CHAPTER 4

Selected Potentially Hazardous Chemical Ingredients, Additives, and Contaminants

Limited information exists about the chemical components of specific MWFs because of the highly competitive and proprietary nature of the metalworking industry. A wide variety of chemicals may be used in each of the MWF classes, and the risk these chemicals pose to workers may vary because of different manufacturing processes, various degrees of refining, recycling, improperly reclaimed chemicals, different degrees of chemical purity, and potential chemical reactions between components. The intent of this criteria document is not to identify and characterize all chemicals in MWFs that may pose health risks to workers. However, several selected chemicals are briefly discussed here.

4.1 Chemical Ingredients and Additives

4.1.1 Triethanolamine

Savonius et al. [1994] stated that triethanolamine (TEA) may be an animal carcinogen and may cause occupational asthma.

Alkanolamines or ethanolamines—TEA, diethanolamine (DEA), and monoethanolamine (MEA)—may be used in MWFs to stabilize pH or inhibit corrosion. Typically, MWFs contain 2% to 3% MEA or DEA and up to 25% TEA. ILMA has recommended using MWFs with 5% MEA or DEA and up to 25% TEA to calculate exposure risk [CMA 1996]. A typical 10:1 dilution of bulk MWF with water gives a final concentration of 0.5% MEA or DEA and 2.5% TEA. Because of the continual addition of make-up water, ethanolamines tend not to concentrate in MWFs [CMA 1996]. On the basis of a 16% absorption factor and a hand/forearm skin-exposure surface area of 2,300 cm^2, a 78.1-kg worker would have an MEA or DEA exposure potential of 0.24 mg/kg and a TEA exposure potential of 1.2 mg/kg over the course of a typical workday [CMA 1996]. In vitro studies by Sun et al. [1996] indicate that the absorption rate may be even less for MEA and DEA. The Chemical Manufacturers Association (CMA) also estimates potential aerosol inhalation of 0.0032 mg/kg for MEA and DEA and 0.016 mg/kg for TEA. These estimates are based on the average daily human air intake of 10 m^3 for a 78.1-kg worker exposed to MWF containing 0.005% MEA and DEA and 0.025% TEA at the

current OSHA permissible exposure limit (PEL) of 5 mg/m^3 for mineral oil mist [CMA 1996].

Kenyon et al. [1993] reported TEA, DEA, and MEA exposures in the same automotive parts manufacturing plants studied by Eisen et al. [1992] and Woskie et al. [1994]. The results are provided from one plant that used insoluble, soluble, synthetic, and semisynthetic fluids. Personal samples were collected from all operations using synthetic, semisynthetic, and some soluble oil MWFs. TEA in particulate mass samples and TEA, MEA, and DEA in bulk fluid samples were collected and analyzed by gas chromatography. TEA did not account for more than 1% of the particulate mass except when the MWF contained more than 10% TEA in the bulk formulation. All three ethanolamines were found in bulk samples of synthetic and semisynthetic fluids. TEA and MEA were found in soluble fluids. No detectable concentrations of ethanolamines were found in mineral oil, and only low concentrations of ethanolamines were found in soluble fluids. Higher airborne TEA concentrations were found with transfer operations (large complex machines that perform several operations) than with other machining operations. The authors concluded that although airborne TEA concentrations generally increase with increasing percentage of TEA in the bulk fluids, the concentration is also operation-specific.

In 1994, the National Toxicology Program (NTP) released a Board Draft regarding two chronic experimental studies in which Fischer 344/N rats and $B_6C_3F_1$ mice were dermally exposed to concentrations of TEA in acetone for 103 weeks [NTP 1994a]. A final report has not been released as of October 1997.

The NTP stated that "equivocal evidence" showed carcinogenic activity in the TEA-treated male rats. The NTP doubted that this result could be attributed to TEA administration, because of the lack of both a clear dose-response relationship and an increase in the total number of proliferative renal lesions in dosed male rats. Since no significant terminal increase in tumors was found in female rats in the treatment or control groups, the NTP concluded that "no evidence" existed of carcinogenic activity induced in these TEA-treated females [NTP 1994a].

The NTP [1994a] also reported a significant increase (P=0.03) in hepatocellular adenomas in high dose male mice compared with the concurrent controls. No differences were observed in incidence of hepatocellular adenomas for the two lower-dose male groups. When the terminal incidences for hepatoblastomas and hepatocellular adenomas and carcinomas were combined for the high-dose males, they also became statistically significant (P=0.018). However, these male mice were infected with *Helicobacter hepaticus*, which has been associated with increased incidences of hepatocellular neoplasms in male mice. This occurrence may be a confounding factor in the interpretation of carcinogenicity studies [Ward et al. 1994a]. This infection in male mice was a significant factor in the NTP's final determination of "equivocal evidence" of carcinogenic activity

in treated male mice based on the possibility that the increased numbers of hepatocellular adenomas were induced by the *Helicobacter* infection.

Elevated hepatoblastoma rates did not occur in the treated female groups. However, the number of hepatocellular carcinomas increased significantly in the 300-mg/kg treated female group (P=0.02), and the number of hepatocellular adenomas increased significantly in the 1,000-mg/kg treated female group (P<0.001). When these hepatocellular adenomas and carcinomas were combined within each female treatment group, they were only statistically significant for the 1,000-mg/kg dose (P<0.001). Because the carcinoma rate among the 300 mg/kg treated female mice was well below the NTP historical control, and there was no consistent dose-related increase in hepatocellular carcinomas for the other treatment groups. Therefore, the NTP decided that the elevated carcinoma rate observed in this experiment was not related to TEA exposures. Ward et al. [1994b] suggested that female mice have a low susceptibility to *Heliobacter* infection compared with males. This difference suggests that the increased incidence of hepatocellular adenomas was related to the TEA treatment. The NTP concluded that "some evidence" existed of an elevated adenoma rate in the treated female mice.

