

**April 5, 2001**

# **Metal Working Fluids**

**Recommendation for Chronic Inhalation Studies**

**National Institute for Occupational  
Safety and Health  
Cincinnati OH USA 45226**

## Nomination of Metal Working Fluids for Testing by the National Toxicology Program

April 5, 2001 Executive Summary Update

The nomination of metal working fluids as a candidate for chronic inhalation studies is based upon their high production volume, the large number of occupationally-exposed workers, and the lack of carcinogenicity and chronic toxicology data for this class of mixtures.

Millions of gallons of metal working fluids are used each day in industry for cutting, milling, drilling, stamping, and grinding. NIOSH and OSHA have estimated that over a million workers are engaged in these activities and are potentially exposed dermally and via inhalation to a wide variety of formulations that have been referred to among other things as cutting oils, machining fluids, metal removal fluids, metal working fluids, etc.

Past exposures to metal working fluids have been associated with a variety of cancers in workers. Past and present exposures are associated with adverse respiratory effects in workers and experimental animals. The distinction between past and present exposures is important because metal working fluid formulations continue to change. Modifications are made to improve performance, reduce cost, meet the need of new applications, and abate health concerns of workers. Despite changing formulations and reduced occupational exposure levels, adverse respiratory effects in workers continue to be a persistent problem. While known or highly suspect carcinogens have generally been reduced or eliminated from metal working formulations, potential cancer risk of presently used formulations is unknown. However, recent studies by NIOSH have demonstrated the capacity of new metal working formulations to cause oxidative stress in liver (Al-Humadi et al., 2000a; b) and cell transformation in vitro (Keshava et al., 2001a; b). Both of these experimental end points can be attributable to carcinogens.

From a toxicological testing perspective, potential hazards in product formulations are typically identified by testing of individual constituents. Recognized carcinogens such as nitrosating agents and short-chained-chlorinated paraffin have been eliminated from metal working fluids and suspect carcinogens such as ethanalamines have been reduced in concentration in some formulations in an attempt to reduce the potential cancer hazard posed by metal working fluid exposure. Presently, epidemiological data are unavailable to determine if these modifications have reduced the cancer risk associated with metal working fluid exposure.

The highly competitive and proprietary nature of metal working formulations has prevented an accurate assessment that would define the specific constituents of formulations, the demographics of their use, and associated occupational exposures. Nonetheless, there is considerable information on the general make up of the metal working fluids and the most widely used constituents, at least in terms of their chemical classes. Because of the extensive industrial use of metal working fluids, available information primarily from the Independent Lubricating Manufacturers Association (ILMA) indicates that many or most constituents are high production volume chemicals (HPV - more than 1 million pounds produced per annum) and hazard assessments of inadequately tested chemicals are being addressed through industry sponsorship of EPA's HPV challenge. Therefore, data from acute toxicity studies will be available for many constituents in the next few years. Not covered under the HPV challenge is assessment of complex metal working fluid formulations via the primary exposure route of inhalation; nor will there be assessment of cancer risk posed by untested constituents.

While the NTP has made a commitment to assess the health hazards posed by exposure to complex mixtures such as dioxin-like chemicals, AIDS therapies, or asphalt fume (Bucher and Lucier, 1997), testing of a formulation in a chronic bioassay is atypical. The present nomination is based on the hypothesis that inhalation of the liquid aerosols of presently used formulations produced by the metal working fluid applications represents an unrecognized potential cancer

hazard for workers. Assessment of this hazard can best be achieved by the testing of metal working fluid formulations in a chronic inhalation bioassay.

NIOSH recognizes that testing of formulations constitutes a formidable challenge to the NTP. The difficulties associated with the testing of one or several formulations available are described in public comment received by NIOSH on a November 14<sup>th</sup>, 2000 Draft Nomination Document for testing metal working fluids. Comments and recommendations were received from formulators, end users, scientists, and government agencies. While some reviewers support the nomination, others raised questions. Numerous reasons and extensive arguments were presented against testing metal working fluids as a complex mixture, but were succinctly summarized by William Watt of DaimlerChrysler who made the following statements: “This task is nearly impossible to perform as proposed. There are hundreds of formulas for MRFs (metal removal fluids), using several of the hundreds of potential ingredients available. . . it would be impossible to pick *a* formula that would represent anything more than a very small percent of MRFs. . . the results of testing one formula could be misinterpreted. . . and would only lead to control of that formula.” Other objections arise from the belief that the real hazard associated with metal working fluids is contamination that occurs after metal working fluids are put into use. It was also noted that resources would be better directed at the primary health effect of acute respiratory irritation, hypersensitivity pneumonitis, and reduced lung function in workers exposed to metal working fluids. Despite the barriers presented to the testing of metal working fluids, there is still a need to determine if exposure to modern metal working formulations exposes workers to an increased risk of cancer. In the absence of epidemiological data on presently exposed workers, testing of metal working fluid formulations in experimental animals is warranted.

### **Recommendation and Suggested Studies**

The objective of the proposed studies is to determine if chronic inhalation exposure to neat metal working fluid formulations causes cancer in experimental animals. While contamination of metal working fluids during use is considered a potential occupational hazard, this hazard cannot be addressed until adequate testing assesses the hazards associated with unused metal working formulations. Therefore, this nomination addresses only unused or neat metal working fluid formulations. As virtually all metal working fluids evaluated have been found to be sensory and pulmonary irritants in experimental animals at some concentration (Ball and Lucke, 2001; Thorne and DeKoster, 1996; Schaper and Detwiler, 1991) assessing acute respiratory effects of metal working fluids is not a primary objective of this testing nomination.

Generally, metal working fluids are put into four categories. These being straight oils, soluble oils, semisynthetic fluids, and synthetic fluids. The distinguishing feature among the fluids is the amount of highly refined oil. Straight oils are 60-100% oil and synthetic fluids contain no oil. The two largest classes, the soluble oils, and semi-synthetic fluids, contain 5-85% oil. While these are often split into two categories, their only distinguishing feature is that semi-synthetic fluids contain less oil than the soluble oils. For this nomination the soluble oils and semisynthetic fluids will be considered as a single class and this soluble/semisynthetic class is recommended as the focus of testing.

As there are an infinite number of formulations, results from the testing of a single or even multiple formulas will not provide information that is directly applicable to untested formulas. Therefore, the objective of the present testing nomination will be to test the hypothesis that a complex formulation of metal working fluid poses a health hazard that is greater than would be predicted based on toxicological evaluation of the individual constituents. To

adequately test this hypothesis it will be necessary to also determine the toxicity of the constituents.

The following testing strategy is being proposed with the understanding that additional discussion on the type(s) and merit of short-term screening tests of the formulations may be warranted: 1) select ten to twelve of the most widely used formulations of soluble/semi-synthetic fluids (e.g., by product sales or end user purchasing) in which a large number of workers are potentially exposed, 2) identify the constituents of the formulations by chemical class and CAS number, 3) conduct *in vitro* assessment for DNA damage, mutagenicity and possible cell transformation on the formulations and key constituents, 4) rank the formulations and constituents based on outcome of *in vitro* tests, 5) among the top ranking formulations, select two-three that encompass most or all of the constituents of the ten to twelve most commonly used formulations, 6) design and conduct 14 day (possibly 90 day) inhalation studies that assess inflammation, DNA damage or other indicators of cancer potential; similar inhalation tests should be conducted on the constituents of each formulation that are suspect to be contributing to the effects of the formulation, 7) perform a 2-year chronic inhalation bioassay on at least one formulation, 8) evaluate short-term test results of constituents for the need to test individual constituents in 2-year chronic inhalation bioassay.

This is not a novel testing approach. In a review of toxicological methodologies for testing mixtures, it is referred to as the “top down” approach (Feron et al., 1998). That is to say the hazard associated with the mixtures is determined first or independent of the components of the mixture. This contrasts with making inferences about the hazard associated with exposure to a mixture based solely on toxicity of the constituents. There is precedence for this approach in the testing of metal working fluids. Schaper and Detweiler (1991) evaluated the acute respiratory effects of ten different aerosolized metal working fluids in a mouse bioassay. Of the ten, the most potent sensory and pulmonary irritant was evaluated in a follow-up study (Detweiler-Okabayashi and Schaper, 1996). The 12 components, including water, were evaluated in the same bioassay for comparison of effects of the individual constituents to that of the metal worker fluid formulation. While only sensory and pulmonary irritation were evaluated, the experimental design could be expanded to include systemic toxicity and carcinogenesis. For example, Ito et al. (1996) successfully assessed the tumor promoting capacity of a mixture of 20 pesticides at two different doses in an 8-week liver cancer model. Results from the mixture study were compared to known effects of the individual pesticides.

The present nomination for testing a metal working fluid as a complex mixture without explicitly defining the specific formulation at the onset is being submitted in order to provide an opportunity for the NTP to interact with NIOSH in defining a testing protocol and the formulations to be tested. Before proceeding to identifying test formulations, it is important that NTP reviewing and approving committees consider the strengths and weaknesses of the conceptual framework of this nomination and provide recommendations and guidance. To reiterate, the primary objective of this testing nomination is to determine if there is a cancer hazard associated with workplace exposure to presently produced metal working fluids. NIOSH believes the best way to determine this is through chronic testing of metal working fluid formulations.

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## **Nomination of Metal Working Fluids for Testing by the National Toxicology Program**

### **Executive Summary**

The nomination of metal working fluids as a candidate for chronic inhalation NTP studies is based upon their high production volume, the large number of occupationally-exposed workers, and the lack of carcinogenicity and chronic toxicology data for this class of mixtures.

Metal working fluids are a complex mixture of chemicals. The identity and proportion of chemical species in this mixture is dependent on a number of factors including the manufacturer and the cooling and lubrication requirements of the machining process. Moreover, a number of additives such as biocides and anti-foaming agents are added to the metal working fluids to enhance their operational lifespan. Also of considerable concern, an unknown number and amount of contaminants become part of the complex mixture during machining operations. These contaminants can include tramp oils, reaction products such as nitrosamines, and microbial agents such as bacteria and fungi.

Metal working fluids have been used since the early 1900s to prolong the tool life of metalworking equipment [Newhouse 1982]. The Independent Lubricant Manufacturers Association (ILMA) has reported that 95 to 103 million gallons of metal working fluids were produced on an annual basis in the United States for the period from 1994 to 1999 [ILMA 1999]. In 1999, five companies each reported manufacturing greater than 5 million gallons of metal working fluids.

Mineral oil-based metal working fluids were the most predominant lubricating/cooling fluids used during the first three-quarters of the 20th century and most toxicological and epidemiology data are derived from studies with mineral oil-based metal working fluids. Soluble and semi-synthetic metal working fluids have overtaken mineral oils as the most frequently used fluids. Today, metal working fluids are grouped into four major classes: straight oil (mineral oil), soluble, semi-synthetic, and synthetic.

Workers can be exposed to metal working fluids through skin contact by (1) exposure to splashes during immersion or flooding of the machine tool or work, and (2) handling parts, tools, and equipment covered with metal working fluids. Workers also receive a significant exposure to metal working fluids by inhalation of aerosols [Bennett and Bennett 1987]. The National Occupational Exposure Survey [NIOSH 1983] lists an estimated 1.2 million workers who are potentially exposed to agents collectively called metalworking fluids. The majority of all workers potentially exposed to metal working fluids are employed in the industrial categories of machinery (except electrical), fabricated metal products, and transportation equipment.

Somewhat limited information exists about the identity of chemical components of specific metal working fluids because of the highly competitive and proprietary nature of the metalworking industry. A wide variety of chemicals may be used in each of the metal working fluid 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.

Refined petroleum products are used as base oils in all metal working fluids except synthetic fluids. The refined petroleum oils are complex mixtures of hydrocarbons (aromatics, naphthenes, paraffins, and cycloparaffins), metal compounds, and organic compounds containing sulfur, oxygen, and nitrogen. The actual constituents in such refined oils depends on the crude oil and the processing/refining techniques. Among the chemicals of greatest toxicological concern, little chronic effects research has been done with the exception of the ethanalamines and untreated or mildly treated mineral oils. NTP has completed chronic studies in mice and rats treated dermally with diethanolamine or triethanolamine. These studies have raised concern regarding the carcinogenic potential of these chemicals which can make up as much as 25% of metal working fluids prior to dilution with water. There is also strong evidence that untreated or mildly treated mineral oils are human carcinogens, although only highly refined mineral oils are used in modern metal working fluids. Thus, there is considerable concern that the chemical constituents of metal working fluids may pose as a risk for chronic adverse health effects in exposed workers.



Epidemiological evidence has determined that metal working fluids are associated with an increased risk of cancer. Given the small number of epidemiologic studies that have adequate exposure characterization, the specific metal working fluid constituent(s) or contaminant(s) responsible for the various site-specific cancer risks remain to be determined. Studies suggest that specific classes of metal working fluids are associated with cancer at certain sites. The studies that provide the bulk of the evidence suggesting an association between metal working fluid exposure and cancer involve workers employed as early as the 1930s and as late as the mid-1980s. Because there is a latency period of 10 to 20 years between initial exposure to a carcinogen and the initial appearance of a solid-organ cancer caused by that carcinogen, the excess cancer mortality observed in these cohort studies most likely reflects the cancer risk associated with exposure conditions in the mid-1970s and earlier. Over the last several decades, substantial changes have been made in the metalworking industry, including changes in metal working fluid composition, reduction of impurities, and reduction of exposure concentrations. These changes have likely reduced the cancer risks. Yet, the risk of cancer from metal working fluid exposures in the mid-1970s and later remains to be determined, because a definitive study has not yet been conducted on workers entering metal working fluid-exposed jobs during this period. Thus, there is an unclear potential for current metal working fluids to pose a similar carcinogenic hazard.

Contaminants must be also considered in the evaluation of the adverse health effects of metal working fluid aerosols. Certain metals and nitrosamines have been strongly associated with carcinogenic effects and are present in metal working fluids. Efforts have been made to reduce precursors of nitrosamine formation, but these efforts have not eliminated nitrosamines from in-use metal working fluids. Particular concern has focused on the health effects of microbial agents which contaminate virtually all in-use metal working fluids. Bacterial endotoxin has been identified in virtually all poorly maintained in-use metal working fluids and has been strongly implicated in the acute adverse respiratory effects of metal working fluid aerosols. Many other microbial compounds are present in metal working fluids, however, and little research has been done in evaluating their role in chronic adverse health effects. For example, recent outbreaks of hypersensitivity pneumonitis have been linked to microbial contamination of metal working fluids, but identification of the responsible agent is unclear. Clearly, inadvertent contaminants of metal working fluid need further evaluation for chronic adverse health effects.

### **Recommendation and Suggested Studies**

The information provided by toxicology and epidemiology studies has raised many concerns with regard to the chronic effects of metal working fluid exposure on human health. Epidemiology studies and the toxicologic evidence of a carcinogenic potential for certain components of metal working fluids strongly suggest that chronic, life-time studies in mice and rats are necessary. Because the major concern for adverse health effects is via exposure of workers to metal working fluid aerosols, these studies should be conducted by the inhalation route using metal working fluid aerosols with a particle size that is respirable for rodents. Subchronic, 13-week inhalation studies on samples from each of the 4 major classes of metal working fluids should be performed first. Based upon the findings of these subchronic studies, one or more metal working fluid type should be chosen to test in the chronic life-time rodent bioassay. The subchronic inhalation study will also provide a database for determining appropriate exposure concentrations for the chronic study. In addition, because of the positive genotoxicity findings for a number of the chemical constituents of metal working fluids, it is recommended that metal working fluids be examined in an array of *in vitro* genotoxicity studies using standard bacterial and mammalian cell line tests.

The choice of the actual metal working fluid that will be evaluated for each class is made extremely difficult due to the variety of components and different concentrations used by the metal working fluid manufacturers. Because it would be impractical to test several metal working fluids from each manufacturer in each class, two obvious choices would be to: 1) purchase a representative metal working fluid for each class (directly from a manufacturer or 'off the shelf'); or 2) develop and use a

representative fluid for each class. This latter choice would require the cooperation of the metal working fluid manufacturers or their trade associations (e.g., ILMA). Although the percentages and identity of each component may vary among the manufacturers, such an approach would permit the toxicological evaluation of complex metal working fluid mixtures. These 'surrogate' mixtures could be made to closely approximate those currently available for use in machining operations. A similar 'surrogate' approach has been used successfully in the development of a reference cigarette for toxicity studies of total and environmental tobacco smoke.

Finally, a powerful and logical argument can be made for the inclusion of actual in-use metal working fluids in the testing protocols. These in-use fluids better represent the complex mixtures to which individuals are exposed in the workplace. They include the reaction/degradation products of the chemical constituents of metal working fluids, biocides, microbial agents, metals, and contaminating fluids such as tramp oil. Addition of in-use metal working fluids to the testing protocol, although important, would be cumbersome and require significant cooperation from manufacturers. Nevertheless, it is recommended that an effort be made to add an in-use fluid to the chronic bioassay study protocol.

## 1.0 BASIS OF NOMINATION

The nomination of metal working fluids as a candidate for chronic inhalation NTP studies is based upon their high production volume, the large number of occupationally-exposed workers, and the lack of carcinogenicity and chronic toxicology data for this class of complex mixtures.

