

# WHITE PAPER

## **Hypersensitivity Pneumonitis: Is There an Association with Triazine Biocides and Mycobacteria in Metalworking Fluids?**

A White Paper Produced by the Safety, Health, Environmental Regulatory Affairs Committee of the *Independent Lubricant Manufacturers Association (ILMA)*

### **DISCLAIMER**

The information contained in this White Paper is being made available by the Independent Lubricant Manufacturers Association (ILMA) in the interest of disseminating knowledge about the management and use of metalworking fluids. Neither ILMA nor the individuals who contributed to this White Paper make any representation or warranty, express or implied, with respect to the accuracy, completeness or usefulness of the information contained in this publication. ILMA assumes no responsibility for liability or damage which may result from the use of any of this information in this White Paper.

TABLE OF CONTENTS

	PAGE
<b>I. ABSTRACT .....</b>	<b>3</b>
<b>II. INTRODUCTION .....</b>	<b>4</b>
<b>III. BACKGROUND .....</b>	<b>5</b>
<b>A. Biocides .....</b>	<b>5</b>
<b>B. What are “s-triazines” .....</b>	<b>5</b>
<b>C. Triazine Biocidal Activity .....</b>	<b>6</b>
<b>D. Biocide Resistance .....</b>	<b>7</b>
<b>E. Mycobacteria and HP .....</b>	<b>8</b>
<b>F. Treatment of Bacteria in MWF Systems .....</b>	<b>10</b>
<b>G. Treatment of Mycobacteria in MWF Systems .....</b>	<b>10</b>
<b>IV. POSSIBLE SOLUTIONS .....</b>	<b>11</b>
<b>V. CONCLUSION .....</b>	<b>13</b>
<b>VI. REFERENCES .....</b>	<b>14</b>

# WHITE PAPER

## **Hypersensitivity Pneumonitis: Is There an Association with Triazine Biocides and Mycobacteria in Metalworking Fluids?**

A White Paper Produced by the Safety, Health, Environmental Regulatory Affairs Committee of the *Independent Lubricant Manufacturers Association (ILMA)*

### **I. ABSTRACT**

Triazine-based biocides used in metalworking fluids are members of a larger class of antimicrobials prepared by reacting an amino alcohol with formaldehyde. They are commonly known as “formaldehyde-condensates.” These biocides are routinely formulated in water-based metalworking fluids and used tankside as a means to reduce a broad range of microbial populations that cause fluid spoilage.

As a result of many years of proven usage, triazines have been shown to be highly effective chemical compounds that increase the useful life of fluids in a cost-effective manner. However, recently, the efficacy of using triazine-based and other formaldehyde-condensate antimicrobials has come into question, because of concerns about their ability to control acid-fast species of the genus *Mycobacterium*. In this regard, there are assertions by some users of metalworking fluids that certain species of mycobacteria are causative agents or are at least strongly associated with hypersensitivity pneumonitis in workers exposed to metalworking fluids in the wet machining environment.

This White Paper discusses four major questions: (1) What is the chemistry of formaldehyde-condensate biocides, including triazines, and what are their *United States Environmental Protection Agency (EPA)* usage recommendations?; (2) What is the biocidal activity of triazine against mycobacteria in in-use metalworking fluids and does overuse of triazine promote the growth of acid-fast species?; (3) Do scientific data support a valid relationship between inhaled mycobacteria and hypersensitivity pneumonitis?; and (4) What should users of metalworking fluids that contain triazines and other formaldehyde-condensate biocides do to use them properly while minimizing potential adverse health effects?

## **II. INTRODUCTION**

A recent, widely-discussed hypothesis states that formaldehyde-condensate biocides, such as triazines and oxazolidines, may cause an imbalance in the microbial flora of in-use metalworking fluids (MWFs). The hypothesis further asserts that this putative microbial imbalance favors the proliferation of certain nontuberculosis mycobacteria (NTM) in MWFs and that the subsequent inhalation of NTM-containing aerosols can cause hypersensitivity pneumonitis in a small percentage of susceptible workers.