Hoshino and Tanooka [1978] reported a significantly increased lymphoma incidence (P<0.05) for combined groups of ICR-JCL female mice. However, the combined groups had a low lymphoma incidence rate compared with historical controls, and the increased lymphoma rates in treated mice reported by Hoshino and Tanooka may not have been induced by chronic ingestion of TEA. Konishi et al. [1992] reported no dose-related increased incidence of any tumor in $B_6C_3F_1$ mice treated with TEA in their drinking water for 82 weeks. MaeKawa et al. [1986] reported no significant increases of tumors in F344 rats administered TEA ad libitum in drinking water compared with controls.

In summary, the NTP Board Draft reported that the elevated carcinoma rate observed in female mice was not related to chronic TEA exposures. However, the elevated adenoma rate for the 1,000-mg/kg female mice was higher than the maximum historical control rate for a single study and provided some evidence of an elevated rate. Until the NTP releases its final report, the final interpretation of these results remains unresolved.

The NTP has released a Preliminary Pathology Working Group Chairperson's Report on selected slides from a 2-year chronic dermal study of DEA in $B_6C_3F_1$ mice [NTP 1994b]. Incidences of multiple hepatocellular adenoma, multiple hepatocellular carcinoma, and hepatoblastoma were greater in treated males than in controls. Incidences of multiple hepatocellular adenoma, hepatocellular carcinoma, and multiple hepatocellular carcinoma were greater in treated females than in controls. In addition, the NTP Working Group confirmed that, with very few exceptions, the lesions diagnosed as hepatocellular neoplasms were clearly neoplasms, and the lesions of *Helicobacter* infections were absent.

Regardless of controversies concerning carcinogenicity, occupational asthma has been associated with TEA in MWFs [Savonius et al. 1994], as well as with other aliphatic amines [Chan-Yeung and Malo 1993b; Ng et al. 1995] that are used as components of MWF.

4.1.2 Mineral Oil

Mineral oils (lubricant base oils) refined from petroleum crude oils are complex mixtures of straight- and branched-chain paraffinic, naphthenic (cycloparaffin) and aromatic hydrocarbons [IARC 1984]. Skin cancer of the hands, forearms, and scrotum was reported to be due to long-term exposure of workers to the poorly or nonrefined mineral oils used before the 1950s [Järvholm et al. 1985, Järvholm and Easton 1990; Cruickshank and Gourevitch 1952; Waldron 1983]. Water-based MWFs have not been associated with scrotal cancer because no cases were observed among the grinders who often use soluble oils [Järvholm and Lavenius 1987]. Experimental animal bioassays demonstrated that the skin tumorigenicity of different refinement classes of mineral oils is related to their polycyclic aromatic content [IARC 1984]. More severe refinery methods used since the 1950s have reduced the PAHs in straight oils [Järvholm and Easton 1990; McKee et al. 1990].

The International Agency for Research on Cancer (IARC) has classified untreated and mildly treated oils as Group 1 human carcinogens; the evidence for carcinogenicity to humans is sufficient for untreated and mildly treated oils and inadequate for highly refined oils. Untreated and mildly treated oils have also been classified as Group 2 animal carcinogens; the evidence for carcinogenicity to animals is sufficient for untreated and mildly treated oils and inadequate for highly refined oils [IARC 1987a]. The OSHA hazard communication standard [29 CFR 1910.1200] requires that employers report on the MSDSs that a substance is a carcinogen or potential carcinogen when (1) OSHA has regulated the substance as a carcinogen, (2) the NTP lists the substance on its annual list of carcinogens, or (3) IARC has evaluated the substance and found sufficient or limited evidence of carcinogenicity. According to the IARC process parameters of mild hydrotreatment, an oil processed at a hydrogen pressure of 800 pounds per square inch (psi) or less at temperatures up to 800°F is subject to the OSHA hazard communication standard. ILMA reports that mineral-oil suppliers provide short-term test results to confirm the low PAH content of dermal carcinogenicity for severely hydrotreated or severely solvent refined oils [ILMA 1996]. If untreated or mildly treated oils are used, worker exposure should be reduced to the extent technologically feasible.

4.1.3 Antimicrobial Agents

Antimicrobial agents are incorporated as components in formulated MWFs or added to MWFs before and during use to prevent microbial growth. These agents can be classified by their general function or by their chemical name [Passman 1995]. Table 4–1 lists antimicrobial agents commonly used in MWFs.

Table 4–1. Antimicrobial agents commonly used in MWFs

Chemical name	Trade name
Tris(hydroxymethyl)nitromethane	Tris Nitro
Hexahydro-1,3,5-tris(2-hydroxyethyl)-S-triazine	Grotan® Onyxide® 200 Busan® 1060 Bioban® GK Triadine® 3
Hexahydro-1,3,5-triethyl-S-triazine	Vancide TH
1-(3-Chloroallyl)-3,5,7-triaza-1-azonia adamantane chloride	Dowicil 75
4-(2-Nitrobutyl)morpholine and 4,4'-(2-ethyl-2-nitrotrimethylene)	Bioban® P-1487
O-Phenyl phenol	Dowicide®-1
Sodium 2-pyridinethiol-1-oxide	Sodium Omadine®, 40% aqueous solution
1,2-BIT; 1,2-benzisothiazolin-3-one	Proxel® MW 300 or MW 200
5-Chloro-2-methyl-4-isothiazolin-3-one-2-methyl-4-isothiazolin-3-one	Kathon® 886
2,2-Dibromo-3-nitrilopropionamide	Dow XD–8254 DBNPA
p-Chloro-m-xylenol	PCMX

Some microbiocidal or microbiostatic activities of antimicrobial agents occur through the release of formaldehyde. Formaldehyde releasers are usually soluble in water rather than oil and are more effective against bacteria than fungi. Tris(hydroxymethyl) nitromethane and hexahydro-1,3,5, tris(2-hydroxyethyl)-s-triazine are examples of formaldehyde-releasing antimicrobial agents. Formaldehyde is an airways irritant and recognized cause of occupational asthma [Chan-Yeung and Malo 1993b]. Studies suggest that exposure to certain antimicrobial agents can cause allergic or irritant contact dermatitis [Zugerman 1986]. Concerns have been raised about the potential carcinogenicity of some of these agents because of their formaldehyde-releasing action, although the actual concentrations of formaldehyde released in MWFs have not been thoroughly studied. Formaldehyde is an OSHA-regulated carcinogen [29 CFR 1910.1048]. NIOSH recognizes formaldehyde as a potential occupational carcinogen (Ca); the

REL is 0.016 ppm (TWA) with a 15-min ceiling of 0.1 ppm [54 Fed. Reg. 2651 (1989); NIOSH 1988b].

