24 Dermal Absorption and Cutaneous Toxicity of Metalworking Fluids

Ronald E. Baynes and Vikrant Vijay
Center for Chemical Toxicology Research and Pharmacokinetics, North Carolina State University, Raleigh, North Carolina, U.S.A.

INTRODUCTION

The use of metalworking fluids (MWFs) started in the early 1900s with the purpose of extending the life of metalworking tools and equipments (1). In a recent study, the total worldwide utilization of MWFs including straight oils and water-based products is approximately 2,055,000 metric tons and European Union consumption of water-based fluids is approximately 178,000 metric tons (2). MWFs represent a business of approximately $800 million in the United States alone (3). National Institute for Occupational Safety and Health (NIOSH) estimates that approximately 1.2 million U.S. workers are exposed to MWFs (1).

MWFs or cutting fluids are an integral part of metal industry operation whether it is a metal producer or a machinery or equipment manufacturer. Machines can be used for several functions including drilling, milling, shaping, sawing, grinding, threading, shaving, and engraving with each of these processes employing MWFs. MWFs serve as coolant, lubricant, or remove the fine particles or swarfs produced during machining process. MWF residues on machined products also impart short-term corrosion protection (4).

MWFs are complex heterogeneous formulations containing a combination of various additives, most of which are organic compounds including biocides, corrosion inhibitors, defoamers, coolants, antioxidants, extreme pressure (EP) agents, lubricants, emulsifiers, couplers, dyes, odor maskers, friction modifiers, oiliness agents, passivators, plasticizers, thickeners, tackiness agents, viscosity index improvers, and diluents (1,5). MWF is a broader term used to represent metal-removal fluids, metal-forming fluids, metal-protecting fluids, or metal-treating fluids. MWFs are divided into four groups (Fig. 1) on the basis of their composition—neat or straight oils (nearly 100% petroleum oil), emulsifiable soluble oil, water-soluble semisynthetic solutions, and water-soluble synthetic (no petroleum oil) solutions.

The base oils used for the MWFs are mainly mineral oils, polyethylene glycol (PEG), and/or synthetic esters. Since the neat oil type of MWF is a good lubricant but a poor coolant, there is an increasing trend of using water-based MWFs because of their better performance over neat oils. The usage of these water-based MWFs, both semisynthetic and synthetic, has increased from 4–5% to 30% in recent years (6). The main components of MWFs are presented in Table 1 (1).

Soluble oil and semisynthetic and synthetic MWFs are generally alkaline solutions (pH ~9) and are diluted with water before use. Proper dilution of the MWF concentrate is required to maximize its performance. Too concentrated mixtures can produce excess foam and residue buildup whereas too diluted mixtures cause rancidity, corrosion, and poor tool life. Similarly, improper pH

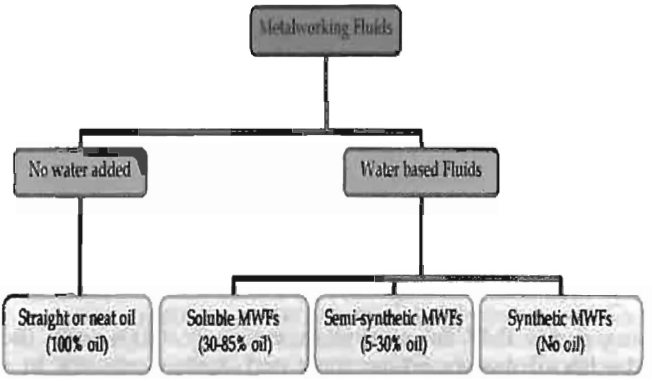

FIGURE 1 Classification of MWFs based on mineral oil contents. *Abbreviation*: MWF, metalworking fluids.

