NIOSH

Current Intelligence Bulletin

Reprints-Bulletins 31 thru 47

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

NIOSH CURRENT INTELLIGENCE BULLETIN
REPRINTS - BULLETINS 31 thru 47

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

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DISCLAIMER

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DHHS (NIOSH) Publication No. 86-122

PREFACE

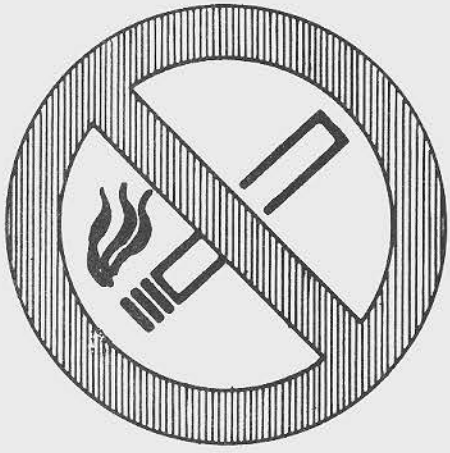
In January 1975, the National Institute for Occupational Safety and Health (NIOSH) developed a Current Intelligence System. Through this system, persons concerned with occupational health are informed of health and safety hazards that have gone unrecognized or are greater hazards than generally known. Since the inception of the NIOSH Current Intelligence System, over 40 Current Intelligence Bulletins have been issued as part of the information dissemination process. It is important to note that the Bulletins have been reprinted essentially as originally published and do not contain information that may have become available since date of publication. Also, for some of the substances, NIOSH may have since issued Criteria Documents with recommended occupational health standards.

NIOSH

Current Intelligence Bulletin 31

February 5, 1979

ADVERSE HEALTH EFFECTS of SMOKING and the OCCUPATIONAL ENVIRONMENT



U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health

The NIOSH Current Intelligence Bulletin is the primary product of the Current Intelligence System. The purpose of the Current Intelligence System is to promptly review, evaluate, and supplement new information received by NIOSH on occupational hazards that are either unrecognized or are greater than generally known. The staff of the NIOSH Technical Evaluation and Review Branch, Office of Extramural Coordination and Special Projects was responsible for the preparation of this Bulletin.

As warranted by this evaluation, the information is capsulized and disseminated to NIOSH staff, other government agencies, and the occupational health community, including labor, industry, academia, and public interest groups. With respect to currently known hazard information this system also serves to advise appropriate members of the above groups of recently acquired specific knowledge which may have an impact on their programs or perception of the hazard. Above all, the Current Intelligence System is designed to protect the health of American workers and to allow them to work in the safest possible environment.

DHEW (NIOSH) Publication No. 79-122

CURRENT INTELLIGENCE BULLETIN

ADVERSE HEALTH EFFECTS OF SMOKING AND THE OCCUPATIONAL ENVIRONMENT

February 5, 1979

There is increasing evidence of adverse health effects due to the combined actions of tobacco use and exposure to chemical and physical agents in the workplace. The National Institute for Occupational Safety and Health (NIOSH) recommends that the use of and/or carrying of tobacco products into the workplace be curtailed in situations where employees may be exposed to physical or chemical substances which can interact with tobacco products. Additionally, curtailment of the use of tobacco products in the workplace should be accompanied by simultaneous control of worker exposure to physical and chemical agents. These recommendations are based on evidence which indicates that smoking can act in combination with hazardous agents to produce or increase the severity of a wide range of adverse health effects. Six ways have been identified by which smoking can interact with workplace exposures, and this Bulletin has been prepared to advise you of the hazards involved. NIOSH requests that chemical producers and distributors transmit the information in this Bulletin to their customers and employees, and that professional associations and unions inform their members.

In this Bulletin, smoking and/or tobacco products are defined as cigarettes, cigars, pipe tobacco, chewing tobacco, and any by-products resulting from their burning and/or use. The discussions and illustrations used in this Bulletin may relate to any one or more of these products. It is important to note that many of the adverse effects can still occur if an exposed tobacco product (contaminated) is subsequently smoked away from the workplace.

BACKGROUND

The National Institute for Occupational Safety and Health recently prepared a chapter entitled "Interaction Between Smoking and Occupational Exposures," for SMOKING AND HEALTH - A Report of the Surgeon General - January 11, 1979 (1). This Bulletin contains a summary of the information in the above chapter of the Surgeon General's Report.

The smoking habits among workers in various occupations provide an opportunity for interaction to occur between smoking and workplace exposure to physical and chemical agents. More blue-collar workers smoke [51%] than white-collar workers

[37%]. Also, the blue-collar workers have the highest risk for workplace exposure to hazardous physical and chemical agents. The use of tobacco products and workplace exposure to industrial agents increased steadily from 1920 to 1960. Since 1966 the percentage of blue-collar workers who smoke has decreased while the number of workplace exposures continues to increase. Studies have shown that more non-whites[22.6%] work in jobs associated with an increased risk of lung cancer than do whites[13.5%](2-5).

Despite increasing recognition that both smoking and workplace exposures contribute to the development of certain disease states, few investigators have addressed the ways in which these two factors can interact to produce or enhance disease in workers. Some of the effects historically attributed to smoking may actually reflect interactions between smoking and workplace exposure to physical and chemical agents. These cannot always be quantified, and it should be noted that the six different mechanisms by which smoking may adversely act with physical and chemical agents found in the workplace are not mutually exclusive and several may prevail for any given agent. The six modes of interaction follow.

ILLUSTRATIONS OF MODES OF ACTION

1. Certain toxic agents in tobacco products and/or smoke may also occur in the workplace, thus increasing exposure to the agent.

   Employees exposed in the workplace to toxic chemicals can receive additional exposures from the presence of those toxic chemicals in tobacco products. For example, cigarette smoking causes increased exposure to carbon monoxide (CO). A CO concentration of 4% (40,000 ppm) in cigarette smoke can lead to a lung CO concentration of 0.04 to 0.05% (400 to 500 ppm), which can produce CO blood concentrations, as measured by the carboxyhemoglobin (COHb) level, of 3 to 10% (6-8).