## 2.0 CHEMICAL PROPERTIES

Metal working fluids are a complex mixture of chemicals. The identity and proportion of chemical species in this mixture is dependent on a number of factors including the manufacturer and the cooling and lubrication requirements of the machining process. In addition, a number of additives are added to the metal working fluids to enhance their operational lifespan. Unfortunately, an unknown number and amount of contaminants also become part of the complex mixture during manufacturing processes.

Mineral oil-based metal working fluids were the most predominant lubricating/cooling fluids used during the first 3/4 of the 20th century. Soluble and semi-synthetic metal working fluids have overtaken mineral oils as the most frequently used fluids. Today, metal working fluids are grouped into four major classes (Table 1):

1. Straight oil metal working fluids are severely solvent-refined petroleum oils (lubricant-base oils) or other animal, marine, vegetable, or synthetic oils used singly or in combination and with or without additives. Straight oils are not designed to be diluted with water. Straight oils (cutting oils) function as lubricants, improve the finish on the metal cut, and prevent rusting [Frazier 1982; CRC 1985]. Depending on the application, the petroleum oils used in straight oil metal working fluids are usually mineral oils from highly refined naphthenic (generally saturated, ring-type structures) or paraffinic oils (straight or branched-chain saturated hydrocarbons) [Bigda and Associates 1980]. The lubricant base oils may also be reprocessed oils from various sources.

Mineral oils may serve as a blending medium or as an additive carrier in straight oils. Mineral oils may be derived from highly refined petroleum stocks or from reprocessed oils of unknown origin. Animal, marine, or vegetable oils may be used singly or in combination with straight oils to increase the wetting action and lubricity [Cookson 1971]. Straight oils containing both fatty oil and sulfur additives provide greater lubricity, whereas those containing sulfochlorinated mineral oils have improved antiweld properties over a wide temperature range. Sulfochlorinated mineral oils with fatty oils added are good for heavy-duty, slow-speed operations [CRC 1985]. ILMA [1996] reports that current formulations have reduced or eliminated the addition of both sulfur and chlorine compounds.

2. Soluble oil (emulsifiable oil) metal working fluids are combinations of 30% to 85% severely refined lubricant-base oils and emulsifiers that may include other performance additives. Soluble oils are diluted with water at ratios of 1 part concentrate to 5-40 parts water. Soluble metal working fluids (emulsions and water soluble oils) cool and lubricate to prevent welding of the cutting tool to the work surface, reduce abrasive wear of the tool at high temperatures, and prevent distortion caused by residual heat [Frazier 1982]. The mineral oils (paraffinic or naphthenic base oils) of soluble metal working fluids are blended from highly refined, high-viscosity oil bases. They contain surface-active emulsifying agents to maintain the oil-water mix as an emulsion [Cookson 1971; Menter et al. 1975]. Superfatted emulsions of soluble metal working fluids are produced by the addition of fatty oils, fatty acids, or esters. Extreme-pressure emulsions for very heavy-duty operations are produced with the addition of sulfur, chlorine, or phosphorus derivatives [CRC 1985].

3. Semi-synthetic metal working fluids contain a lower amount of severely refined lubricant-base oil in the concentrate (5% to 30%), a higher proportion of emulsifiers, and 30% to 50% water. The transparent concentrate is diluted with 10 to 40 parts water. Semi-synthetic metal working fluids may be

formulated with fatty acids, sulfur, chlorine, and phosphorus derivatives to provide lubrication for higher speeds and feed rates [CRC 1985].

4. Synthetic metal working fluids contain no petroleum oils and may be water soluble or water dispersible. The synthetic concentrate is diluted with 10 to 40 parts water. The simplest synthetics are made with organic and inorganic salts dissolved in water. They offer good rust protection and heat removal but usually have poor lubricating ability. Others may be formulated with synthesized hydrocarbons, organic esters, polyglycols, phosphate esters, and other synthetic lubricating fluids [CRC 1985]. Synthetics are stable, can be made bioresistant [Passman 1992], and provide effective cooling capacity at high speeds and feeds. They eliminate smoking, reduce misting, and provide detergent action and oxidative stability [Vahle 1982].

### **2.1 Deterioration and Contamination of MWFS during Use**

Physical, chemical, and microbial effects can cause the chemical components of in-service metal working fluids to deteriorate. Contaminants such as wear debris, rust, weld spatter, lint, metal chips and abrasives, as well as contaminants entering through broken seals, dirty oil filter pipes, chemical residue on metal parts, or the addition of incorrect additives can accelerate metal working fluid breakdown. Depending on the alloy being machined and the machining process, metal particles or dissolved metal will contaminate the metal working fluids. Machining or parts manufacture includes a variety of process operations during which process chemicals and ancillary lubricants can contaminate the metal working fluids. Industrial lubricants and in-process cleaners may leak into or be carried by parts being machined and contaminate the fluids. The industrial lubricants that are used around machine tools and that may leak into and contaminate the metal working fluids are referred to as tramp oils. These tramp oils include hydraulic oils, spindle oils, slidway lubricants, greases, and wire rope lubricants.

Additionally, oil may degrade from excessive temperatures. The oxidation of metal working fluid oils and constituents can lead to the formation of acids, resins, varnishes, sludges, and carbonaceous deposits. Additives such as biocides and anticorrosives may be depleted with use, requiring routine product addition or supplemental additions to maintain metal working fluid performance.

### **2.2 Microbial Contamination**

Additional contaminants from the working environment such as food scraps, floor sweepings, cigarette butts, etc. can cause changes in metal working fluids. Historically, microbial contamination of metal working fluids has been a problem in the metalworking industries, primarily because of potential adverse health effects and microbial growth effects on fluid quality and performance. Fluid degradation from microorganisms may result in changes in fluid viscosity, and the acid products of fermentation may lower the pH of the fluids, causing corrosion and leaks in the metal working fluid 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. More importantly, the microbial contaminants may result in adverse health effects in workers exposed to metal working fluid aerosols.

Water-based metal working fluids are excellent nutritional sources for many kinds of bacteria and fungi. The predominant microbial species routinely recovered from metal working fluids 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 metal working fluid 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. For example, 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.

### **3.0 PRODUCTION VOLUMES**

Metal working fluids were first used in the early 1900s to prolong the tool life of metalworking equipment [Newhouse 1982]. The Independent Lubricant Manufacturers Association (ILMA) has reported that 95 to 103 million gallons of metal working fluids were produced on an annual basis in the United States for the period from 1994 to 1999 [ILMA 1999]. In 1999, five companies each reported manufacturing greater than 5 million gallons.

### **4.0 USES**

Metal working fluids (a.k.a. cutting oils, machining fluids, lubricants, and coolants) reduce friction between the cutting tool and the work surface, reduce wear and galling, protect surface characteristics, reduce surface adhesion or welding, carry away generated heat, and flush away swarf, chips, fines, and residues [Nachtman and Kalpakjian 1985]. Metal working fluids are designed for use in various machining operations such as turning, grinding, boring, tapping, threading, gear shaping, reaming, milling, broaching, drilling, hobbing, and band and hack sawing [Weindel 1982]. Metal working fluids can be manually applied to the cutting zone of the tool and the work or delivered as a mist in a high-velocity air stream. A continuous stream of metal working fluid delivered by a low-pressure pump can be directed through a nozzle to the cutting edge of the machine tool or through the tool and over the work to carry away the metal chips or swarf. A variety of fluid nozzle designs are available, depending on the application needed [Smits 1994]. A distribution system may be used to control metal working fluid flow volume and flow pressure. The metal working fluid recirculating system and sump can be complex and may contain large amounts (over 100,000 gallons) of metal working fluids. The metal working fluids are routinely collected through gravity flow, velocity flow, or conveyORIZED trenches. They are then recirculated to the cutting zone of the machine tool through filtration systems, chip-handling conveyors, belt skimmers or decantation tanks (to remove contaminating substances such as tramp oils), and chillers or plate-and-frame heat exchangers.

### **5.0 HUMAN EXPOSURES**

#### **5.1 Exposure Categories**

Workers can be exposed to metal working fluids through skin contact by (1) exposure to splashes and aerosols during immersion or flooding of the machine tool or work, and (2) handling parts, tools, and equipment covered with metal working fluids. Workers may also be exposed to metal working fluids by inhalation of aerosols [Bennett and Bennett 1987]. During machining of parts, workers are exposed by metal working fluids flow through fluid circulation systems, air cleaners in a recirculating local exhaust ventilation system, adjacent operations, and persistence of fugitive emissions in workroom air. The National Occupational Exposure Survey [NIOSH 1983] lists an estimated 1.2 million workers who are potentially exposed to agents collectively called metalworking fluids in 39 industry codes (2-digit Standard Industrial Classification [SIC] Codes). Approximately 70% of all workers potentially exposed to metal working fluids were employed in the industrial categories of machinery (except electrical), fabricated metal products, and transportation equipment.

Since 1967, NIOSH has conducted more than 70 health hazard evaluations (HHEs) of industries with occupational exposures to metal working fluids or mineral oil aerosols. Skin disorders (skin irritation, eczema, rashes, oil acne) were the most frequently reported health problems, followed by complaints of eye, nose, and throat irritation (mucous membrane irritation) and respiratory symptoms or disorders (breathing problems, cough, chest tightness, asthma).

## 5.2 Exposure Levels

Exposure data from 38 HHEs indicate that airborne metal working fluid exposures have generally decreased over time. The arithmetic mean personal exposure concentrations (total particulate mass) were 1.23 mg/m<sup>3</sup> (n=21 plants) in the 1970s, 0.57 mg/m<sup>3</sup> in the 1980s (n=15 plants), and 1.0 mg/m<sup>3</sup> in the 1990s (n=2 plants). The latter increase is based on only two plants. The overall mean concentration for the 38 plant-based HHEs was 0.96 mg/m<sup>3</sup>. The exposure data collected at these 38 plants show airborne concentrations similar to those in the OSHA IMIS data set. These two data sets indicate an overall reduction in airborne metal working fluid exposures since 1980.

In the automotive industry, Kriebel et al. [1994], Greaves et al. [1995a,b; 1997], and Robins et al. [1994] have examined the respiratory effects and associated metal working fluid airborne exposures for component manufacturing workers. All three investigators reported an arithmetic mean metal working fluid airborne exposure concentration of <1.0 mg/m<sup>3</sup>. Kriebel et al. [1994] reported mean exposure concentrations of 0.24 mg/m<sup>3</sup> (total aerosol mass, 7-hole sampler) for straight oil metal working fluid aerosols and 0.22 mg/m<sup>3</sup> for soluble oil metal working fluids. Greaves et al. [1995a,b; 1997] reported similar concentrations with mean concentrations (thoracic fraction) for several plant surveys. The mean concentration ranged from 0.2 to 0.68 mg/m<sup>3</sup> for straight oil metal working fluids, from 0.35 to 0.65 mg/m<sup>3</sup> for soluble oil metal working fluids, and 0.41 mg/m<sup>3</sup> for synthetic fluids. Likewise, Robins et al. [1994] reported soluble metal working fluid exposures for automotive parts manufacturing workers of 0.1 to 0.6 mg/m<sup>3</sup> (thoracic fraction). Airborne metal working fluid concentrations significantly declined during the period 1958-87, with an arithmetic mean concentration of 5.42 mg/m<sup>3</sup> (total aerosol mass) observed before 1970 and 1.82 mg/m<sup>3</sup> after 1980 [Hallock et al. 1994]. The three data sources (OSHA IMIS, NIOSH HHEs, and the epidemiologic studies mentioned earlier [Kriebel et al. 1994; Greaves et al. 1995a, 1997; Robins et al. 1994, 1997; Sprince et al. 1997]) suggest that the average airborne aerosol exposures in the 1990s are lower (<1.0 mg/m<sup>3</sup>) than the 1.8 mg/m<sup>3</sup> aerosol exposures recorded for the 1980s by Hallock et al. [1994].

## 6.0 POTENTIALLY HAZARDOUS COMPONENTS

Only limited information exists about the chemical components of specific metal working fluids because of the highly competitive and proprietary nature of the metalworking industry. A wide variety of chemicals may be used in each of the metal working fluid 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. Because it is beyond the scope of this document to identify and characterize all chemicals in metal working fluids, information on several selected components are presented below. These potentially hazardous components include chemicals which are added to the metal working fluids for a particular purpose as well as chemical and microbial factors which contaminate the fluids during use.

### 6.1 Chemical Ingredients/Additives

#### 6.1.1 Ethanolamines

Alkanolamines or ethanolamines (triethanolamine (TEA), diethanolamine (DEA), and monoethanolamine (MEA)) may be used in metal working fluids to stabilize pH or inhibit corrosion. Typically, metal working fluids contain 2% to 3% MEA or DEA and up to 25% TEA. ILMA has recommended using metal working fluids with 5% MEA or DEA and up to 25% TEA to calculate exposure risk [CMA 1996]. A typical 10:1 dilution of bulk metal working fluid 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 metal working fluids [CMA 1996].

There has been considerable concern regarding the carcinogenic potential for TEA or DEA and that TEA may cause occupational asthma. The National Cancer Institute nominated triethanolamine for

study by NTP because of its widespread use in consumer products, its high potential for worker exposure due to its many industrial uses, and its potential for conversion to the carcinogen N-nitrosodiethanolamine. Dermal application was chosen as the route of exposure to mimic a principal means of human exposure to triethanolamine and because considerable systemic exposure is achieved with this route. Male and female F344/N rats and B6C3F1 mice received triethanolamine (purity 98% or greater) by dermal application for 2 years. Under the conditions of these dermal studies, there was equivocal evidence of carcinogenic activity of triethanolamine in male F344/N rats based on a marginal increase in the incidence of renal tubule cell adenoma. There was no evidence of carcinogenic activity in female F344/N rats receiving 63, 125, or 250 mg triethanolamine per kilogram body weight. The study in male and female B6C3F1 mice was considered inadequate, because the presence of a *Helicobacter hepaticus* infection complicated interpretation of the relationship between triethanolamine administration and liver neoplasms in these animals.

Diethanolamine was also studied by NTP. Under the conditions of a 2-year dermal studies, there was no evidence of carcinogenic activity of diethanolamine in male or female F344/N rats administered 8 to 64 mg/kg diethanolamine. However, there was clear evidence of carcinogenic activity of diethanolamine in male and female B6C3F1 mice based on increased incidences of liver neoplasms in males and females and increased incidences of renal tubule neoplasms in males. Based upon these dermal findings, there is concern regarding the carcinogenic potential of ethanolamines if delivered via the inhalation route of exposure.

### **6.1.2 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 has been reported to result from long-term exposure of workers to the poorly or nonrefined mineral oils used before the 1950s [Jarvholm et al. 1985; Jarvholm and Easton 1990; Cruickshank and Gourevitch 1952; Waldron 1983]. Water-based MWFs have not been associated with scrotal cancer - no cases were observed among the grinders who often use soluble oils [Jarvholm 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 [Jarvholm 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, based upon their findings that 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, whereby the evidence for carcinogenicity to animals is sufficient for untreated and mildly treated oils and inadequate for highly refined oils [IARC 1987a].

### **6.1.3 Antimicrobial Agents**

Antimicrobial agents are incorporated as components in formulated metal working fluids or added to metal working fluids 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 2 lists antimicrobial agents commonly used in metal working fluids. 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 1993]. 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 concentration of formaldehyde released in MWFs has not been thoroughly studied. Formaldehyde is an OSHA-regulated carcinogen [29 CFR 1910.1048] and 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 1988a].

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. 1989a]. Sodium 2-pyridinethiol-1-oxide and o-phenyl phenol are examples of non-formaldehyde-releasing biocides.

Nitrated antimicrobial agents such as Bronopol (2-bromo-2-nitro-1,3-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 metal working fluids. 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 metal working fluid concentrate can directly form N-nitrosomorpholine (NMOR) (an animal carcinogen [IARC 1978a]), which can increase in concentration over time [Mackerer 1989]. Whether this action could result in any measurable worker exposure is unclear.

#### **6.1.4 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 piece and work to prevent destructive welding, excessive metal transfer, and surface breakdown [Nachtman and Kalpakjian 1985].

The National Cancer Institute (NCI) selected long-chain chlorinated paraffins (C23, 43% chlorine; a mixture of C22-26 chlorinated paraffins, with an average chain length of C23) and short-chain chlorinated paraffins (C12, 60% chlorine; a mixture of C10-12 chlorinated paraffins with an average chain length of C12) 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 (C23, 43% chlorine) in male B6C3F1 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 EPA 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 (C12, 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 B6C3F1 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].



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

## **6.2 Hazardous Contaminants**

Exposure to hazardous contaminants in metal working fluids 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 metal working fluids to hazardous end products as well as elaborate endotoxins, exotoxins, and tissue-damaging enzymes. A few selected chemical and biological contaminants of metal working fluids are discussed in the following subsections.

### **6.2.1 Nitrosamines**

Potentially carcinogenic nitrosamines have been identified in metal working fluids studied in the 1970s and early 1980s. The formation and concentration of nitrosamines in metal working fluids 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 metal working fluid, (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 the conditions of 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 1978b; 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 metal working fluids 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 metal working fluids containing sodium nitrite and DEA or TEA [Jarvholm et al. 1986; Spiegelhalter 1980]. Fan et al. [1977] reported 0.02% to 3% concentrations of NDELA contamination in several unused synthetic metal working fluids 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 metal working fluids 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 metal working fluids 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. Importantly, however, some studies have shown that nitrosamines may form in metal working fluids that contain TEA or DEA even though nitrites have not been added [Challis et al. 1978].