Cohen [1995] studied the use of the antimicrobial agent triazine hexahydro-1,3,5,tris(2-hydroxyethyl)-s-triazine. His study examined approximately 550 air samples, 300 of which were obtained from workers. All of the personal air samples were below the OSHA action level of 0.5 ppm for formaldehyde [29 CFR 1910.1048], including workers exposed to triazine-containing MWFs [Cohen 1995]. Thorne et al. [1995] reported that airborne concentrations of formaldehyde (formaldehyde-yielding antimicrobial agents as the primary source) ranged from below the detection limit to 0.62 mg/m^3 at an automotive engine plant.

Non-formaldehyde-releasing antimicrobial agents are generally more effective against fungi than formaldehyde releasers but are also effective against bacteria. The phenolic compounds are oil soluble, and the antimicrobial agent derivatives of morpholine and the dioxanes are partially soluble in oil and water [Zugerman 1986; Pryce et al. 1989b]. Sodium 2-pyridinethiol-1-oxide and o-phenyl phenol are examples of non-formaldehyde-releasing biocides.

Nitrated biocides such as Bronopol® (2-bromo-2-nitro1,3-propanediol), 2-methyl-2-nitro-1,3-propanediol, and 5-methyl-5-nitro-1,3-dioxane, which have been shown to release nitrite, can act as nitrosating agents in MWFs. Bioban® P–1487, which is composed of 70% 4-(2-nitrobutyl) morpholine and 30% 4,4'-(2-ethyl-2-nitrotrimethylene) dimorpholine, can dissociate to form nitrite ions. Bioban® P–1487 added to MWF concentrate can directly form N-nitrosomorpholine (NMOR) (an animal carcinogen [IARC 1978b]), which can increase in concentration over time [Mackerer 1989]. Whether this action could result in any measurable worker exposure is unclear.

Antimicrobial agents chosen for the application should be compatible with the MWFs. The chemical reactivity of MWFs may destroy antimicrobial activity; pH, extreme temperatures, and contact with some metals may inactivate or destabilize antimicrobial agents in MWFs. These agents can be combined in a mixture to produce a synergistic effect that is broad spectrum enough to kill or control both bacteria and fungi. In addition, the use of lower concentrations of synergistic antimicrobial agents would reduce worker exposure to these toxic agents; furthermore, microorganisms are not likely to develop resistant mutants to two biocides simultaneously [Rossmoore and Rossmoore 1994].

The U.S. Environmental Protection Agency (EPA) lists more than 70 chemicals as preservatives (antimicrobial agents) and more than 200 active products used as material preservatives in MWFs. EPA is developing exposure assessment methods to evaluate

both dermal and inhalation exposures to 10 commonly used antimicrobial agents. Dang [1997] estimated acute dose rates and lifetime average daily doses for acute (short-term risks) and chronic (long-term cancer risks) exposures.

4.1.4 Chlorinated Paraffins

Chlorinated paraffins are a group of chemicals with carbon chain lengths of 10 to 30 atoms and 40% to 70% (by weight) chlorination. Chlorinated paraffins are used as extreme-pressure additives that are activated by the heat generated during metalworking to form a film between the tool and work to prevent destructive welding, excessive metal transfer, and surface breakdown [Nachtman and Kalpakjian 1985]. Fifty percent of the chlorinated paraffins produced are used as extreme-pressure additives. In 1988, 79.1 million lb of chlorinated paraffins (C_{10-30}, 35% to 64% chlorine) was produced in the United States [USITC 1989].

Nilsen et al. [1981] reported that short-chain chlorinated paraffins (C_{10-13}, 49% to 71% chlorination) administered intraperitoneally to male Sprague-Dawley rats increased liver weight compared with controls. Chlorinated paraffins containing more than 17 carbon atoms did not increase the liver weights. However, the increased liver concentration of microsomal cytochrome P–450 was related to the degree of chlorination rather than the carbon chain length.

The National Cancer Institute (NCI) selected long-chain chlorinated paraffins (C_{23}, 43% chlorine; a mixture of C_{22-26} chlorinated paraffins, with an average chain length of C_{23}) and short-chain chlorinated paraffins (C_{12}, 60% chlorine; a mixture of C_{10-12} chlorinated paraffins with an average chain length of C_{12}) for toxicity and carcinogenicity evaluation. The NTP reported that under the conditions of 2-year gavage studies, clear evidence existed of the carcinogenicity of the long-chain, chlorinated paraffins (C_{23}, 43% chlorine) in male $B_6C_3F_1$ mice, as shown by a dose-related induction of malignant lymphomas [NTP 1986a]. Re-evaluation of this study by the Experimental Pathology Laboratories, Inc. (November 3, 1983) and the Pathology Working Group (February 21, 1984) resulted in the conclusion by the EPA that there is insufficient evidence to conclude that the malignant lymphomas observed in male mice were treatment related and that long-chain chlorinated paraffins should not be classified as potential carcinogens [59 Fed. Reg. 61462]. The Agency further concluded that there was insufficient evidence to list long-chain chlorinated paraffins on the Emergency Planning and Community Right-to-Know Act (EPCRA) Section 313 list [59 Fed. Reg. 61462].