   Workers are frequently exposed to carbon monoxide as part of their job and workers who smoke in those situations have increased exposure to CO. For example, in a study of COHb levels in British steelworkers, the average end-of-shift COHb concentration found in non-smoking blast furnace workers was 4.9% compared to 1.5% in non-smoking unexposed controls. For heavy cigarette smokers, the average COHb levels were 7.4% for exposed blast furnace workers and 4.0% for unexposed controls (9). The COHb levels of blast furnace workers who smoked were in a critical range. Studies have shown that levels of COHb in excess of 5% can cause cardiovascular changes which are dangerous for persons with coronary heart disease (10-11). Also, since a significant number of workers have coronary heart disease and many smoke, additional occupational exposure to carbon monoxide may increase cardiovascular morbidity and mortality.

   Other chemicals found in tobacco which workers might be exposed to at their jobs, include: acetone, acrolein, aldehydes (e.g. formaldehyde), arsenic, cadmium, hydrogen cyanide, hydrogen sulfide, ketones, lead, methyl nitrite, nicotine, nitrogen dioxide, phenol, and polycyclic aromatic compounds (12).

2. Workplace chemicals may be transformed into more harmful agents by smoking.

The heat generated by burning tobacco can transform workplace chemicals into more harmful substances. Investigations of outbreaks of polymer fume fever (PFF) provide a clear illustration of this effect.

Polymer fume fever is a disease caused by inhalation of degradation product fumes from heated Teflon® (polytetrafluoroethylene). The particular chemical agents responsible for PFF have not been identified; however, temperatures in excess of 315°C (600°F) have been sufficient to cause their production. It is important to note that the temperature of burning tobacco in a cigarette is approximately 875°C (1600°F) (13,14). This disease is characterized by effects such as chest discomfort, fever, increased number of white blood cells, headache, chills, muscular aches and weakness (15). Because these symptoms are similar to those of other diseases, such as influenza, polymer fume fever may go undiagnosed. It has been suggested that repeated attacks of polymer fume fever may lead to permanent lung damage (16).

One report describes aviation employees whose work involved contact with door seals that had been sprayed with an unspecified fluorocarbon polymer. In one case, a worker smoking during a break realized by the taste of his cigarette that it had become contaminated. Although the worker extinguished the cigarette, he experienced shivering and chills lasting approximately six hours, beginning one-half hour after smoking (17).

Another illustrative report describes outbreaks of polymer fume fever among smokers whose hands were contaminated with polytetrafluoroethylene used as a mold release agent. There was no recurrence of symptoms among these workers after smoking at the plant was prohibited (18).

Other examples of workplace chemicals which can possibly be transformed into more toxic substances by smoking after tobacco is contaminated include a number of chlorinated hydrocarbons that have the potential for conversion to phosgene, a highly toxic chemical.

3. Tobacco products may serve as vectors by becoming contaminated with toxic agents found in the workplace, thus facilitating entry of the agent into the body by inhalation, ingestion, and/or skin absorption.

Tobacco products can become contaminated by chemicals used in the workplace thus increasing the amount of toxic chemicals entering the workers' bodies.

The effects of smoking cigarettes contaminated in the workplace with known amounts of tetrafluoroethylene polymer have been studied with the assistance of human volunteers. Nine out of ten subjects were reported to exhibit typical

polymer fume fever symptoms after each had smoked just one cigarette contaminated with 0.40 mg tetrafluoroethylene polymer.

Some other toxic chemicals found in the workplace, identified in NIOSH criteria documents as potential contaminants of tobacco products include boron trifluoride (20), carbaryl (21), dinitro-ortho-creosol (22), inorganic fluorides (23), formaldehyde (24), lead (25,26), inorganic mercury (27), methyl parathion (28), and organotin (29).

4. Smoking may contribute to an effect comparable to that which can result from exposure to toxic agents found in the workplace, thus causing an additive biological effect.

Smoking can add to the damaging biological effects which result from exposure to toxic chemicals found in the workplace. For example, combined worker exposure to chlorine and cigarette smoke can cause a more damaging biological effect than exposure to chlorine alone. In a plant producing chlorine by electrolysis of brine, 55 of 139 workers required oxygen therapy at least once during their employment after accidental exposure one or more times to high concentrations of chlorine. The maximal mid-expiratory flow (MMF) values of these workers with accidental chlorine exposures were compared with those of non-exposed smokers and non-smokers. A reduction in normal lung function is indicated by low MMF values, while a normal lung function is reflected by higher MMF values. MMF values decreased when chlorine and smoking were considered as additive toxic agents. Average MMF values in liters per second [L/sec] decreased in the following sequence: unexposed non-smokers [4.36], unexposed smokers [4.13], exposed non-smokers [4.10], and exposed smokers [3.57] (30). Other agents which can act additively with tobacco smoke include cotton dust (31), coal dust (32,33), and beta radiation (34).

5. Smoking may act synergistically with toxic agents found in the workplace to cause a much more profound effect than that anticipated simply from the separate influences of the occupational exposure and smoking.

Smoking can interact with worker exposure to toxic materials found in the workplace resulting in more severe health damage than that anticipated from adding the separate influences of the occupational exposure and smoking. Asbestos provides one of the most dramatic examples of severe health damage resulting from interaction between the smoking of tobacco products and workplace exposures. In a prospective study of 370 asbestos insulation workers, 24 of 283 cigarette smokers died of bronchogenic carcinoma during the four year period of the study, while not one of the 87 non-cigarette smokers died of this cancer (35). This study suggested that asbestos workers who smoke have eight times the risk of lung cancer as compared to all other smokers and 92 times the risk of non-smokers not exposed to asbestos. This same group of insulation workers was restudied five years later, at which time 41 of the 283 smokers had died of bronchogenic cancer. Only 1 of the 87 non-cigarette smokers, a cigar smoker, died of lung cancer (36).

Other chemicals and physical agents which appear to act synergistically with tobacco smoke include radon daughters (37), gold mine exposures (38), and exposures in the rubber industry (39).