IARC has classified N-nitrosodiethylamine (NDEA) and NDMA as 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].

### **6.2.2 Microbial Contamination**

Although frankly pathogenic organisms such as Salmonella, Staphylococcus, and Legionella have been isolated from metal working fluids [Hill and Al-Zubaidy 1979; Herwaldt et al. 1984], most of the organisms associated with metal working fluids are characterized either as nonpathogens or as opportunistic pathogens (those that primarily infect persons with a major abnormality in their natural defenses).

The bacterial genus most commonly isolated from metal working fluids is Pseudomonas (*P. aeruginosa* and *P. oleovorans*). Despite the frequency and severity of Pseudomonas infections in susceptible persons, healthy adults with intact immunity are rarely affected. No reports have been published of work-related Pseudomonas infections in metal working fluid workers. One study of a worksite with a demonstrated viable count of  $1 \times 10^8$  colony-forming units per ml of metal working fluid showed no evidence of Pseudomonas colonization of the workers' respiratory tracts, even though the organisms were cultured from the metal working fluid [Hill and Al-Zubaidy 1979]. It is likely that organisms are rapidly cleared from the lungs of healthy persons. Other bacteria identified to contaminate metal working fluids include Klebsiella pneumoniae, Micrococcus pyogenes (now Staphylococcus aureus), Escherichia coli, Proteus vulgaris, Aerobacter (now Enterobacter) aerogenes, and members of the Citrobacter and Achromobacter genera.

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., hypersensitivity pneumonitis, also known as extrinsic allergic alveolitis). Interest has focused on the possible involvement of microbial antigens in recent clusters of hypersensitivity pneumonitis among workers exposed to metal working fluid aerosols in operations using synthetic and soluble oil metal working fluids [Kreiss and Cox-Ganser 1997]. However, the cause of hypersensitivity pneumonitis in metal working fluid-exposed workers may not be limited to bacterial antigens (see Section 7.1.1).

Endotoxins are heat-stable lipopolysaccharide-protein complexes contained in the cell envelopes of all gram-negative bacterial 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]. Metal working fluids that have high levels of gram-negative bacteria also have high levels of endotoxins [Mattsby-Baltzer et al. 1989a; Milton et al. 1990].

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; Gordon and Galdanes 1999; 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 metal working fluids 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 metal working fluid aerosols [Hill and Al-Zubaidy 1979; Hill 1983; Kennedy et al. 1989; Mattsby-Baltzer et al. 1989b; Gordon 1992; Sprince et al. 1994; Robins et al. 1997].

Fungi (yeasts and molds) also contaminate water-based or water-contaminated metal working fluids. Generally, the fungi isolated from metal working fluids are common saprophytic species that live on decaying organic matter in the environment and are not usually the major microbial contaminant in

metal working fluids. Although no reports have been published about fungal diseases from contaminated metal working fluid exposures, some known health hazards are associated with fungi exposure. Given the opportunity, fungi may infect susceptible hosts (such as immunocompromised persons) or may cause allergic disease in persons previously sensitized. *Cephalosporium*, a genus commonly isolated from metal working fluids, has reportedly caused hypersensitivity pneumonitis in exposed persons [Patterson et al. 1981]. *Penicillium* and *Aspergillus* species, have likewise been implicated in hypersensitivity pneumonitis and both are common metal working fluid contaminants. In addition, several fungal species isolated from metal working fluids are known to cause allergic reactions including asthma, but the relationship between fungal contamination and occupational asthma associated with metal working fluid exposures is uncertain.

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

### **6.2.3 Metals and Metal Alloy Contaminants**

Depending on the type of metal working fluid, the grinding or machining process and tools, and the metals or alloys being machined, metals may dissolve into the metal working fluid. 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 metal working fluid. Higher metal working fluid 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 metal working fluids include lead from leaded steel, aluminum, and 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 metal working fluids [Kennedy et al. 1995a].

## **7.0 OCCUPATIONAL HEALTH RISKS**

### **7.1 Nonmalignant Chronic Respiratory Effects**

Occupational exposure to MWF aerosols is associated with a variety of nonmalignant respiratory conditions. The major known adverse effects are discussed below.

#### **7.1.1 Hypersensitivity Pneumonitis**

Hypersensitivity pneumonitis, also known as extrinsic allergic alveolitis, involves an immunologic reaction to inhaled antigen and is believed to require prior sensitization to the antigen. This disease is characterized in its acute phase by alveolar inflammation and influenza-like symptoms. In its chronic phase (following repeated exposures), it is characterized by pulmonary fibrosis associated with respiratory impairment. Common antigens associated with hypersensitivity pneumonitis in nonmetalworking occupational settings include airborne microbes (especially bacterial spores of *Saccharopolyspora* spp., spores of *Thermoactinomyces* spp., fungal spores of *Alternaria* and *Aspergillus* spp., and various large-molecular-weight compounds, including proteins). Two cases of hypersensitivity pneumonitis associated with metal working fluids were reported during a 3-year period to an occupational respiratory disease surveillance program operating in the United Kingdom [Meredith and McDonald 1994]. Many more cases in North America have been recently recognized [Rosenman et al. 1994; Bernstein et al. 1995; Rose et al. 1996; Kreiss and Cox-Ganser 1997]. Until these recent cases, this lung parenchyma disease appeared to have been relatively unusual in workers exposed to metal working fluid aerosols. However, hypersensitivity pneumonitis has generally not been systematically studied among workers exposed to metal working fluid aerosols, and the recent emergence of hypersensitivity pneumonitis-like disease associated with metal working fluid aerosol and the large numbers of workers exposed justify considerable concern [Blanc 1995; Kreiss and Cox-Ganser 1997]. It is possible that

hypersensitivity pneumonitis has been occurring in metal working fluid-exposed workers for many years but has not been detected because hypersensitivity pneumonitis is sometimes difficult to diagnosis and has only recently been targeted for study among workers exposed to metal working fluid. However, it is also possible that recent changes in the work environment, fluid composition, or biocide use have increased the risk of hypersensitivity pneumonitis among these workers [Kreiss and Cox-Ganser 1997].

### **7.1.2 Asthma**

In general, concerns about the respiratory hazards of occupational exposure to metal working fluid aerosols have focused on conducting airways disorders even more than on hypersensitivity pneumonitis. A variety of components, additives, and contaminants of metal working fluid are sensitizers or irritants known to induce new-onset asthma, aggravate pre-existing asthma, or irritate the airways of nonasthmatic workers. These sensitizers, irritants, or toxicants include ethanalamine and other amines, colophony, pine oil, tall oil, metals and metallic salts (e.g., chromium, nickel, cobalt, and tungsten carbide), castor oil, formaldehyde, chlorine, various acids, and fungal and other microbial contaminants (including gram-negative bacterial endotoxin) [Chan-Yeung and Malo 1993; Hendy et al. 1985; Kennedy 1992; Michel et al. 1992]. However, only a few of these agents have been carefully documented as causes of metal working fluid-associated asthma.

Considered in aggregate, several studies provide evidence indicative of an elevated risk of asthma among workers exposed to metal working fluid aerosol exposure concentrations currently found in large metalworking shops. As suggested by published clinical case reports, asthma induced by metal working fluids appears to involve known sensitizers in some cases; but various other agents, possibly acting through irritant or inflammatory mechanisms, may be responsible for a high proportion of metal working fluid-associated asthma cases. Some evidence from cross-sectional studies strongly suggests a tendency for affected workers to transfer away from jobs with exposure to metal working fluid.

With respect to metal working fluid type, exposure to metal working fluid aerosols in operations using synthetic metal working fluids has been associated with asthma [Rosenman et al 1997b; Greaves et al 1995b; Eisen et al 1997]. There is also evidence suggesting a causal association between asthma and exposure to soluble metal working fluid aerosols, but it is somewhat less consistent than that for synthetic metal working fluid exposures. Case reports have documented asthma caused by exposure to soluble oil metal working fluid [Hendy et al. 1985; Robertson et al. 1988] or to common components of soluble oil metal working fluids [Savonius 1994]. A surveillance program in Michigan received 13 case reports of occupational asthma attributed to soluble oil metal working fluids during 1988-94 [Rosenman et al. 1997b], although some of the plants in which these cases worked may have also been using straight oil metal working fluid. Of the seven relevant epidemiologic studies, results consistent with statistically significant elevated risk estimates were presented only by Greaves et al. [1995b, 1997] (for cumulative exposure) and Rosenman et al. [1997b]. Findings of three of the other five studies indicated elevated, though not statistically significant, risk estimates for asthma, with point estimates ranging upward from 2.1 [Kriebel et al. 1994, 1997; Robins et al. 1994, 1997; Massin et al. 1996]. Thus, the overall evidence also suggests an association between asthma and exposure to straight oil metal working fluid aerosol [Rosenman et al 1997b; Forbes and Markham 1967; Robertson et al. 1988].

### **7.1.3 Symptoms of Airways Disorders**

With the exception of one early study [Ely 1970], epidemiological studies of respiratory symptoms present generally consistent and, in the case of the more recent studies, compelling epidemiologic evidence indicating that occupational exposure to metal working fluid aerosols causes symptoms consistent with airways irritation, chronic bronchitis, and asthma. The evidence suggests that at least 3 classes of metal working fluids (straight oil, soluble oil, and synthetic) are capable of inducing respiratory symptoms at metal working fluid aerosol exposure concentrations that are currently typical of large metalworking shops. To date, there is no convincing evidence that identifies any particular

component or components of MWF aerosol as the predominant cause of these symptoms, although some irritant components of metal working fluid are clearly suspect [Sprince et al. 1997]. One recent, large multiplant study in the U.S. (with mean exposures for the major types of metal working fluids ranging from 0.41 to 0.55 mg/m<sup>3</sup> [thoracic fraction]), found statistically significant quantitative exposure-response relationships between cumulative concentration of metal working fluid aerosols and respiratory symptoms [Greaves et al. 1995b, 1997]. Likewise, another U.S. study found significant exposure-response relationships between aerosol exposure concentration and chest symptoms [Sprince et al. 1997]. In addition, the onset or worsening of many symptoms over a work shift [Kriebel et al. 1994; Sprince et al. 1997; Rosenman et al. 1997b], and the reported substantial symptomatic improvement experienced by many affected workers when away from work [Greaves et al. 1995b, 1997]. Thus, controlling worker exposures can prevent chronic effects induced by metal working fluid aerosol exposure and may reverse early metal working fluid-induced airways effects.

#### **7.1.4 Cross-Sectional Studies of Lung Function**

Whereas occupational exposure to metal working fluid aerosols is associated with reduced pulmonary function, results of cross-sectional studies of lung function generally parallel those from studies of respiratory symptoms among workers exposed to metal working fluid aerosols. Although the observed reductions in pulmonary function may, in part, be acute and reversible, their stronger relationship with past exposures than with current exposures [Greaves et al. 1995a] suggests that they may well be substantially chronic and irreversible. The observed adverse lung function effects are attributable to straight oil, soluble oil, and synthetic metal working fluids at exposure concentrations recently observed in large metalworking shops. Moreover, evidence from the largest study [Greaves et al. 1995a] involving several different plants using three different major types of metal working fluids at mean aerosol exposures ranging from 0.41 to 0.55 mg/m<sup>3</sup> (thoracic fraction) suggests that the pulmonary function effects associated with cumulative exposure to metal working fluid aerosols occur in a dose-related manner. Some pulmonary function evidence suggests possible interaction between smoking and exposure to metal working fluid aerosol in reducing lung function [Ameille et al. 1995]. Although the actual degree of self-selection away from metal working fluid exposure by affected individuals is not known, such a phenomenon would bias cross-sectional studies toward underestimating the effects of exposure. The lack of association between metal working fluid aerosol exposure and lung function observed in some studies may be attributable to such selection, to statistical power limitations related to study size, to aerosol concentration, to exposure duration, and/or to MWF aerosol composition.

### **7.2 Malignant Health Effects**

#### **7.2.1 Carcinogenic Effects in Animals**

Few animal data have been published on the tumorigenicity of metal working fluids. Six animal studies have examined the tumorigenicity of metal working fluids [Gilman and Vesselinovitch 1955; Desoille et al. 1973; Jepsen et al. 1977; Wang and John 1988; Gupta and Mehrotra 1989; McKee et al. 1990]. Three of these studies reported only findings related to the skin [Gilman and Vesselinovitch 1955; Jepsen et al. 1977; Gupta and Mehrotra 1989]. Of these three studies, one examined unrefined cutting oil [Gilman and Vesselinovitch 1955], one examined solvent-extracted cutting oil [Jepsen et al. 1977], and the third study did not specify how the cutting oil was refined (although the cutting oil was probably highly refined, as the PAH content was only 5.22%) [Gupta and Mehrotra 1989]. The study by Gilman and Vesselinovitch [1955] found that among mice receiving a skin application of soluble cutting oils formulated from unrefined distillates three times weekly for 310 days, 61% developed skin tumors (of whom 22% had carcinomas) compared with no tumors present in the unexposed control group. Jepsen et al. [1977] found that among mice receiving skin applications of solvent-extracted cutting oils, 80% and 0% of mice developed papillomas after exposure to undiluted and diluted soluble oil, respectively. Jepsen

et al. [1977] also studied paraffin-based and naphthalene-based straight oil metal working fluids. They found that 45% and 0% of mice developed papillomas after exposure to unused and used paraffin-based solvent-refined straight oil metal working fluid (level of refining unspecified), respectively. They also found that 40% and 100% of mice developed papillomas after exposure to unused and used naphthalene-based straight metal working fluid (level of refining unspecified), respectively. Another study found that both unused and used cutting oils were potent skin tumor initiators [Gupta and Mehrotra 1989]. These investigators found that among mice given a single application of the cutting oil and three times weekly application of a promoting agent (12-0-tetradecanoyl-phorbol 13-acetate [TPA]), 90% and 60% of mice developed benign skin tumors after exposure to unused and used cutting oil.

Three other animal studies examined the tumorigenic effects of metal working fluid exposure on the skin and other organs [Desoille et al. 1973; Wang and John 1988; McKee et al. 1990]. One study of 20 mice receiving a skin application of used cutting oils (type of refining was not specified) one to three times weekly for 6 months found that two developed pulmonary cancer, and one of the two mice also developed skin cancer [Desoille et al. 1973]. None of the 20 control mice developed cancer. In another animal study, pancreatic carcinoma was found in 9 of 40 Wistar rats orally given undiluted rust-proof cutting fluid consisting of sodium nitrite, TEA, and polyethylene glycol for 2 years, whereas none of the 40 control rats developed pancreatic cancer ( $P < 0.01$ ) [Wang and John 1988]. All three of the components reported to be in the rust-proof cutting fluid (sodium nitrite, TEA, and polyethylene glycol) are components that can be found in some metal working fluids used in the United States. Finally, one other study found no evidence of carcinogenicity from solvent-extracted cutting oils [McKee et al. 1990].

The animal data are limited in the types of metal working fluids tested and the outcomes examined. The variety and complexity of metal working fluids are immense. Even within general classes of metal working fluids, one can find a wide variety in terms of composition and component concentration. Specific components (e.g., DEA, TEA, nitrosamines, and formaldehyde), however, have been evaluated for carcinogenic potential on an individual basis. Understandably, it would be difficult to select representative samples of metal working fluids for use in animal studies whose findings could be generalized to a wide variety of metal working fluids. To add to the complexity, chronic application of unused metal working fluids in animal studies would not be representative of worker exposure to in-use fluids. In conclusion, there is inadequate animal evidence for the carcinogenicity of metal working fluids currently in use. Because the carcinogenic activity of individual metal working fluids depends on the severity of processing of the base oils, and because of the nature and concentration of additives and contaminants and the conditions of use, the existing animal data have provided only limited utility in interpreting the human epidemiology data.

### **7.2.2 Carcinogenic Effects in Workers**

Substantial evidence exists for increased risk of cancer at several sites (larynx, rectum, pancreas, skin, scrotum, and bladder) associated with at least some of the metal working fluids used before the mid-1970s. The inconsistencies between studies with respect to the organ sites that were affected, and the variation in the strength of association between the surrogates of exposure and specific sites are most likely related to the diverse nature of metal working fluid mixtures studied, the absence of detailed exposure information, and the limitations of the epidemiologic tools with which metal working fluid exposures have been studied. The evidence is equivocal for an association between metal working fluid exposure and cancer at several other sites, including the stomach, esophagus, lung, prostate, brain, colon, and hematopoietic system.

As described earlier, there are four classes of metal working fluids. The types and amounts of chemical constituents can vary across these classes. Furthermore, within each class are many formulations that vary in composition and may contain many different additives and impurities. Some metal working fluid constituents are considered carcinogenic in animals (including N-nitrosamines [IARC 1978b] and PAHs [IARC 1983]). Efforts to reduce these potential carcinogenic exposures have been ongoing. Removal of PAHs from metal working fluids began in the 1950s, and EPA regulations in

the 1980s were directed at reducing nitrosamine exposures. Because different epidemiologic study populations may have been exposed to different classes and formulations of cutting fluids, some lack of consistency in site-specific results between studies should be expected when evaluating the carcinogenicity of these substances. Similarly, when comparing studies with limited information about the intensity of exposure, we would expect variation in the strength of association between exposure and the risk of cancer.