The NTP also reported clear evidence of the carcinogenicity of the short-chain chlorinated paraffins (C_{12}, 60% chlorine) in F344/N rats [NTP 1986b]. This evaluation was based on increased incidences of hepatocellular neoplasms in males and females, combined adenomas and adenocarcinomas of the kidney tubular cells in males, and combined follicular cell adenomas and carcinomas of the thyroid gland in females. The NTP

study reported evidence of the carcinogenicity of the short-chain chlorinated paraffins for $B_6C_3F_1$ mice, as shown by increased incidences of hepatocellular adenomas in males and females, and combined hepatocellular adenomas or carcinomas in males and females. Female mice also developed increased incidences of follicular cell adenomas and of combined follicular cell adenomas or carcinomas of the thyroid gland [NTP 1986b].

Ashby et al. [1990] tested the same grade of C_{12} chlorinated paraffin used in the NTP study [1986b] and determined that it did not induce unscheduled DNA synthesis activity in rat liver at doses up to 2 g/kg of body weight.

Two short-chain chlorinated paraffins (C_{10-13}, 60% chlorine) and one medium-chain (C_{14-17}, 40% chlorine) chlorinated paraffin were shown to be peroxisome proliferators in Fischer rat and $B_6C_3F_1$ mouse liver. The long-chain (C_{20-30}, 43% chlorine) chlorinated paraffin did not elicit peroxisome proliferation. These studies suggest that short- and medium-chain chlorinated paraffins are associated with nongenotoxic induced peroxisome proliferation and hepatocarcinogenesis [Ashby et al. 1990; Ashby et al. 1994].

EPA agreed in its EPCRA Section 313 list and Section 6607 of the Pollution Prevention Act that for short-chain chlorinated paraffins, the kidney tumors observed in rats were not likely to be relevant to tumor formation in humans. However, EPA did not question the use of $B_6C_3F_1$ mice or the results of the cancer bioassays. EPA did not believe that nongenotoxicity is a sufficient reason to dismiss the relevance to humans of tumor formation by the short-chain chlorinated paraffins. EPA also did not agree that the lack of liver growth, peroxisome proliferation in hepatocytes, and stimulation of replicative DNA in guinea pigs are proof that these effects are specific to rats and mice and have no bearing on tumor formation in humans. Therefore, EPA found sufficient evidence for listing short-chain chlorinated paraffins [EPCRA Section 313 list pursuant to EPCRA section 313(d)(2)(B)] based on the available carcinogenicity data for those chemicals. Thus EPA added the short-chain (C_{10-13}) polychlorinated alkanes (chlorinated paraffins/α-olefins) to EPCRA Section 313. EPA believes that no significant structural differences exist between chlorinated paraffins and chlorinated α-olefins. Both are primarily linear hydrochlorocarbons, and the degree of chlorination of both groups of substances can be controlled. The main difference between chlorinated paraffins and chlorinated α-olefins is that chlorinated paraffins typically manufactured from paraffin mixtures are also mixtures, whereas individual chlorinated α-olefins can be manufactured in moderate-to-high purity. Since EPA has determined that only the short-chain species meet the listing requirements of EPCRA Section 313, the polychlorinated alkanes category will be defined by the following formula and description:

$$C_xH_{2x-y}Cl_y$$

where x=10–13, y=3–12, the average chlorine content ranges from 40% to 70%, and the limiting formula structure is set at $C_{10}H_{19}Cl_3$ and $C_{13}H_{16}Cl_{12}$ [59 Fed. Reg. 61462].

Many MWF manufacturers have reported the removal of short-chain chlorinated paraffins from MWF formulations by substituting chemicals made from other feedstocks such as α-olefins or fats or other chlorinated materials not subject to EPCRA Section 313.

4.1.5 Potential Sensory or Pulmonary Irritants

MWFs may contain ingredients or additives that can be irritating through respiratory or dermal contact. Because of limited research in this area, potentially irritating ingredients and additives have not been completely identified.

In a study by Schaper and Detwiler [1991], aerosols generated from seven unused and undiluted MWFs and three used MWFs (soluble, straight [insoluble], synthetic, and semisynthetic) produced sensory and pulmonary irritation in male Swiss-Webster mice exposed to aerosolized mist at 20 to 2,000 mg/m^3 in a single 180-min inhalation period with a 20-min pre-exposure control time and a 20-min recovery period. Sensory irritants (which stimulate trigeminal nerve endings in the nasal mucosa) produce a lengthening of the expiratory phase of each breath in mice. Pulmonary irritants, which stimulate the vagal nerve endings, produce a pause between breaths in mice [Alarie 1981a; Schaper 1993]. Alarie [1981b] reported that both sensory and pulmonary irritants decrease respiratory frequency proportionally to exposure concentration.

Schaper and Detwiler [1991] observed pulmonary irritation after 2 hr with all MWF aerosol exposures. The mean respiratory frequency rapidly decreased with exposures to all MWF aerosolized mists, plateauing at 2 hr. In low-exposure animals, recovery of respiratory frequency to control levels was prompt following discontinuation of exposure. However, slower recovery occurred in animals exposed at higher concentrations. At high exposure concentrations, mean tidal volume decreased by 30% to 50% and respiratory frequency decreased 70% to 80%. Little change occurred in lung weight or lung volume displacement in mice exposed to concentrations capable of inducing a 50% reduction in respiratory frequency. The most significant histopathologic changes were found 24 hr after exposure. Mild interstitial pneumonitis occurred in animals exposed to unused and used soluble oil fluids, unused and used semisynthetic fluids, and unused and used straight oil fluids. Moderate interstitial pneumonitis and bronchopneumonia occurred in animals exposed to a second unused soluble oil MWF sample. No histopathologic changes were seen in mice exposed to a third unused soluble oil MWF sample or in mice exposed to an unused synthetic fluid sample. On the basis of the 50% reduction in respiratory frequency, the three semisynthetic/synthetic MWFs were more irritating than the five soluble oil fluids. All eight were more potent than the two straight oil fluids. There was no significant difference in potency between the three neat fluids and

their corresponding in-service fluids. Schaper and Detwiler [1991] concluded that these results do not imply that other sets of straight oil and in-service fluids are equally potent or that the relative order of potency will always be the following: synthetic/semisynthetic>soluble>straight.