6. Smoking may contribute to accidents in the workplace

Studies have shown that smoking contributes to accidents in the workplace. In a nine-month study of job accidents, the total accident rate was more than twice as high among smokers as among non-smokers (40). It has been suggested that injuries attributable to smoking were caused by loss of attention, preoccupation of the hand for smoking, irritation of the eyes, and cough (41). Smoking can also contribute to fire and explosions in occupational settings where flammable and explosive chemical agents are used; however, in many of these areas smoking is prohibited.

Some other situations where interaction between smoking and workplace exposure have been hypothesized include:

A. Cadmium - Several studies suggests that exposed smokers had poorer lung function and a higher incidence of urinary abnormalities than did exposed non-smokers (42,43).

B. Chloromethyl Ether - Chronic cough and expectoration showed a dose response relationship with chemical exposure and smoking. For each smoking category, chronic cough was more common for exposed than for unexposed men (44).

C. beta-Naphthylamine and other Aromatic Amines - There are reports of associations between cigarette smoking and bladder cancer (45,46). Since aromatic amines, which are known bladder carcinogens, are also found in cigarette smoke (12), a smoker who works with this group of gases receives exposure to bladder carcinogens from two sources. The interaction between smoking and exposure to aromatic amines should be further assessed.

Research Considerations

1. Studies on the adverse health effects from smoking should take occupational exposures into consideration and vice versa. Whenever possible, studies should include data on exposed and unexposed smokers and non-smokers.

2. The increasing rates of lung cancer in non-white males compared to white males should be investigated further with respect to occupational exposures and smoking habits.

3. The change in smoking habits of blue collar workers over the last decade provides an opportunity to more critically assess the contribution of smoking vs. occupational exposure to hazardous agents to certain disease states. Cohorts should be identified and followed prospectively for this purpose.

4. Workplace physical and chemical agents which interact with the smoking of tobacco to produce adverse health effects should be identified.

5. Further investigation into the mechanisms of synergism between smoking and occupational exposures is needed.

6. The impact of the combination of smoking and workplace exposures upon reproductive functions needs further study.

7. The impact of smoking on workplace accidents merits further study.

8. The lack of information on the effect of side stream smoke in the development of occupational disease in non-smoking workers merits attention.

9. The effects of cessation of smoking upon lung cancer risk among those occupationally exposed to toxic workplace agents requires investigation.

RECOMMENDATIONS

The National Institute for Occupational Safety and Health (NIOSH) recommends that the use of and/or carrying of tobacco products into the workplace be curtailed in situations where employees may be exposed to physical or chemical substances which may interact with tobacco products. Additionally, curtailment of the use of tobacco products in the workplace should be accompanied by simultaneous control of worker exposure to physical and chemical agents. These recommendations are based on evidence which indicates that smoking can act in combination with hazardous agents to produce or increase the severity of a wide range of adverse health effects.

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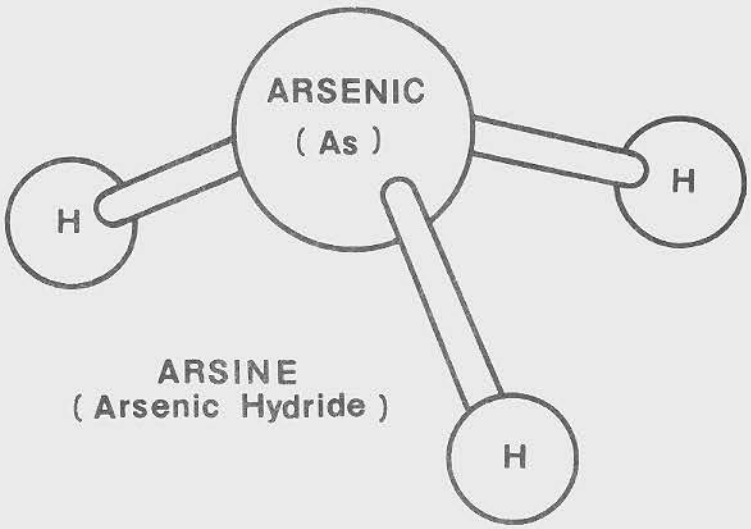
NIOSH

Current Intelligence Bulletin 32

AUGUST 3, 1979

ARSINE (Arsenic Hydride) POISONING IN THE WORKPLACE



ARSINE
(Arsenic Hydride)

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health

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IDENTIFIERS AND SYNONYMS FOR ARSINE

Chemical Abstracts Service Registry Number: 7784-42-1
NIOSH RTECS Number: CG6475000
Chemical Formula: AsH_3

Arsine
Arsenic hydride
Arsenic trihydride
Arseniuretted hydrogen
Arsenous hydride
Hydrogen arsenide

The above information was obtained from the National Institute for Occupational Safety and Health's computerized Registry of Toxic Effects of Chemical Substances (RTECS), and from the National Library of Medicine's computerized chemical dictionary file CHEMLINE. Registered trademark information is not included in these files. Therefore, some of the above synonyms and identifiers may be trademarked but are not so indicated above.

DHEW (NIOSH) Publication No. 79-142

CURRENT INTELLIGENCE BULLETIN

ARSINE (Arsenic Hydride) POISONING IN THE WORKPLACE

The National Institute for Occupational Safety and Health (NIOSH) recommends that appropriate workpractices be implemented to reduce the risk of worker exposure to arsine (AsH_3) gas. There is a high potential for the generation of arsine gas when inorganic arsenic is exposed to nascent (freshly formed) hydrogen. This recommendation is based on several reports of worker exposure to arsine resulting in severe toxic effects or death. Most of the reported cases occurred when arsine was accidently generated during an industrial process. NIOSH would like to inform the occupational health community of some of the circumstances in which workers have been poisoned by arsine, with particular emphasis on the underlying mechanisms of generating the gas. We request that producers and distributors of arsenic and materials containing arsenic transmit information to their customers and employees, and that professional associations and unions inform their members.

Stibine (SbH_3), another toxic gas, is formed when antimony is exposed to nascent hydrogen. In most situations where arsine can be formed, stibine can also be formed if antimony is present. Therefore, similar workpractices should be implemented to reduce the risk of worker exposure to stibine.