TABLE 1 Major Additives (% Composition) Used in Different Types of Metalworking Fluids

Lubricity ←

→ *Cooling*

		Straight oils	Soluble oils	Semisynthetics	Synthetics
1	Dilution with water	No dilution	5–40 parts	10–40 parts	10–40 parts
2	Mineral oils	60–100%	30–85%	5–30%	Nil
3	Emulsifiers	Nil	5–20%	5–10%	5–10%
4	Surfactants	0–10%	5–20%	10–20%	10–20%
5	Corrosion inhibitors	0–10%	3–10%	10–20%	10–20%
6	Extreme pressure agents	0–40%	0–20%	0–10%	0–10%
7	Biocides	Nil	0–2%	0–2%	0–2%

Source: Adapted from Ref. 1.

can cause instability, rancidity, and poor corrosion control (7). Because of the presence of water in the MWF, it is liable to microbial contamination. The major microbes seen in MWFs are bacteria, fungi, and yeasts. These microorganisms produce foul smell by generating H_2S in the fluid, cause corrosion, emulsion instability, fluid degradation, generate toxins, reduce coolant, and lubricant life. Various classes of biocides are added to MWFs to prevent the growth of microorganisms. These biocides include, but are not limited to, the following classes: phenols, isothiazolinones, morpholines, triazines, oxazolidines, formaldehyde-releasing biocides, and nitrated biocides (1).

MWFs are applied to working tool and metal interface through a nozzle with the help of a low-pressure pump. Dermal and inhalational exposure to MWFs can occur either via mist, aerosols, and droplets generated during machining process or by splashing of MWFs on exposed skin of workers (8). Excessive exposure to MWFs can occur due to high pressure or excessive MWF application, poorly designed equipment and ventilation system, inadequate machine enclosures, and lack of maintenance and personal protective equipment (1). Serious health problems have been associated with exposure to MWFs. These range from irritation of the skin, lungs, eyes, nose, and throat to more severe

conditions such as dermatitis, acne, asthma, hypersensitivity pneumonitis, irritation of the upper respiratory tract, and a variety of cancers. A variety of factors including time of exposure, pH of the fluid, presence of contaminants, and personal sensitivity can influence the severity of these problems (9).

DERMAL ABSORPTION

It has been documented that different components of MWFs contribute to adverse health effects, especially biocides that are associated with carcinogenesis as well as irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD) (1,10–12), which may be positively correlated to their dermal absorption and may cause systemic toxicity if absorbed in significant amount, in workers involved in metalworking operations. In a study on six-week-old B6C3F1 mice, dermal exposure of neat semisynthetic MWFs resulted in increased oxidative damage to the liver indicated by elevated levels of malondialdehyde. The skin histamine levels and mast cell numbers were also elevated. This showed that the components of MWFs are absorbed through skin and produce liver toxicity (13). Further, another study showed that the topical application of MWFs along with vitamin E–deficient diet produced more marked oxidative stress when compared with oxidative stress produced by vitamin E–deficient diet without topical MWFs application (14). Some biocides act by releasing formaldehyde and some by releasing nitrite, which can combine with ethanolamines to form nitrosamines (potential carcinogen) that are hazardous to human health (15). Therefore, these biocides are of significant concern as they are occupational health hazards.

Recent work in our laboratory determined that the biocide additive (e.g., triazine) is more permeable in skin than the surfactant additive (e.g., linear alkylbenzene sulfonate, LAS) or the lubricant additive (ricinoleic acid, RA) (16–18). In these eight-hour in vitro studies, triazine absorption ranged from 2.24% to 3.89% with limited levels recovered on the skin surface (1.34–2.84%) because of triazine evaporation, and even less was retained in the stratum corneum (SC) (0.21–1.15%) and viable skin (0.19–1.02%) (17). Triazine is one of the more water-soluble biocides used in the MWF industry and thus less likely to readily diffuse or partition in skin, therefore these data should not be extrapolated to other more lipophilic biocides such as the phenolics.

LAS absorption was limited to <0.5% with the majority of the surfactant being retained on the skin surface (27.97–73.41%), SC (1.3–21.66%), and viable skin (0.56–9.66%) (16). The limited LAS permeability in skin can be attributed to its large molecular weight and charge which limit its diffusion across the lipid matrix of the SC. This is reflected in almost similar permeability values in both silastic (inert) membrane and porcine skin. Anionic surfactants such as LAS and sodium lauryl sulfate (SLS) can form micelles or spherical aggregates above the critical micelle concentration (CMC), which are effectively too large to diffuse across a membrane. RA absorption (<0.3%) was even less than LAS absorption with only 0.75% to 16% retained in the SC and 0.31% to 5.22% in the viable skin (18). It should be noted that RA is a major component (90%) of castor oil, which is formulated with many MWFs to enhance lubricity and is known to illicit an inflammatory response in skin (19).