Hypersensitivity pneumonitis (HP), or extrinsic allergic alveolitis, is an immunologically mediated inflammatory lung disease that affects the distal portions of the lungs. Summarily, polymorphonuclear leukocytes (PMN) accumulate in the alveoli and airways as a result of antigen exposures. Subsequently, there is an influx of mononuclear cells in the affected sites and the formation of non-necrotizing granulomas that reduce functional lung tissue. Individuals who are susceptible to HP contract the disease through repeated exposures to low or high molecular weight environmental antigens. In order of increasing severity, there are three stages of HP; acute, subacute, and chronic. The chronic form of HP - a focus of this paper - is associated with irreversible pulmonary fibrosis. Symptoms of HP include flu-like illness accompanied by chronic dyspnea, i.e., difficult or labored respiration. The immunologic mechanisms associated with this disease are not well understood. For a comprehensive examination of what is presently known about the pathogenesis and epidemiology of HP, the reader is directed to suggested papers.<sup>(1,2)</sup>

It has been known for some time that the etiologic agents of HP are derived from a variety of sources including animals and plants, insects, water-based mechanical systems, medications, and chemicals. The interpretation of data from epidemiological investigations that seek to identify the etiology of HP in occupational settings is confounded by the reality that afflicted individuals have been constantly exposed to numerous antigens on a regular and daily basis in both domestic and occupational environments. Further, in cases where discrete substances are suspected etiologic agents of HP, there have been no dose-response relationships established for provocative antigens. Indeed, there may be synergistic interactions among several antigens that cause individuals with particular genetic susceptibilities to become symptomatic for HP disease.

### **III. BACKGROUND**

#### **A. Biocides:**

Industrial biocides are chemicals that are added to MWF formulations or mixes to kill and/or retard the growth of bacteria and fungi. The EPA regulates biocides under the Pesticide Act of 1972 through the administration of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Under FIFRA, biocides require extensive toxicological testing, since each biocide is registered for a particular application. This registration process is similar to the federal Food and Drug Administration (FDA) registration for pharmaceuticals and is more extensive than the notification requirements of the Toxic Substances Control Act (TSCA) for non-pesticide chemicals.

Over a period of time MWFs may lose their desired functional characteristics because of spoilage, i.e., rancidity, caused by a variety of microorganisms. Unless the deterioration of MWFs is controlled, infected fluids may cause dermatitis and respiratory problems among some workers. Rancid fluids also will cause a decline in optimal machining performance requirements that will result in increased tool wear and poor parts quality.

The formaldehyde-releasers have found increasing use in many industrial processes requiring the preservation of materials such as cutting fluids. For example, the imidazoles, and hexamine derivatives are widely used. Isothiazolinones, oxazolidines and chemicals in the dioxane family are also used globally. One of the most popular categories of biocides consists of the formaldehyde-condensates that have been in use for over three decades. Some specific biocides in this group are Bioban<sup>®</sup> CS-1246, Bioban<sup>®</sup> CS-1135, and Vancide<sup>®</sup> TH. A related category of biocidal formaldehyde-condensate compounds is the nitroalcohols. Their antimicrobial action is due to the release of formaldehyde in aqueous alkaline systems; the product tris(hydroxymethyl) nitromethane (TRIS NITRO<sup>®</sup>) is representative of this class.

#### **B. What are “s-triazines”?:**

As a class of organic compounds, s-triazines are characterized by a symmetrical hexametric (6-member) ring with three carbon atoms and three nitrogen atoms alternating in the cyclic structure. Also attached to the triazine ring are carbon chains that may or may not be oxygenated.