BACKGROUND

Identified in 1775, arsine is a highly poisonous, colorless, nonirritating gas with a mild garlic odor. It is soluble in water, and slightly soluble in alcohol and alkalies. When nascent hydrogen is generated in the presence of arsenic, or when water reacts with a metallic arsenide, arsine evolves. Most cases of arsine poisoning have been associated with the use of acids and crude metals, one or both of which contained arsenic as an impurity. Ores contaminated with arsenic can liberate arsine when treated with acid (1). Arsine is commercially produced for use in organic synthesis, and the processing of solid state electronic components.

In industrial settings arsine poisoning generally results from the accidental formation of arsine gas. Most reported cases of exposure to arsine have occurred during the smelting and refining of metals. However, there are many other situations where exposures to lethal concentrations of the gas have been reported, including galvanizing, soldering, etching and lead plating operations. Arsine can be produced by fungi (especially in sewage) in the presence of arsenic. The renewed interest in coal as a source of energy causes concern for a possible increase in the number of exposures to arsine, because coal contains considerable quantities of arsenic. The processes for converting coal to gas and other by-products should include preventative measures aimed at reducing the chance of transformation of the arsenic impurities into arsine (1).

OCCUPATIONAL STANDARDS AND EXPOSURES

The current Department of Labor, Occupational Safety and Health Adminstration (OSHA) standard for occupational exposure to arsine is 0.05 ppm (0.2 mg/cu m of air) as a time-weighted average in any 8-hour work shift of a 40-hour work week. The present OSHA standard for occupational exposure to stibine is 0.1 ppm (0.5 mg/cu m of air) in any 8-hour work shift of a 40-hour work week (2). The 1975 NIOSH Criteria Document on inorganic arsenic recommended that worker exposure to inorganic arsenic and to arsine be limited to 0.002 mg (2.0 μg) of arsenic/cu m of air as determined by a 15-minute sampling period. The document states that the short-term limit is intended to achieve the greatest practicable reduction in worker exposure while avoiding spurious sampling results which can be produced by natural background concentrations of inorganic arsenic (3). The 1978 NIOSH criteria document on antimony recommended the retention of the specific Federal limit for occupational exposure to antimony, without recommending a limit for stibine (4).

The NIOSH National Occupational Hazard Survey (NOHS) estimates that approximately 900,000 workers are occupationally exposed to identified sources of arsenic for varying periods of time during the workday. This estimate is not, however, based on actual workplace environmental exposure measurements. However, arsenic is a widespread element, and therefore unidentified exposures can occur in unsuspected work situations. The NOHS estimate for occupational exposure to antimony is approximately 1,700,000 workers (5).

TOXICITY

The first case of arsine poisoning was reported in 1815 after a German chemist died from an exposure to arsine in his laboratory. From 1815 to 1928, 247 cases of arsine poisoning were reported. From 1928 to 1974 an additional 207 cases were reported, of which 51 (25%) were fatal (1).

Acute Arsine Toxicity - Arsine is the most acutely toxic form of arsenic and one of the major industrial causes of sudden extensive hemolysis (destruction of red blood cells). It has the ability to combine with hemoglobin within the red blood cell, causing destruction or severe swelling of the cell, rendering it nonfunctional (1). Inhalation of 250 ppm (800 mg/cu m) of arsine gas is instantly lethal. Exposures of 25-50 ppm (80-160 mg/cu m) for one-half hour are lethal, and 10 ppm (32 mg/cu m) is lethal after longer exposures. The Mean Lethal Dose (MLD) is unknown for man, but in small mammals it is about 0.5 mg/kg body weight (6).

The characteristic features of acute arsine poisoning are abdominal pain, bloody urine, and jaundice (yellow discoloration of the skin). Initial symptoms of arsine

poisoning are headache, malaise, weakness, dizziness, difficult breathing, abdominal pain, nausea, and vomiting, which are usually first noticed 2 to 24 hours after exposure. Bloody urine, light to dark red, is frequently noticed 4-6 hours after exposure to arsine and is often followed by jaundice 12-48 hours later. An unusual bronze discoloration of the skin can often be observed accompanying the jaundice. If the arsine exposure is severe, the products resulting from the breakdown of red blood cells and hemoglobin will clog the kidneys, causing a reduction in the amount of urine formed, sometimes to the point of complete blockage of urine formation. Other toxic effects of arsine include damage to the liver and heart, either by direct actions of arsine in the cells or due to the formation of arsenic (1,7).

Chronic Arsine Toxicity - Most reported cases of arsine poisoning have been acute or sub-acute in nature, usually resulting from a single short exposure or from breathing the gas for a few hours. In one report of chronic arsine poisoning, it was noted that arsine in very small concentrations appeared to exert a cumulative, damaging effect. This was manifested by a progressive drop in the number of red blood cells and in the hemoglobin level. The exposed victims experienced shortness of breath on exertion, and a general feeling of weakness. However, in relation to the degree of blood destruction, the degree of known disability experienced by the victims of chronic arsine poisoning was less than expected (8).

Chronic Arsenic Toxicity - Since inorganic arsenic is needed to generate arsine, prolonged exposures to low levels of arsine are likely to occur under conditions where workers are also exposed to inorganic arsenic. Once arsine is inhaled, it breaks down, releasing inorganic arsenic into the blood stream. The worker's risk of arsenic poisoning is therefore increased by the combination of inorganic arsenic exposure and the breakdown of arsine. A number of signs and symptoms are associated with arsenic poisoning. When ingested, arsenic compounds can cause nausea, vomiting and diarrhea within a few hours. Dermatitis may be observed after chronic ingestion, but the typical signs include increased pigmentation, and thickening of the skin on the palms and soles of the feet. Changes in the heart's performance, as measured by the electrocardiogram (ECG) have been reported after chronic arsenic intoxication. Observed ECG changes regressed after arsenic exposure ceased. Decreased numbers of red and white blood cells were reported in cases of chronic intoxication, but these changes also regressed after arsenic ingestion ended. Skin cancer has long been considered a consequence of arsenic exposure, however multiple cancers of the internal organs have also been reported (3).