The dermal absorption of these biocides and other MWF additives can be modulated by the presence of different additives in the cutting fluid formulations. Consequently, dermal disposition of an aqueous biocide solution

may vary when compared with biocides in mixtures, where mixture components can either physicochemically or chemicobiologically alter the percutaneous absorption of biocides. The dermal absorption of important industrial chemicals (e.g., biocides) has been shown to be significantly altered in mixtures (MWFs) because of the presence of different components such as surfactants and alkanolamines (17,20–25).

This research identified *significant mixture interactions* that are unique for each of the three cutting fluid additives in soluble oil and synthetic cutting fluid surrogate mixtures, and which clearly influenced additive disposition in skin. Triazine permeability in both silastic (inert) membranes and porcine skin (Fig. 2) was significantly increased in both mineral oil–based and synthetic (PEG 200)-based aqueous mixtures when the *complete additives package* was added to the formulation (17). Synergistic interactions were identified between triethanolamine (TEA) and sulfated ricinoleic acid (SRA) that enhanced triazine permeability in both membranes. It is conceivable that the alkanolamine and fatty acid interaction led to formation of lipophilic ion pairs that resulted in statistically significant enhanced permeability. At the same time, triazine enhanced LAS absorption, but the presence of RA decreased the CMC of the formulation thus decreasing LAS absorption. A more surprising observation was that RA absorption was significantly reduced in the presence of any of the MWF additives (18). While the latter interaction may suggest limited risk for systemic absorption in workers exposed to MWF formulations, this does not rule out the fact that greater retention of RA can occur in the upper epidermis to illicit an irritant response.

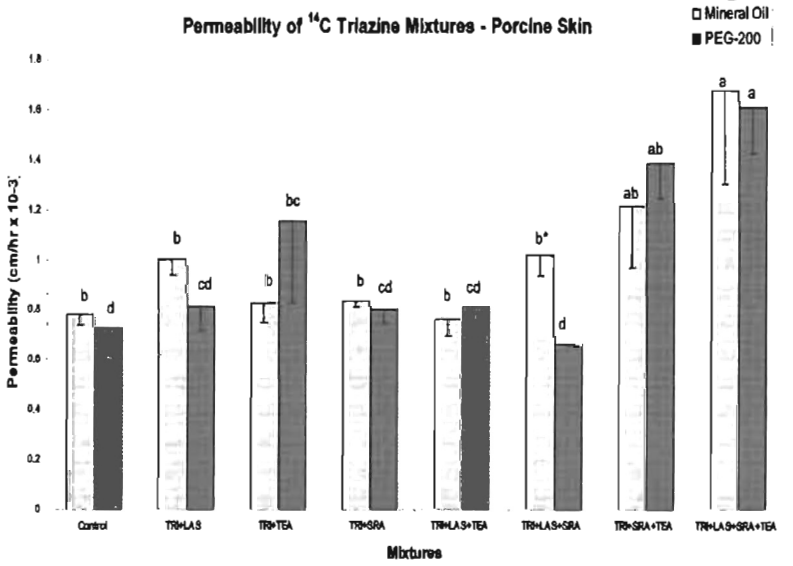

FIGURE 2 Influence of cutting fluid additives on permeability of triazine (permeabilities with different letters are statistically different and those with same letters are not statistically different within the formulation and across the mixtures, $p < 0.05$). *Abbreviations*: TRI, triazine; LAS, linear alkylbenzene sulfonate; TEA, triethanolamine; SRA, sulfated ricinoleic acid; PEG, polyethylene glycol.

MWF can become contaminated with various metals from the grinding and cutting processes, solvents from the degreasing process, and nitrosamines formed in several nitrite and even nitrite-free formulations (26). Although recent research demonstrated that little or no nickel or the nitrosamine (*N*-nitrosodiethanolamine, NDELA) was absorbed across skin, the presence of these contaminants in MWFs can significantly enhance triazine absorption from a soluble oil MWF when compared with absorption from a synthetic MWF (23). It is plausible to assume that although NDELA is insoluble in a soluble oil MWF, it behaves as an effective cosolvent for the polar biocide, triazine, than if the skin was exposed to synthetic MWF similarly contaminated with NDELA. Workers in the metal machining industry often use a solvent degreaser similar to trichloroethylene (TCE) to remove the MWF, which results in chronic and/or simultaneous exposure to TCE and MWF additives. Our research demonstrated that TCE pretreated skin was almost twice as permeable (×2) to triazine as normal skin, but simultaneous exposure to TCE had little or no effect on triazine absorption (24). Solvent-induced compromised epidermal barriers have been associated with altered lipid domains of the SC and lipid extraction (27–29).