Given the small number of epidemiologic studies that have adequate exposure characterization, the specific metal working fluid constituent(s) or contaminant(s) responsible for the various site-specific cancer risks remain to be determined. The study with the most statistical power and detailed exposure information [Tolbert et al. 1992] suggests that specific classes of metal working fluids are associated with cancer at certain sites. However, within these metal working fluid classes, the specific formulations responsible for the elevated cancer risks remain to be identified. Within the Tolbert et al. [1992] study, straight oil exposure was modestly associated with an increased risk for laryngeal and rectal cancer, and there was limited evidence that synthetic oil metal working fluid exposure was associated with an increased risk for pancreatic cancer. Subsequent case-control studies based on the original cohort have confirmed the association of laryngeal cancer with straight oil metal working fluid [Eisen et al. 1994], and the association of pancreatic cancer with synthetic metal working fluid [Bardin et al. 1997]. The Tolbert et al. study found less evidence that soluble oil exposure is associated with cancer at any specific site. Yet, it is premature to conclude that all members of the soluble oil class of metal working fluids were free from carcinogenic risks in the past, since soluble metal working fluids contain many of the ingredients found in straight oil metal working fluids but in different concentrations. Also, many of the epidemiologic studies with positive findings involved exposures to more than one class of metal working fluid.

Non-metal working fluid exposures are unlikely to be responsible for the cancer findings described in this chapter. Smoking and alcohol are associated with some of the cancers observed to be associated with metal working fluid exposure. However, most of the case-control studies controlled for these exposures when appropriate or determined that these exposures were unlikely confounders. Although information about these lifestyle factors are not often collected in occupational cohort mortality or PMR studies, it has been demonstrated that smoking is unlikely to account for RRs >1.3 for lung cancer and other smoking-related diseases [Siemiatycki et al. 1988]. Non-metal working fluid occupational exposures are unlikely to explain the majority of findings, as the common exposure across all of the studies was metal working fluid. Although some non-metal working fluid exposures may have interacted synergistically with metal working fluid exposure to produce some of the observed risks, the existence or extent of such synergism remains to be determined.

The studies that provide the bulk of the evidence suggesting an association between metal working fluid exposure and cancer involved workers employed as early as the 1930s and as late as the mid-1980s. Because there is a latency period of 10 to 20 years between initial exposure to a carcinogen and the initial appearance of a solid-organ cancer caused by that carcinogen, the excess cancer mortality observed in these cohort studies most likely reflects the cancer risk associated with exposure conditions in the mid-1970s and earlier. Over the last several decades, substantial changes have been made in the metalworking industry, including changes in metal working fluid composition, reduction of impurities, and reduction of exposure concentrations. These changes have likely reduced the cancer risks. However, since the epidemiologic data do not usually identify the metal working fluid composition and impurities associated with the cancer risks observed in earlier cohorts, there is insufficient data to conclude that these changes will have eliminated all carcinogenic risks. The risk of cancer from metal working fluid exposures in the mid-1970s and later remains to be determined because a definitive study has not yet been conducted on workers entering metal working fluid-exposed jobs during this period. Thus, there is an unclear potential for current metal working fluids to pose a similar carcinogenic hazard.

### **7.2.3 Genetic Effects**

Only one epidemiologic study was identified that examined genotoxicity among workers exposed to metal working fluid [Fuchs et al. 1995]. In a German study of 65 male metal workers exposed to synthetic metal working fluids in seven small-to medium-sized plants, those who worked in areas having a NDELA concentration greater than 500 ng/m<sup>3</sup> had a significantly ( $p < 0.01$ ) elevated mean number of DNA strand breaks in mononuclear blood cells compared with workers employed in areas with less than 50 ng/m<sup>3</sup> NDELA ( $1.69 \pm 0.34$  workers versus  $0.76 \pm 0.05$ , respectively) [Fuchs et al. 1995]. The average concentration of NDELA present in the cutting fluids at these plants was 20.6 ppm (range 2 - 135 ppm). In addition, nonsmokers who worked more than 4.5 hr/day had a significantly elevated mean number of DNA strand breaks compared with nonsmokers who worked less than 4.5 hr/day ( $1.34 \pm 0.12$  versus  $0.91 \pm 0.12$  respectively,  $p < 0.02$ ). Airborne concentrations of metal working fluids were not reported. NDELA is a contaminant that may be present in some metal working fluids and can be formed in metal working fluids when DEA or TEA reacts with a nitrosating agent (e.g., nitrite). This study provides evidence that nitrosamine exposure may be genotoxic. However, in 1984, EPA prohibited the addition of nitrosating agents to metal working fluids.



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**Table 1. Components of the four MWF classes (undiluted)\***

Component	Function	Amount			
		Straight oils	Soluble oils	Semisynthetic s	Synthetics
Water	Acts as coolant solvent, diluent	Dissolved 10–500 ppm/ wt <sup>†</sup>	5–40 parts/ 1 part concentrate	10–40 parts/ 1 part concentrate	10–40 parts/ 1 part concentrate
Mineral oil	Carries lubrication	60%–100%	30%–85%	5%–30%	‡
Emulsifier	Emulsifies	‡	5%–20%	5%–10%	5%–10%
Chelating agents	Tie up ions in solution	‡	0%–1%	0%–1%	0%–1%
Coupling agents	Stabilize	‡	1%–3%	1%–3%	1%–3%
Viscosity index improvers	Maintain viscosity	§	‡	‡	‡
Detergent	Prevents deposit formation	§	§	§	§
Plasticizer	Reduces tackiness	‡	§	§	§
Antimist agent	Reduces misting	§	§	‡	‡
Antiweld agent	Prevents welding	0%–20%	0%–20%	0%–10%	0%–10%
Oiliness agent	Increases film strength	§	‡	‡	‡
Surfactant wetting agent	Reduces surface tension	0%–10%	5%–20%	10%–20%	10%–20%
Dispersants	Prevent fine agglomeration and deposit formation	§	‡	‡	‡
Passivator	Prevents staining	§	‡	‡	‡
Anti-foaming agents	Prevent foaming	0–500 ppm	0–500 ppm	0–500 ppm	0–500 ppm

<b>Component</b>	<b>Function</b>	<b>Amount</b>			
		<b>Straight oils</b>	<b>Soluble oils</b>	<b>Semi-synthetics</b>	<b>Synthetics</b>
Alkaline reserve	Acts as buffer control	‡	2%–5%	2%–5%	2%–5%
Dyes	Identify, leak detection	‡	0–500 ppm	0–500 ppm	0–500 ppm
Odorant	Masks odor	§	§	§	§
Corrosion inhibitors, anti-rust	Prevent rust film barrier	0%–10%	3%–10%	10%–20%	10%–20%
Biocides, bioresistant components	Control bacterial and fungal contaminants	‡	0%–2%	0%–2%	0%–2%
Extreme pressure additives	Act as reaction lubricant films	0%–40%	0%–20%	0%–10%	0%–10%

\*Adapted from Key et al. [1983], Niemeier [1990], and ILMA [1994].

†CRC [1985]. Dissolved water concentrations in mineral oils range from 10 to 100 mol per million carbon atoms, depending on ambient humidity and temperature.

‡Not present in this MWF class.

§Usually present in this MWF class.

**Table 2. Biocides commonly used in MWFs**

<b>Chemical name</b>	<b>Trade name</b>
Tris(hydroxymethyl)nitromethane	Tris Nitro
Hexahydro-1,3,5-tris(2-hydroxyethyl)-S-triazine	Grotan <sup>®</sup> Onyxide <sup>®</sup> 200 Busan <sup>®</sup> 1060 Bioban <sup>®</sup> GK Triadine <sup>®</sup> 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-4,4'-(2-ethyl-2-nitrotrimethylene) dimorpholine	Bioban <sup>®</sup> P-1487
O-Phenyl phenol	Dowicide <sup>®</sup> -1
Sodium 2-pyridinethiol-1-oxide	Sodium Omadine <sup>®</sup> , 40% aqueous solution
1,2-BIT; 1,2-benzisothiazolin-3-one	Proxel <sup>®</sup> MW 300 or MW 200
5-Chloro-2-methyl-4-isothiazolin-3-one-2-methyl-4-isothiazolin-3-one	Kathon <sup>®</sup> 886
6-Acetoxy-2,4-dimethyl-m-dioxane	Givgard <sup>®</sup> DNX
2,2-Dibromo-3-nitrilopropionamide	Dow XD-8254 DBNPA
p-Chloro-m-xylenol	PCMX

Public Comment  
to

**Metal Working Fluids**

**Recommendation for Chronic Inhalation Studies**

**National Institute for Occupational  
Safety and Health  
Cincinnati OH USA 45226  
November 14, 2000**

# Independent Lubricant Manufactures Association

Independent Lubricant Manufacturers Association (ILMA)

January 31, 2001

By Telefax

Mr. Mark Torasson  
National Institute of Occupational Safety  
and Health Administration  
Cincinnati, Ohio 45226

**Re: November 14, 2000 Draft: Metal Working Fluids, Recommendation for  
Chronic Inhalation Study**

Dear Mr. Torasson:

The Independent Lubricant Manufacturers Association ("ILMA") appreciates the opportunity to provide these comments to NIOSH on the Draft Metal Working Fluids Recommendation for Chronic Inhalation Study ("Draft Recommendation"). These comments are provided by the ILMA Health & Safety Task Force.

ILMA strongly opposes a NIOSH recommendation to the National Toxicology Program ("NTP") for Metal Working Fluid chronic inhalation studies. ILMA supports relevant and scientifically valid research on metalworking fluids, but cannot support this proposal because ILMA does not believe that metalworking fluids are an appropriate candidate for chronic inhalation NTP study at this time. ILMA believes that NIOSH's focus should be driven by its

1998 document: "Criteria for a Recommended Standard: Occupational Exposure to Metalworking Fluids" (Criteria Document), which states that current-day metalworking fluid formulations do not present a cancer risk, but rather, present a risk of non-malignant respiratory disease.<sup>1</sup> Any NIOSH recommendation should thus focus on non-malignant chronic respiratory endpoints.

Moreover, ILMA believes that NIOSH should delay any recommendation to NTP until the Environmental Protection Agency ("EPA") High Production Volume ("HPV") testing program is complete to determine whether any suspect components are identified. In the absence of additional data regarding metalworking fluid components, NIOSH does not have the ability to prioritize representative compositions for study and thus cannot sufficiently focus its testing recommendation.

ILMA offers specific comments in support of its opposition to the proposal:

1. Cancer is not the greatest occupational health concern with the use of metalworking fluids.
2. None of the major chemicals used in metalworking fluids are suspect carcinogens.
3. There are too many different metalworking fluids commercially available for this approach to reach any definitive answers about their cancer risk.
4. Other information and programs in progress need to be reviewed to properly prioritize test subject for this approach.
5. Metalworking fluids are complex mixtures.
6. The NTP bioassay approach is an unproved tool for commercial mixtures.

A. Metalworking Fluids Should Not Be Addressed By NTP

1. Association Of Cancer To Occupational Use Of Metalworking Fluids Is Weak At Best

NIOSH states that there have been a small number of epidemiological studies that have adequate exposure characterization, and that the metalworking fluid constituent responsible for the site-specific cancer "remains to be determined." ILMA believes that none of these studies has adequate exposure characterization. Those studies that reported statistically significant effects found only very weak effects. None of the studies rigorously meet criteria for establishing a cause-effect relationship. The next sections discuss the criteria for establishing such a relationship.

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<sup>1</sup>ILMA commissioned Dr. Daniel Hoffman of George Washington University School of Public Health to review the cancer studies cited in the NIOSH Criteria Document. The final document will be sent to NIOSH upon its submission to ILMA.



a. **Strength** There should be a strong association between exposure and an effect. Epidemiologists recognize risk ratios greater than 3 as strong. Risk ratios of 1.21.5 are classed as weak.<sup>2</sup> This is the range reported in the study with the best design.<sup>3</sup>

b. **Consistency** All studies should give the same result. This criterion is clearly not met. The type of cancer supposedly found and the subgroup at risk varies with each study. Admittedly, this could reflect the variation in fluid composition and the type and degree of contamination, but it definitely reflect inadequate study design.

c. **Specificity** The toxic effect should occur only in those exposed to the putative cause. Each of the cancers reported is common in the general population. This makes the statistical treatment of the data even more critical. Comparison of cancer rates in occupations using metalworking fluids with those of other occupations with little or no chemical exposures suggests there is no difference in rates; machinists have a lower risk of rectal cancer than mechanical engineers, electrical engineers or bartenders<sup>4</sup>. Similarly, lathe operators had similar or lower rates of digestive organ cancer when compared to public relations specialists, glaziers, optometrists or astronomers. Colon cancer rates for grinder operators are comparable to those of women who work in the home and urban planners.

d. **Temporality** Exposure should precede the disease. This is consistently lacking in retrospective studies.

e. **Gradient** A doseresponse relationship should be shown. Again, this is lacking in the published studies. Approximations have been attempted by using time of service as a surrogate for exposure, but the increased rate of cancer with increasing age is an important confounding factor. Attempts have been made to estimate mist exposures at past dates, but these are not a replacement for hard data.

f. **Biological plausibility** The effect should reflect the route of exposure. Primary exposure to metalworking fluids is through skin absorption and by inhalation. Thus, it would seem probable that any carcinogenic action would be primarily manifest in the skin and respiratory tract. In fact, none of the studies reports excesses of skin or lung cancer.<sup>5</sup> (NIOSH does find a significant association with laryngeal cancer, but only for straight oils.) The alleged associations involve the digestive system, at sites wellremoved from the site of original exposure.

g. **Coherence** The effect reflects the known properties of the components. The only plausible carcinogens associated with metalworking fluids are the shale oils and nitrosamines. Shale oils have not been used for decades. Skin and scrotal cancers are no longer current issues. Use of nitrites in metalworking fluids began in about 1950. Replacement began in 1977 and was complete by 1985. The period of use, 1950-1985 is exactly the period covered by the epidemiology studies, which find only weak effects, at best.

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<sup>2</sup>Richard R. Monson, "The Interpretation of Epidemiologic Data", *Occupational Epidemiology*, CRC Press, Boston, MA, p. 88 (1990).

<sup>3</sup>P.A. Eisen, *et.al.* "Mortality Studies of Machining Fluid Exposure in the Automobile Industry I: A Standardized Mortality Analysis," *Amer. Jour. Med.*, pp. 809-824 (1992).

<sup>4</sup>Mortality by Occupation, Industry, and Cause of Death: 24 Reporting States (1984-1993) NIOSH Publication Np. 97-114.

<sup>5</sup>See note 2.

Nitrosodiethanolamine ("NDELA") is a liver carcinogen in rats. It is sitespecific because  $\beta$ -hydroxynitrosamines cannot form carbonium ions by direct decomposition. The actual carcinogenic chemical is formed only after metabolism in the liver. Excess liver cancer is not reported in the studies.

d. **Experiment**—The effect should be confirmed in controlled trials. This criterion cannot be met without experiments involving humans. The past use of fluids containing nitrosamines could be looked at as an unintentional experiment with negative results. As long as these criteria are not met, it is presumptive and misleading to maintain that any real carcinogenic risks have been established and should be explained.

## 2. Most Suspect Carcinogens Used In The Past Are No Longer Used In Metalworking Fluids

Although a carcinogenic risk from the occupational use of metalworking fluids has not been established, there have been many changes in commercial metalworking fluids over the last 50 years that would also serve to reduce carcinogenic risk.

Even though responsible companies began making strides in the 1970s to make metalworking fluids safer, one cannot minimize the importance of the OSHA Hazard Communication Standard (effective 1985) in altering the way chemicals are used in the workplace. This regulation, with especially strong provisions to assure label and Material Safety Data Sheet ("MSDS") statements for carcinogens contained at greater than 0.1% in a chemical product, created a strong incentive for manufacturers to provide their customers less hazardous industrial and commercial chemical products.

The purity of mineral oils has drastically improved over last few decades through great strides in refining technology. The carcinogenicity of mineral oils is a purity issue. Most toxicologists agree that carcinogenic activity is due to the presence of polynuclear aromatic and nitro-aromatic impurities. A landmark was established in the understanding of the carcinogenicity issue with the IARC monograph in 1984. After a review of all the available data on mineral oil, IARC classified a "severely-refined solvent oil" as not carcinogenic to experimental animals. OSHA quickly adopted this definition as guidance to the industry.

In the absence of any valid, positive evidence from sources other than IARC regarding the carcinogenicity of severely hydro-treated or severely solvent-refined oils, no reference to carcinogenicity need be included on the MSDS and the label for such materials, IARC has concluded that when an oil is refined using sequential processing of mild hydro-treatment and mild solvent refining, there is no evidence of carcinogenicity.<sup>6</sup>

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<sup>6</sup>OSHA Directive CPL 2-2.38D - Inspection Procedures for the Hazard Communication Standard (1998). [http://www.osha-slc.gov/OshDoc/Directive\\_data/CPL\\_2-2\\_38D.html](http://www.osha-slc.gov/OshDoc/Directive_data/CPL_2-2_38D.html). Appendix A, d(4).

Responsible lubricant formulators reviewed their mineral oil specifications and put processes into place to assure that only severely-refined and severely hydro-treated solvent oils were used in metalworking fluids and other lubricants.