In a recent study by Schaper and Detwiler-Okabayashi [1995a], the authors examined the sensory and pulmonary irritant properties of the three major components (tall oil fatty acids, sulfonic acid, and paraffinic oil) of one of the three unused soluble oil MWFs described earlier. As in the previous study, male Swiss-Webster mice were administered generated aerosol mists (particulate mass median aerodynamic diameter of 1 to 2 μm, standard deviation [SD] 2.0) for 180 min with 20-min pre-exposure and 20-min postexposure recovery times. Sensory and pulmonary irritation were evaluated through the recordings of tidal volume and respiratory frequency. In this study, tall oil fatty acid acted mainly as a sensory irritant, and sulfonic acid acted as a pulmonary irritant. Animals exposed to either agent did not fully recover normal breathing patterns, and the mean respiratory frequency remained below control levels. Paraffinic oil produced sensory irritation at the beginning of exposures, with pulmonary irritation effects occurring between the second and third hour. Recovery was incomplete, although respiratory frequency returned toward control levels.

Schaper and Detwiler-Okabayashi [1995a] also assessed the sensory and pulmonary effects of two component mixtures (sulfonic acid/tall oil fatty acids, sulfonic acid/paraffinic oil, and tall oil fatty acid/paraffinic oil). Mixtures containing sulfonic acid provoked pulmonary irritation earlier in the exposures than did the tall oil fatty acid/paraffinic oil. Likewise, recovery was poor for all the mixtures but the latter, for which some recovery was observed. The sensory and pulmonary effects of the unused soluble oil MWF closely matched those of paraffinic oil and tall oil fatty acid/paraffinic oil.

The decreases in respiratory frequency for each of the components and mixture are proportional to the logarithms of exposure concentrations. This result suggests (at least with these components) that the sensory and pulmonary irritation effects of all three components are additive and not synergistic. These studies provide evidence that some components of arbitrarily selected MWFs are pulmonary irritants in experimental animals. These findings are consistent with the adverse health effects observed in the studies of respiratory symptoms and pulmonary function in exposed workers. Schaper and Detwiler-Okabayashi [1995b] has suggested an approach to using the results of these studies to derive an occupational exposure limit. However, NIOSH has relied primarily on the epidemiologic data to establish an REL for MWFs.

4.2 Hazardous Contaminants

Exposure to hazardous contaminants in MWFs may present health risks to workers. Contamination may occur from (1) process chemicals and ancillary lubricants

inadvertently introduced, (2) contaminants, metals, and alloys from parts being machined, (3) water and cleaning agents used for routine housekeeping, and (4) contaminants from other environmental sources at the worksite. Bacterial and fungal contaminants may metabolize and degrade the MWFs to hazardous end products as well as elaborate endotoxins, exotoxins, and tissue-damaging enzymes. A few selected chemical and biological contaminants of MWFs are discussed in the following subsections.

4.2.1 Nitrosamines

Potentially carcinogenic nitrosamines have been identified in MWFs studied in the 1970s and early 1980s. The formation and concentration of nitrosamines in MWFs depend on: (1) the concentrations of amine and nitrosating agent, (2) the type of amine (primary, secondary, or tertiary), (3) the presence of catalysts or inhibitors, (4) the pH of the MWF, (5) the temperature of the fluid, and (6) the time of contact between amine(s) and nitrosating agent(s) [Loeppky et al. 1983]. Some nitrosamines may form under work conditions such as the extreme heat and pressure generated by machinery [Fan et al. 1977; Kipling and Waldron 1976; NIOSH 1976]. Lijinsky et al. [1972] demonstrated that TEA could be nitrosated to form N-nitrosodiethanolamine (NDELA), a nitrosamine that IARC has classified as a Group 2B carcinogen (possibly carcinogenic to humans) [IARC 1978a; Lijinsky et al. 1980, 1984; Lijinsky and Kovatch 1985; Preussman et al. 1982; Lijinsky and Reuber 1984]. Lucke and Ernst [1992] reported that the concentrations of NDELA found in MWFs are related to the amount of DEA in the fluids. Certain biocides can dissociate to form nitrite ions, which may react with alkanolamines to form nitrosamines [Mackerer 1989].

NDELA has reportedly occurred in MWFs containing sodium nitrite and DEA or TEA [Järvholm et al. 1986; Spiegelhalder 1980]. Fan et al. [1977] reported 0.02% to 3% concentrations of NDELA contamination in several unused synthetic MWFs containing the alkanolamines TEA or DEA and nitrites. The presence of nitrosamines in these samples was reported before the EPA prohibited the addition of nitrosating agents to MWFs containing the triethanolamine salt of tricarboxylic acid, mixed monoamides and diamides of an organic acid, or a TEA salt of a substituted organic acid [40 CFR 747.115 (1990)]. These prohibitions were intended to eliminate or reduce the concentration of contaminating nitrosamines by controlling the precursors. Analysis of some MWFs following the EPA prohibition showed reduced concentrations of nitrosamines. Garry et al. [1986] reported 1 to 5 ppm of N-nitrosodimethylamine (NDMA), N-nitrosodibutylamine (NDBA), and NMOR.