Our research has also identified *solute-micelle interactions* in these cutting fluid mixtures. Although linear LAS did not readily diffuse across either membrane system in either solvent system (16), this anionic surfactant reduced triazine partitioning into the SC but had little effect on its dermal permeability. This was also observed with the cutting fluid lubricant SRA. While it is hypothesized that micellar interactions reduced additive partitioning into the SC, we also discovered that several of the cutting fluid additives, especially the fatty acid additive, significantly reduced the CMC for LAS (16). This interaction was also supported by the inhibitory effect of SRA + LAS on triazine partitioning and permeability in skin. In addition to these interactions, SRA partitioning into the SC and diffusion in skin was significantly inhibited by additives other than LAS.

The absorption of biocides among different classes of MWFs (soluble oil, synthetic, and semisynthetic) has been shown to differ statistically (30) where highest permeability was observed in synthetic MWFs and lowest in soluble oil MWFs (Fig. 3). This suggests that a soluble oil MWF may be safer than a synthetic MWF in regard to dermal permeation of phenolic biocides/solutes to allow for an increased potential of systemic toxicity. Therefore, one may conclude that a synthetic type of formulation has more potential to cause contact dermatitis and possibly induce systemic toxicological effects (30). Differences in permeability were expected, since the chemistry of synthetic, semisynthetic, and soluble oil MWFs is different. This result demonstrated that more lipophilic chemicals (e.g., biocides) have comparatively less permeation into skin from lipophilic vehicles, which was in agreement with previous studies (8,31). MWF biocide permeability in skin and inert membranes can be significantly reduced as the MWF concentration increases (30,32). This can be of occupational concern as MWF dilutions in the workplace can range from 1% to 20% with the *more dilute formulation enhancing permeability* of some classes of biocides.

The fact that the mixture effects described above occurred in both inert and biological membrane systems and because these additives affected formulation pH and CMC provided strong evidence of dominant physicochemical interactions modulating solute permeability in skin. However, these studies did not identify or quantify the precise physicochemical mechanism (e.g., hydrogen

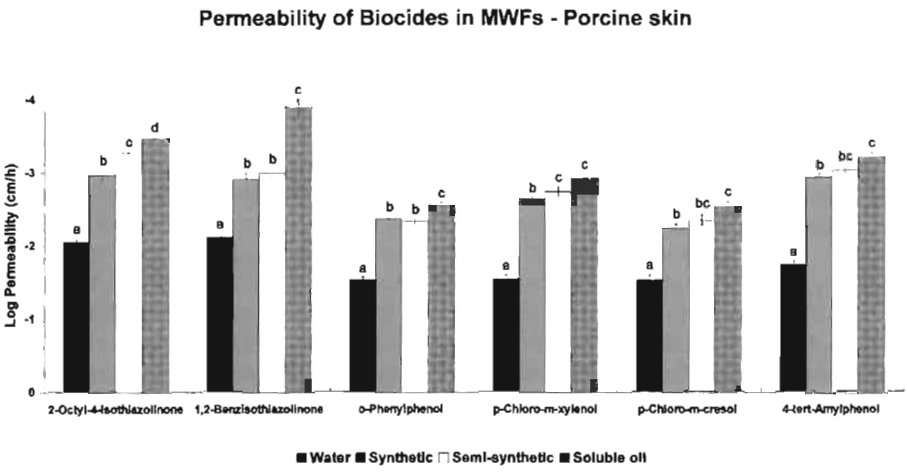

FIGURE 3 Permeability of phenolic and isothiazolinone biocides in water, synthetic, semi-synthetic, and soluble oil MWFs [permeabilities with different letters are statistically different and those with same letters are not statistically across the mixtures (water, synthetic, semisynthetic, and soluble oil MWFs) for each biocide, $p < 0.05$]. *Abbreviation*: MWF, metalworking fluids.

bonding or polarity changes) responsible for these interactions. The inert membrane studies strongly suggested that physicochemical interactions contribute significantly to solute permeability in skin. There are many possible physicochemical interactions between various additives and contaminants seen in MWF systems and the components of that particular MWF being used and cannot be ignored. Such interactions include (*i*) alterations to the solubility and ionization of chemicals within the MWF, (*ii*) changes in the alkalinity or pH of the formulation, or (*iii*) ionic or covalent interactions between biocides and other additives that may all change the partitioning behavior (17,18).

