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Potential Health Effects Associated with Dermal Exposure to Occupational Chemicals

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ABSTRACT: There are a large number of workers in the United States, spanning a variety of occupational industries and sectors, who are potentially exposed to chemicals that can be absorbed through the skin. Occupational skin exposures can result in numerous diseases that can adversely affect an individual's health and capacity to perform at work. In general, there are three types of chemical–skin interactions of concern: direct skin effects, immune-mediated skin effects, and systemic effects. While hundreds of chemicals (metals, epoxy and acrylic resins, rubber additives, and chemical intermediates) present in virtually every industry have been identified to cause direct and immune-mediated effects such as contact dermatitis or urticaria, less is known about the number and types of chemicals contributing to systemic effects. In an attempt to raise awareness, skin notation assignments communicate the potential for dermal absorption; however, there is a need for standardization among agencies to communicate an accurate description of occupational hazards. Studies have suggested that exposure to complex mixtures, excessive hand washing, use of hand sanitizers, high frequency of wet work, and environmental or other factors may enhance penetration and stimulate other biological responses altering the outcomes of dermal chemical exposure. Understanding the hazards of dermal exposure is essential for the proper implementation of protective measures to ensure worker safety and health.

KEYWORDS: dermal, chemical, toxicity, occupational

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Incidence of Occupational Dermal Exposure

The Centers for Disease Control and Prevention (CDC) estimates that more than 13 million workers in the United States, spanning a variety of occupational industries and sectors, are potentially exposed to chemicals that can be absorbed through the skin. Approximately 82,000 chemicals are in industrial use with an estimated additional 700 new chemicals being introduced annually resulting in a high potential for dermal exposure to chemicals.[1] Occupational skin exposures can result in numerous diseases, which can adversely affect an individual's health and capacity to perform at work resulting in significant economic losses, including decreased productivity, medical expenses, and loss of work because of illness with associated costs estimated to exceed $1 billion annually in the United States alone.[2,3] In 2012, skin diseases alone accounted for 34,400 cases at a rate of 3.4 per 10,000 employees as reported by the Bureau of Labor Statistics (BLS), exceeding occupational respiratory illnesses (19,300 cases with a rate of 1.9 per 10,000 employees).[4] This review uses examples of chemicals from each of the National Institute for Occupational Safety and Health (NIOSH) National Occupational Research Agenda (NORA) sectors to provide a review of the known and emerging issues associated with occupational skin exposures and to increase awareness about potential health hazards.

Functions of the Skin

The skin is the body's largest organ accounting for more than 10% of total body mass. It is a very complex and dynamic organ composed of an outer epidermis and inner dermis with functions well beyond that of just a barrier to the external environment. Skin functions include but are not limited to barrier protection, water preservation, tactile sensation, thermal regulation, endocrine activity and vitamin D synthesis, immunological affector, and biotransformation of xenobiotis.[5] Dermal absorption depends largely on the barrier function of the stratum corneum, the outermost superficial layer of the epidermis, and is modulated by factors such as skin integrity, hydration, density of hair follicles and sebaceous glands, thickness at the site of exposure, physiochemical properties of the substance, chemical exposure concentration, and duration of exposure.[6] Low molecular weight (LMW) chemicals (molecular weight <500 Da) that have good solubility in both water and fat penetrate the skin more readily than large, highly hydrophilic or highly lipophilic compounds.[7] However, evidence suggests that reduced integrity or barrier dysfunction of the skin, through factors such as physical or chemical damage, may increase dermal absorption of chemicals leading to the entrance of larger molecules such as proteins,[8] inorganic metal compounds,[9] or nanoparticles.[10] For example, dermal exposure to solvents has been shown to reduce barrier function of skin by altering lipid and protein structures of the stratum corneum, thus promoting the systemic uptake of the solvent itself or other chemicals.[11] Enhanced systemic absorption of carbon disulfide, dimethylformamide, aromatic amines, 2-(2-butoxyethoxy)ethanol, and xylene was found in workers with skin abnormalities caused by previous exposure to these solvents.[12–16] In the workplace, dermal exposure to chemicals may occur through direct contact with contaminated surfaces, deposition of aerosols, immersion, or splashes and can often occur without being noticed by the worker. This is particularly true for non-volatile chemicals, which remain on work surfaces for long periods of time. Prolonged exposures may result from contamination of clothing or permeation of chemicals through gloves, potentially resulting in enhanced absorption secondary to occlusion. Therefore, it is critical for workers to understand the significance of dermal exposure and what measures to take for prevention.

Types of Disease

Chemical agents are the main cause of occupational skin diseases, and dermal exposure to chemicals can result in a wide range of other adverse health effects.[17] In general, there are three types of chemical–skin interactions of occupational concern: direct skin effects, immune-mediated skin effects, and systemic effects. Direct skin effects occur when exposure to the chemical produces a local effect such as irritation, necrosis, or corrosion. Dermal exposure may also lead to chemical sensitization, which occurs through complex immune processes. Once sensitized, subsequent exposure may lead to allergic reactions [eg, allergic contact dermatitis (ACD), urticaria or asthma] in the skin or sites remote from the skin, such as the respiratory tract. Systemic toxicity occurs when skin exposure contributes to the overall body burden, resulting in other organ toxicities.