Not all s-triazines are pesticides (e.g., melamine is used as a thermosetting plastic). There are approximately 30 s-triazines registered and approved by the EPA. Only two s-triazines are currently registered and approved by EPA for use in MWF as antimicrobial agents. A commodity type s-triazine is Hexahydro-1,3,5-tris-(2-hydroxyethyl)-s-triazine (CAS No. 4719-04-4). The single active ingredient and 78% active versions are Busan<sup>®</sup> 1060 (Buckman Laboratories, Inc.), Grotan<sup>®</sup> (Troy Corporation), Triadine<sup>®</sup> 3 (Arch Chemicals, Inc.), and Onyxide<sup>®</sup> 200 (Stepan Company). There are other single active component triazines of lower concentrations, and “private label” sub-registration biocides that the EPA does not list on its website. A biocide that is not widely used but is, nevertheless, still actively registered is Hexahydro-1,3,5-triethyl-s-triazine (CAS No. 7779-27-36): Vancide<sup>®</sup> TH (R.T.Vanderbilt Company, Inc.).

### **C. Triazine Biocidal Activity:**

Triazine-based biocides are formed from a condensation reaction between equimolar amounts of alkanolamine and formaldehyde. Insofar as the ultimate “mode of action” of triazine biocidal activity is concerned, this mechanism is not as clear-cut as the disruption of specific metabolic sites by antimicrobial agents that are utilized in chemotherapy.<sup>(3)</sup> However, it is known that the hydrolysis of formaldehyde-condensates at the cell boundary (wall) effectively denatures this peptidoglycan structure and, thus, leads to cellular death.<sup>(4)</sup> Mechanistically, aldehydes are electrophilic active agents and, because of the electron deficiency of the carbonyl atom, a reaction with nucleophilic cell entities (e.g., amino and thiol groups) leads to antimicrobial activity.<sup>(5)</sup>

Though the biochemistry of the cell walls of various bacterial species differs slightly according to genetic variability and the availability of environmental nutrient factors, triazine biocidal activity is effective against a wide spectrum of organisms at the EPA approved dosage of 1500 ppm. In addition to their biocidal effectiveness, triazines have been used extensively in water-based MWF formulations, because of favorable cost/dose considerations as compared to many other biocides. The efficacious use of triazine in MWF concentrates or as a tankside additive as part of an overall fluid management program to control microbial contamination has a long and proven history in the MWF industry. It should be noted that a form of triazine called Hexahydro-1,3,5-tris-(3-methoxypropyl)-s-triazine (CAS No. 3960-05-2) is used for pH buffering and emulsion stability. Though this product is not marketed as a biocide, it does have some antimicrobial properties.

Many of the EPA registered s-triazines provide buffering, pH adjusting, corrosion inhibition, rancidity control, and a variety of other desirable properties for metalworking fluids. There are producers of s-triazines or products containing s-triazines that make no antimicrobial claims. Metalworking fluid formulators and end-users should be mindful of all the properties and the potential cumulative effects that additives might have on the microorganisms in a given MWF distribution system.

#### **D. Biocide Resistance:**

As a matter of survival, some procaryotic microorganisms, such as bacteria, have inherent mechanisms to combat the lethal effects of biocides. Many of these mechanisms are based on plasmids (i.e., small circular deoxyribonucleic acid (DNA) molecules in bacteria that replicate independently of the chromosome).<sup>(6,7)</sup> Plasmids can carry the genes that confer resistance to recipient bacteria against biocides. Some microorganisms have cell walls that are not reactive to certain biocides. Other microbes have cell membranes that will not allow the passage of biocide molecules that function in the interior of the cell. Under some conditions, bacteria can accept DNA from other bacteria that encodes for resistance to metals (e.g., mercury, and antimicrobials such as biocides and antibiotics through a direct exchange (conjugation)), from the environment (transformation), or from viruses (transduction). By one of these genetic exchanges a bacterial cell that was previously sensitive to antimicrobial treatment may now be resistant to it. Bacteria also undergo genetic mutations that make them capable of resisting chemicals. Mutations occur rarely and at an average of 1 in  $10^8$  (1/100,000,000) cells. These mutated cells may then acquire a genotype that confers resistance to biocides or antibiotics. For example, mutations may change as many as 70 or more ribosomal proteins in a cell.