The permeation of a chemical through skin is influenced by its physicochemical characteristics and the biological characteristics of the skin, which can be predicted using a QSAR (quantitative structure-activity relationship) approach (33). Various scientists have developed QSAR models for dermal permeation and have proposed different mathematical models to correlate physicochemical and biological interactions occurring in the process of permeation. Studies have shown that hydrophobicity, polarity, molecular volume, and hydrogen bonding capability of chemicals are among the most important predictors for predicting permeability of chemicals (34–36). QSPR (quantitative structure-permeability relationships) has been utilized in predicting skin permeability and is the subject of continuous reviews (37–41). LSER (linear solvation energy relationship) is a type of QSAR, which statistically correlates physicochemical properties related to solvation of chemicals (solvatochromic parameters) to any free energy–related biological properties and represents a subset of broader class of linear free energy relationship (LFER). Dermal permeability of pesticides in mixture has been predicted using a modified LSER (42,43) that included a mixture factor as a molecular descriptor in the multiple linear regression analysis. Recently, Vijay et al. used LSER to predict the dermal permeability of biocides in soluble oil and synthetic type of MWFs where LSER approach also provided chemical insights for understanding the importance of

specific interactions occurring in the permeation/partitioning process between two phases (skin and MWFs) as well as explained the difference in the interactions between two different systems (skin/synthetic MWF, skin/soluble oil MWF, and skin/water are three different systems) (25).

FUNCTION AND SKIN TOXICOLOGY OF METALWORKING FLUID ADDITIVES

MWFs include a myriad of additives belonging to several classes, which comprise of different functions. The selection of additives of specific chemistry to provide required performance without impacting the functions of other ingredients is very challenging for MWF formulators (44). Therefore, because of formulation limitations, it is almost impossible to include all the additives that are safe from health perspective, and it is inevitable to include some additives that may cause health hazard.

NIOSH (1998) has conducted more than 70 health hazard evaluations of occupational exposure of MWFs and has found that the most frequently reported health problems were skin disorders followed by eye, nose, and throat irritations as well as respiratory disorders. Also, there was an overall reduction in airborne MWF exposures since 1980 (1).

The information about exact composition and concentrations of additives in commercial MWFs is limited and not revealed due to proprietary reasons. Health risks associated with these additives may vary due to difference in formulation techniques and level of concentration used. Therefore, assuming that all the ingredients can be toxic at a certain concentration, the functions and possible toxicities of most of the ingredients or additives used in MWFs are discussed below.

Mineral oils act as lubricants and carry lubrication. Neat oils cause acne and folliculitis in metalworkers (1). When the skin is exposed to oils, the hair follicles are blocked. As a result the dead keratin cells and sebum from sebaceous glands are trapped inside the skin leading to inflammation and formation of pustules. *Corrosion inhibitors* such as calcium sulfonate, alkanolamines, amine carboxylate, amine dicarboxylates, boramides, arylsulfonamido acids, sodium molybdate, sodium metasilicates, succinic acids, benzotriazoles, benzothiazoles, and thiadiazoles prevent rust formation by forming a protective film between metal surface and corrosive agents or by neutralizing them. TEA (45) and aliphatic polyamines (46) are associated with causation of occupational asthma.