Contact dermatitis is one of the most common types of occupational illnesses accounting for approximately 90–95% of all occupational skin disorders in the United States and resulting in a significant socioeconomic impact. Common symptoms of acute dermatitis include itching, pain, redness, swelling, and/or formation of a rash with the potential for chronic changes, including alteration in pigmentation, skin thickening, and cracking following repeated or prolonged exposure. Contact dermatitis can result from direct effects of the chemical on the skin, irritant contact dermatitis (ICD), or immune-mediated effects, including urticaria and ACD. The symptoms and presentation of ICD and ACD are similar, which often makes it difficult to distinguish between the two without clinical testing such as patch testing. The severity of contact dermatitis is highly variable and, similar to dermal absorption, depends on many factors including chemical properties of the hazardous agent, exposure concentration, duration and frequency of exposure, environmental factors, and condition of the skin. Chemicals responsible for direct or immune-mediated effects are capable of crossing the epidermal barrier and have certain physiochemical features such as lipophilicity, molecular size, and shape and reactivity that enable them to activate innate or adaptive immunity through the stimulation of secondary stimuli such as danger signals.[18,19] ICD is a non-immunologic reaction that manifests as a local inflammation of the skin caused by direct damage to the skin following exposure to a hazardous agent. The reaction is typically localized to the site of contact. Available data indicate that ICD represents approximately 70–80% of all cases of occupational contact dermatitis.[20] ICD may be caused by acute exposures to highly irritating substances such as acids, bases, and oxidizing agents; high frequency of wet work; or chronic cumulative exposures to mild irritants such as detergents and weak cleaning agents. Hundreds of chemicals present in virtually every industry (metals, epoxy and acrylic resins, rubber additives, chemical intermediates) have been identified to cause immune-mediated skin disorders such as ACD, which is the second most commonly reported occupational illness accounting for 10–15% of all occupational diseases and urticaria. ACD and urticaria have two essential phases, the induction (or sensitization) phase, which primes the allergic response; and the elicitation phase, which is mediated by the immunological memory response. Allergic urticaria is considered as a Type I (IgE-mediated) hypersensitivity reaction, and ACD is classified as a cell-mediated or Type IV delayed hypersensitivity response. For immune-mediated skin disorders to occur, an individual must be first sensitized to the chemical allergen. This requires the chemical (often an LMW hapten) to cross the stratum corneum and

associate with an epidermal protein to form a chemical hapten–protein conjugate, which is recognized by antigen presenting cells such as Langerhans cells (LC). The conjugate is then internalized by the LC, modified, transported to the lymphatics, and presented to other immune cells that expand to form effector and memory cells. Subsequent exposures of the skin to the chemical may elicit an immunologic reaction resulting in inflammation of the skin. These reactions are based on memory responses and are not confined to the site of contact. ACD is an inflammation of the skin caused by an immunologic reaction triggered by dermal contact with a skin allergen. In ACD, the cytotoxic damage to the skin produced by the inflammatory mediators and the cell infiltrates leads to the clinical symptoms of ACD, which may occur within 24 hours of exposure in a previously sensitized individual and reach its maximum response between 48 and 72 hours.[21] Allergic urticaria is a complex release of inflammatory mediators, including histamine, following cross-linking of IgE bound to cutaneous mast cells, resulting in an immediate skin presentation of hives.

Although not as common, other skin conditions may occur as a result of occupational chemical exposures. These comprise <10% of occupational skin disease and include non-allergic urticaria, eczema, folliculitis, and skin cancer. In addition to skin disorders, dermal exposure to many commonly used occupational chemicals, such as solvents and pesticides, may result in systemic effects such as acute poisonings; neurotoxicity;[22] lung, liver, and kidney toxicity;[23] cardiovascular and respiratory toxicity;[24] reproductive toxicity; carcinogenicity;[25] and potentially death.[26]

Emerging evidence suggests that dermal exposure to some chemicals, initially thought to be safe, may result in immune, reproductive, and/or developmental effects as well as cancer, diabetes, and obesity because of their endocrine disrupting properties.[27] Endocrine disrupting compounds (EDCs) are synthetic chemicals that can mimic or block hormones and disrupt the body's normal function, resulting in the potential for numerous health effects. They can act through nuclear hormone receptors, non-steroid receptors, transcriptional coactivators, and other enzymatic pathways involved in steroid biosynthesis and metabolism. Similar to hormones, EDC can function at very low doses in a tissue-specific manner and may exert non-traditional dose–response because of the complicated dynamics of hormone receptor occupancy and saturation. Therefore, exposure to low doses of an EDC may produce a greater impact than exposure to high doses. While this is a new and emerging area of research, potential health effects related to dermal exposure to EDC are just beginning to be identified and investigated in animal and epidemiology studies. Increased awareness about exposures to these types of chemicals and their predicted health effects is warranted. The potential health effects related to dermal exposure to these types of chemicals are described in more detail below.

Regulation of Occupational Dermal Chemical Exposures

There are at least 14 federal regulations and 3 agencies, including the Environmental Protection Agency (EPA), Food and Drug Administration (FDA), and the Occupational Safety and Health Administration (OSHA), that are involved in the regulation of occupational skin exposure in the United States.[28] Historically, efforts to control workplace exposures to hazardous agents have focused on inhalation rather than skin exposures. As a result, assessment strategies and methods are well developed for evaluating inhalation exposures in the workplace; however, standardized methods are currently lacking for measuring and assessing skin exposures.[29] There are currently no occupational exposure limits (OELs) set for dermal exposures; however, chemicals with risk associated with dermal penetration are given a skin notation assignment (S) as a guidance to warn against potential for increased risk of systemic toxicity because of dermal penetration in additional to inhalation exposure. NIOSH has 142 skin notations assigned to chemicals, OSHA lists 159 notations in the PocketGuide, and over 219 chemicals have a skin notation assigned by the American Conference of Industrial Hygienists (ACGIH). Historically, the main goal of the skin notation is to communicate the potential for dermal absorption; however, the criteria and protocol for the assignment of skin notations vary among the different agencies and have many limitations. Among these limitations are (1) lack of information about the inherent toxicity of the chemical, which could result in the same skin notation for highly toxic chemicals and chemicals with limited toxicity that are absorbed through the skin; (2) no warning about chemicals that produce direct damage to the skin (ie, irritants, sensitizers, corrosives); (3) the perception that chemicals that are not assigned a skin notation are safe following exposure via the dermal route; and (4) detailed information about the rationale behind the skin notation assignment. In 2009, NIOSH published a strategy intended to address many of the limitations in the historic approaches applied to establish skin notation.[30] The NIOSH Skin Notation (SK) Profile uses a unique tiered approach to provide information about systemic and direct effects, including dermal absorption, corrosivity, irritation and sensitization, and systemic toxicity specific for the chemical, and is ultimately the determination of a substance's hazard potential or its potential for causing adverse health effects as a result of skin exposure.[29] The NIOSH SK assignment involves use of scientific data on the physicochemical properties of a chemical, epidemiology, toxicology and data from mechanistic studies, and computational techniques, including predictive algorithms and mathematical models by means of analytical or numerical methods. Skin Notation Profiles are intended to inform occupational health practitioners, researchers, employers, and workers in potentially hazardous workplaces about potential health effects associated with dermal exposures, with the ultimate goal of better protecting workers from the risks of skin contact with hazardous chemi-