In natural environments, microorganisms commonly live in ecological clusters called “biofilms” where they form symbiotic relationships, e.g., the sharing of nutrients. A biofilm is a consortium of microorganisms that is produced when slime-forming bacteria extrude a sticky slime exopolymer consisting of protein and carbohydrates. Biofilms are found throughout MWF distribution systems and, though the biochemical compositions of different biofilms vary according to their microbial constituents, the result is the same; the slime exopolymer protects microorganisms by reacting with intruding chemicals. Biofilms in MWF systems cause the microorganisms

within them to be more resistant to biocides. Inorganic materials also stick to the exopolymer and present a further challenge to biocide treatments. In aged biofilms that adhere to the surfaces of MWF reservoirs, sumps and machine parts, there is eventually a sloughing off of sections of embedded cells that are impacted in slime exopolymer. Subsequently, this detached cellular material will find its way into fluids and aerosols.

Some microorganisms do not become resistant to but, instead, become “tolerant” of biocides, i.e., they tolerate high doses of biocide(s) but are not killed. This phenomenon is demonstrated by raising the applied dosage several fold higher than the typically applied dosage, causing the susceptible cells to die. If the cells were truly resistant, they would not be killed by the higher dosage. In some cases, resistant microorganisms will metabolize a biocide through various biochemical degradative pathways and then utilize the released biochemical energy in the form of adenosine triphosphate (ATP). “Tolerant cells” lack this capability.

#### **E. Mycobacteria and HP:**

The bacterial genus *Mycobacterium* is typically represented by an aerobic, acid-fast bacillus that measures 0.2-0.7 x 1.0-10 µm depending on the species and growth conditions. In nature, mycobacteria are widely distributed in soil and water. Many *Mycobacterium* species grow slowly in microbiological media, e.g., 2-60 days under optimal temperature. Faster growing mycobacteria such as *M. chelonae*, *M. fortuitum*, *M. phlei*, and *M. smegmatis* can grow up on subculture in 7 days or less. As a result of the ubiquity of mycobacteria in the ambient environment, it is not unusual for humans to inhale these microbes in aerosols in a variety of everyday settings. Significantly, the inhalation of aerosolized mycobacteria does not result in pulmonary disease in most exposed individuals, and exposure rates are much more frequent than incidences of HP.

In recent years, some researchers have focused on certain fractions of airborne microbial exposures as possible etiologic agents of HP. In this regard, acid-fast, NTM mycobacteria such as *Mycobacterium chelonae* and a relatively newly proposed NTM species, *M. immunogenum*, have been investigated. (Note: “Acid-fastness” is a laboratory staining characteristic of certain bacteria in which the stained cell wall is not easily decolorized by acids.) Selected studies of machining facilities that have had incidences of HP report a tenuous association between the presence of these organisms in machining environments and HP. This association is based on the

assumption that HP is caused by mycobacterial species that have “recently appeared” in some MWF systems. Rossmore and Bassett have suggested that these organisms arise because they are resistant to formaldehyde-releasing biocides and colonize sites formerly occupied by Gram-negative bacteria, as is evidenced by endotoxin accumulations in fluid samples.<sup>(8)</sup> The use of biocides like p-chloro-m-cresol (PCMC) and chlorinated isothiazolone may be indicated for the reduction of NTM when triazines are not effective.<sup>(9)</sup>

In 1997, under the sponsorship of the *United Auto Workers (UAW)-Chrysler National Joint Committee on Health and Safety*, and the *Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health (CDC/NIOSH)* facilitated a workshop in Detroit, Michigan (January 28-29) dealing with the prevention of HP in the workplace. This meeting of representatives from the corporate, union, industry, and academic sectors, was prompted by outbreaks of HP in various automotive plants and parts manufacturing facilities.<sup>(10,11,12)</sup> A published summary of this meeting concluded that NTM and fungi were “strong candidates” for HP, but confirmatory data was not presented.<sup>(13)</sup> A recent CDC/NIOSH report described HP cases of machinists at an automobile brake manufacturing facility in which NTM were implicated but not confirmed as etiologic agents.<sup>(14)</sup> CDC/NIOSH published a widely distributed criteria document in 1998 which stated that the etiologic agents of HP in workers in machining environments were unknown.<sup>(15)</sup> During bronchoscopic examinations, pulmonologists routinely find mycobacteria and other types of bacteria, and also various fungi in the lungs of HP patients.