Emulsifiers emulsify or mix two immiscible liquids (such as oil and water) so that one liquid is in dispersed phase and the other in continuous phase. The examples of emulsifiers are ethanolamines, nonionic ethoxylates, synthetic sulfonates, fatty acid amides, fatty acid soaps, petroleum sulfonates, sodium sulfonates, amphoterics etc. *Surfactants* or surface-active agents reduce surface tension of dispersed phase. An emulsion is not stable and over a period of time the droplets coalesce to form separate layer. Surfactants increase the kinetic stability of emulsion and stabilize it. Most commonly used MWF surfactants are alkoxylated alcohols and alkoxylated nonylphenols. Emulsifiers and surfactants can act as direct irritant and may change the structure and function of skin by dehydrating the skin or removing lipids or denaturing keratins causing dryness, fissuring, and eczematization (47). Physicochemical interactions between additives in defined MWF mixtures can influence the availability of a surfactant, linear LAS for absorption and distribution in skin, and could ultimately influence toxicological responses in skin (16).

Biocides such as phenols, triazines, isothiazolinones, oxazolidines, morpholines, sodium omadine, bromonitriles, and halogen carbamates are used to control bacterial and fungal growth. Although biocides prevent microbial growth and prevent the workers from diseases caused by microbes, they are responsible for causing adverse health effects. The United States Environmental Protection Agency (U.S. EPA) has listed more than 70 chemicals as antimicrobial agents and over 200 active products to be used as preservatives in MWFs (1). Biocides, such as glutaraldehyde and benzalkonium chloride, have long been associated with the causation of ACD (48,49). Although benzalkonium chloride primarily displays irritant activity, it may also produce ACD of the hands (50). Biocides like formaldehyde releasers and isothiazolinones such as benzisothiazolinone (BIT) and octylisothiazolinone (OIT) are being used as preservatives in water-based MWFs, and corresponding cases of sensitization have been observed. Potter and Whittle suggested that the isothiazolinones bind to protein by different mechanisms (51). Potter and Maguire explained these mechanisms as follows: 5-chloro-2-methyl-4-isothiazolin-3-one is activated by thiols to form intermediates that bind to protein whereas the 2-methyl-4-isothiazolin-3-one appears to primarily bind to the sulfahydryl moiety of cysteine to form a semistable mixed disulfide protein adduct (52). Protein binding of biocides is required for the induction and elicitation of an immunological response while unbound isothiazolinone was sequestered in skin without immunological consequence. Lymph node proliferation, which indicates immunological response, was dependent on concentration of isothiazolinones and type of vehicle used in the application (53). However, some of these biocides are difficult to patch test because the test reactions are often weak and poorly reproducible (54). Garcia et al. observed that a biocide (2-butanone peroxide) used in hospital environment showed negative results in the acute dermal irritation test and skin sensitization test (55).

EP additives such as sulfurized fatty acid esters, sulfurized hydrocarbons, chlorinated paraffins, chlorinated waxes, chlorinated esters, phosphate esters, zinc dithiophosphate, and lead naphthenate are used as boundary lubricity additives that can operate at higher temperatures of up to 1000°C. Increased friction between moving metal parts may lead to wearing and finally welding. EP additives adsorb to the metal surface to form a film even at very high temperature and pressure and prevent the contact of work piece and metal tool (44). Short- and medium-chain chlorinated paraffins are associated with non-genotoxic-induced peroxisome proliferation and hepatocarcinogenesis (56). *Detergents* such as metal sulfonate and metal phenate prevent deposition to maintain insoluble particles in suspension, neutralize acid buildup, and clean the metal surface. Detergents may act as irritant and may cause ICD.

CONTAMINANTS IN MWFs

MWFs can be contaminated with metal chips; leaking of tramp oils and in-process cleaners; and formation of polycyclic aromatic hydrocarbons (PAH), nitrosamines, and microbial toxins. All these contaminants in MWFs can further augment deleterious health effects. During metalworking process, a lot of fine particles, swarfs, *metal chips*, lints, and weld spatters are generated that can act as abrasives, irritants, and potential sensitizers (57). Irritation caused by these metal chips further adds to the occurrence of irritant and allergic dermatitis and may also lead to infection by microorganisms.

Tramp oils are industrial lubricants such as greases, gear and slideway lubricants, and hydraulic and machine oils that enter into MWFs through broken seals or damaged oil filter pipes (1) and contribute to the occurrence of acne or folliculitis. *In-process cleaners* such as acidic, alkaline, and hydrocarbon terpene solvents are used during routine machining or manufacturing process in many intermediate cleaning steps and may contaminate MWFs. Many of these solvents may cause contact dermatitis or other skin disorders (58). Despite of the use of biocides, sometimes bacteria and fungi can grow in MWFs and may release endotoxins and mycotoxins (*microbial toxins*). Contamination by a variety of species of pathogenic bacteria and fungi can cause respiratory, dermal, and systemic infections as well as allergies, fever, and inflammation in metalworkers (1). Fusarium mycotoxins have been shown to produce dermal toxicity (59).