cals. Under the new NIOSH strategy, there are 47 published skin notation profiles expected by the end of 2014 with another 130 currently in the review process.

Occupations With the Highest Potential for Dermal Chemical Exposure

NIOSH estimates that 13.2 million workers in the United States are exposed to chemicals with an OSHA skin notation. Workers at risk of potentially harmful exposures of the skin include, but are not limited to, those working in the following industries and sectors: agriculture, manufacturing, cosmetology, health care, cleaning, painting, mechanics, printing/lithography, and construction. Chemicals known to cause ICD and ACD are present in virtually every sector, and the association of chemical exposures with other types of systemic diseases continues to be identified and mechanisms are being elucidated. In an attempt to increase awareness, the sections below describe some of the most common chemicals encountered in sectors and the potential health effects resulting from occupational dermal exposure.

Cosmetology

Hairdressers and cosmetologists represent a large occupational group with a high incidence of occupational skin diseases.[31] Among the most common disorders are skin irritation and dermatitis with a higher reported incidence among hairdressers compared to cosmetologists. Epidemiology studies have identified the rates for allergic and ICD to range between 27.3 and 72.7%, and 20.0 and 51.1%, respectively, with the hand being the most common body site of involvement.[31–33] Somewhat unique to this industry, in several of the studies, ACD was found to be more prevalent than ICD.[31,33] These skin disorders have been associated most commonly with chemical exposures from the detergents/surfactants/colors/fragrances present in shampoos (isopropyl myristate and triethanolamine), additives such as preservatives or biocides (formaldehyde, isothiazolinones, dibromosalicylanilide, methyldibromo glutaronitrile, methylisothiazolinone), permanent wave solutions (cysteamine hydrochloride, glyceryl monothioglycolate, diglyceryl thioglycolate), bleaching agents (persulfate salts), fragrances or dyes present in other hair product formulations (p-toluenediamine, para-phenylenediamine, 4-aminoazobenzene, pyrogallol), acrylates used for nail art acrylic products, and nickel sulfate used in the cosmetology equipment.[32–36]

In the majority of the available epidemiological data, persulfate salts were reported as one of the most common allergens. Persulfate salts (ammonium, potassium, and sodium) are inorganic salts used as oxidizing agents in hair bleaches and hair-coloring preparations at concentrations up to 60%.[37] Persulfates have been reported to cause both delayed-type and immediate skin reactions, including irritant dermatitis, allergic dermatitis, urticaria, rhinitis, and asthma.[36] Allergies to hairdressing chemicals such as persulfates have also been shown to be enhanced by detergents or other irritants present in shampoos. Chronic exposure to irritants in these products can enhance allergic contact sensitization to dyes, waving solutions, and other chemicals. These effects may be further enhanced by the frequent wetting and drying of the hands that occur in these professions.

Acrylates are plastic materials formed by the polymerization of monomers derived from acrylic or methacrylic, commonly used by nail technicians for artificial nails. Although acrylates have been well characterized to induce irritant and ACD in other industries such as painting, printing, and health care, their use in the cosmetology sector is increasing.[38] In a seven-year study with 2,263 patients evaluated for dermatitis caused by acrylates, cosmetologists working with artificial nails were identified as 80% of all occupational cases of ACD.[39]

Health Care

Occupational skin diseases, including ACD, ICD, and urticaria, occur commonly among healthcare workers. Some of the most common allergens in the healthcare profession include biocides commonly used for applications such as the sterilization of medical devices that are sensitive to normal heat or steam sterilization processes [glutaraldehyde and *ortho*-phthalaldehyde (OPA)] and the disinfection of surfaces (quaternary ammonia compounds).[40] Medical gloves containing certain rubber accelerators (thiuram mix and carba mix), and antibacterial hand sanitizers and soaps (chloroxylenol and cocamide diethanolamine) have also been identified as common sources of allergens.[40] In general, there are increased rates of ACD for healthcare workers compared to non-healthcare workers for the majority of the above-mentioned allergens.[41]

For over 40 years, glutaraldehyde was the primary choice for disinfecting heat-sensitive medical devices with 376,330 workers exposed to glutaraldehyde from 1981 to 1983;[42] its toxicity has been well described, and its use has been associated with dermatitis and occupational asthma.[43] ACD from glutaraldehyde often causes chronic dermatitis, which frequently forces patients to leave their jobs. Owing to the known toxicities of glutaraldehyde, less offensive and presumably safer alternatives such as OPA have been introduced. OPA, the active ingredient present in Cidex OPA, has shown superior antimycobactericidal activity compared to that of glutaraldehyde, allowing for its use at lower concentrations. While there is limited toxicity data in humans and animals, there is evidence that similar to glutaraldehyde, OPA exposure can induce anaphylaxis and IgE-mediated allergic responses.[44–46] Fujita et al reported a case involving a female nurse who exhibited slight dyspnea and dry cough with a subsequent diagnosis of bronchial asthma and serous papules, and urticaria after working with OPA.[47] Animal studies also suggest that dermal exposure to OPA induces significant irritation and sensitization.[48] Owing to its low volatility, it is presumed that the skin may be a significant route of exposure. While direct associations of

dermal exposure to triclosan on human health have not been fully established, the above-mentioned studies raise concerns about exposure to this chemical.

