatitis in a female worker who assembled PVC bags for intravenous fluids. Cyclohexanone was used to seal the outlet tube to the PVC bag. Bruze et al [294] reported four cases of occupational dermatitis in workers who manufactured cyclohexanone resin.

Methyl-n-butyl ketone

Methyl-n-butyl ketone (MBK) is used primarily as a solvent. It is also mixed with toluene, benzene, and acetone and used in glues, inks, laminates, paints, and paint thinners. Di Vincenzo et al [295] found skin absorption of 4.8 and 8.0 mg/cm^2/h in two human volunteers exposed to radioactively labeled solvent. Both methyl butyl ketone and n-hexane are metabolized to a common intermediate 2,5-hexanedione that is neurotoxic. Chronic ethanol use induces the cytochrome P 450 system, enhancing the metabolism of MBK and leading to increased amount of 2,5-hexanedione.

Methyl ethyl ketone

Methyl ethyl ketone (MEK) is used as a solvent in the electronics industry; for vinyl and acrylic resins; and in pharmaceuticals, cosmetics, and fabric coatings. MEK is a mild irritant and defatting agent that is rapidly absorbed through skin. Varigos and Nurse [296] described an Australian painter with contact urticaria, a positive patch test, and severe irritation from exposure to MEK.

Fiserova-Bergerova and Pierce [192] calculated a percutaneous absorption rate of 2.45 mg/cm/h for MEK based on physicochemical properties. Munies and Wurster [297] found MEK in expired air in less than 3 minutes when the solvent was applied to the skin of volunteers continuously. However, in their system, steady state was not reached for 2 to 3 hours. Brooke et al 1998 estimated that dermal absorption of MEK contributed about 3% of the total body burden.

Methyl isobutyl ketone

Methyl isobutyl ketone is a solvent for many natural and synthetic resins; pesticide concentrates; an extractant for metals and metal chlorides; and is used in the purification and extraction of penicillin. It is an important constituent

of epoxy resin paints and is also used in alkyd resin and acrylic and polyurethane paints.

Other solvents

Acetonitrile

Acetonitrile, an aliphatic nitrile, is a common solvent and extractant. It is used in the biotechnology industry in high-performance liquid chromatography. Acetonitrile is toxic by any route of exposure: dermal, inhalation or accidental ingestion [298–300]. However, intoxication and death may be delayed for hours. Acetonitrile is metabolized by cytochrome P450 enzymes to cyanohydrin, which undergoes peroxidation, releasing hydrogen cyanide [301–303]. Cyanide is then eliminated by oxidation of endogenous thiosulfate to thiocyanate, which can also contribute to toxicity. Symptoms begin with headache, nausea, and vomiting 3 or more hours after exposure. After a latent period of up to 12 hours, symptoms may progress to stupor, bradycardia, respiratory depression, shock, and death. The central nervous system, blood, and kidneys are the main systems affected. Cyanide and thiocyanate blood levels do not correlate well with the lower doses that one would expect in a dermal exposure [301].

Carbon disulfide

In the United States, carbon disulfide is used primarily in the production of rayon (33%), agricultural and other chemicals, and rubber chemicals [304]. It also has a wide range of applications as a solvent. The textile industry is changing the production methods for viscose rayon to a solvent spun cellulosic fiber that replaces carbon disulfide with an amine oxide solvent.

Carbon disulfide is highly volatile and flammable. Although most occupational exposures occur by vapor inhalation, both vapor and liquid are absorbed through intact skin. Carbon disulfide is a potent solvent for lipids and is one of the strongest skin irritants known. Repeated skin exposure can lead to erythema, pain, dermatitis, and fissuring. Skin contact has also caused second and third degree burns [305]. Skin absorption leads to many of the same symptoms as acute inhalation headache, nausea, dizziness, cardiac dysrhythmias and even coma.

The neurologic and psychologic problems that result from exposure to high levels of carbon disulfide have been well known for over a century. Several epidemiologic studies have confirmed that chronic exposure can also lead to hypertension and changes in blood lipids [306,307] and an increased incidence of cardiovascular disease in carbon disulfide workers [308,309]. The exact mechanism remains unclear but may be due to atherosclerosis, a direct cardiotoxic effect, or a direct thrombotic effect.

Proper protective gear is essential for workers who are exposed to carbon disulfide. This includes chemical-resistant clothing, gloves, and respiratory protection (self-contained breathing apparatus) above 50 ppm. Urine should be monitored for thiazolidine-2-thione-4-carboxylic acid, a carbon disulfide metabolite.

Phenol

In the past, phenol was used widely as a skin antiseptic because of its bactericidal effects at 0.5% to 1% aqueous solution. It was also used as an antipruritic (1%–2% aqueous solution) and in deep face peels (up to 10% aqueous solution). Now its main use in the United States is in the production of phenol-formaldehyde resins for the housing/construction industries and for binders in insulation materials and chipboard.

Phenol is rapidly absorbed through skin as a liquid and a vapor. Levels of skin absorption can equal or exceed inhalation levels. The threshold for human skin damage is a 1.5% solution; higher concentrations denature skin proteins [80]. There is a nonlinear relationship between concentration and the permeability coefficient: the permeability coefficient for a 5% phenol solution is 50 times higher than for a 1% solution [310].