Historically, nitrosamine contamination has been suspect as a possible source of cancer risk in metalworking fluids. Once it was discovered that the source of the nitrosamines was the use of inorganic nitrite salts as a rust preventative, responsible companies discontinued use of nitrites. EPA subsequently issued a rule under TSCA to prohibit the use of nitrites in metalworking fluids (40 C.F.R. § 721.4740). Since 1976, nitrosamine levels in metalworking fluids have been reduced from levels of parts-per-hundreds to parts-per-billion. Levels of NDELA in metalworking fluids are below the accepted *de minimis* level by three orders of magnitude.

Chlorinated paraffins have been another source of carcinogenic concern in metalworking fluids. Bioassays by the NTP have indicated that the activity is limited to short chain paraffins as opposed to longer chain paraffins. Again responsible formulators took early action to assure that only long chain-chlorinated paraffins were used in metalworking fluids.

### 3. None Of The Major Metalworking Fluids Components In Use Today Are Suspect Carcinogens

As explained below, metalworking fluids are complex mixtures manufactured by hundreds of small blenders. It is not known with certainty how many different metalworking fluids are available in the marketplace nor how many different chemicals are used in metalworking fluids. Steigerwald, *et al.* (1994) compiled a list of over 100 separate chemicals or mixtures components commonly used in metalworking fluid compositions. ILMA members have reviewed this list recently and believe the 100 chemicals on this list represent the major chemicals used to formulate metalworking fluids. Toxicologists from ILMA member companies have examined the list and none of the chemicals are suspect carcinogens.

A number of comments can be made on these chemicals: Mineral oil and chlorinated paraffins are more fully discussed in the section above. The data on diethanolamine ("DEA") and triethanolamine ("TEA") were recently reviewed by the International Agency for Research on Cancer ("IARC") and the expert body did not conclude that the evidence on these chemicals warranted a carcinogenic classification. IARC has reviewed the existing data for DEA and TEA, including the NTP studies. (<http://193.51.164.11/past&future/evaltab77.html>) IARC assigned both amines to Group 3: Insufficient Data to Determine Human Carcinogenicity Potential. For TEA, there was inadequate evidence for carcinogenicity in both humans and animals. TEA was also placed in class 3 and has been found to be a non-sensitizer in human studies. It is widely and safely used in personal care products.

Many different fatty acids and fatty acid derivatives appear on the list. The scientific evidence indicates these chemicals are fairly innocuous and are not suspect structures for carcinogenicity.

Various alkyl alcohols and glycols (CAS 112-27-6, 107-21-1, 56-81-5, 107-41-5, 57-55-6) are also not suspect structures for carcinogenicity.

Several alkyl sulfides (CAS 68425-16-1, 68515-88-8, 72162-15-3) Alkylbenzene sulfonates (CAS 61789-86-4, 68608-26-4) are being voluntarily reviewed by individual companies or industry consortiums under the EPA HPV Chemical Testing Program. These chemicals are not mutagenic or genotoxic and there is no other data to indicate that they are suspect carcinogens.

#### 4. Cancer Is Not The Top Health Concern Of Usage Of Modern MWF

NIOSH acknowledges that over the last several decades, the metalworking fluid industry has made substantial changes including changes in MWF composition and reduction in metalworking fluid impurities and exposure concentrations.

With respect to studies that have shown association between occupational exposure to metalworking fluids and asthma (Rosenman et al 1997b; Greaves et al 1995b; Eisen et al), these investigations conducting the UAW-GM studies did not consider semi-synthetics as a separate class, but regarded them as synthetic fluids. With the exception of one early study (Ely 1970), epidemiological studies of respiratory symptoms present generally consistent, and in the case of more recent studies, compelling epidemiological evidence indicating that occupational exposure to metalworking fluid aerosols have been associated with symptoms that may be consistent with airway irritation, chronic bronchitis, and asthma. ILMA believes that these non-malignant respiratory effects should be the target for research.

#### 5. Many MWF Components Are In The EPA HPV Test Program And The Results Could Help NTP Prioritize

Approximately 2000 chemicals are being reviewed voluntarily under the EPA HPV Program. Attachment 1 indicates which of the major metalworking components are being reviewed. Several are not being reviewed because of low concern or because they have gone through a similar review under the OECD SIDS Program.

Although it is believed that these chemicals are not suspect carcinogens, new data may be uncovered or generated during the HPV program. In view of the complexity of assessing hundreds of complex mixtures for carcinogenicity as explained below, new information from the HPV Program may help prioritize the metalworking fluids or the types of metalworking fluids that should be examined for carcinogenicity. (Attachment 1).

#### 6. Biocides Have Been Fully Evaluated By EPA

Biocides are required to be registered with EPA under the Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA"). Before using any biocides in a cancer bioassay, the data submitted to EPA should be reviewed to determine whether any biocides are suspect carcinogens.

#### B. Technical Difficulties In Using The NTP Approach To Study This Problem

## 1. Metalworking Fluids Are Complex Mixtures

Each type is represented by hundreds of complex mixtures of variable composition each of which consist of several of as many as 800 different components. As NIOSH is aware, metalworking fluids are commonly identified as one of four types: straight oils or neat oils; soluble oils; semisynthetics; and synthetics. Foltz (1990) defined these four types of fluids.

Straight oils are metalworking fluids that typically consist of a severely solvent refined petroleum oil, a severely hydrotreated petroleum oil, or other oil of animal, marine, vegetable or synthetic origin used singly or in combination, or with other additives. These products are not designed to be diluted with water before use. Historically, the oldest class of engineered metalworking products, straight oils provide excellent lubricity, good rust control, and long sump life. Depending on the intended application, straight oils may have:

- "oiliness agents" such as the vegetable oils identified above or polyol esters
- extreme pressure additives such as sulfurized fatty materials or chlorinated paraffins
- antioxidants, such as an alkylated phenol
- a metal passivator, such as a triazole
- other corrosion inhibitors, such as a calcium sulfonate
- an antimist agent, such as a polymethacrylate polymer
- dispersants
- odorants
- a dye

Some lower viscosity straight oil products, such as those designed for an application such as honing, will use middle distillate petroleum fractions, rather than the more viscous vacuum distilled fractions.

Soluble oil (or emulsifiable oil) is a combination of between 30-85% severely refined lubricant base oil and emulsifiers that may include other performance additives. Such products are supplied as concentrates that are diluted with water at ratios of one part concentrate to five to forty parts water. In addition to the base oil, soluble oils can contain:

- oiliness agents, such as an ester
- extreme pressure additives, such as a chlorinated olefin or ester or sulfurized fatty material
- emulsifiers, very typically including a sodium petroleum sulfonate, salts of fatty acids, and/or nonionic surfactants
- alkanolamines to provide "reserve alkalinity"
- a biocide, such as a triazine or oxazolidene
- a "coupler," such as a fatty alcohol
- a defoamer, such as a long chain organic fatty alcohol or salt
- possibly, corrosion inhibitors, antioxidants, dyes, and/or metal passivators, such as may be found in straight oils as previously described.

“Reserve alkalinity” is a term used to describe alkaline materials present in a composition that are available to react with, for example, short chain organic acids produced by bacteria.

Soluble oils as a class provide good lubrication as well as improved cooling (as compared to straight oils). On the other hand, soluble oils may have poor corrosion control, may be “dirty” (*i.e.*, machine tool surfaces and adjacent areas become covered with oil or difficult-to-remove product residues), may smoke (because of insufficient ability to cool), and may have poor mix stability or short sump life. A distinction needs to be made between “commodity” soluble oils, containing few if any performance enhancing additives, and “premium” soluble oils, which offer the user higher performance and extended fluid life.

A semi-synthetic metalworking fluid contains a lower amount of severely refined base oil, for example, 5-30% in the concentrate. These products also contain a higher proportion of emulsifiers as well as 30-50% water, resulting in a transparent concentrate, and are typically transparent or translucent when they are diluted with ten to forty parts water. Perhaps the most complex of metalworking fluid formulations, semi-synthetics offer good lubrication, good heat reduction, good rust control, and have longer sump life and are cleaner than soluble oils. Conversely, this class of products have a greater tendency to foam in softer water and can be unstable in hard water. Comprised of many of the same ingredients as soluble oils, semi-synthetics will contain a more complex emulsifier package, often including fatty amides, additional corrosion inhibitors such as an amine salt of boric acid, and sometimes a chelator, such as a salt of ethylenediamine tetraacetic acid (“EDTA”).

Synthetic metalworking formulations do not contain any petroleum oil. Among the four classes of fluids, they are the cleanest, offer the best heat reduction, have excellent rust control and long sump life, are transparent (allowing the operator to see his or her work), and are largely unaffected by hard water. On the other hand, synthetics offer poor physical lubrication, can be more difficult to waste-treat, and can foam in some applications. Like the other classes of water-miscible fluids, synthetics are designed to be diluted with water, from ten to forty parts per part of fluid concentrate. Besides water, synthetics can contain ethylene oxide - propylene oxide polymers, amides, and /or organic esters as lubricants, amine salts of mono- and dicarboxylic and boric acids as corrosion inhibitors; alkanolamines to provide reserve alkalinity; a plasticizer, such as a glycol ether, and, as in other classes of water-miscible fluids, chelators, defoamers, odorants, biocides, and or dyes can be optionally included.

Steigerwald, *et al.* (1994) compiled a list of components commonly used in metalworking fluid compositions. Categorized as described above, this list of components consisted of over 100 separate chemicals or mixtures. Because of survey methodology, this list did not include all examples of all chemicals which might be used. Based on an annual volume survey, ILMA believes that over one-half of its regular members (around 75 – 80 companies) compound and market metalworking fluids; however, not all metalworking fluid producers are ILMA members.

Those familiar with the market estimate that the actual number of formulas in commercial use easily number in the thousands, varying substantially from one another. Even within one lubricant manufacturer’s line, formulations sold under the same trade name, may have differing blend formulas. For example, it is generally acknowledged that semi-synthetics are the most complex formulas and can comprise upwards to fifteen individual ingredients or mixtures. As

NIOSH is aware, water-miscible fluids such as a semi-synthetic are diluted 10 to 40 parts with water. Because of varying water conditions (*e.g.*, in hardness), a semi-synthetic product sold under the same trade name by one manufacturer may in fact have different blend formulas so the products are usable with these varying water conditions. Given the complexity of the technology, the diversity of components that might be used in a formulation, and the thousands of formulas likely to be in commercial use, it is difficult to conceive how any one (or a few) could be chosen that would represent all those formulations now in use.

## 2. A Study Of Virgin Fluids Does Not Address In-Use Fluid Changes

A study of virgin fluids does not address the myriad of fluid changes that occur while the fluids are in use in a facility. When a metalworking fluid is charged into a sump, the composition is known. Unfortunately, this is true for only a short time. A number of chemical, physical and biological processes cause depletion or accumulation of individual components over time. A system typically loses 10% of its volume daily through evaporation of water. Replacing the lost water can reverse this, but this leads to an increase in the ionic strength of the mix as dissolved salts in the make up water build up.

Metalworking fluid are shipped as a pure mixture. Once the container is opened and used, there are changes to the metalworking fluid as contaminants, some of which are microbial in nature, enter and grow in the system. The metalworking fluid as received is thus a completely different mixture within hours, days, and weeks of use. The same metalworking fluid will exhibit microbial changes differently depending on the water properties, the cleanliness of the system, the purity of the air, the hygiene and housekeeping of the employees, the length of use, and the material being machined.

Contamination of a fluid in use is inevitable. A common source of contaminations are other lubricants used in other machinery such as hydraulic fluids and greases. This source of contamination is commonly caused "tramp oil." A system will occasionally have a higher content of tramp oil than of the primary metalworking fluid. These tramp oils are often formulated products themselves. The tramp oils often introduce chemicals such as antioxidants, zinc dialkylthiophosphates and mercaptobenzothiazole into the fluid. Other common contaminants are cleaners, rust preventatives, degreasers, particulate and dissolved metals, dirt and anthropogenic wastes. As a rule of thumb, it can be assumed that any material present in a workplace will wind up in the fluid at some time.

Machining and grinding generate vast areas of nascent metal surface that are chemically reactive. Many fluid components, especially corrosion inhibitors, are stripped from the mix by these sites and are replaced by (largely unknown) reaction products. Many chemicals, especially biocides, are not stable at the pH levels commonly found in metalworking fluids. They decompose over time to form products that were not present in the original blend.

Fatty acids and monoethanolamine are known to be readily consumed by microorganisms. Other chemicals, like mineral oil, may be degraded more slowly. The resulting metabolic products may be innocuous, like carbon dioxide, or irritating, like ammonia.

In soluble oils and semi-synthetics, the constituents can be present in the oil phase of the emulsion, in the water phase or both. As synthetic fluids become contaminated with tramp oil, the organic components will become distributed between the oil and the water. As the ionic strength of a used fluid increases with salt build up, organic molecules will be increasingly forced into the oil phase. As tramp oil is removed from the fluid, the more oil-soluble components will be depleted from the mix and their relative concentrations will decrease.

Even when this does not happen, the change in the oil-water distribution of an ingredient will make the effective dose of that ingredient in a used fluid different than the effective dose in a fresh fluid, at the same applied dose level.

Microbes are the contaminant of greatest concern from a health effects perspective. Animal models have shown that contaminated fluids have a greater irritation potential than fresh fluids. Anecdotal evidence from epidemiology studies have reported that fluids generate more complaints after several weeks of use. Respiratory problems and hypersensitivity pneumonitis have been observed at very low exposure levels, in the presence of highly contaminated fluids. In many of these incidents, heavy contamination of the ventilating systems as well as the metalworking fluid have been reported. In those cases, it is valid to ask if the fluid has contaminated the air system or vice versa.

The microbial population is not well defined. Historically, levels have based on counts of planktonic gram-negative bacteria on culture plates. Recent studies have shown that gram-negative bacteria may represent as little as 10% of the actual population in a fluid system. Further, the planktonic organisms are only a fraction of the total biomass present. Most of the population is present in huge masses of biofilm growing in the fluid, in splash areas or under machines.

The overall impact of microbial exposure is unknown and is an important area for future study. Any testing should be conducted to determine the magnitude of risk and should not involve the metalworking fluid as a chemical entity, but rather, as a vehicle for the microbial exposure.

### 3. NTP Cancer Bioassays Are Not The Proper Approach For Assessing Commercial Mixtures

The NTP bioassay has traditionally studied relatively pure single chemicals. Studying mixtures in a laboratory animal inhalation cancer bioassay presents a number of procedural and interpretative issues. Aerosols of mixtures may not be of uniform composition. Volatility of mixture components could add complexity to the exposure profile in the study. The analyte to determine exposure needs to be carefully chosen. Several analytes may be necessary to obtain a true picture of exposure. Any positive effects will cast a shadow of doubt on all components in the experimental mixture which will not be able to be resolved until all the components can be tested separately. It will take a number of years to run these bioassays. If these results are inconclusive, simpler mixtures may need to be studied. This level of testing will also require an additional number of years. If the original effect is an anomalous effect due to the animal species chosen, millions of dollars could be wasted on an effect that is not relevant to human health effects.



#### 4. It May Be Difficult To Attain Aerosol Levels That Approach Maximum Tolerated Dose

ILMA members have conducted a number of studies on the acute inhalation toxicity of their products, as well as a few sub-acute studies. In acute studies, it has been impossible to achieve exposure levels high enough to cause acute effects after a one-hour exposure. The general practice has been to expose the animals for one hour at 200 mg/l and report the products as "non-toxic."

In 28-day studies, using exposure at 20 mg/l to a semi-synthetic fluid and a synthetic fluid, no toxic effects were observed in the exposed animals. A major obstacle to conducting inhalation studies has been the inability to achieve exposure levels high enough to cause toxic effects, even for a 28-day sub-acute studies. Any choice of a small number of fluids to be tested would not result in a valid surrogate for all fluids.

Evaluation of a number of metalworking fluids by the mouse bioassay showed RD50 levels of 100-1000 mg/m<sup>3</sup> for three hours exposure with the observation of sensory and pulmonary irritation. No significant differences were observed that could be attributed to differences in composition or fluid type. It seems reasonable to suspect that the over riding factor in this irritation is the alkaline nature of the fluids.

The maximum tolerated dose must be less than 100-1000 mg/m<sup>3</sup> to avoid effects of pulmonary irritation. Since the epidemiology studies suggest that any carcinogenic effect must be very weak, it must be asked if these exposure levels would be high enough to give results that would be accepted if negative.

#### 5. The Studies Cited By NIOSH Do Not Support the Proposal

The studies cited in the NIOSH Proposal do not provide compelling evidence that chronic, irreversible health hazards are caused by normal exposure to metalworking fluids. In every case, there is a degree of uncertainty, usually resulting from an experimental design that does not account for confounding factors. Authors suggest interpretations that cannot be ruled out but cannot be proven. A greater degree of appreciation of the complexity of the issues has resulted from the two symposia sponsored by American Automobile Manufacturers Association in 1995 and 1997. As a result, studies are now in progress or planning that will be more comprehensive and avoid some of these deficiencies.

NIOSH, itself, under Dr. Vincent Castronova, has conducted a series of studies on the effects of dermal and inhalation exposure of animals to an unused semi-synthetic metalworking fluid. In a series of poster papers, they report no significant differences between control and exposed groups, unless the exposed animals have been impaired by sensitization with ovalbumin or fed diets deficient in Vitamins C and E. This work is continuing and promises to shed further light on the mechanisms of injury from metalworking fluid exposure.