Additional biocides such as quaternary ammonium compounds are ubiquitous in healthcare settings as they are active ingredients in many sprays and wet-wipe products used for disinfecting surfaces and floors, resulting in the exposure to these chemicals in cleaning staff, nurses, physicians, and technicians. Epidemiological data and case studies indicate that healthcare workers have an elevated risk for development of sensitization and allergic asthma from either dermal or inhalation exposure to these chemicals. Among the identified quaternary ammonium compounds, benzalkonium chloride (BAC) [alkyldimethylbenzylammonium chloride (ADBAC)], benzethonium chloride (BEC), and didecyldimethylammonium chloride (DDAC) are known sensitizers in humans.[40,43,49] A study evaluating 142 patients with suspected allergies to BAC and BEC confirmed sensitization by patch test to these compounds in 20% of the patients and identified potential co-reactions between the two quaternary ammonium compounds in 85% of the subjects who tested positive.[50] Contradictory to the human data, animal data typically describe these compounds as irritants and/or very weak sensitizers.[51,52] However, these animal models may lack the complexity associated with actual occupational exposures. With regard to hand hygiene, healthcare workers have very high frequencies and durations of wet hands (70–100 times per shift) and glove use (1.5 hours per shift).[53] Repetitive exposure to wet work and repetitive glove use are significant factors in development of occupational ICD among healthcare workers, and the development of ICD may predispose these individuals to induction of sensitization and subsequent ACD because the skin is more susceptible to chemical penetration.[54,55] Research has begun to bring to light the importance of danger signals in sensitization. These early signaling events in the skin (potentially a result of barrier breakdown or irritation caused by excessive hand washing, exposure to chemical irritants, glove usage, and wet work) are thought to provide a bridge between the innate and adaptive immune systems, and are of pivotal importance for the initiation of cutaneous immune responses, including those to chemical allergens resulting in skin sensitization.[56]

In addition to the frequent glove use contributing to decreased barrier integrity, gloves are one of the more frequent sources of chemicals inducing ACD.[57] Although the prevalence of latex allergy has been reduced by decreasing powder and protein content of gloves, the use of rubber accelerators such as carbamates and thiurams still persists in latex and nitrile gloves. A study conducted by Cao et al evaluated 23 patients with ACD because of rubber accelerators in gloves. Each had a positive patch-test reaction to one or more rubber accelerators, including carbamates, thiurams, 2-mercaptobenzothiazole, and 1,3-diphenylguanidine. Owing to the prevalence of allergies to these chemicals in the healthcare sector, there are alternative or accelerator-free glove options available for sensitized workers.

While it is generally well recognized that healthcare workers are exposed to biocides and antimicrobials that induce sensitization, they are also exposed to high levels of antimicrobials such as triclosan that are not generally recognized to cause sensitization. A study conducted by MacIsaac et al found that use of triclosan-containing antibacterial soaps in healthcare settings represents a substantial and potentially biologically relevant source of occupational triclosan exposure.[58] Triclosan (2,4,4′-trichloro-2′-hydroxydiphenyl ether) is generally recognized as an EDC.[59–61] Owing to the endocrine disputing properties, emerging evidences suggest that triclosan exposure may contribute to an increased cancer risk[62] and development effects such as decreased birth length.[63] In addition, it has been suggested that exposure to EDCs, including triclosan, may be at least in part responsible for recent increases in the frequency of asthma and allergic disease. A recent study found levels of urinary triclosan to be positively associated with aeroallergen, and food sensitization and asthma exacerbation.[64,65] Animal studies support these findings and suggest that while triclosan may not be allergic itself, it may act as an adjuvant and enhance allergic responses to an known allergen.[66] Owing to the potential for high exposure to triclosan and the suspected health effects mentioned above, triclosan is currently under review by the national toxicology programs for developmental, immune, and reproductive toxicity.

Agriculture and Forestry

The Agriculture, Forestry and Fishing sector contains nearly 50% of the world labor force, and these numbers are expected to increase along with increased exposure to the rising number of pesticides and fertilizers used to enhance crop protection and production. In addition to pesticides, individuals working in this sector can potentially be exposed to solvents, fuels, oils, vehicle exhaust, dusts, and microbes. The BLS estimates that the Agriculture and Forestry sector has the highest incidence of occupational skin disease with 155 cases reported per 100,000 workers.[67] For the purpose of this review, however, only pesticide exposure will be discussed. Pesticide expenditures in the United States totaled $12.5 billion in 2007 and accounted for 32% of total world pesticide expenditures.[68] Pesticides can be classified or grouped according to the target organism (insecticides, fungicides, and herbicides), chemical structure (organochloride, organophosphates, pyrethroids), or type of health hazard involved. Dermal exposure to pesticides is one of the most relevant routes of exposure in the agriculture industry and can occur during mixing and loading, application, and clean up. End users of pesticides include workers who are involved in the application of pesticides and agricultural workers, urban pest controllers, municipal and public utility workers, park and garden workers, and foresters. Pesticide formulations vary broadly in physicochemical properties, and hence, in their capacity to be absorbed through the skin, and this can be influenced by amount and duration of exposure, presence of other material on the skin, temperature