In general, there is a low incidence of infectious disease outbreaks in industries that utilize metalworking fluids.<sup>(16)</sup> There have been relatively low incidences of diagnosed HP in workers who are employed in automobile manufacturing facilities. One widely quoted estimate puts the incidence of HP in these industries at between 2.3 per 10,000 (clinically documented) to 4.9 per 10,000 (inclusive of surveillance cases).<sup>(17)</sup> In an attempt to explain these cases, investigators have looked at water-soluble metalworking fluid exposures of workers in automobile plants. Workers may be exposed to a wide variety of chemical and biological antigens in MWF as well as other antigens from intramural and extramural environments associated with a given facility. Previous investigations of some HP incidents in machining operations indicate that there was a loss of microbial control in fluid systems that resulted in increases in colony-forming units per ml (CFU/ml) of not

only mycobacterial species, but also of *Pseudomonas*, *Actinomycetes*, fungi and numerous other species. The microflora of metalworking fluid grab samples commonly consists of fungi, mycobacteria, and Gram-positive and Gram-negative bacteria. Interestingly, though fungi as a group are found in great abundance in practically all MWF systems, these eucaryotes have not been implicated thus far as causative agents of HP in machining operations.

#### **F. Treatment of Bacteria in MWF Systems:**

It is important for fluid management personnel to determine what types of microorganisms will be eliminated from a given system. For example, if one's goal is to decrease the total count of aerobic bacteria and all of these bacteria are in the flowing fluids (i.e., they are planktonic) a low dose of standard nonoxidizing biocides should suffice. However, in most MWF systems, the bacteria are also present in large numbers in biofilms, i.e., sessile formations. Thus, in this case it is necessary to treat a given system with a biodispersant and nonoxidizing biocides. Though nonoxidizing biocides decrease the concentrations of many types of bacteria, no specific nonoxidizing biocide will kill all bacteria. Therefore, it is important to use more than one biocide in a system to maintain low levels of bacteria and fungi, and to eliminate known problematic bacterial species.

Some biocide suppliers share Minimum Inhibitory Concentration (MIC) data for specific microorganisms. The MIC is the lowest treatment dose that will prevent a laboratory test culture population from proliferating, or otherwise contributing to biodeterioration. Typically, a kill dose is two to six times greater than the MIC dose. Several slug doses may be required to kill a mixed population of microorganisms entrenched in biofilms and a combination of biocides is usually needed. If certain bacteria or fungi are problematic in a given system, the fluid manager can select a biocide based on the product technical information provided by the supplier in order to plan treatment strategies to eliminate these organisms. These strategies are highly dependent on the results of prior microbiological testing of representative fluid samples. Biocide users should consult with their MWF suppliers and follow manufacturers' labeled directions.<sup>(18)</sup>

#### **G. Treatment of Mycobacteria in MWF Systems:**

If a MWF system is contaminated with mycobacteria that the fluid manager wants to eliminate, it is usually treated with heavy doses of the appropriate biocide and allowed to stand for a recommended period of time; then it is drained, cleaned and recharged (DCR). Biocides used for MWF

applications must have EPA approval and should be targeted against the specific microorganisms of concern.

A metalworking fluid system is dynamic, because of continually changing contamination and environmental conditions. Therefore, microbial treatment practices should be re-evaluated on a regular basis in accordance with fluid management control parameters. System evaluations should always include the following:

- **Identify** the type of contamination.
- **Quantify** the microbial contamination.
- **Determine**, through visual inspection, the presence and severity of biofilm.
- **Evaluate** the efficacy of the current biocide treatment vs. specifically targeted microorganisms (e.g., mycobacteria, *Candida* yeast, *Aspergillus* mold).