However, some studies show that nitrosamines may form in MWFs that contain TEA or DEA even though nitrites have not been added. Challis et al. [1978] demonstrated the rapid nitrosation of primary and secondary amines by nitrogen oxides; oxygen accelerates nitrosation by converting NO through NO_2 to either of two nitrosating agents, N_2O_3

or N_2O_4. In addition, nitrosamine formation from NO and amines is accelerated under specific conditions by formaldehyde, paraformaldehyde, thiocyanate, nitrophenols, and certain metal salts (e.g., ZnI_2, CuCl, $AgNO_3$, $SnCl_2$, $CoSO_4$, and $HgCl_2$) [Challis et al. 1978; Keefer and Roller 1973; Boyland et al. 1971; Davies and McWeeny 1977; Loeppky et al. 1983; Okun and Archer 1977].

Keefer et al. [1990] reported NDELA contamination (0.05 to 58.8 ppm) of synthetic, semisynthetic, straight oil, and soluble concentrates (Table 4–2).

Table 4–2. NDELA and nitrite/nitrate concentrations in unused MWF concentrates*

MWF	NDELA (ppm)	NO_2/NO_3 (ppm)
Synthetic	0.05–58.80	9–111
Semisynthetic	0.43–4.55	15–17
Petroleum-based	0.11–0.16	10–72

*Adapted from Keefer et al. [1990].

In May 1993, EPA issued the Significant New Use Rule for alkali metal nitrites intended for use in MWFs. Manufacturers or companies that plan to manufacture, import, or process alkali metal nitrites (i.e., nitrites of lithium, sodium, potassium, rubidium, cesium, and francium) for use in MWFs must comply with the reporting requirements under Section 5(a)(2) of the U.S. EPA Toxic Substances Control Act.

4.2.1.1 NIOSH Reports of Nitrosamine Contamination

On the basis of a report on NDELA contamination in new and used MWFs [Keefer et al. 1990], NIOSH researchers began a preliminary nitrosamine contamination survey of MWFs [NIOSH 1992]. They collected bulk fluid and personal air samples during HHEs [NIOSH 1992] of the metalworking industry. During 1992–93, 47 samples of straight, soluble, semisynthetic, and synthetic MWFs (both new and used) were collected at 4 sites, and 29 air samples were collected at 2 sites.

The air samples were analyzed for seven nitrosamines, including NMOR, which may be formed from NDELA by dehydration and cyclization. The results were negative (limit of detection ranged from 0.01 to 0.04 μg per sample) except for one sample in which NMOR was detected at 0.12 μg per sample (air concentration about 0.1 $\mu g/m^3$). That sample was from a site using a straight oil MWF [NIOSH 1992].

All MWF bulk samples were analyzed for NDELA. In addition, the samples from one site (designated Site A) were reanalyzed for NDELA and for seven other nitrosamines; only NMOR was found. The results (Table 4–3) ranged from undetected to 4.7 ppm for NDELA and 0.04 to 17 ppm for NMOR. NMOR was found in all six samples analyzed, and NDELA and NMOR were found in all three samples of straight oils. NDELA was detected in only one of eight MWF concentrates, but it was found in half (22 of 44) of the used fluids produced from those concentrates. These results suggest that NDELA may form during use. Also, the results for Fluid G at site C suggest that some process factors influence nitrosamine formation.

The degradation of nitrosamines in MWFs is less well understood, but (like the formation) it may also depend on the pH of the fluids, the type of machining operation, types of microbial species and numbers, metal and alloys being machined, and length of fluid use.

4.2.1.2 Carcinogenicity of Nitrosamines

IARC has classified N-nitrosodiethylamine (NDEA) and NDMA. Group 2A agents—*probably carcinogenic to humans*. This group classification includes agents for which limited evidence exists of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals [IARC 1987b]. IARC has classified NDBA, NDELA, and NMOR as Group 2B carcinogens—*possibly carcinogenic to humans*. This category includes agents for which inadequate evidence exists of carcinogenicity in humans, but sufficient evidence exists of carcinogenicity in experimental animals [IARC 1987b].

The NTP has determined that sufficient evidence exists for the carcinogenicity of NDBA, NDELA, NDMA, and NMOR in experimental animals based on animal studies cited by IARC [NTP 1991].

OSHA has classified NDMA as a *cancer suspect agent* (29 CFR 1910.1003 and 1910.1016). Without establishing a PEL, OSHA promulgated standards in 1974 to regulate the industrial use of NDMA, identified as an occupational carcinogen. The changes in MWF composition since the EPA prohibitions in 1984 and 1990 have reduced the concentration of nitrosamine, as demonstrated by Garry et al. [1986], Keefer et al. [1990], and NIOSH [1994a]. However, as these studies show, low concentrations of nitrosamines are still found in some MWFs.

4.2.2 Microbial Contamination

4.2.2.1 Ecology

Historically, microbial contamination of MWF has been a problem in the metalworking industries, primarily because of microbial growth effects on fluid quality and performance. Fluid degradation from microorganisms may result in changes in fluid viscosity,

Table 4–3. Concentrations of NDELA and NMOR found in MWF field samples from four sites

MWF type and identification	Sample site	Sample condition	Nitrosamine concentration (ppm)	
			NDELA	NMOR
Straight oil:				
Fluid A	A*	Unused	0.14, 0.35	0.04
Fluid B	A	Unused	0.44, 4.7	17.0
Unknown	A	Used	3.00, 0.18	0.16
Soluble oil:				
Fluid C	B	Concentrate	ND†	NA‡
		Used	ND	NA
		Used	ND	NA
		Used	ND	NA
		Used	ND	NA
	C	Concentrate	ND	NA
		Used	ND	NA
		Used	ND	NA
		Used	ND	NA
		Used	ND	NA
Fluid D	D	Concentrate	1.90	NA
		Used	0.05	NA
		Used	0.66	NA
Semisynthetic oil:				
Fluid E	D	Concentrate	ND	NA
		Used	ND	NA
		Used	0.48	NA
		Used	0.29	NA
		Used	0.61	NA

See footnotes at end of table.