and humidity, and the use of personal protective equipment.[69] Systemic toxicity and health effects associated with exposure to crop protection chemicals include neurological and mental health effects,[70] mutagenic or reproductive effects, endocrine effects,[71] cancer,[72,73] or death.[74] The major classes of insecticides include organophosphosphates, organochlorides, pyrethroids, neonicotinoids, and ryanoids. Organophosphosphates (chlorpyrifos, diazinon, parathion, malathion, methyl bromide, strychnine, and *N,N*-diethyl-*m*-toluamide (DEET)) are the most commonly used pesticides and function by irreversibly inactivating acetylcholinesterase, which is essential to nerve function in insects, humans, and many other animals. There are more than 40 organophosphate pesticides registered in the United States, and the EPA estimates about 33 million pounds of organophosphate insecticides were applied in 2007.[68] While the EPA banned most residential uses of organophosphates in 2001, they are still heavily used in the agricultural sector for insect control on fruits and vegetables. Chlorpyrifos and malathion are considered by the EPA to be the two top most widely used organophosphate insecticides in the Agriculture and Forestry Sector in the United States.[68] Owing to the cholinesterase inhibition in humans, which can cause overstimulation of the nervous system, individuals exposed to high levels of organophosphate pesticides can develop acute cholinergic syndrome, characterized by a variety of symptoms, including rhinorrhea, salivation, lacrimation, tachycardia, headache, convulsions, and death.[75] Individuals may also develop a proximal and reversible paralysis called intermediate syndrome, organophosphate-induced delayed polyneuropathy, or long-term neurologic sequelae.[76] Symptoms of repeated low-dose exposures in pesticide workers and applicators include impaired memory and concentration, disorientation, severe depression, irritability, confusion, headache, speech difficulties, delayed reaction times, nightmares, sleepwalking, drowsiness, insomnia, and flu-like conditions.[77]

Chlorpyrifos is an organophosphate insecticide used to control soil-borne insect pests on a variety of food and feed crops. According to the EPA, approximately 10 million pounds of chlorpyrifos are applied annually in agricultural settings, which is almost half of the total annual usage of corn (~5.5 million). The Agriculture Health Study reported that agricultural workers exposed to chlorpyrifos in the United States have greater levels of urinary metabolites of chlorpyrifos (3,5,6-trichloro-2-pyridinol) compared to the general population.[78] However, true estimations of occupational exposure are difficult because of other potential sources of exposure to the pesticide or its metabolite, especially through dietary ingestion. A longitudinal assessment of chlorpyrifos exposure identified an increase in self-reported neurological symptoms such as behavioral changes, cognitive motor and sensory functions in adolescent pesticide applicators,[79] and delayed polyneuropathy in Iranian farm sprayers.[80] It has been reported that dermal exposure can cause neurotoxicity in mice based on glial fibrillary acidic protein expression.[81]

Malathion is another commonly used oganophosphate insecticide. It is used in agriculture to protect food/feed crops such as wheat and corn from insects such as aphids, leafhoppers, and Japanese beetles. Self-reported work behaviors (ie, wearing protective clothing and hand washing) and urinary metabolite (malathion dicarboxylic acid) data for malathion workers were collected as part of a community-based participatory research intervention study conducted at two strawberry farms. In the year this study was conducted, 497,383 pounds of organophosphate pesticides were applied and approximately 30,000 farmworkers were employed. Despite protective work behaviors, participants had significantly higher levels of exposure compared with those of a national reference sample.[82] In animal studies, significant neurobehavioral deficits and neuronal degeneration were identified in the brain of rats following dermal exposure to malathion.[83] While there is also weak evidence associating malathion exposure with non-Hodgkin's lymphoma in animal and epidemiology studies, these data are inconsistent and contradictory.[84]

Paraquat is one of the most common commercially used herbicides according to the EPA. It exerts its toxicity through a series of redox reactions, generating active oxygen species, which induces lipid peroxidation and oxidation of both NADPH and NADH (role of redox cycling and lipid peroxidation in bipyridyl herbicide cytotoxicity). The most severe cases of paraquat poisoning are most commonly because of inhalation or oral ingestion. Although not thought to passively penetrate the skin, dermal penetration of paraquat can occur as a result of reduced skin integrity or prolonged exposure to this corrosive chemical. While not common, there have been reports describing paraquat poisoning by skin absorption most often as a result of accidental exposure. A case report described skin burns resulting from minimal accidental paraquat exposure, which subsequently lead to acute renal and respiratory failure and ultimately death.[74] Another report described prolonged dermal paraquat exposure as a result of a crop-dusting accident, also resulting in death.[85] Epidemiology studies have also associated self-reported paraquat usage with Parkinson's disease, most likely because of the increased production of reactive oxygen species resulting from the toxicity of the herbicide.[86] While this information only represents a small fraction of some of the most commonly used crop protection chemicals, it underscores the potential detrimental health effects that can occur in these industries if proper exposure controls are not employed.

Manufacturing

The Manufacturing sector has the highest number of cases (26,000) and the second highest reported incidence (139 per 100,000) of occupational skin diseases among major industries.[67] This sector includes a number of professions, including printing, petroleum and coal products manufacturing, chemical manufacturing, plastic and rubber products manufacturing, metal manufacturing, and furniture

manufacturing in which a high potential for dermal exposure to toxic chemicals exists. As examples, this section will only focus on some of the chemicals most well recognized to produce adverse health effects following dermal exposure.