#### **IV. POSSIBLE SOLUTIONS**

Hypersensitivity pneumonitis occurs as a result of repeated airborne exposures to antigens that may be of viable and/or non-viable origin. Therefore, based on the best available scientific evidence, mycobacteria alone cannot be definitively implicated as the etiologic agents of HP in machining operations.<sup>(19,20)</sup> Obviously, individuals who work in machining facilities and who are diagnosed with HP have had a variety of inhalational exposures. In order to better understand the role(s) of etiologic agents in HP, a proper analysis of these exposures requires a multifactorial analytical approach. The application of this method recognizes the reality of the exposure environments that contain antigens that cause HP. On the other hand, the use of a singular approach to elucidate the cause(s) of HP, i.e., the implication of a single agent (*Mycobacterium* species) from a single source (MWF) as a result of a single cause (triazine), overlooks the importance of applying the proper scientific methods. Classical pathogen-disease associations that are encountered in clinical settings are commonly elucidated by *Koch's Postulate*-type reasoning: (I) a specific bacterium is found in all subjects that experience a specific disease; (II) the bacterium is isolated from the diseased host and grown in pure culture; (III) the disease is reproduced when the pure bacterial culture is inoculated into a healthy host; and (IV) the bacterium is recovered from the infected host. However, worker health problems related to occupational exposures are difficult to

ascribe to a sole etiologic agent. In this regard, aside from the suggestions made by Rossmore and Bassett as noted earlier, there have been no published microbial ecology studies of fluids in active systems to test the hypothesis that triazine biocides routinely favor the proliferation of NTM over other species. Also, no explanation is given for the absence of HP among workers who are exposed to fluids in systems that have relatively high NTM CFU/ml. Further, most studies of HP in plants give little or no data on antigen concentrations in extramural air or other non-MWF sources of airborne exposures.

It is incumbent upon MWF managers in machining facilities to assure that the proper engineering controls (e.g., ventilation systems, machine enclosures), fluid management practices, industrial hygiene measures, and facility housekeeping standard operating procedures are in place to protect workers. Again, the need for good housekeeping in machining industries is universally recognized, because we have known for many years that this simple yet effective measure works.<sup>(21)</sup> Vigilant housekeeping practices provide a low-tech and highly effective method to reduce the possibility of adverse health effects in machining environments. By and large, clean industrial environments are usually healthy workplace environments.

The proper dosing of a coolant system and maintaining an acceptable concentration of biocide in a MWF system are measures that do not always guarantee that all microorganisms will be controlled. It is important to evaluate biocide treatment practices, and analyze fluids with appropriate microbiological tests. Moreover, systems should be regularly inspected to evaluate whether the desired fluid conditions have been achieved. The effectiveness of a responsible fluid management program should be re-evaluated periodically. If the existing program is not effective, an alternative biocide should be added, or the biocides used should be changed to prevent bacterial resistance. One should keep in mind that a change(s) in the chemical or physical factors in a given system may cause problems with a normally effective biocide program. For example, changes in a contaminant, raw material, or a new additive can decrease the effectiveness of a biocide that was once effective in the same MWF system. Therefore, careful and frequent monitoring of the system is required. In order to eliminate the potential for problems, immediate follow-up based on the results of inspections is needed. This approach is much more economical than paying undue DCR and attendant disposal charges.

The role(s) of endotoxin in promoting HP problems is(are) not a focus of this White Paper. However, it is briefly mentioned here because of the potential for endotoxin to cause serious respiratory problems in many different industries where bacterial growth creates problems. Endotoxin - a constituent of the cell membranes of Gram-negative bacteria - is a powerful immune system potentiator. Rossmore and Bassett have suggested that exposure to aerosols containing endotoxin antigens, along with mycobacterial cell wall fragments and biocides may cause some workers (including those with pre-existing lung diseases from non-occupational and occupational exposures) to eventually manifest HP symptoms.<sup>(8)</sup> Therefore, it is recommended that future investigations of HP incidents in workplaces include data collection of endotoxin concentrations in fluids and aerosols (area and personal samples).