(Continued)

Table 4–3 (Continued). Concentrations of NDELA and NMOR found in MWF field samples from four sites

MWF type and identification	Sample site	Sample condition	Nitrosamine concentration (ppm)	
			NDELA	NMOR
Synthetic oil:				
Fluid F	A	Concentrate	ND, ND	0.09
		Used[§]	ND, ND	0.23
		Used[§]	0.34, ND	0.10
Fluid G	B	Concentrate	ND	NA
		Used	0.48	NA
		Used	0.05	NA
		Used	0.40	NA
		Used	0.43	NA
		Used	ND	NA
		Used	0.49	NA
		Used	0.39	NA
		Used	0.56	NA
	C	Concentrate	ND	NA
		Used (steel)	ND	NA
		Used (steel)	ND	NA
		Used (steel)	ND	NA
		Used (steel)	ND	NA
		Used (stainless steel)	0.07	NA
		Used (stainless steel)	0.48	NA
		Used (stainless steel)	0.31	NA
		Used (stainless steel)	0.30	NA

See footnotes at end of table.

(Continued)

Table 4–3 (Continued). Concentrations of NDELA and NMOR found in MWF field samples from four sites

MWF type and identification	Sample site	Sample condition	Nitrosamine concentration (ppm) NDELA	NMOR
Synthetic oil (continued):				
Fluid H	D	Concentrate	ND	NA
		Used	0.67	NA
		Used	0.59	NA
		Used	0.34	NA
		Used	0.61	NA

*Only Site A samples were subsequently analyzed for NMOR and reanalyzed for NDELA (second values).
†ND=not detected; estimated limit of detection=0.05 ppm.
‡NA=not analyzed.
§Water-based fluids presumed to have been prepared from Fluid F concentrate.

and the acid products of fermentation may lower the pH of the fluids, causing corrosion and leaks in the MWF system. Anaerobic bacteria, specifically the sulfate reducers, may produce hydrogen sulfide and other disagreeable and toxic gases. Excessive microbial growth may result in clogged filters and ports and may interfere with the metalworking operation.

Water-based MWFs are excellent nutritional sources for many kinds of bacteria and fungi. The predominant microbial species routinely recovered from MWFs are virtually identical to those routinely recovered from natural water systems. As a group, they exhibit great nutritional diversity. Moreover, many species that grow well on MWF components secrete waste products that serve as nutrients for microorganisms with more restricted nutritional capabilities. Environmental conditions such as alkaline pH, elevated temperature, and the presence of metals favor the development of a population able to survive and grow in conditions generally considered hostile for microorganisms. Attempts to manage microbial growth by the incorporation or addition of biocides may result in the emergence of biocide-resistant strains. Complex interactions may occur among different member species or groups within the population. The growth of one species may result in conditions that are more (or less) favorable to the subsequent establishment of other species. The elimination of one group of organisms may permit the overgrowth of another. All these factors contribute to the establishment of a unique microbial community and to the continuation of change in the population.

4.2.2.2 Hazards

Microbial contamination of MWFs may pose occupational hazards for exposed workers. Tant and Bennett [1956] isolated 29 different bacterial species from emulsion oils, including many that are pathogenic or potentially pathogenic for humans. The most commonly cultured species belonged to the genus *Pseudomonas (P. aeruginosa* and *P. oleovorans)*. Others identified included *Klebsiella pneumoniae, Micrococcus pyogenes* (now *Staphylococcus aureus*), *Escherichia coli, Proteus vulgaris, Aerobacter* (now *Enterobacter*) *aerogenes*, and members of the *Citrobacter* and *Achromobacter* genera. In a later study, Bennett [1972] again identified *Pseudomonas* and *Desulfavibrio* as the two most common genera isolated. Wort et al. [1976] examined samples of soluble oil emulsions and also reported that *Pseudomonas* was the predominantly cultured genus. *Cephalosporium* (*Acremonium*) was the most common fungus isolated [Bennett 1972]. Rossmoore [1986] found *Pseudomonas, Enterobacter, Moraxella, Aeromonas, Acinetobacter, Flavobacterium*, and *Alcaligenes* and the fungi *Cephalosporium, Fusarium, Penicillium, Aspergillus, Cladosporium, Trichoderma, Candida, Botrytis, Saccharomyces, Trichosporon*, and *Cryptococcus* in MWFs from an automotive engine plant.

Although frankly pathogenic organisms such as *Salmonella, Staphylococcus*, and *Legionella* have been isolated from MWFs [Hill and Al-Zubaidy 1979; Herwaldt et al. 1984], most of the organisms associated with MWFs are characterized either as nonpathogens or as "opportunistic" pathogens (those that primarily infect persons with a major abnormality in their natural defenses). Conditions and situations that may result in compromised host defenses include predisposing disease such as diabetes, cancer (especially leukemia), or cystic fibrosis; alcoholism; inherited or acquired immune deficiency; burns, skin cuts and abrasions, or other trauma; invasive medical procedures; and certain medications (e.g., some antibiotics and immunosuppressive drugs).

The bacterial genus most commonly isolated from MWFs is *Pseudomonas*. Despite the frequency and severity of *Pseudomonas* infections in susceptible persons, healthy adults with intact immunity are rarely affected. One study of a worksite with a demonstrated viable count of 1×10^8 colony-forming units per ml of MWF showed no evidence of *Pseudomonas* colonization of the workers' respiratory tracts, even though the organisms were cultured from the MWF [Hill and Al-Zubaidy 1979]. The reason is probably that organisms are rapidly cleared from the lungs of healthy persons. No reports have been published of work-related *Pseudomonas* infections in MWF workers.