#### C. Industry Studies May Yield Important New Information

The Metalworking Fluid Product Stewardship Group ("MWFPSG"), which is a subsidiary of ILMA, has initiated two studies that may yield information to facilitate NIOSH's efforts. The first study, which will be complete within the next 2 months, reviews the mammalian and *in vitro* toxicology of formulated metalworking fluid products.

The author of the report reviewed 180 company toxicology studies on 99 formulated metalworking fluids to create a compilation and evaluation of the mammalian and *in vitro* toxicology. The second project, which has just begun, will track and analyze the toxicological, chemical, and microbial changes in an in-use fluid. Simultaneous health and mist exposure surveys of the workplace will allow identification of the root causes of any health effects found. The preliminary results of the second study should be available within a year.

It is reasonable to assume that other studies are also in progress and will lead to a better understanding of the extent and degree of health risks posed by metalworking fluids. Within a short time, there may be a better understanding of the risks of fluid exposure and the critical factors in avoiding those risks.

ILMA again urges NIOSH to reconsider its proposal and redirect its focus. ILMA looks forward to working with NIOSH on this important issue.

If you have questions about these comments, please call Dr. Richard Kraska, at (440) 943-1200 or Dr. John Howell, (630) 743-7340, of the ILMA Health & Safety Task Force.

Sincerely,

Michael C. Metallo  
Executive Director

Enclosures

cc: ILMA Health & Safety Task Force  
Stephanie Siegel, Collier Shannon Scott  
Frank White, Organization Resources Counselors

Organization Resource  
Counselors, INC.

Task Force on  
Metal Removal Fluids

January 31, 2001

Mark Toraason, Ph.D., DABT  
National Institute for Occupational Safety and Health (NIOSH)  
4676 Columbia Parkway (C23)  
Cincinnati, OH 45226-1998

Re: ORC MRF Task Force Comments on Carcinogenicity Testing of MRFs

Dear Dr. Toraason:

In response to your request, the Organization Resources Counselors Task Force (Task Force) on Metal Removal Fluids (MRFs) is pleased to submit these comments on the November 14, 2000, draft proposal, "Nomination of Metal Working Fluids for Testing by the National Toxicology Program" (NTP).

The Task Force has reviewed the proposed recommendation of testing of complex MRF formulations through the NTP. In light of our current knowledge about the health effects associated with MRFs and the limited potential for cancer risk posed by current MRF formulations, we believe such testing will have limited value in improving workplace health and safety. We also believe – if NIOSH recommends any program to NTP – that NIOSH must include in its recommendation steps to ensure the quality and value of information obtained from such testing. Most importantly, we believe that any NIOSH recommendation to NTP should focus on evaluation of components of MRFs, not the finished formulations themselves.

NIOSH already recognizes that the number of potential choices for testing individual MRF formulations is vast and MRFs are highly complex. There is a large number of possible selections within each category of additives that formulators might choose to use. This complexity makes testing one or even a few of the most widely used MRF formulations for possible adverse interactions, as has been suggested, problematic. While such an approach may indicate carcinogenic risk associated with specific MRF formulations before and – if somehow they could be tested - after use, it would provide very little information as to the specific components of concern. As a result, there would be little or no new information for those who use and/or formulate MRFs to help them select low risk components.

The MRF Task Force believes that a focused, systematic approach to identifying constituents of concern and selecting these specific substances for bioassay is the most likely to produce results that can be acted upon by users and formulators to minimize occupational health risk. The best use of time and resources involves:

- Screening specific categories of components for potential risk,
- Selecting for bioassay a subset of components that show potential risk.

#### Screening categories of components for potential risk:

Questions have been raised about the possible cancer risk of certain categories of MRF components by inhalation either individually or in combination with other agents. These include petroleum sulfonates, non-ionic surfactants, base oils, and alkanolamines, specifically triethanolamine. The Task Force believes that NIOSH should build its testing strategy using these categories. A great many substances that may be of concern can be included in the study by identifying the individual chemicals in each category that are used in MRF formulations and screening them for potential cancer risk. This includes conducting reviews of existing studies on these chemicals for information on cancer risk by inhalation and identifying chemicals for which further information is needed.

#### Selecting for bioassay a subset of components that show potential risk

Chemicals for which further information is needed on inhalation cancer risk would be screened further. The use of computational tools such as TOPKAT and MultiCASE for determining cancer risk based on quantitative structure activity relationships (SAR), provides valuable information for focusing inhalation bioassays. The National Institute for Environmental Health Sciences (NIEHS), where the NTP resides, has a program to develop alternatives to traditional toxicological testing, which include computational methods. For example, the EPA High Production Volume Chemical Challenge Program seeks to screen 2,800 chemicals for their toxicological risk, a task resembling the difficulty of a complete assessment of the toxicological risk of MRFs; commitments for some components of MRFs have already been made. To accomplish the screening in a cost-effective and timely manner, EPA is also proposing to use SARs.

Substances identified through the SAR process as potential cancer risks by inhalation should be prioritized for testing based on the degree of exposure found in most workplaces, and the potential level of risk indicated by the SAR analysis. To ensure the validity and usefulness of information obtained from the NTP research, laboratory animal models used to evaluate the toxicological risk of MRF components must be exposed by the same primary routes as workers. Oral and pulmonary instillation studies (following uptake and distribution studies) are inadequate substitutes for true inhalation exposures. There is ample evidence from

Mark Toraason  
January 31, 2001  
Page 3

instillation studies of particulate material (fiberglass, for example) to demonstrate that instillation studies can show false positive results which conflict with results from the more definitive inhalation studies.

Since the goal of the NIOSH project is to improve the safe use of MRFs in the workplace, the best approach to testing these substances is one which would allow users and formulators alike to take action by substituting less hazardous ingredients once risks are known. When information on inhalation toxicity of MRF components becomes available, users and formulators will be enabled to analyze their work environments and products to determine and minimize exposure risks to their customers and employees. As a result, the ORC MRF Task force recommends that NIOSH recommend a program focused on selection of components for evaluation, not on evaluating finished MRF formulations.

Sincerely,

Frank A. White  
Vice President

John K. Howell

Castrol Industrial  
North America, Inc.

January 29, 2001

Mark Toraason, Ph.D., DABT  
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Cincinnati, OH 45226-1998

**VIA FAX: 513-533-8138**

Dear Dr. Toraason:

Thank you for the opportunity to offer these thoughts in response to your request for comments on the November 14, 2000, draft proposal, "Nomination of Metal Working Fluids for Testing by the National Toxicology Program" (NTP). I do expect you will also be hearing shortly from the Organization Resources Counselors' Metal Removal Fluids Task Force and from the Independent Lubricant Manufacturers Association Health & Safety Task Force. I myself appreciate the opportunity you and NIOSH have given us to meet with you, understand the background of this proposal, and offer comments.

Throughout these next paragraphs, I refer not to "metalworking fluids," but to "*metal removal fluids*," the subset of the larger category of metalworking fluids that are used for wet machining or grinding to produce the finished part. I believe all agree that these are the particular fluids addressed by this proposal.

I strongly urge NIOSH *not* recommend to National Toxicology Program that metal removal fluids be tested for chronic inhalation. I do recommend an alternative approach that NIOSH may want to consider before submitting this proposal.

NIOSH, in 1998, published the document, "Criteria for a Recommended Standard: Occupational Exposure to Metalworking Fluids." NIOSH's recommendation for reducing MWF aerosol exposures is supported by what is said to be "substantial evidence associating some MWFs used before the mid-1970s with cancer at several organ sites" and NIOSH's continuing concern for the "potential for current MWFs to pose a similar carcinogenic hazard." NIOSH also states, however, that the "primary basis of the NIOSH recommendation is the risk that MWFs pose for *nonmalignant respiratory disease (emphasis added)*. While there may be no actual test data on formulated products that show that current-day formulations *do not* pose any significant risk of cancer, there is



certainly no evidence to suggest that the components of current-day formulations *do pose* a significant cancer risk. Thus I recommend NIOSH's *principal* focus in any recommendation be on *non-malignant chronic respiratory endpoints* and not be on cancer.

As NIOSH is aware, metal removal fluids are complex mixtures of chemicals that - in the plant - change in use as contaminants, some of which are microbial in origin, enter or grow in the metal removal fluid system. As NIOSH is also aware, there are literally thousands of formulations in use. Even if cancer were a significant risk, it is impractical to select any one or even several fluids and believe that results of any evaluation by inhalation for cancer of a few of these as-manufactured fluids could be generally applied to the broad class of metal removal fluid products. And, given that it is the "in-use" metal removal fluids to which occupational exposure occurs, any extension of results – positive or negative – to such "in-use" fluids is fraught with difficulty.

NTP has had other opportunities to evaluate mixtures for chronic effects via inhalation and, in all previous situations with which I am aware, has decided not to proceed. The comment in the "Report on Carcinogens, Ninth Edition," Table 1, page IV-46, for "paint dust" is of interest: "No testing planned - - because of the diverse nature of this category of substance, and because any sample selected for testing would be representative of only a limited class of potential samples." I submit, and I believe you would agree, that metal removal fluids – because of the reasons enumerated above – are not candidates for testing by NTP for essentially identical reasons.

If testing metal removal fluid mixtures via inhalation for chronic cancer endpoints is problematic, what, then can be recommended? I suggest that the focus be on *components and microbiological by-products*, not metal removal fluid mixtures. Indeed, the United Auto Workers (UAW) nominations to NTP in this area have focused on metalworking fluid constituents, not on formulated products. Specifically, UAW has nominated petroleum sulfonates, non-ionic surfactants, oil mist (in conjunction with detergents) and triethanolamine, all by inhalation. Each of these components are commonly used materials in soluble oil formulations. And, although no specific non-ionic surfactants were nominated, candidates for evaluation could be selected. There is certainly an argument to be made as to why triethanolamine *should not* be evaluated, particularly while skin painting studies are still outstanding. As a result, I would suggest NIOSH recommend for nomination:

- *Sodium petroleum sulfonate, CAS#68608-26-4*: this component is found in virtually all soluble oil formulations, and in concentrations from 5 – 15%, as active ingredient in the as-manufactured product concentrate.
- *Non-ionic surfactant, such as octylphenoxypolyethoxyethanol (poly(oxy-1,2-ethandiyl), alpha-[(1,1,3,3-tetraethylbutyl)phenyl]-omegahydroxy), CAS#9036-*

- 19-5: this is but an example of hundreds (if not thousands) of “non-ionic surfactants” which could have been chosen, but is useful/has been used in metal removal fluid formulations.
- *Fatty acids, tall oil, compounds with triethanolamine (CAS#68132-46-7) or fatty acids, tall oil, compounds with ethanolamine, CAS#68132-47-8.* These salts (the potassium salt is also often used) of tall oil fatty acids are commonly used co-emulsifiers with sodium petroleum sulfonates and non-ionic surfactants in a soluble oil formulation. In such formulations, tall oil fatty acids are always neutralized with a base.

Combined with severely hydrotreated or severely solvent refined petroleum oil, and small amounts of "couplers," such as glycerine, (*1,2,3-propanetriol, CAS#56-81-5*) or *dipropylene glycol, CAS#25265-71-8*, these materials could be formulated into a soluble oil product.

Further support for selection of components such as these comes from the work of Schaper and Detweiler-Okabayashi and Ball and Lucke, as reported in "The Industrial Metalworking Environment - - Assessment and Control: Proceedings of the Symposium in Dearborn, Michigan, November 13-16, 1995, by the American Automobile Manufacturers Association, Washington, D.C.: AAMA, 1996. Schaper and Detweiler-Okabayashi found that sodium (petroleum) sulfonates and tall-oil fatty acids (evaluated in the un-neutralized form) produced the most significant sensory or pulmonary irritation in mice. Ball and Lucke, while not able to construct a model which would explain field-observed irritation, also found that sulfonates, tall-oil fatty acids, ethanolamine and fatty acids amides produced sensory irritation in mice. The findings are not that surprising, given the surface activity or alkalinity of the components. However, if irritation resulting from exposure to in-use metal removal fluids should somehow lead to chronic effects in the lung, it makes sense to begin with components, evaluate for non-malignant effects, and after understanding those results, proceed from there.

In any experimental design, *microbiological by-products*, such as *endotoxin*, must be included to offer a basis for comparison to “real life.”

I would be pleased to respond to further questions and am open to further discussion if you would like.

Cordially,

John K Howell, Ph.D.

DiamlerChrysler

# DAIMLERCHRYSLER

Mark Toraason, Ph.D., DABT  
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Dear Dr. Toraason,

Thank you for the opportunity to comment on NIOSH's proposed chronic study on metal working fluids (MWF) through the National Toxicology Program. This letter represents both my opinion and that of Jack Hartwig of the DaimlerChrysler Industrial Hygiene staff. Although the NIOSH recommendation references metal working fluids, our comments are directed at studying metal *removal* fluids. Our interpretation of the many important studies done in this area is that the majority concentrate on fluids used in the metal removal processes and there is enough difference between MWFs and MRFs to warrant the distinction.

Although NIOSH acknowledges typically testing individual constituents, the NIOSH document recommends the testing of MRFs as a complex mixture and seeks suggestions as to how such a mixture can be selected. While testing the MRF mixtures seems appropriate initially, further analysis leads to the conclusion that this task is nearly impossible to perform as proposed. There are hundreds of formulas for MRFs, using several of the hundreds of potential ingredients available for use. Consequently, it would be impossible to pick *a* formula that would represent anything more than a very small percent of the MRFs in use. Furthermore, the results of the testing of one formula could be misinterpreted and used incorrectly to characterize other mixtures. Finally, the results of testing a given formula lead only to control of that formula, and do little to help evaluate the other fluid formulas.

The best approach is to test selected constituents of MRFs. It avoids the complexity of the mixtures and provides for the most useful control strategy, substitution of less harmful components. In addition, knowledge of harmful ingredients allows for sampling of those specific ingredients and less reliance on the use of mist as a surrogate for the harmful ingredients.

The NIOSH Criteria Document and other reviews of MRFs indicate that nonmalignant respiratory disease is the primary concern. MRFs' relationship to cancer is questionable and NIOSH recognizes a link with earlier formulas but only a concern with the current potential. Nonetheless, the higher mortality and greater emotional impact of cancer generates more concern for that aspect, and it is a valuable endpoint to evaluate. Since the main route of exposure is inhalation, a chronic inhalation study of suspected carcinogenic MRF components is appropriate.

Several MRF components such as base oils, chlorinated paraffins, alkanolamines, etc. have already been recommended for carcinogenic evaluation. Selection of which components to study should be based on a review of all potential MRF constituents using whatever screening tools are available (invitro tests, structural relationships, etc.), as well as consideration of earlier recommendations.

Since nonmalignant respiratory disease is a key issue, the study design should take advantage of evaluating selected components, where feasible (e.g. petroleum sulfonate; alkanolamines) for both endpoints of interest, thereby answering several questions. Since there are so many constituents to test for, selection of the appropriate test ingredients is important to increase the existing knowledge base and to resolve existing concerns.

Sincerely,

William D. Watt, Ph.D., CIH  
Manager, Industrial Hygiene & Toxicology  
DaimlerChrysler

Oscar Hernandez

EPA

Office of Pollution  
Prevention and Toxics

## NIOSH Nomination of Metal Working Fluids for Testing: EPA/OPPT Comments and Recommendations

The selection of a “representative” chemical mixture for carcinogenicity testing is no doubt one of the most difficult toxicological problems because of the infinite variations of chemical components and concentrations in chemical mixtures. The November 14 2000 NIOSH document has provided an excellent summary of the complex issues associated with testing of metal working fluids (MWFs) and recommended *in vitro* genotoxicity and 13-week subchronic inhalation toxicity testing of a representative MWF from each of the four major classes of MWFs as a basis to determine the choice of one or two MWFs for long-term carcinogenicity testing by the National Toxicology Program. The exact representative MWF from each class remains to be determined.

Given the fact that it will never be possible to pick a MWF which is truly representative of all MWFs and given the fact that the high cost of testing will allow testing of only one or two MWFs, it will be imperative for NIOSH to develop a clear strategy to select the appropriate MWF for testing. EPA/OPPT is of the opinion that NIOSH should gather all available information on all potential candidate MWFs with known or probable worker exposure, rank their carcinogenic potential, and select the most hazardous MWF for testing in order to minimize the possibility of getting false negative. Two approaches may be taken to rank the carcinogenic potential of candidate MWFs: (a) short-term tests suggestive of carcinogenic potential and (b) scientifically based prediction of carcinogenic potential of chemical mixtures based on consideration of chemical components present.

### (A) Short-term tests

Short-term tests are essential for ranking of carcinogenic potential of MWFs. In addition, they could be used as inexpensive, time-saving surrogate tests if and when they can be demonstrated to correlate to carcinogenic activity of MWFs. In addition to the usual genotoxicity batteries mentioned in the NIOSH documents, the following should prove to be useful:

(1) *In vitro* Syrian Hamster Embryo (SHE) cell transformation assay: This assay is particularly recommended because it can also detect nongenotoxic carcinogens and tumorigenesis promoters depending on 24-hour or 7-day exposure protocol (e.g., Kerckaert et al., *Mutat. Res.* 356, 65, 1996). This test can supplement the usual genotoxicity batteries. In addition, there is possibility that this test can be used to detect potential interaction effects (e.g., synergism, promotion, etc.) among the various chemical components in the MWF mixtures. A pilot study using simpler mixtures known to act synergistically or antagonistically should be conducted to ensure the effectiveness of SHE cell in detecting interaction effects.