Case Reports - Most cases of arsine poisoning occur after the accidental generation of the gas in the workplace. During recent years many incidents have involved a reaction between arsenic and aluminum, with the subsequent release of hydrogen in the presence of water to permit the formation of arsine gas (9). Tables 1, 2, and 3 list examples of accidental arsine poisoning reported in the literature.

TABLE 1. Examples of workers poisoned by arsine in smelting and refining operations.

o Three workers were poisoned while using a jackhammer to remove slag from ladles. To reduce dust, water was sprayed on the slag. The water reacted with the arsenide of the alkali metal, generating arsine (9).
o A worker was poisoned while cleaning an obstructed industrial drain which contained acid liquors with arsenic impurities. A galvanized shovel and bucket were used to carry the sludge from the drain. The acidic arsenic liquor reacted with the zinc coating of the bucket and produced arsine (10).
o Thirteen workers were poisoned (3 died) during the purification of lead alloys. Arsine fumes were generated by moisture reacting with aluminum arsenide in metal dross (11).
o A worker was poisoned during reclamation of metal from flue dust obtained from blast furnaces. Zinc, water, and sulphuric acid had been added to the dust. Upon heating with steam, arsine was formed because arsenic impurities and nascent hydrogen were both present (12).

TABLE 2. Examples of workers poisoned by arsine in enclosed spaces.

o Two workers were poisoned while cleaning an aluminum trailer tank with a phosphoric acid solution. The tank had been used 6 months previously for the transport of a 42% solution of sodium arsenite (weed killer). Since that time it had been cleaned with steam and detergent, and used for storage and transportation of alcohol and other industrial solvents. Before assigning the trailer to another client, a thorough cleaning job was ordered, which required the hand application of the acid cleaner. Subsequently, arsine was generated by a reaction between the acid cleaner and the aluminum which had arsenic impurities (13).
o Three workers were poisoned while using an aluminum ladder to descend into a chemical evaporation tank containing a few inches of sodium arsenite. The aluminum ladder reacted with the sodium arsenite, liberating arsine (14).
o Eight sailors were poisoned when a cylinder containing arsine developed a leak, emitting the gas into the airspace of a cargo hold on board a freighter (15).

TABLE 3. Examples of workers poisoned by arsine in miscellaneous occupational settings.

o A worker was poisoned while pouring freshly diluted commercial hydrochloric acid through the pipes of a water jacket. The manufacturer had added sodium arsenite and aniline hydrochloride to the acid to act as inhibitors to the corrosive action of the acid. Subsequently the mixture of water and sodium arsenite under these conditions led to the generation of arsine (16).
o Five workers were poisoned while washing aluminum slag to dissolve out soluble constituents. Apparently, the copper in this mixture was contaminated with arsenic (17).
o Eight children and one adult were poisoned on a farm while cleaning a dipping vat. Two years before, arsenic had been used in the vat as an insecticide. Later, with another insecticide, superphosphate was added to create an acid medium, thereby leading to arsine production (18).
o Two workers were poisoned after a commercial drain cleaner was added to a drain which contained water and arsenic residues. The drain cleaner contained sodium hydroxide, sodium nitrate, and aluminum chips. These chemicals reacted to produce nascent hydrogen, which bonded with the arsenic, leading to generation of arsine (19).

Although the accidents illustrated in the above tables differ with respect to the surrounding circumstances, the basic reactions leading to arsine formation are similar. Arsine usually evolved when nascent hydrogen was generated in the presence of arsenical compounds, or by the hydrolysis of a metallic arsenide in contact with water. Invariably, there was an acid medium where metal was present (e.g., dross residues, galvanized implements, aluminum tanks or implements) thereby creating the key ingredients necessary for arsine formation.

A more recent area of concern involves the recycling of batteries. Lead alloys in car batteries contain antimony as a hardener, with arsenic and silver added to inhibit corrosion. In the production of "maintenance-free" batteries, calcium is added to the lead alloys as a hardening agent. During recycling, arsine can be released if scrap containing arsenic is melted down with the "maintenance-free" batteries containing calcium. When the scrap mixture is in the molten state, calcium arsenide is formed. As cooling occurs, the calcium arsenide floats to the surface as part of the dross, and in the presence of water, arsine evolves (20).

OTHER CONSIDERATIONS

Stibine (SbH_3; hydrogen antimonide; antimony hydride; antimony trihydride)- Antimony (Sb) can be converted to stibine by a similar series of reactions required to convert arsenic to arsine. Stibine equals or surpasses arsine in toxicity, and causes a specific toxic action which closely resembles that of arsine (21). Although stibine is chemically similar to arsine, it is less stable. Probably because of this instability fewer cases of stibine poisoning have been reported (22). Stibine can evolve when certain alloys containing antimony (Sb) are treated with acid and subjected to electrolytic action, when certain antimony compounds are treated with steam, or whenever nascent hydrogen comes in contact with metallic antimony or with a soluble antimony compound.

When stibine enters the bloodstream, it reacts with the hemoglobin of red blood cells, leading to destruction of the cells (21). Stibine exerts a direct effect on the brain tissue cells, leading to various degrees of degeneration (23). Victims of stibine poisoning have experienced marked weakness, headache, nausea, severe abdominal and lower back pain, and blood in the urine. These symptoms are similar to those caused by arsine toxicity (24).

NIOSH RECOMMENDATION

In light of the serious and accidental nature of exposure to arsine and/or stibine, NIOSH recommends that steps be taken to prevent exposure to these gases. Whenever the possibility exists for either gas being generated, such as when working with metals (crude, drosses, or implements made of metal) care should be taken to assure that arsenic and antimony do not react with any sources of fresh hydrogen. Similarily, when working with arsenical compounds, care should always be taken to prevent the inadvertant generation of hydrogen gas in the presence of arsenicals. In all occupational settings where there is arsenic, workers should be informed of the possibility of arsine formation when there is nascent (freshly formed) hydrogen present. Likewise, workers exposed to antimony compounds should be informed of the possibility of exposure to stibine when freshly formed hydrogen is present.