Infections are not the only health risks associated with occupational exposure to microorganisms. All microorganisms produce antigens—molecules, often proteins or polysaccharides, that stimulate the immune system. A single exposure to an antigen may result in sensitization. If the sensitized person is exposed again to the same antigen, a hypersensitive or allergic response may occur to an antigenic dose that would elicit little or no reaction from nonsensitized persons. Allergic reactions to inhaled antigens may be

limited to the upper respiratory tract (e.g., allergic rhinitis), or they may affect the airways (e.g., allergic asthma) or the distal portions of the lung (e.g., HP, also known as extrinsic allergic alveolitis). Interest has focused on the possible involvement of microbial antigens in recent clusters of HP among workers exposed to MWF aerosols in operations using synthetic and soluble oil MWFs [Kreiss and Cox-Ganser 1997]. However, the cause of HP in MWF-exposed workers may not be limited to bacterial antigens (see Section 5.3).

Endotoxins (the principle surface antigens in gram-negative bacteria) are heat-stable lipopolysaccharide-protein complexes contained in the cell envelopes of all gram-negative species. Exotoxins are secreted by viable cells as a physiological function. In contrast, endotoxins are released from cells generally as a result of the death of the cell, or the lysis or disruption of the integrity of the outer membrane/cell wall structure [Galanos et al. 1979]. MWFs that have high levels of gram-negative bacteria also have high levels of endotoxins [Mattsby-Baltzer et al. 1989a; Milton et al. 1990].

Endotoxins exhibit similar biological activities (pyrogenicity and increased capillary permeability) regardless of the species of bacteria from which they are derived [Budavari et al. 1989]. Endotoxins were first implicated in occupational disease in 1942 [Neal et al. 1942]. Subsequently, various animal, human, and epidemiologic studies have established a link between exposure to airborne endotoxins and respiratory problems in various workplace environments [Pernis et al. 1961; Cavagna et al. 1969; DeMaria and Burrell 1980; Snella 1981; Burrell and Rylander 1982; Brigham and Meyrick 1986; Castellan et al. 1987; Rylander and Beijer 1987; Jacobs 1989; Burrell and Ye 1990; Gordon et al. 1991; Fogelmark et al. 1992; Rylander and Fogelmark 1994; Rylander and Jacobs 1997]. Also, animal exposure studies conducted by Gordon [1992] demonstrated that the endotoxin content of MWFs predicted respiratory toxicity in a guinea pig model of acute airways obstruction. Therefore, aerosolized endotoxins are suspect causative agents of occupationally related adverse respiratory effects (e.g., chronic bronchitis, abnormal cross-shift declines in pulmonary function, asthma, and other long-term effects) among workers exposed to MWF aerosols [Hill and Al-Zubaidy 1979; Hill 1983; Kennedy et al. 1989; Mattsby-Baltzer et al. 1989b; Gordon 1992; Gordon et al. 1992; Sprince et al. 1994; Robins et al. 1997].

For some time, the Food and Drug Administration has regulated the measurement of endotoxin (pyrogen) in parenteral solutions and on various medical devices manufactured by the pharmaceutical industry [USP 1985; FDA 1988]. However, no standard method exists for measuring airborne endotoxin in environmental samples. Therefore, reported measurements of airborne endotoxin concentrations often exhibit high variability because of differences in collection media, sampling methods, and assay procedures [Milton et al. 1990; Gordon et al. 1992].

Bacteria also secrete other toxins and extracellular enzymes that may present health hazards, although to date no evidence exists that exotoxins or other microbial enzymes have produced adverse health effects in MWF-exposed workers. Theoretically, toxic metabolites and tissue-damaging enzymes may accumulate to concentrations that constitute a threat to exposed workers. In addition to tissue-damaging enzymes, bacterial enzymes are also potentially associated with ill effects. They are highly antigenic and have caused asthma in some work settings [Chan-Yeung and Malo 1993b]. The growth of certain bacteria may result in the production of gases such as ammonia and hydrogen sulfide, which can have toxic or irritant effects.

Fungi (yeasts and molds) also contaminate all water-based or water-contaminated MWFs. Generally, the fungi isolated from MWFs are common saprophytic species that live on decaying organic matter in the environment and are not usually the major microbial contaminant in MWFs. Although no reports have been published about fungal diseases from contaminated MWF exposures, some known health hazards are associated with fungi exposure. Given the opportunity, fungi may infect susceptible hosts (such as the immunocompromised persons discussed earlier) or may cause allergic disease in persons previously sensitized. *Cephalosporium*, a genus commonly isolated from MWFs, has reportedly caused HP in exposed persons [Patterson et al. 1981]. *Penicillium* and *Aspergillus* species, have likewise been implicated in HP and both are common MWF contaminants. In addition, several fungal species isolated from MWFs are known to cause allergic reactions including asthma, but the relationship between fungal contamination and occupational asthma associated with MWF exposures is uncertain.

Fungi also produce toxic metabolites called mycotoxins. *Fusarium* (one of the fungal genera isolated from contaminated MWFs) produces toxins that cause dermal toxicity [Bhavanishankar et al. 1988]. Other genera, including *Cephalosporium,* may also produce these toxins.

4.3 Metals and Metal Alloy Contaminants

Depending on the type of MWF, the grinding or machining process and tools, and the metals or alloys being machined, metals may dissolve into the MWF. In general, straight oils absorb fewer metals than water emulsions, whereas semisynthetics may be less reactive than synthetic fluids. The amount of metal absorbed is directly related to the total metal surface area exposed to the MWF. Higher MWF operating temperatures can result in greater metal solubility. Smaller sumps become more quickly saturated with soluble metals, and concentrations of metals (and other chemicals) increase the longer the fluids are in use. Soluble metals that may contaminate MWFs include lead from leaded steels, leaded aluminum and leaded brass; nickel and chrome from stainless steel; zinc from galvanized steel; and mercury, lead, zinc, and copper from cast and ductile irons [Burke 1994]. Cobalt may also contaminate MWF [Kennedy et al. 1995a].