Oxidation and presence of nitrites and amines in MWFs may lead to formation of *nitrosamines*, for example NDELA, which has been classified as group 2B carcinogen. These nitrosamines had first been identified in MWFs in 1970 to 1980s studies of MWFs. The formation of nitrosamines depends on a variety of factors such as pH and temperature of MWFs, concentration and time of contact between amine and nitrosating agents, and type of amine (1). However, the concentration of nitrosamines in MWFs is decreasing because of reduction in the use of nitrosating agents and better formulation practices. PAH can be formed from the degradation of base oil at high temperature, which may be carcinogenic. PAH content was more in early used straight oils, but refinement techniques such as severe hydrotreatment of mineral oils have limited the concentration of PAH in MWFs (60).

CURRENT TREND OF ADDITIVE USAGE IN MWFs

Many MWF formulators are limiting the use of chlorine-containing compounds, phenols, nitrites, amines, polychlorinated biphenyls (PCBs), and heavy metals. Chlorine- and sulfur-containing additives were used extensively in the 1970s, but have been mostly eliminated except use of long-chain chlorinated alkanes (C_{14}–C_{30}) as EP additives and petroleum sulfonates as emulsifying agents. The use of short-chain chlorinated alkanes (C_{10}–C_{13}) has been eliminated because of their suspected carcinogenicity (1).

SKIN DISORDERS ASSOCIATED WITH MWFs

Several skin disorders have been reported to be associated with MWF exposure. These disorders include contact dermatitis, squamous cell carcinoma, acne, folliculitis, keratosis, pigmentary changes (e.g., melanoderma), granuloma, mechanical injuries from metal chips, nail disorders, and photosensitivity reactions (57). Folliculitis, acne, keratosis, carcinoma, and granuloma are mainly associated with neat (straight oil) MWFs and contact dermatitis is caused by water-based MWFs (58). Since the use of straight oils is decreasing, only contact dermatitis will be discussed in detail as follows.

Contact Dermatitis

The most common skin problem due to exposure of water-based MWFs is contact dermatitis (1). A recent study in Finland reported that occupational skin diseases including both ICD and ACD were most common among metalworking machinists, whereas occupational respiratory disease was very rare (61). Contact dermatitis is the most frequent occupational dermatosis. Contact dermatitis can

be of two types: *ICD* and *ACD* (see chap. 17). Occupational irritant dermatitis is more frequently observed than ACD (62). Clinically, it is very difficult to differentiate ICD and ACD, and in most cases, the occupational skin disease is a mixture of ICD and ACD (63). To make a distinction between ACD from ICD, patch testing using several chemicals and allergens is performed and the difference between ICD and ACD is more conceptual than demonstrable (64). There are many other factors that influence the development of contact dermatitis such as individual susceptibility, lack of personal protective equipments, climate, type of machine and control methods, factory environment, and most important the extent and duration of MWF exposure (1,65).

Occupational ICD is a nonimmunological cutaneous inflammatory response generally resulting from exposure to a wide range of irritants in the workplace, such as solvents, cleansers, and MWFs without the production of specific antibodies. Higher alkalinity of the MWFs can also promote skin irritation. The irritancy of a particular substance, such as detergents and biocides, depends on its ability to remove the protective lipid layer (intercellular lipids of the SC) and/or the ability to produce damage of proteins in the outer layer of skin. Once surface corneocytes are damaged with loss of lipids, the skin water retention ability reduces, leading to dry and inflamed skin. Damage in ICD depends on three factors: duration of contact, strength of irritant, and frequency of contact (66). ICD involves antigen-independent activation of T cells. The damaged keratinocytes release a variety of inflammatory mediators and cytokines, which activate T cells. T cells further promote inflammation by releasing cytokines in a similar fashion as described below for allergic reactions (67). Besides, fissuring and damage of the keratin layer leads to increased permeability and can lead to sensitization with resultant ACD subsequent to the original irritant effect (68). The biocide, triazine, was found to be the most potent of the four performance additives used in MWFs in causing dermal irritation and exhibited highest toxicity toward human keratinocyte cell culture, which correlated well with the in vivo irritation and morphology results (69).