Further research on the chronic and acute effects of exposure to arsine and stibine is needed. Although the acute toxicity of arsine in humans is fairly well defined, very little information is available on long term effects of exposure to arsine with simultaneous exposure to other arsenic compounds. In addition, more research into methods of sampling for the presence of arsine and stibine in air is needed, for both monitoring and documentation purposes.

In the event arsine and/or stibine is generated, immediate steps should be taken to remove workers from the contaminated environment. In cases of exposure, or when any symptoms are first observed, prompt medical attention is imperative. Treatment of arsine poisoning should include: (a) immediate blood exchange transfusion to replace the destroyed red blood cells, and also to remove arsenic

(24)

and the hemoglobin-arsine complex; (b) the adminstration of therapeutic amounts of dimercaprol (BAL); and (c) dialysis should be started if the patient has suffered kidney damage. Exchange transfusions lower blood arsenic levels, but dialysis, though it may be life-saving, does not remove arsenic from the patient. Therefore, efforts should be made to remove arsenic from the victim's body (25). Other medical support measures should be utilized as indicated.

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JOINT

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RADIOFREQUENCY (RF) SEALERS AND HEATERS:

POTENTIAL HEALTH HAZARDS AND THEIR PREVENTION

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health

U. S. DEPARTMENT OF LABOR
Occupational Safety and Health Administration

This Current Intelligence Bulletin is a joint effort of the National Institute for Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Administration (OSHA), and is a product of the NIOSH Current Intelligence System. The staff of the NIOSH Technical Evaluation and Review Branch, Office of Extramural Coordination and Special Projects, was responsible for the preparation of the Bulletin. Major contributions to the content of the Bulletin were made by NIOSH Division of Criteria Documentation and Standards Development and Division of Biomedical and Behavioral Science and by staff of the Occupational Safety and Health Administration.

The purpose of the NIOSH Current Intelligence System is to promptly review, evaluate, and supplement new information received by NIOSH on occupational hazards that are either unrecognized or are greater than generally known. As warranted by its evaluation, the information is capsulized and disseminated to NIOSH staff, other government agencies, and the occupational health community, including labor, industry, academia, and public interest groups. With respect to currently known hazard information this system also serves to advise appropriate members of the above groups of recently acquired specific knowledge which may have an impact on their programs or perception of the hazard. Above all, the Current Intelligence System is designed to protect the health of American workers and to allow them to work in the safest possible environment.

"Employers in every state who want help in recognizing and correcting safety and health hazards in their workplaces can get it from a free onsite consultation service funded by the Occupational Safety and Health Administration. The service is delivered by state governments or private sector contractors using well trained professional staff. Employers can obtain from OSHA the name, address, and phone numbers of the state agency or contractor that provides this service."

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JOINT NIOSH/OSHA
CURRENT INTELLIGENCE BULLETIN: #33

Radiofrequency (RF) Sealers and Heaters: Potential Health Hazards and Their Prevention

December 4, 1979

The National Institute for Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Administration (OSHA) are concerned about potential health hazards to workers exposed to radiofrequency (RF) energy emitted from RF dielectric heaters (more widely known as RF sealers and heaters). RF energy is nonionizing electromagnetic radiation and should not be confused with X-rays and other ionizing radiation. RF energy, when absorbed in sufficient amounts by workers, may produce adverse thermal effects resulting from heating of deep body tissue which may include potentially damaging alterations in cells. Absorption of RF energy may also result in "nonthermal" effects on cells or tissue, which may occur without a measureable increase in tissue or body temperature. "Nonthermal" effects have been reported to occur at exposure levels lower than those that cause thermal effects. While scientists are not in complete agreement regarding the significance of reports of "nonthermal" effects observed in laboratory animals, NIOSH believes there is sufficient evidence of such effects to cause concern about human exposures. NIOSH and OSHA recommend that precautionary measures be instituted to minimize the risk to workers from unwarranted exposure to RF energy. Section V of the Appendix to this Bulletin lists engineering controls, such as shielding, and other immediate actions that should be taken. Also, NIOSH and OSHA are issuing this Bulletin to alert employers and workers to the potential for overexposure of workers to RF energy from RF sealers and heaters, and to recommend control technology that can prevent unwarranted exposures.

Workers near RF sealers may be unaware of their exposure to RF emissions, because the RF energy from sealers and heaters can penetrate deeply into the body without activating the heat sensors located in the skin. A false sense of employee safety may exist; in many instances, worker exposures to RF energy may not have been properly assessed. This has been due, largely, to the complex problems of measurement and thus the misapplication of the instruments available for monitoring RF energy levels. Recently, monitoring instruments that facilitate accurate measurement of worker exposure have been developed. Federal survey teams, equipped with these new instruments, have detected excessive exposures of workers to RF energy.

NIOSH is seeking additional information about the adverse effects of RF energy and effective control technology. The Institute would appreciate receiving information concerning adverse health effects among workers which might be associated with their exposure to RF energy in the workplace and information on methods for retrofitting existing RF sealers and heaters in order to control the

emission of RF energy. NIOSH and OSHA request that manufacturers, distributors, and users of RF sealers and heaters transmit the information in this Bulletin to their customers and employees, and that professional societies, trade associations, and unions inform their members.

BACKGROUND

RF sealers have been used for more than 30 years, but there are no reliable, documented estimates of the number of units in present use or of the number of workers operating RF sealers. However, it is generally believed that the number of RF sealers and heaters in use is approximately 20,000 and that there are about 30,000 to 40,000 workers operating these units. A list of companies believed to manufacture RF sealers and/or heaters appears in Section I of the attached Appendix.

RF sealers are used to heat, melt, or cure materials such as plastic, rubber, or glue. Specific uses include: 1) the manufacture of many plastic products such as toys, vinyl loose-leaf binders, rain apparel, waterproof containers, furniture slip covers, and packaging materials; 2) wood lamination and veneer processes, including glue setting; 3) embossing and drying operations in the textile, paper, plastic, and leather industries; and 4) curing of various materials including plasticized polyvinyl chloride, wood resins, polyurethane foam, concrete binder materials, rubber tires, and epoxy resins. An extensive list of occupations involving the use of RF sealers and heaters is presented in Section II of the attached Appendix.