## **V. CONCLUSION**

The recent hypothesis which states that there is an association between the proliferation of *M. chelonae* and *M. immunogenum* in MWF systems and HP, as a result of triazine usage, has not been rigorously tested.<sup>(22)</sup> This hypothesis becomes problematic in situations where *M. immunogenum* or other mycobacterial species are present in fluids - sometimes in relatively high concentrations - but there is not a single case of diagnosed HP in exposed workers. Therefore, until more scientific data are available, this hypothesis must be viewed with some skepticism. A ban on triazine in MWF concentrates appears to be an attempt to respond to a problem. In this regard, MWF end-users would perhaps be better served by encouraging well-designed scientific studies that will provide solutions to a problem that many consider complicated and perplexing. The unfortunate outcome of a ban on triazine from MWF formulations is that an effective biocide has been hastily implicated as the cause of a serious respiratory disease, and that the focus of the underlying cause(s) of HP has been shifted from needed research to speculation. The historical record clearly shows that triazines have consistently functioned well as biocidal chemicals.

For the future welfare of its workforce, it is incumbent upon the MWF industry as a whole to study many machine shops and to compare the incidences of HP. In particular, data should be gathered on differences between shops with outbreaks and those without outbreaks. An organization like CDC/NIOSH would be an ideal research partner to initiate such a study, as a follow-up to data that was presented in the 1998 NIOSH MWF criteria document. In this regard, a protocol should be developed that stresses the

need for periodic measurements of mycobacteria, Gram-negative and Gram-positive bacteria, endotoxin, and fungi (the major microflora in MWF).

The exact underlying causes of the recent incidences of HP in the workplace are still unknown. The seriousness of this disease compels end-users and metalworking fluid suppliers to work together to better understand the etiology of the disease. This cooperative association should begin by designing good scientific studies. The sporadic nature of HP incidents in the workplace requires the implementation of rigorous scientific methods that will foster an understanding of the contributory factors that cause HP outbreaks among some workers but not others who are exposed to similar workplace conditions. An investigational approach that includes basic research and intensive field studies is the most effective way to eventually eradicate HP from the workplace.

The initiative by some to ban triazines from concentrates has elicited widespread discussions and a sharing of ideas and opinions, as is evidenced, in part, by the writing of this White Paper. Industry stakeholders will, undoubtedly, observe the results of this initiative with involved interest. However, regardless of the outcome of the matter, resultant data can be used towards finding solutions that contribute to the provision of healthier work environments for MWF workers.

## VI. REFERENCES

1. Wild, L.G., and Lopez, M. 2001. Hypersensitivity Pneumonitis: A Comprehensive Review. *J Invest Allergol Clin Immunol* 11(1):3-15.
2. Bourke, S.J., Dalphin, J.C., Boyd, G., McSharry, C., Baldwin, C.I., and Calvert, J.E. 2001. Hypersensitivity Pneumonitis: Current Concepts. *Eur Respir J* 18 (Suppl 32):81s-92s.
3. Rossmore, H.W., and Sondossi, M. 1988. Applications and Mode of Action of Formaldehyde Condensate Biocides. *Adv Appl Microbiol* 33:223-277.
4. Holtzman, G.H., and Rossmore, H.W. 1977. Evaluation of Action of a Formaldehyde Condensate Germicide. *Dev Ind Microbiol* 18:753-758.
5. Paulus, W. 1993. Substance Classes: Properties-Effectiveness-Applications (Aldehydes), p. 37. In: *Microbicides for the Protection of Materials: A Handbook*. Chapman & Hall (Kluwer Academic) Publishers, London.
6. Candal, F.J., and Eagon, R.G. 1984. Evidence for plasmid-mediated bacterial resistance to industrial biocides. *Intl Biodeterioration* 20(4):221-224.
7. Sondossi, M., Rossmore H.W., and Wireman, J.W. 1986. The Effect of Fifteen Biocides on Formaldehyde-Resistant Strains of *Pseudomonas aeruginosa*. *J Ind Microbiol* 1:87-96.
8. Rossmore, H., and Bassett, D. 2002. Oil Mist Exposures and the Development of Hypersensitivity Pneumonitis. Presentation: Health Effects of Mineral Oil Mist & Metalworking Fluids Symposium (October 2-4, 2002), Cincinnati, OH, American Conference of Governmental Industrial Hygienists (ACGIH), Cincinnati, OH.
9. Rossmore, H.W., Rossmore, L.A., Cuthbert, C., and Cribbs, C.E. 2002. Detection and Control of *Mycobacterium* sp. in Metalworking Fluids. Presentation: Society of Tribologists and Lubrication Engineers (STLE) 57<sup>th</sup> Annual Meeting, May 19-23, 2002, Houston, TX.
10. Muilenberg, M.L., Burge, H.A., and Sweet, T. 1993. Hypersensitivity Pneumonitis and Exposure to Acid-Fast Bacilli in Coolant Aerosols. Abstract 682. *J Allergy Clin Immunol* 91:311.
11. Bernstein, D.I., Lummus, Z.L., Santilli, G., Siskosky, J., and Bernstein, I.L. 1995. A Hypersensitivity Pneumonitis Disorder Associated with Exposure to Metalworking Fluid Aerosols. *Chest* 108:636-641.
12. Centers for Disease Control and Prevention (CDC). 1996. Biopsy-Confirmed Hypersensitivity Pneumonitis in Automobile Production Workers Exposed to Metalworking Fluids – Michigan, 1994-1995. *Morbidity and Mortality Weekly Reports (MMWR)* 45:606-610.
13. Kreiss, K., and Cox-Ganser, J. 1997. Metalworking Fluid-Associated Hypersensitivity Pneumonitis: A Workshop Summary. *Am J Ind Med* 32:423-432.
14. Centers for Disease Control and Prevention (CDC). 2002. Respiratory Illness in Workers Exposed to Metalworking Fluid Contaminated with Nontuberculosis Mycobacteria---Ohio, 2001. *Morbidity and Mortality Weekly Reports (MMWR)*, April 26, 2002, 51(16):349-352.