A common factor contributing to the development of ACD is a preexisting skin condition, such as ICD, because this disrupts the skin barrier and leads to increased penetration of allergenic substances (66). The mechanism of contact allergy from most of the biocides or other MWF additives can be explained on the basis that they act as a hapten (partial antigen) that causes allergic contact hypersensitivity by binding to protein, which ultimately makes it immunogenic. But to produce these effects, the biocides have to penetrate nonviable SC and enter the viable epidermis (31,70). Moreover, the chemistry and metabolized product of biocides or other potential chemical additives are also very important to determine whether it can act as an allergen. Most of the allergens are electrophilic (poor in electrons), which are positively charged. Sometimes nonenzymatic processes (e.g., ultraviolet irradiation) and the metabolizing enzymes present in skin could convert harmless nucleophiles (electron rich) into allergenic electrophiles. Since MWFs are mixture of a variety of chemicals, there is a possibility of cross-allergic reactions that depend on their structural and chemical similarity as well as similarity of metabolized products. Skin can be considered as electron rich, because a very large amount of biological structures such as nucleic acids and proteins contain electron-rich groups (nitrogen, sulfur, oxygen, or phosphorus) and are negatively charged. All these electrophilic haptens form very stable covalent bonds with nucleophilic proteins to act as complete antigen and trigger hypersensitivity reactions (70).

The allergenic chemicals form a complete antigen after conjugating with protein in viable epidermis. In response to these antigens, epidermal immunocompetent cells such as keratinocytes and Langerhans cells and dermal immunocompetent cells such as mast cells, fibroblasts, dermal antigen-presenting cells, and endothelial cells are activated to release cytokines, which in turn activate the T lymphocytes. Activated T lymphocytes and other immunocompetent cells as mentioned above release a variety of cytokines such as interleukin-1 (IL-1), IL-2 (induces T-cell proliferation), IL-3, IL-4, and IL-6 eliciting an inflammatory immune reaction (see chap. 16).

The allergic immune reaction (also known as type IV delayed type of hypersensitivity) responsible for causing ACD undergoes two phases namely sensitization followed by elicitation phase and involves antigen-dependent T-cell activation. The sensitization phase involves antigen presentation to T cells and formation of memory T cells. The degree of sensitization depends on the extent of hapten-protein conjugation and thus on the structure of allergens (70). The major antigen-presenting cells in epidermis are Langerhans cells, which contain class II major histocompatibility complex (MHC-II). T cells can only recognize antigen when presented in association with MHC-II molecules. Langerhans cells engulf hapten-protein conjugate (complete antigen) and digest it with the help of lysozymes. The Langerhans cells then leave epidermis and migrate to the paracortical area of the regional lymph nodes through lymphatic vessels to present processed antigens in association with MHC-II molecules to T cells. T cells are activated and this results in monoclonal expansion of antigen-specific T cells and formation of memory T cells (antigen-specific), which are distributed throughout the body and are ready for future antigen challenge. In elicitation phase, when the skin is rechallenged with the same chemical, antigen-specific memory T cells are activated to release a variety of cytokines resulting in inflammatory reaction and upregulation of the immune response (i.e., an allergic skin rash) as well as keratinocyte proliferation (i.e., epidermal hyperplasia) (67).

SUMMARY

Workers in the metal fabrication industry are more often exposed to MWFs and their components such as biocides via the skin that can cause harm to the skin and/or the entire body if absorbed by the dermal route. This chapter demonstrated why MWFs are still a major occupational concern in the metal machining industry. Several of the many performance additives such as the biocides in MWFs are readily absorbed across the skin and can illicit an inflammatory response. Research in our laboratory has demonstrated that dermal absorption and cutaneous response can be modulated by the presence of other additives in the MWF formulation. Understanding how these various additives interact with each other and the skin barrier will ultimately help inform the development and risk assessment of MWF formulations that afford greater protection to workers in the metal machining industry.

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Edited by

Nancy A. Monteiro-Riviere
North Carolina State University
Raleigh, North Carolina, U.S.A.

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