Experiments in animals suggest that the potential consequences of absorbing excessive amounts of RF energy may include changes in: the eye, the central nervous system, conditioned reflex behavior, heart rate, chemical composition of the blood, and the immunologic system. Effects on reproduction and on the development of offspring of females exposed during pregnancy have also been reported.

As previously mentioned, a false sense of employee safety may exist in many industrial settings because worker exposures to RF energy may not have been properly assessed. The recent development of monitoring instruments that facilitate accurate measurement of worker exposure to RF energy allowed for a series of studies at workplaces where RF sealers and heaters are used. The results of a NIOSH study indicate that the majority of the workers surveyed were exposed to RF energy at levels exceeding values citable by OSHA.[1] RF energy in the immediate area of a worker has been measured at levels as great as ten times the values citable by OSHA.[1,2] A list of manufacturers of instruments suitable for measurement of RF energy is presented in Section III of the attached Appendix.

This Bulletin will provide an overview of the potential adverse health effects associated with the use of RF dielectric heaters. The Appendix contains technical information to assist research, engineering, and manufacturing personnel in evaluating this potential hazard and for initiating appropriate modification and controls to prevent unwarranted worker exposure.

BIOLOGICAL EFFECTS OF RF ENERGY

Excess amounts of RF energy absorbed by workers may produce adverse thermal effects resulting from heating of deep body tissue. These thermal effects may include potentially damaging alterations in cells caused by localized increases in tissue temperature. Scientists involved in this work have generally agreed that exposures of humans to levels of RF energy at or above a far-field power density of 10 mW/cm^2 (see Section IV.C of the attached Appendix) can cause net increases in tissue or body temperatures, and that exposures at or above these values should be avoided.[3] In the far field, a power density of 10 mW/cm^2 is equivalent to a mean squared electric field strength of 40,000 $volts^2/meter^2$ or a mean squared magnetic field strength of 0.25 $amperes^2/meter^2$. Because the body's surface heat sensors, located in the skin, are not activated when RF energy is absorbed deep within body tissues, RF sealer workers may be unaware that they are absorbing RF energy.

Absorption of RF energy may also result in "nonthermal" effects on cells or tissue, which may occur without a measurable increase in tissue or body temperature. "Nonthermal" effects are reported to occur from exposure to RF energy at field strengths lower than those necessary to cause thermal effects.[4,5] While scientists are not in complete agreement regarding the significance of reports of "nonthermal" effects observed in laboratory animals, NIOSH believes there is sufficient documentation of such effects to cause concern.

For radiation frequencies similar to those commonly used with RF sealers and heaters, reported observations at relatively low energy levels in laboratory rats or rabbits included changes in: electroencephalographic (EEG) recordings of electrical activity of the brain,[6] conditioned reflex behavior,[6,7] chemical composition of the blood,[6] the endocrine (hormonal) system,[6,8] and the immunologic (infection defense) system.[6,9] Details of these experiments are summarized in Section IV.E of the attached Appendix. For the frequencies at which these observations have been made the rates of energy absorption in man are much greater than in the laboratory animals.[10] Therefore, the biological effects observed in the laboratory animals *may* occur in humans at exposure levels even lower than those reported for the animals.

Other adverse health effects on the eye, heart rate, and the central nervous system have been observed in laboratory animals exposed to electromagnetic energy at higher frequencies in the microwave region of the electromagnetic spectrum (see Section IV.A of the attached Appendix). The extent to which these latter effects may also be caused by absorption of energy at the lower frequencies employed by RF sealers is not known.

There is no convincing evidence to indicate that RF energy can cause cancer in humans.[4] Reports have described chromosomal abnormalities in animal and human cells cultured in the laboratory after exposure to RF energy.[11,12] However, the relevance of such studies to humans is not known and must be determined through additional research.

There have been reports which suggest an association between RF exposure and reproductive damage in animals and humans. These reports, primarily from

Eastern Europe and the Soviet Union, list a variety of reproductive and developmental effects resulting from occupational exposures of workers and experimental exposures of laboratory animals to electromagnetic energy at frequencies in the RF and microwave ranges. Reported effects from exposure of women to fields of relatively high intensity RF and microwave energy have included changes in menstrual pattern, increased incidence of miscarriage, and decreased lactation in nursing mothers.[13] Retarded fetal development and increased congenital anomalies have been noted among exposed offspring.[13] Laboratory studies have shown that exposure of pregnant rats to RF energy (at levels believed to have been relatively high) resulted in numerous fetal malformations including abnormalities of the central nervous system, eye deformities, cleft palate, and deformation of the tail.[14]

There is a report of changes in spermatogenesis (production of male germ cells in the testicles) among workmen exposed to nonionizing electromagnetic energy.[15] Reproductive effects in male experimental animals, including testicular damage, debilitated or stillborn offspring and changes in spermatogenesis, have been reported to be related to exposure to electromagnetic energy at microwave frequencies.[16,17] Similar studies have not been reported for the lower frequencies of RF sealers and heaters.

NIOSH surveys indicate that a large majority of the workers using RF sealing and heating equipment are women of child-bearing age.[18] NIOSH is beginning an epidemiologic study of potential reproductive effects among operators of RF sealers, and is conducting laboratory research to study the possibility that teratogenic effects (malformations) in animals may result from exposure to RF radiation.

PRESENT OCCUPATIONAL EXPOSURE STANDARD

The Occupational Safety and Health Administration radiation protection standard for occupational exposure to RF and microwave radiation (29 CFR 1910.97) applies to the frequencies 10 - 100,000 MHz. It establishes as a limit for occupational exposures a maximum power density of 10 mW/cm^2, as averaged over any possible 6-minute period.[19] In the far field, a power density of 10 mW/cm^2 is equivalent to a mean squared electric field strength of 40,000 $volts^2/meter^2$ or a mean squared magnetic field strength of 0.25 $amperes^2/meter^2$. OSHA is presently enforcing both of these mean squared field strengths averaged over any 0.1-hour period, as exposure limits for RF energy, under its occupational standard for nonionizing radiation (29 CFR 1910.97).