Phenol can cause burns and necrosis; absorption from the site of contact continues until decontamination or debridement occurs [311]. Bentur et al [312] reported a case in which a 90% liquid phenol spill occurred over 3% of the body surface area; the half-life after the exposure was prolonged to 13.9 hours. The patient had cardiac dysrhythmias, ventricular ectopy, hypalgesia, hypesthesia, and a blue-black skin discoloration that persisted for 4 months. The clinical picture is similar regardless of the route of exposure, and systemic toxicity occurs within minutes to hours [313]. Fatalities have been reported in 10 minutes when 25% of the body surface area was exposed to liquid phenol [314,315].

Rapid decontamination is critical for the prevention of dermal burns and systemic toxicity, but water may enlarge the contact area thereby increasing absorption [312]. The best decontaminant is a 50% solution of polyethylene glycol (PEG-300 or PEG-400) because it stops absorption and prevents systemic toxicity. The recommended steps in decontamination are: (1) remove all contaminated clothing; (2) irrigate the contact area extensively with water; (3) apply PEG-300 or PEG-400 to the contact area for 10 to 20 minutes; and (4) observe the worker closely for any medical complications [314]. Protective clothing and gloves (made from neoprene, polyethylene, or rubber) and a face shield (or full face mask if airborne concentrations exceed 20 mg/m^3) are recommended.

Chronic low-level skin exposure may lead to a burning sensation, erythema, pruritus, and ultimately ochronosis, in which skin collagen becomes discolored. Chronic exposure (over 6 months) to phenolic compounds, especially those containing hydroquinones, may lead to leukoderma.

Terpenes

D-limonene

D-limonene is increasingly used as a solvent for lacquers, inks, and polishes and in degreasing agents, cleaners, printing inks, perfumes, rubber compounds, paints, and enamels. It is promoted as a "natural" cleaning agent because it was originally extracted from citrus peel. D-limonene has a pleasant orange odor that

adds to its appeal as an "eco-friendly" cleaner. It is also a powerful irritant and sensitizer with many case reports of allergic contact dermatitis [316–321].

Turpentine

Turpentine is used in paint solvents, polishes, varnishes, perfumes, and ceramic painting. Concentrations of β-pinene, the major constituent of turpentine, vary depending on the country of origin. β-pinene is higher in Portuguese turpentines and lower in turpentines from Indonesia. Turpentine acts as a skin irritant by defatting the skin, leading to dryness and fissuring. Oxidation products of delta-3- carene develop when turpentine is exposed to air and are potent sensitizers [318,322–325].

Prevention

Gloves and clothing designed to protect workers from hazardous materials may have the opposite effect. If the gloves and clothing cause occlusion, the SC may become overhydrated, reducing its barrier properties. Solvents that penetrate the gloves can then permeate the skin, because the glove acts as an occlusive agent. This may lead to irritation, dermatitis, and ultimately higher levels of systemic absorption [326–328].

Workers with dry skin may be more likely to use gloves and protective clothing. Long-term use can lead to further damage to the skin barrier and aggravation of the underlying skin problem [329,330].

Some have advocated the use of cotton gloves under impermeable gloves, but this can be a double-edged sword. Although the cotton gloves can absorb perspiration, they also can exert a "wick effect": drawing solvent in through breaches in the glove and causing extensive skin contact and damage.

Proper glove selection is essential so that solvent does not dissolve, swell, or penetrate the glove. Permeability is often expressed as the milligrams of solvent that penetrates 1 m2 of material per minute. The ideal glove material for a given solvent has a permeability of less than 1 mg/m2/min. Glove materials are rated on a 5-point scale in which the best glove material for a given solvent has a permeability index number of 0.

Breakthrough time is the time in minutes for a measurable amount of a given solvent to penetrate a protective material. A glove or other protective material with a permeability index number of 0 should have a breakthrough time of at least 8 hours. Workers should inspect their gloves frequently for holes, cuts, cracks, or any signs of material degradation such as hardening or change in color or texture.

Mixtures of solvents may have different properties than their pure components. A glove that protects against one solvent does not necessarily protect against other components of a mixture. All gloves are not created equal. Thickness and quality of gloves can vary tremendously from one manufacturer to another. Manufacturers may produce several grades of glove from the same material, and permeability can vary within a single lot [331]. Ideally, gloves

should be tested under the conditions of use, because temperature as well as other factors can affect permeability.

Summary

The skin has assumed a more prominent role as a potential route for solvent exposure and uptake as respiratory exposure has been reduced through engineering controls and personal protective equipment. Skin architecture plays an important role in regulating solvent absorption. Key epidermal variables that influence solvent absorption include: SC thickness; cell packing/organization; lipid content; skin hydration; and the number/density of hair follicles and sweat glands. Solvent physical and chemical characteristics (molecular structure, pH, pK_a, hydrophobicity, volatility) as well as solvent vehicle, solubility, duration of contact, occlusion and concentration are all important in assessing potential for skin penetration.

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