Solvents. Solvents are frequently used by numerous occupations to dissolve, dilute, or disperse materials that are insoluble in water. As such, they are widely employed across many occupational sectors as degreases and as constituents of paints, varnishes, lacquers, inks, aerosol spray products, dyes, and adhesives. They are also used as intermediates in chemical synthesis, and in fuels and fuel additives. In 1981, OSHA estimated that there were approximately 350 solvents. Inhalation is the major route of solvent exposure because of their vapor pressures, but their physical properties also allow for ready absorption across the skin,[87] especially in compromised skin. Solvents may also enhance the penetration of other chemicals by disrupting the protective lipid layer of the skin. Limited studies exist but do suggest that exposure of human skin to vapors may contribute to total body burden for some solvents.[88] Common industrial solvents include glycol ethers, aromatic hydrocarbons (benzene, toluene, xylene), alcohols (ethanol and methanol), glycols (ethylene glycol, diethylene glycol, propylene glycol, hexylene glycol), chlorinated hydrocarbons (trichloroethylene, methylene chloride, carbon tetrachloride), alkanes, and ketones. Although varying widely in chemical structure and physical properties, solvents produce a rather stereotypical set of toxicological manifestations resulting in temporary or long-term alterations of central nervous system function following acute exposure. There is also concern for reproductive or carcinogenic effects.[89]

The aromatic hydrocarbon benzene has been used extensively over the years as a raw material in the manufacture of polymers, detergents, pesticides, dyes, plastics, and resins, and as a solvent for waxes, oils, natural rubber, and other compounds. In addition, it is a component of gasoline. Headaches, dizziness, nausea, and vomiting are all symptoms of benzene overexposure. Exposure to benzene at high concentration can lead to blurring of vision, unconsciousness, convulsions, ventricular irregularities, and respiratory failure. Death as a result of exposure to extremely high concentration of benzene may occur because of respiratory failure or cardiac arrhythmias.[89] Long-term exposure to benzene has been shown to produce several adverse health effects, including an increased risk of acute myeloid leukemia[90] and hematotoxicity.[91] Benzene is recognized as an occupational carcinogen by OSHA, NIOSH, and ACGIH, and is readily absorbed through the skin.[92]

n-Hexane, another well-described toxic solvent with the potential for inhalation and skin exposure, is used in industrial applications such as printing, low temperature thermometers, adhesives, extractions, and cleaning processes. Dermal exposure to n-hexane and other solvents (benzene, toluene, xylene) was analyzed in farm machinery maintenance workers performing repair and maintenance tasks using a solvent sampling patch. All organic solvents were extracted and detected from the patches indicating the potential for dermal exposure.[93] Potential health effects associated with exposure include neuropathy, CNS effects, and skin irritation.[89] Occupational exposures have been associated with damage to motor and sensory nerves often resulting in symptoms such as numbness and paresthesia in the distal extremities, which tend to improve over time.[94]

Diisocyanates (DIC). DIC such as toluene diisocyanate (TDI), 4,4′-methylenebis-(phenyl isocyanate) (MDI), and hexamethylene diisocyanate (HDI) are another class of chemicals commonly used in the manufacture of many products, including flexible and rigid polyurethane foams, polyurethane rubbers and elastomers, adhesives, paints, coatings, insecticides, and rock consolidation media. The world production of isocyanates is estimated to be three billion pounds annually, and 280,000 workers in the United States are potentially exposed to them.[95] The major route of occupational exposure to isocyanates is by inhalation of the aerosol, but exposure may also occur through the skin during the production and use of isocyanates. While they are commonly known to induce occupational asthma, there have also been reported cases of ACD. Occupational allergic dermatitis to isocyanates was confirmed by patch test in workers manufacturing flooring laminate boards coated with isocyanate lacquer[96] and in sculptors working with polyurethane sculpting materials.[97] Skin exposure has been suggested to be an important route for inducing immune sensitization, which may promote subsequent airway inflammatory responses and asthma pathogenesis. In a mouse model of asthma, skin exposure to MDI resulted in specific antibody production and promoted subsequent respiratory tract inflammation in animals challenged intranasally with MDI–mouse albumin conjugates.[98]

Metalworking fluids (MWF). Approximately 1.2 million workers are potentially exposed to MWF in machine finishing, machine tooling, and other metalworking and metal-forming operations.[99] MWF have been used since the early 1900s to reduce heat and friction associated with industrial machining and grinding operations, and to ultimately improve product quality. There are numerous types of MWF ranging from straight oils to water-based fluids, including soluble, semi-synthetic, and synthetic fluids.[100] MWF are often complex mixtures of oils, emulsifiers, anti-weld agents, buffers, biocides, and other additives. The fluid complexity is compounded by contamination with substances from industrial use that encourage microbial growth, which can introduce biological contaminants such as endotoxins, exotoxins, and mycotoxins.[101] MWF exposure can occur through inhalation of the aerosols generated in the machining process or through skin contact when parts, tools, and equipments covered with the fluids are handled. Dermal absorption to biocides in MWF has also been well documented.[102] Dermatologic exposures are most commonly associated with, but not limited to, allergic and irritant dermatitis and most often with the water-based MWF.[103] Studies have shown the prevalence of dermatitis to

be between 20 and 30% among workers who handle MWF, much higher than the 4% prevalence recorded among the general population.[104] The causes of dermatitis in these workers are likely to be multifactorial and include exposure to a wide variety of metal types, different types of MWF solvents, biocidal additives, and exposure to damaged skin, demonstrating the complexity of exposure to mixtures. Chronic dermal exposures to MWF have also been identified to cause a variety of other skin and systemic health effects, including squamous cell carcinoma, folliculitis, keratosis, pigmentary changes, granuloma, photosensitivity reaction, and an increased incidence of certain kinds of cancers such as breast, lung, liver, pancreatic, bladder, brain, and prostate.[105] In many cases, little information is provided by manufacturers about the chemical makeup of specific MWF because of industry competition and trade secrets; however, analytical techniques can be used to separate, identify, and study MWF constituents.[106]