(2) <sup>32</sup>P-Postlabeling DNA binding. This method has been used to detect the *in vivo* genotoxic potential of chemical mixtures and should be used in combination with *in vitro* genotoxicity data for ranking MWFs.

(3) Skin painting studies. For some classes of chemicals (e.g., polycyclic aromatic hydrocarbons, PAHs), there is a reasonably good correlation between the pulmonary and dermal carcinogenic activities. Although not fool-proof, such tests could be used as surrogate for ranking of carcinogenic potential of MWFs particularly if they contain substantial amounts of PAHs. Ultra-sensitive strains (e.g. Sencar) or transgenic mice may be used to cut down the time needed for these assays. These assays are much more cost effective and less time consuming as compared to two-year inhalation studies.

#### (B) Component-based risk assessment

If information on the chemical components in MWFs is available, it may be possible to rank the carcinogenic potential of various MWFs by evaluating the inherent carcinogenic hazard based on the carcinogens present and by estimating the possible interaction effects. EPA/OPPT has developed a computerized Integral Search System (ISS) which may be useful in this respect if the components in MWFs are covered in the ISS. The details of the ISS are described in the publication by Woo et al. (*Environ. Health Persp.* 102 (Supp. 9), 113-118, 1994). Essentially, the ISS, with input by human experts, assesses the carcinogenic potential of chemical mixtures by evaluating:

(1) The Inherent Cancer Hazard: This can be done by identifying, to the extent possible, all the chemical carcinogens present, assessing the cancer hazard for each carcinogen ( $q_1^*$  data or structure-activity relationship analysis), and combine by simple additivity.

(2) The Hazard Modification Potential: This can be done by entering all the chemical components of a mixture into the ISS system. The ISS automatically generates all possible binary pairs of chemicals and compared with its database of virtually all available literature binary interaction data on carcinogen-carcinogen, carcinogen-promoter, and carcinogen-inhibitor. By calculating the balance between hazard enhancing interactions (e.g., synergism, promotion, cocarcinogenesis) and hazard-reducing interactions (e.g., antagonism, inhibition), a weighting ratio can be generated and used to modify the inherent cancer hazard mentioned above.

Besides the ISS system, a rough estimate of possible interaction effect may also be assessed by mechanistic consideration or solvent effect consideration (e.g., Warshawsky et al., *Fund. Appl. Toxicol.* 20, 376, 1993) depending on the nature of components present.

Greg Piacitelli

NIOSH



(e-mail January 12, 2001)

Mark-

I offer the following few comments concerning the subject proposal for conducting a chronic inhalation study of metalworking fluids (MWFs) under the National Toxicology Program.

1. The association between exposures to *past* MWF formulations and cancer has been clearly demonstrated in several epidemiologic studies. MWF manufacturers contend, however, that any carcinogenic components or precursors have been eliminated from present formulations and therefore the carcinogenic potential has been eliminated. This is disputable. For example, as widely known and cited in the proposal, triethanolamine and diethanolamine, both of which there are concerns about their carcinogenicity and in their role as precursors for carcinogenic nitrosamines, are still used in some formulations of presently-used MWFs.

A recent meeting with representatives from MWF formulators confirmed my belief that very little is known within the MWF industry about the chronic toxicity of their products. The potential for respiratory irritancy seems to be the focus of present concerns. Attendees indicated that there is a strong reliance on toxicological data (such as results from genotoxicity assays) for individual fluid ingredients (if and as provided by suppliers of these ingredients) when assessing the chronic toxicity of their MWF products. However, it is recognized that there may be unavailable and/or incomplete information for many components of these complex mixtures. Also, the chemistry and toxicity of individual components may change when used together in fluid formulations. It is therefore apparent that there is a paucity of information available about the mutagenic or carcinogenic potential of essentially all of the MWF products presently used. NTP studies are clearly necessary to provide empirical evidence which help to address the uncertainties concerning the carcinogenic risks associated with *present* MWF formulations.

2. As mentioned in the proposal, the selection of appropriate metalworking fluids for evaluation remains one of the most difficult and challenging issues in planning the proposed NTP study. Since there are literally thousands of MWF formulations presently used, it is virtually impossible to select a limited number of fluids for study which are specifically representative of all MWFs. However, I suggest that a logical strategy would be to initially select formulations which are most commonly purchased by major users, particularly those involving work populations which might also be suitable for follow-up epidemiologic research. Representatives from MWF manufacturers have suggested that a soluble fluid initially be selected since it is the most commonly used class and the simplest in composition. This seems reasonable. A "specification fluid" such as that presently used by Ford Motors would be generic version of a soluble fluid which should be relatively simple to develop as a "reference" fluid for comparison. Additionally, the significant number of exposed workers in the automotive industry provides a relatively accessible study population for complementary epidemiologic research, if warranted.

Incidentally, in the NIOSH study of small machine shops using MWFs (a manuscript which is currently in press is attached), straight fluids were observed to be the most frequently used class of MWF. The percentages of sampled workers using different fluid types were as follows:

straight (42%); soluble (28%); semi-synthetic (18%); and synthetic (12%). (Bob Glaser can provide a listing and categorization of all the fluid products (n>200) obtained from the 79 shops in the study). This higher frequency of straight fluids compared to soluble fluids in the NIOSH study is based only on the presence of the fluid and not on the actual volume of MWF used (these data were not available). Most data on the volume of MWF usage that I have seen indicate that soluble (followed by semi-synthetic) MWFs are most frequently used at the present time. (The OSHA Office of Regulatory Analysis has also prepared an analysis of MWF usage based on economic data which was presented to the MWF Standards Advisory Committee).

3. Any NTP testing protocol for MWFs should be designed to model representative workplace exposure levels. MWF aerosol exposures in most recent exposure studies in the automotive industry have been well below 1.0 mg/m<sup>3</sup>. The NIOSH study of small machine shops indicated about 80% of exposures to MWF particulate were less than 0.5 mg/m<sup>3</sup> (a frequency distribution of exposure levels is presented in the attached manuscript). Chronic inhalation studies should be designed to model these "real-world" exposure levels to improve the applicability of research results to actual human populations.

Hope these comments are helpful--feel free to call to discuss further. Also, if there is additional information from the NIOSH study which you believe may possibly be useful for preparing the NTP proposal, please let me know.

Greg

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# Robert Park

## NIOSH

Comments on:

***Metal Working Fluids  
Recommendations for Chronic Inhalation Study***

[NIOSH; draft:11-4-00]

This document describes the general characteristics of metalworking fluids (MWFs), and the reported health effects associated with MWF exposures, for the purpose of guiding selection of test materials in NTP testing programs. The resulting focus is on materials to be evaluated primarily in animal inhalation studies.

**Major Issues**

***Selection of Materials for testing***

The draft document identifies priority classes of MWF components and proposes testing both generic MWFs or specially prepared surrogates as well as in-use materials but does not identify which materials to test, or propose a specific procedure or sampling scheme to select such materials. How are these selections to take place?

***Target health effects***

Respiratory

Respiratory problems appear to be the primary concern in metalworking operations. These problems result from both in-use and possibly new fluids. Although most effects appear to be microbiological in origin, there are some formulation components that themselves are suspect for acute and potentially chronic respiratory effects, such as formaldehyde-releasing and other biocides, tall oil-derivatives and ethanolamines. To address these concerns, it may be best to test individual components or defined mixtures.

For investigating endotoxin-mediated pulmonary effects and hypersensitivity pneumonitis, clearly used fluids (or new fluids added to contaminated coolant systems) are required because the originating organisms and conditions favoring their presence are poorly described or understood. A sampling scheme that offers reasonable probability of capturing unusual microbiological episodes within typical metalworking operations would be needed for both generating animal exposure aerosols and for characterizing the general microbiological environment. However, sampling that is sufficient to recover a representative spectrum of causative agents may not also feasibly be able to retrieve adequate coolant system history to allow inferences regarding the evolution of such systems to generating toxic conditions.

Based on the diversity of MWF environments, this reviewer suggests that 100 to 200 samples be taken for respiratory effect testing from each of 25 industrial sites. The sampling should be divided into 2-4 monthly installments over a two year period and should span several basic industries (automotive, farm equipment, aerospace, appliance...). (For example, 12 coolant systems at a plant might be sampled approximately every 3 months, producing 96 samples after two years.) For sampling strategies that involve periodic sampling from the same coolant systems, a protocol should be developed for documenting system management over the period of sampling (fluid changes, additions, biocide use, symptom episodes, etc.). Fewer samples would be needed for inhalation studies if rapid-response sampling could be triggered by MWF-related complaints of workers. However, attempts by others at complaint-responsive sampling have not been particularly successful (see Sprince et al., below). For acute and sub-acute effects testing, presumably 100s of liters of used MWF could be required in each sample (appropriately preserved and stored). Animal models for acute inflammatory effects and sensitization would be needed. From these same samples several other testing modules could be conducted, as described below. The sampling at each site should be planned using an inventory of central coolant systems as well as stand-alone machine sumps. The strategy for taking samples should not be disclosed in advance.

#### Other chronic diseases

Elucidating the etiology of digestive tract cancer, including stomach, liver, pancreas and other sites, would require long term animal bioassays or *in vitro* tests. Priority test materials might include chlorinated oils (both paraffinic and naphthenic), ethanolamines, PAHs and nitrosamines, which should be tested as both defined preparations and as new MWFs containing complex mixtures. Using in-use MWFs probably would not be very meaningful in chronic bioassays as they vary unpredictably across time, unless each sample were characterized. There is probably little justification in attempting to replicate crude MWF preparations used in the past, such as petroleum base oils through which elemental chlorine (Cl<sub>2</sub>) was bubbled for the purpose of generating extreme pressure additives. For *in vitro* tests, large numbers of samples of used fluids

representative of the diversity of metalworking environments should be examined from each of the 25 sites that were proposed above for testing respiratory effects (samples might include aliquots taken from the large-volume samples). In addition to the respiratory test samples, a larger number of small samples from all coolant systems/individual sumps should be acquired. These studies could include large-scale DNA-chip screening for enzyme activation pathways and would constitute a pioneering effort in applying this new technology to a complex environmental assessment for which animal toxicology was also being performed.

Inhalation studies would model one route of entry; skin spray/painting or warm immersion might be considered to address skin contact exposures.

### ***Process Focus***

Metal removal processes constitute the majority of MWF usage. However, many other processes also generate MWF exposures. Cold forming work such as stamping, punching, cold-heading and tube fabrication also utilize fluids for lubrication and cooling purposes, usually called drawing compounds. MWF aerosols are present on stamping lines, and there may also be considerable skin contact from manual handling of stamped parts. Some sampling of these operations should be included in the NTP assessment.

Besides production settings, there are other important venues for MWF exposure. Maintenance activities including tool grinding, jig and fixture, tool and die production and repair, and machine repair generally involve activities with MWF exposure, usually from stand-alone machine sumps. The MWF materials in use may differ from those in routine production settings. Although in smaller groups, these activities across entire industries involve significant numbers of exposed workers. The limited epidemiology that addresses skilled trades workers supports the presence of MWF-related hazards in their work.

### ***Other aspects of process that can affect presence of hazardous agents***

In metalworking environments, other processes can contribute to the composition of MWFs. For example, parts washers sometimes operate between machining steps, potentially adding ingredients to the downstream fluids, such as corrosion inhibitors. Nitrites are still present in some washer solutions. Tube fabrication often involves cold forming a tube from a flat steel strip using drawing lubricants that resemble machining fluids, followed immediately by a continuous welder, usually welding right through the fluid-coated surface, producing uncharacterized air contaminants. Unintended uses of MWFs also occur. For example, synthetic MWFs have been observed in use as quench media following heat treatment

(into which hot parts are dropped for rapid controlled cooling); perhaps corrosion inhibitors were advantageous in these applications.

### ***Trends in MWF composition***

There are multiple trends that confuse the evaluation of MWF risk. Base oil refining has generally improved over time; on the other hand recycled oil and higher operating temperatures with advancing tool technology favor the accumulation of thermal degradation products. Some biocides have been restricted on the other hand, concern over endotoxins may have generally increased biocide use (possibly increasing endotoxin release) and altering the ecology of the systems.

New additives are appearing almost continuously, presenting whole new classes of agents with no epidemiologic or toxicologic evidence of long term safety in humans, materials such as: polyalkylene glycols, specialty amides and esters. Many exotic additives have been developed to replace traditional materials with suspect safety, e.g., chlorinated oils. These state of the art additives are usually proprietary. Large-scale sampling of in-use MWF would tend to capture materials reliably representative of those currently in use. A possible problem in this NTP assessment might be that MWF vendors would avoid marketing new products to plants included in the NTP sampling scheme.

### **Specific Comments on Manuscript**

1. see attached edited document for minor suggested text changes
2. p.7: additives are also used for pH control (try to keep it alkaline).
3. p.10: TEA and occupational asthma: I'm aware of asthma associated with triethylamine ("TEA-gas") in foundries but not with triethanolamine.
4. p.14: NDEA is derived from diethylamine; is there diethylamine in MWFs?
5. p.14 (last paragraph): MWF-originating microbial infections are a small although perhaps not insignificant problem compared to the direct toxic (endotoxin) and immunologic (asthma, HP) effects.
6. A number of recent and other citations should be added for a more complete review.

- a. on hypersensitivity pneumonitis:

Zacharisen MC, et al. The spectrum of respiratory disease associated with exposure to metal working fluids. *Am J Ind Med* (1998) 40:640-647.

b. on digestive cancers – stomach and esophagus:

Park RM, Wegman DH, Silverstein MA, Maizlish NA, Mirer FE (1988): Causes of death among workers in a bearing plant. *Am J Ind Med* 13:569-580.

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Schaefer, Michelle: multiple publications in tox literature using Ives Alarie animal model for respiratory and pulmonary irritation (see AAMA Second Symposium on MWFs for references).

1. p.21 (last paragraph): give NDELA concentration in  $\text{ng/m}^3$  as well as in ppm.
2. p.21:  $0.76 \pm 0.05$  .. is this correct? a very precise estimate of mean strand breaks.
3. citations for Key et al. [1983], Niemeier [1990], and ILMA [1994] in Table 1 are not included in References.



**Bill Lucke**

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Mar 23, 2001

EVALUATION OF SENSORY IRRITATION POTENTIAL FOR  
COMMERCIALY AVAILABLE METALWORKING FLUIDS

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ABSTRACT

Seventeen commercially available metalworking fluids were submitted for evaluation by the mouse bioassay for respiratory irritation potential. One fluid was submitted under two sample numbers. Sixteen of the fluids were sensory irritants; all but one were pulmonary irritants. The synthetic fluids, as a class, appeared to have less irritation potential than the semisynthetics, the soluble oils or the synthetic emulsions. It is likely that when the universe of metalworking fluids is considered, there is no difference between the fluid classes.

Two of the fluids could not be aerosolized at levels high enough to reduce the respiratory rate by 50%.

## INTRODUCTION

During the last decade, there has been an increasing awareness of operator complaints about eye, nose, and throat irritation, as part of an increased concern in health effects of exposure to metalworking fluids; specifically those associated with metalworking fluid mists/aerosols.

Sensory irritation is the result of stimulation of the trigeminal nerve endings in the corneal, nasal and oral mucosae because of the action of airborne chemicals.<sup>1</sup>

An effect of the irritation is a decrease in respiratory rate. Alarie has developed an animal bioassay used to predict sensory irritation of chemicals in humans<sup>2</sup>. He found that the decrease in respiration was proportional to the exposure level of the chemical. It is thus possible to calculate an exposure concentration that evokes a 50% reduction in respiration rate, expressed as the RD<sub>50</sub>. Animal responses to individual chemicals, expressed as RD<sub>50</sub>, have been shown to be correlated to Threshold Level Values (TLV) and Permissible Exposure Levels (PEL) set by ACGIH and OSHA, respectively<sup>3,4</sup>.

Kennedy *et al.*<sup>5</sup> reported on pulmonary function measurements performed at the beginning and end of the shifts on Mondays and Fridays in workers exposed to mists of straight oils, soluble oils, or synthetic fluids. Crossshift reductions in FEV<sub>1</sub> (Forced Expiratory Volume, 1 second) were observed on Mondays and Fridays. There was no obvious decrease in FEV<sub>1</sub> observed over the workweek. The study concluded that changes were caused by acute airway obstruction induced by metalworking fluid mist concentrations above 0.2 mg/m<sup>3</sup>, specifically that portion with droplet diameter size < 9.8 μm. Fluid type did not influence the consistency of the results.

Schaper *et al.*<sup>6</sup> have calculated RD<sub>50</sub> values for 10 metalworking fluids using a previously developed mouse bioassay<sup>1,2,7,8</sup>. For the fluids tested, synthetic fluids were the most irritating class, followed by semisynthetics, soluble oils and straight oils. Since the compositions of the fluids were not known, it was not possible to determine which particular chemicals or combination of chemicals might have contributed to the observed irritation.

In the present study, 17 commercially available metalworking fluids of known composition were tested using the mouse bioassay so that chemical origins of irritation effects could be estimated.