15. Centers for Disease Control and Prevention (CDC). 1998. **Criteria for a Recommended Standard: Occupational Exposure to Metalworking Fluids.** Cincinnati, OH: NIOSH; Publication No. 98-102.
16. Passman, F.J., and Rossmore, H.W. 2002. **Reassessing the Health Risks Associated with Employee Exposure of Metalworking Fluid Microbes.** *Lubrication Engrg* 58(7):30-38.
17. American Automobile Manufacturers Association (AAMA). 1998. **The Industrial Metalworking Environment: Assessment and Control of Metal Removal Fluids, Symposium II.** In: *AAMA Symposium Proceedings (September 15-18, 1997)*, Felinski, D.A., and D'Arcy, J.B., eds., Detroit, MI.
18. American Society for Testing and Materials (ASTM). 2001. **Standard Practice for Selecting Antimicrobial Pesticides for Use in Water-Miscible Metalworking Fluids.** ASTM Standard E 2169-01, West Conshohocken, PA.
19. Woskie, S., Virji, M.A., Hallock, M.F., Hammond, S.K., et al. 2002. **A Summary of Findings from the Exposure Assessment Components of MWF Mortality and Morbidity Studies in the Transportation Manufacturing Industry. Presentation: Health Effects of Mineral Oil Mist & Metalworking Fluids Symposium (October 2-4, 2002), Cincinnati, OH, American Conference of Governmental Industrial Hygienists (ACGIH), Cincinnati, OH.**
20. Shelton, B.G., Flanders, W.D., and Morris, G.K. 1999. ***Mycobacterium* sp. As a Possible Cause of Hypersensitivity Pneumonitis in Machine Workers.** *Emerging Infect Dis* 5(2) (internet serial publication), <http://www.cdc.gov.ncidod/eid/vol5no2/shelton.htm>.
21. Russ, G.A. 1979. **Coolant Control of Large Central Systems.** *J Amer Soc Lubr Engrs* 36(1):21-24.
22. Wallace, R.J., Zhang, Y., Wilson, R.W., Mann, L., and Rossmore, H. 2002. **Presence of a Single Genotype of the Newly Described Species *Mycobacterium immunogenum* in Industrial Metalworking Fluids Associated with Hypersensitivity Pneumonitis.** *Appl Environ Microbiol* 68(11):5580-5584.