Exposure to proprietary mixtures is often the case in the manufacturing sector, and this can complicate things when trying to identify the offensive agent(s). The use of analytical methods and animal models for contact sensitization such as the murine local lymph node assay (LLNA) helps to overcome these obstacles.[107] For example, an outbreak of contact dermatitis among employees at an ink ribbon manufacturing plant was investigated by scientists from NIOSH. Employees in the process areas of the plant were exposed to numerous chemicals, and many had experienced skin rashes since introduction of a new ink ribbon product. Following chemical analysis of the solvents used in the manufacturing process, the LLNA was used to identify the potential of the chemicals used in the manufacture of the ink ribbon to induce ACD. Polyvinyl butyral tested positive in the LLNA and was identified as a potential sensitizer.[108] The identification of the offending chemical is an important step in understanding the hazard and also in protecting workers from exposure.

Plasticizers. Plasticizers, most commonly phthalate esters, are added in the manufacture of plastics for improved flexibility and durability. They are used to manufacture building materials, household furnishings, clothing, cosmetics, pharmaceuticals, nutritional supplements, medical devices, dentures, children's toys, glow sticks, modeling clay, food packaging, automobiles, lubricants, waxes, cleaning materials, and insecticides.[109] As the phthalate plasticizers are not chemically bound, they can leach, migrate, or evaporate into indoor air and atmosphere, foodstuff, other materials. Therefore, in addition to occupational exposure, exposure to the general public can potentially occur through ingestion, inhalation, and dermally through direct contact. Commonly used phthalates include bis(2-ethylhexyl) phthalate (DEHP; construction materials and medical devices), diisononyl phthalate (DINP; flooring materials, garden hoses, shoes, toys, and building materials), di-n-butyl phthalate (DnBP, DBP; cellulose plastics, food wraps, adhesives, perfumes, cosmetics, nail polishes, shampoos, sunscreens, skin emollients, and insect repellents), butyl benzyl phthalate (BBzP; vinyl tiles, traffic cones, food conveyor belts, artificial leather, and plastic foams), diisodecyl phthalate (DIDP; insulation of wires and cables, car undercoating, shoes, carpets, pool liners), dioctyl phthalate (DOP or DnOP; flooring materials, carpets, notebook covers, and high explosives), diisooctyl phthalate (DiOP; all-purpose plasticizer for polyvinyl chloride, polyvinyl acetate, rubbers, cellulose plastics, and polyurethane), diethyl phthalate (DEP; additive to adhesives or printing inks as well as cosmetic formulations), and di-n-hexyl phthalate (flooring materials, tool handles, and automobile parts). As a consequence of the ubiquitous use and contamination with phthalates, phthalate metabolites can be detected in urine samples of the majority of the general population.[110]

Occupational exposure to phthalates was evaluated by analyzing their metabolites in urine samples from workers in a car manufacturing plant engaged in seam sealing with a DINP-based plastisol suspension. All plastisol workers had post-shift values of DINP and DIDP metabolites [mono-(hydroxyisononyl) phthalate, mono-(oxo-isononyl) phthalate, and mono-(carboxy-isooctyl) phthalate]. Those were approximately 10–20 times higher than those of a control exposure population at the same manufacturing plant. Owing to the high potential for dermal exposure to phthalates in this unique plastisol suspension, these findings suggest that the skin might be an important and relevant route of exposure.[111] Another study evaluated skin surface levels of commonly used phthalates using human skin wipes. The levels of phthalates in skin wipes can provide information on dermal exposure from the surrounding environment as a consequence of contact with contaminated surfaces, direct absorption from air, and particle deposition. Skin wipes were collected from the forehead, forearm, back-of-hand, and palm of 20 participants. DiBP, DnBP, and DEHP were most frequently detected; DEHP levels (200–10,200 g/m^2) were substantially higher than DnBP (18–1865 $\mu g/m^2$) and DiBP (98–860 $\mu g/m^2$) levels. The levels differed at different body locations, with palm > back-of-hand > forearm ≥ forehead. These findings also suggest that dermal exposure may contribute significantly to the uptake of these phthalates.[112]

In general, phthalates are generally regarded as having low acute toxicity, and are not considered to be mutagenic. However, because of their endocrine disrupting properties, there are concerns for reproductive and developmental toxicities, and these are currently being evaluated by the NTP. There is very limited epidemiology data for phthalate exposure and adverse outcomes, but animals studies have suggested that phthalate exposure can result in developmental and reproductive effects, cancer, immunotoxicity, diabetes, and obesity.[27] While data support the potential for dermal exposure to these compounds,[113] additional studies are necessary for a complete understanding of the potential toxicities following exposure and to identify the mechanism of action.

Similar to phthalates, bisphenol A (BPA) is a large production volume endocrine disruption compound with levels detected in the majority of the population.[114] It is used in the productions of plastics and epoxy resins, and is used in a variety of common consumer goods, such as water bottles, sports equipment, CDs, and DVDs. Epidemiology and animal studies have identified potential reproductive, developmental, metabolic, and immune effects following exposure.[115] Epoxy resins containing BPA are used to line water pipes and as coatings on the inside of many food and beverage cans. In addition to manufacturing, BPA exposure can occur through dermal contact with thermal paper such as receipts where it is used as a color developer. Absorption of BPA via the skin while handling thermal papers is believed to be a significant route of exposure, particularly for cashiers who were shown to have higher estimated levels compared to the general population.[116]