## EXPERIMENTAL

Methods (ASTM Designation E 98184) <sup>9</sup>

### Animals

Male, Swiss Webster mice were used during the entire study. A new group of four mice was used for each experiment.

### *Mouse Chamber Exposure*

Each mouse was placed in a body plethysmograph with the head protruding into a glass (2.5 liter) exposure chamber. A latex collar was fitted around the neck of each animal, keeping its head within the exposure chamber. Each animal had a rubber stopper placed behind its tail to keep it confined within the body plethysmograph. Details of the plethysmograph and exposure chamber may be found in Barrow *et al.*<sup>10</sup>. Ventilation of the exposure chamber at an exchange rate of 20 liters per minute provided a constant source of fresh air and removal of generated carbon dioxide. Metalworking fluids were aerosolized and directed into the chamber as desired.

### *Mouse Respiration Measurement and Data Collection*

Pressure changes in the plethysmographs were measured continuously using pressure sensitive transducers (Gaeltec 8T2). The pressure changes corresponded with changes in thoracic displacement or tidal volume and provided an easy means to detect respiratory cycles.

Respiratory rate and tidal volume were calculated every 15 seconds for each of four animals at each exposure level. The mean respiratory frequency for the four animals was calculated from these data. The reduction in the frequency for an exposure group was found by dividing by the frequency for an unexposed group.

### *Exposure*

The metalworking fluids were tested as the product concentrates, except for Semisynthetic 3 and Semisynthetic 4 which were diluted prior to testing with double distilled water (e.g., 20% v/v) to assist in their aerosolization. Each of the metalworking fluids was drawn into a syringe, then fed into a Pitt No. 1 <sup>11</sup> or Pitt No. 4 <sup>12</sup> generator using a Harvard Apparatus syringe pump at a known flow rate. Varying the flow rate generated different aerosol exposure concentrations. Output from the Pitt generator was directed into the glass exposure chamber (described above).

The aerosol concentration for each exposure was determined by gravimetric analysis of collected chamber air samples. Samples were pulled from the exposure chamber at a rate of 2.0 liters/minute on to 47 mm Gelman Type A/E glass fiber filters. All exposure concentrations were expressed in mg/m<sup>3</sup>, representing only the nonvolatile (non-aqueous) components of the aerosolized metalworking fluid. Particle size distributions would be expected to be similar to those found for other fluids by Schaper <sup>6</sup>.

Animals were exposed for a total of 220 minutes. The exposure time was divided into three periods, *Pre-exposure* (air only), 20 minutes; *Exposure* (aerosolized metalworking fluid), 180 minutes; *PostExposure Recovery* (air only), 20 minutes.

Respiratory frequency and tidal volume baseline values were obtained for each animal during the pre-exposure and postexposure periods. Recovery was indicated by a return of respiration rate to baseline values.

Changes in breathing patterns specific to sensory and/or pulmonary irritation <sup>6</sup> were specifically noted on the plethysmographic tracings. These changes are characterized as follows: sensory (nose and throat) irritation is indicated by a hesitation before exhalation; pulmonary (lung) irritation is shown by pauses (i.e., apneic periods) between breaths. The net result of either effect is a reduction in respiratory frequency.

#### *Calculation of RD<sub>50</sub>*

Each metalworking fluid was tested at a minimum of four different exposure concentrations. Responses were plotted against the logarithm of exposure concentration. A straight line was fitted to the data points. The RD<sub>50</sub> was calculated by interpolation for each fluid from the corresponding concentrationresponse relationship (TABLE I).

## RESULTS

The  $RD_{50}$  values and composition for the 17 commercially available metalworking fluids tested are summarized in TABLE I. The fluids include two synthetic emulsions, six semisynthetics, two soluble oils and seven synthetics. All fluids evoked sensory irritation immediately at the beginning of exposure, accompanied by a rapid decrease in respiratory frequency. As the length of exposure increased, sensory irritation persisted. For most fluids, evidence of pulmonary irritation was seen, particularly after 12 hours of exposure. After three hours, the predominant respiratory effect was pulmonary irritation. There were two exceptions to this observation. Neither Semisynthetic 5 nor Synthetic 7 showed any signs of being pulmonary irritants. Inspection of the metalworking fluid compositions given in TABLE I does not suggest any chemical cause for these differences.

The animals did not return to a full recovery of normal respiratory frequency during the 20-minute postexposure observation period. However, the degree of recovery was inversely proportional to the exposure concentrations; animals exposed at lower concentrations showed greater degrees of recovery.

Two of the synthetic fluids (Synthetic 6 and Synthetic 7) could not be aerosolized sufficiently to achieve mist concentrations that would depress the breathing rates of the animals by 50%.

Replicate determinations were done for Semisynthetic 6 and Synthetic 5 so that experimental error could be estimated. The standard error for Synthetic 5 was 29% of the mean while the standard error for Semisynthetic 6 was 18%.

The magnitude of the  $RD_{50}$  values are in general agreement with those reported by Schaper and Detweiler<sup>6</sup> for other fluids. However, that study found that irritation potential increased from soluble oils to semisynthetic fluids to synthetic fluids. That ranking was not found for the present fluid group (Figure 1). When the data from Schaper and Detweiler are included with the present data, the synthetics and the soluble oils both are equivalent as classes and are less irritating than the semisynthetics and the synthetic emulsions (Figure 2). It seems questionable to attempt a general classification of the irritation potential of metalworking fluids based on generic class.

One sample of Semisynthetic 6 was submitted as a 10% mix. The reported  $RD_{50}$  (126 mg/M<sup>3</sup>) was comparable to that of the undiluted samples and confirms the earlier findings<sup>6</sup> that the mist in the exposure chamber consists of the non-aqueous portion of the fluid. Further, this supports the decision to test the fluid concentrates instead of using diluted mixes.

Through circumstance, a sample of used fluid mix was obtained from a workplace that was reporting severe respiratory irritation problems. The fluid was similar to Semisynthetic 6. Samples of the used mix and of a 5% control mix were submitted for RD<sub>50</sub> determination. The measured RD<sub>50</sub> for the control mix was 196 mg/M<sup>3</sup>; consistent with the values found for Semisynthetic 6. While there was not enough sample of the used mix to allow calculation of an RD<sub>50</sub> level, a respiratory rate decrease of 52% was observed at 575 mg/M<sup>3</sup>. Based on this limited data, there was no indication that the used fluid was more irritating than the control, based on the animal response.

Statistical analysis of the RD50 values showed that the remaining fluids fell into two normally distributed groups. (Figure 3) The fluids can thus be grouped as shown:

<b>Fluids</b>	<b>Mean RD<sub>50</sub> (mg/m<sup>3</sup>)</b>	<b>Standard Deviation</b>
SY1, SY4, SY5	730	196
SY6, SY7	NA	NA
All others	202	197

There are no obvious chemical reasons for this distinction.

## DISCUSSION

Respiratory irritation is not health threatening in the sense of causing permanent injury, but it does represent an imposition on the exposed worker and should not be dismissed lightly. Based on our field experience, whenever workplace mist levels exceed 3 mg/M<sup>3</sup>, complaints of irritation can be expected. This observation appears to hold regardless of the fluid type or composition. In general, such high levels of workplace mist exposure are found only in extreme cases; where ventilation is poor, machines are crowded into a small area or where ceilings are unusually low. The keys to resolving or minimizing complaints of irritation include adjustment of fluid flows, provision of splashguards and proper ventilation of the work area. If these underlying causes of high mist are not addressed, fluid reformulation or replacement will be futile.

RD<sub>50</sub> values have been suggested as a basis for setting TLVs for metalworking fluids, using a multiplier of 0.01 as a “safety factor”<sup>6</sup>. Proposed values have ranged from 217 mg/M<sup>3</sup>. These are predicted to be levels at which no irritation effects would be

expected. Based on the observations discussed above, this safety factor seems inadequate at the higher levels.

## CONCLUSIONS

A normal probability plot of the RD<sub>50</sub> values clearly shows that the data can be described as two separate distributions (Figure 3).

The chemicals most commonly identified as likely causes of respiratory irritation, the alkanolamines and formaldehyderelease biocides were not significant causes of irritation. Further, the alkalinity of the fluids was not a significant causative factor.

The RD<sub>50</sub> has proven to be a reliable predictor of irritation and toxic inhalation effects for pure chemicals in the gas phase. Its utility in the present case for particulate mists appears to be questionable.

The observation that most of the fluids tested are pulmonary irritants is cause for concern. Although the responses are seen at mist levels orders of magnitude higher than common workplace levels, the possibility of cumulative injuries should not be discounted. Since pulmonary irritation is signaled by a change in the breathing pattern more subtle than the respiratory rate, a more sophisticated means of analyzing the respiratory response than simple breathing rate is needed to determine the chemical causes of pulmonary irritation. Efforts to expand and improve the mouse bioassay and to develop other test methods capable of determining these chemical causes should be supported by suppliers and users.

## ACKNOWLEDGMENTS

The RD<sub>50</sub> data (obtained in mice) were generated at the University of Pittsburgh.



## Appendix

### Raw Material Effects

If the assumption is made that the differences in irritation potential of these fluids reflects differences in chemical composition, it is possible to postulate a model which expresses the irritation potential as a function of the irritation potential of each chemical and its concentration in the fluid:

$$\mathbf{RD50 = k_1c_1 + k_2c_2 + \dots + k_n c_n + C_0}$$

where **k<sub>n</sub>** represents the irritation potential of the nth component and **c<sub>n</sub>** is the concentration of the nth component and **C<sub>0</sub>** would represent some level of irritation expected in the absence of any chemical exposure. Given the possibility that two or more components have the potential to interact with one another through salt formation or other reaction, the model should also allow for possible second order terms of the form **k<sub>xy</sub>c<sub>x</sub>c<sub>y</sub>**. Since a higher value of RD50 indicates that a material must be present at a higher level to cause a response, a positive value for a given c<sub>n</sub> indicates that substance n reduces the irritation potential of a mixture in which it is present.

The ability of such a model to describe the experimental observations can be evaluated using multiple regression techniques. To that end, the components of the fluids have been grouped as shown in Table 1 into chemicals or classes of chemicals that are representative of those commonly used in metalworking fluid formulations. In addition, the total base number (TBN) of each fluid was included as a variable to determine the significance of alkalinity as a possible cause of irritation. Pure chemicals in the fluids included ethanolamine (MEA), triethanolamine (TEA) and aminomethylpropanol. (AMP). Many components are natural mixtures or have no definite chemical structure. These were included in the models as classes: tall oil fatty acids (TOFA), sulfonates, fatty amides, short chain organic acids and fatty esters. Those biocides that act through the release of formaldehyde were also included as a class ("H<sub>2</sub>CO"). The levels for the biocides were defined as the theoretical amount of formaldehyde present in the fluid.

The mathematical model representing the best statistical description of the relationship between the chemicals and RD50 values was developed by use of stepwise regression analysis. Only two significant factors were found. The results are expressed by the equation:

$$\mathbf{RD50 = 187.0 + 5.8 \times [MEA] \times [Acids] + 2.6 \times [TEA] \times [Acids](Model 1)}$$

with the following statistical attributes:

Coefficient of Determination	0.936
Lack of Fit	0.03
Error	0.03

As a purely mathematical concept, this model explains a large portion of the variation in the data and has low contributions from lack of fit and error. From a practical aspect, it has no value in that it offers no explanations for the origins of product irritation (no negative coefficients present). The prediction that irritation has no chemically assignable cause is sufficient grounds to reject the model whatever the mathematical attractions.

As noted above, RD50 values are calculated by fitting lines through the measured reductions in respiratory rates at different mist levels. In this process, many data points are compressed into a single value and the variation in those data points is suppressed. As a result, there is less variation for a model based on RD50 to explain and model fitting is misleading. The 17 reported RD50 values are, in fact, derived from 92 separate measurements.

These individual data points represent the measured respiratory depression (RD) observed for a specific level of mist exposure. By using the measured RD values as the dependent variable, the full data set can be used as the basis for the regression model. When this is done, including the data from Synthetics 6 & 7 (for which RD50 could not be determined) and regression techniques are applied to the raw data, a new expression results:

$$\mathbf{RD = 22.2 + 0.63 \times [Sulfonates] + 1.86 \times [Amides] + 0.58 \times [TOFA] - 1.05 \times [AMP] + 0.63 \times [Acids](Model 2)}$$

The predicted parameter is the reduction in respiration rate predicted for the fluid in question at an exposure concentration of 100 mg/M<sup>3</sup>. In this model, higher values of RD reflect greater degrees of irritation and those substances with positive values of **cn** would be irritants, those with negative values of **cn** would reduce irritation. The coefficient of determination (0.633) for this model is much lower than for Model 1, but the model now predicts that irritation has assignable causes. The result of a full regression including all variables is given in Table 2.

Model studies with pure chemicals have suggested that the receptor sites in the respiratory tract where irritation occurs exhibit both polar and hydrophobic

character<sup>1,12</sup>. The sulfonates, amides and fatty acids in the products tested are all surface active agents and function as emulsifiers. These are exactly the types of chemicals that would be expected to interact with the receptor sites. On the other hand, experience has shown that use of high levels of the short chain acids in fluids leads to complaints by users of odor and irritation problems. Thus, even though Model 2 explains less of the experimental variance; it does identify possible causes of the observed irritation that are consistent with known chemical properties and field experience. The apparent ability of AMP to mitigate irritation is unexpected. In addition, the coefficients for the other amines, TEA and MEA, were negative but not statistically significant at the 95% confidence level. While it cannot be certain that the coefficients for these amines is not zero, there is a strong implication that those values are not greater than zero and the amines are not likely to be irritants.

In calculating Model 2, mineral oil was arbitrarily excluded as one of the variables. If included, oil would be identified as a source of irritation, replacing the sulfonates. The exclusion was rationalized because straight oil mists are not irritating (4), suggesting that it was a confounding factor rather than a direct cause of irritation.

In evaluating these models, it should be considered that the model

$$RD_{50} = C0(\text{Model } 0)$$

is potentially valid. For the full data set, this model accounts for only 65% of the total variance, with 35% assigned to lack of fit. However, if only those fluids with  $RD_{50} < 400 \text{ mg/m}^3$  are included in the analysis, 95.4% of the total variance is explained. All raw material effects originate in only 4 data points, making any conclusion about chemical effects very suspect.

If Model 0 is accepted, it must be concluded that metalworking fluids of any composition are inherently irritating or that the animal model is not sensitive enough to differentiate chemical effects.

Table 1 RD<sub>50</sub> TEST RESULTS AND FLUID COMPOSITION (wt%)

Fluid <sup>a</sup>	RD <sub>50</sub>	TBN <sup>b</sup>	MEA <sup>b</sup>	TEA <sup>b</sup>	Sulfonate	AMP <sup>b</sup>	Amide	"H <sub>2</sub> CO" <sup>c</sup>	TOFA <sup>d</sup>	Acids	Es
SE1	220	51.0	0	8.5	0	1.15	0	0.3	17.0	0	48
SS1	262	36.4	1.3	5.0	6.0	0	4.0	0	0	0	0
SE2	192	86.0	3.0	0	0	3.0	0	3.0	21.5	2.2	55
SO1	146	20.6	0	4.0	15.5	0.3	0	0	4.5	0	0
SO2	275	33.0	0	5.0	14.6	1.5	0	0.5	0.4	0	0
SS2	227	10.0	0	0	4.8	0.4	4.0	0.1	0.4	0	0
SS3	236	58.0	6.4	0	3.7	0	2.0	1.0	4.9	0	0
SS4	215	62.0	6.3	0	3.7	0	2.3	0.9	7.6	0	0
SY1	433	79.0	5.0	6.0	0	0	0	0	0	6.0	0
SY2	780	123.2	6.0	15.0	0	2.2	0	0.7	0	8.0	0
SS5	200	75.0	3.2	7.3	0	0	4.5	0.9	2.2	1.3	0
SS6	144	69.8	4.0	1.3	3.4	0	7.6	1.8	3.3	0	0
(mix)	170 126										
SY3	193	86.0	5.6	0	0	0	0.5	0	0	1.2	0
SY4	170	69.8	2.0	0	0	0	1.8	0	0	2.8	0
SY5	709 953	173.0	21.0	0	0	0	0	0	0	5.3	0
SY6		112.4	8.3	9.0	0	0	0	0.7	0	8.2	0
SY7		151.2	7.5	25.0	0	0	0	0	0	6.5	0

<sup>a</sup> SE = synthetic emulsion, SO = soluble oil, SS = semi-synthetic, SY = synthetic fluid <sup>b</sup> TBN = Total Base Number, MEA = methyltriethanolamine

AMP = Aminomethylpropanol <sup>c</sup> Calculated level of formaldehyde, based on biocide content <sup>d</sup> tall oil fatty acids



**Table 2. Regression Coefficients for Chemicals/Classes**

Variable	Coefficient	Significance Level
Constant	28.27	0.0000
Sulfonates	0.67	0.0000
Amides	1.78	0.0000
Tall oil Fatty Acids	0.66	0.0001
Acids	1.38	0.0186
AMP	-2.48	0.0443
TBN	-0.09	0.1069
MEA	-1.04	0.3009
Esters	0.04	0.3323
TEA	-0.10	0.6105
"H <sub>2</sub> CO"	0.19	0.8041







**Figure 3**  
**Normal Probability Plot of RD<sub>50</sub> Values**

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