Perfluorinated compounds (PFCs). Another class of compounds suspected to function as EDC includes PFCs, which are synthetic, highly stable chemicals used in manufacturing of protective coatings for carpets, stain- and grease-resistant clothing, paper coatings, and non-stick pans.[117] PFC includes chemicals such as perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluorohexane sulfonate (PFHxS), and perfluoroundecanoic acid (PFUnA). Their high stabilities and extremely low surface tensions, which lend them to be useful in consumer and industrial applications, have also led to their environmental persistence. Increased concerns have focused specifically on occupationally exposed individuals as their serum PFC concentrations have been found to be up to 1,000 times higher than that of the general population.[118] PFCs have been associated with a number of health effects related to reproductive function and thyroid dysfunction in the general public[119,120] and cancer in a contaminated community.[121] While inhalation and oral are common exposure routes, studies support the potential for skin absorption of these compounds.[122] Occupational exposure has been linked to health effects such as prostate cancer and non-hepatitis liver diseases, malignant and nonmalignant renal diseases, diabetes mellitus, chronic renal disease, and female hypothyroidism.[123,124]

Metals. Numerous metals, including gold, chromium, cobalt, platinum, nickel, beryllium, palladium, and mercury, are known to induce hypersensitivity responses resulting in dermal, respiratory, and systemic diseases. Occupational exposure to these metals results in varying levels of morbidity and mortality from chronic ACD to potentially fatal pulmonary disease or anaphylaxis. There is the potential for exposure to metals in not just manufacturing but across the majority of sectors. For example, exposure potential exists in release from dental tools and alloys,[125] scissor and nail instruments used by cosmetologists and nail technicians,[33] coin handling operations,[126] and metal processing.[127] Patch-test results from the North American Contact Dermatitis Group (NACDG) identified numerous metals responsible for ACD.[128] Following patch testing of 4,454 patients, nickel sulfate (19.0%), cobalt chloride (8.4%), and potassium dichromate (4.8%) were among the most common allergens with nickel being identified as the most frequent positive allergen. Occupational exposure to significant levels of nickel, chromium, and cobalt was identified among carpenters, locksmiths, and cashiers using an acid wipe sampling technique.[129] In addition to the potential for ACD, exposure to hexavalent chromium salts (potassium dichromate or chromic acid) can result in chemical burns, chrome ulcers, and potential systemic effects such as liver damage, shock, coma, gastrointestinal bleeding, renal failure, intravascular hemolysis, and death.[77] While severe acute chromium poisoning related to dermal involvement is rare, it has been reported. In one such case, chromium poisoning occurred through skin exposure as a result of a chemical burn of 15% of the body surface area and resulted in multiple organ failure. Treatment required medical interventions and chelation therapy.[26]

Although not as common as exposure to nickel, chromium, and cobalt, sensitization to beryllium is an important occupational concern. Metal alloys containing beryllium exhibit desirable properties that make them useful in critical applications in diverse industries such as nuclear, aerospace, telecommunications, electronic, metal alloy, biomedical, and semiconductor industries. The presence of beryllium sensitization in some exposed worker populations has been reported to be as high as 12%.[127] In some of the exposed individuals, beryllium sensitization can precede the development of chronic beryllium disease, a slowly progressive respiratory disease characterized by the formation of granulomas. Following regulations set to reduce inhalation exposures, the incidence of beryllium sensitization was not reduced, suggesting that the skin may play an important role in the etiology of the disease.[130] Subsequent to these findings, it was suggested that reducing skin and inhalation exposures may be critical for the protection of workers exposed to beryllium. Indium is another metal that has drawn recent attention because of the occurrence of a rare pulmonary disease, characterized by severe alveolar proteinosis, seen in workers exposed to indium tin oxide (ITO).[131] Indium is a rare metal with unique electrical conductive properties, resulting in its use in thin-film coatings used in the production of solar panels, solders, alloys, and semiconductors. Potential worker exposure to indium and indium compounds occurs during mining, production, and reclamation processes. While inhalation exposure is the primary concern in relation to the development of alveolar proteinosis following ITO exposure, the role of dermal absorption of this metal has not been fully investigated. Animal studies have shown immune stimulation following dermal exposure to ITO.[132]

Summary

Large numbers of individuals from every occupational sector are exposed to potentially hazardous chemicals, and these

numbers are expected to increase with the increasing number of chemicals in use. Skin and inhalation are the two most common occupational routes of chemical exposure. Historically, efforts have been aimed at regulating respiratory exposures; however, the contribution of skin exposure in the development of systemic disease is gaining increased recognition. In particular, studies are beginning to demonstrate the contribution of skin exposure to the development of respiratory sensitization and altered pulmonary function. The skin is the largest organ of the body, and while less volatile chemicals are known to directly penetrate the skin to induce toxicity, there is also evidence of a contribution from vapors or aerosolized chemicals that should not be overlooked. While contact dermatitis is one of the most common and well-understood occupational diseases, increasing the awareness about potential systemic effects following skin exposure to chemicals is also of occupational importance. Not only does skin exposure have the potential to contribute to total body burden of a chemical but also the skin is a highly biologically active organ capable of chemical metabolism and the initiation of a cascade of immunological events, potentially leading to adverse outcomes in other organ systems.

Workers should be aware not only of the hazards associated with the chemicals in their environment but also of conditions that are likely to enhance the systemic absorption of these chemicals. Factors such as excessive hand washing, use of hand sanitizers, high frequency of wet work, exposure to chemical mixtures, or wearing occlusive gloves can change the integrity or function of the skin and play a role in enhancing chemical penetration or sensitization by influencing additional biological responses.

Author Contributions

Wrote the first draft of the manuscript: SEA. Contributed to the writing of the manuscript: SEA, BJM. Made critical revisions and approved final version: SEA, BJM. Both authors reviewed and approved of the final manuscript. SEA, BJM.

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