Existing national health standards for RF energy have been based on evidence of the thermal effects which result from the body's absorption of RF energy and the subsequent heating of deep body tissue. However, in recent years since the development of existing national standards, concern has increased over reported "nonthermal" effects, which may occur at exposure levels lower than those causing measurable thermal effects.

NIOSH RECOMMENDATIONS

NIOSH and OSHA are concerned about potential health hazards to workers exposed to RF energy emitted from RF sealers and heaters. The present Federal standard was derived using data principally from experiments with animals at microwave frequencies, not at the lower radiofrequencies. The standard was intended to prevent thermal effects.

The extent to which biological effects attributed to the absorption of RF energy by animals reflect an occupational hazard to workers is not fully known. There are uncertainties in extrapolating experimental results from animals to humans and to frequencies other than those used in the experiments. These problems have been compounded by the difficulty in properly measuring near-field RF energy exposures, which has been only recently resolved. NIOSH recommends that future research projects dealing with RF energy meet requirements for: 1) better exposure dosimetry and quantification of biological results, 2) use of adequate experimental controls, and 3) uniform reporting of experimental parameters and results.

While scientists are not in complete agreement on the interpretation of available data on biological effects, NIOSH believes there is sufficient evidence of such effects to cause concern about human exposures. NIOSH and OSHA recommend that precautionary measures, as listed in Section V of the attached Appendix, be instituted to protect workers from unwarranted exposure to RF energy.

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Administration

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APPENDIX

JOINT NIOSH/OSHA CURRENT INTELLIGENCE BULLETIN #33

Radiofrequency (RF) Sealers and Heaters:

Potential Health Hazards and Control

I. Manufacturers of Radiofrequency Sealing and/or Heating Equipment

Mention of company name or product does not constitute endorsement by National Institute for Occupational Safety and Health or the Occupational Saf and Health Administration.

Chemetron Corp. (Voltator),	Louisville, Kentucky
Compo Industries, Inc.	Waltham, Massachusetts
Cosmos Electronic Machine Corporation	Farmingdale, New York
Duomatic Electronics Corporation	Brooklyn, New York
Gallery Services Fara-Dine	So. El Monte, California
Gerling Moore, Inc.	Santa Clara, California
Guild Electronics, Inc.	Brooklyn, New York
Hall Dielectric Machine Company	Deer Park, New York
J.A. Callanan Company	Chicago, Illinois
Kabar Manufacturing Corporation	Farmingdale, New York
Lepel High Frequency Laboratories, Inc.	Maspeth, New York
Mann-Russell Electronic Devices, Inc.	Tacoma, Washington
Pillar Corporation	Milwaukee, Wisconsin
P.S.C. Inc.	Cleveland, Ohio
Radio Frequency Company, Inc.	Medfield, Massachusetts
Seal-Pac Services and Machine, Inc.	Brooklyn, New York
Solidyne, Inc.	Bay Shore, New York
Divisions: Thermatron Sealomatic Faratron Stanelco, Ltd Colpitt, B.V.	
Thermo Dielectric Machine Company, Inc.	Brooklyn, New York
Welduction, Inc.	Plymouth, Michigan
W.T. LaRosa and Associates, Inc.	Troy, New York

*This list is complete and accurate to the best knowledge of NIOSH; howe there may be other manufacturers of this equipment of which the Institute is aware.

II. Occupations Which May Involve Use of Radiofrequency Sealing and Heating Equipment

Automotive workers
- Drying of trim base panels
- Embossing of heel pads to carpets
- Heat sealing body interior trim panels
- Heat sealing convertible tops and vinyl roofs
- Heat sealing upholstery covers for seats and backs

Furniture and wood workers
- Decking assembly
- Door lamination
- Fabrication of posts and rafters
- Fiberboard fabrication
- Laminated beams
- Lumber edge glueing
- Plywood panel patching
- Plywood or particleboard scarf glueing
- Ski lamination
- Veneer panel glueing

Glass fiber workers
- Drying and curing sizing on machine packages
- Drying coatings on continuous moving strands
- Drying glass fibers on forming tubes
- Drying roving packages

Paper product workers
- Correcting moisture profile on continuously moving webs
- Drying resin coatings
- Drying twisted twine packages
- Gluing paper
- Heating coating on continuous webs

Plastic heat-sealing workers involved in the manufacture/fabrication of:
- Acetate box covers
- Advertising novelties
- Appliance covers
- Aprons
- Baby pants
- Beach balls
- Belts and suspenders
- Blister packages
- Book covers
- Capes
- Charge cards
- Checkbook covers
- Convertible tops
- Cushions
- Diaper bags
- Display boxes
- Electric blankets
- Food packages
- Fountain pens
- Garment bags
- Gas masks
- Goggles (industrial)

Plastic heat-sealing workers (continued)
- Handbags
- Hat covers
- Index cards
- Lampshades
- Liquid containers
- Luggage
- Machine covers
- Mattress covers
- Mild cartons
- Oxygen tents
- Packages
- Pharmaceuticals
- Pillowcases
- Pillow packages
- Plastic gloves
- Pool liners
- Protective clothing
- Racket bags
- Rain apparel
- Refrigerator bags
- Shoe bags
- Shoes
- Shower curtains
- Slipcovers
- Splatter mats
- Sponge backings
- Sport equipment
- Tobacco pouches
- Toys
- Travel cases
- Umbrellas
- Wallets
- Waterproof containers
- Wire terminal covers

RF/microwave application workers
- Advertising. RF-excited gas display signs
- Ceramics. Drying of ceramic objects
- Chemical. Activation of chemical reactions
- Electronics. Tube aging and testing
- Laser. RF-excited gas lasers
- Medical. Diathermy and (experimental) cancer therapy
- Scientific equipment. Low temperature ashing of samples
- Welding. RF-stabilized welding

Rubber products workers
- Drying latex foams
- Gelling latex foams
- Preheating prior to curing latex foams
- Preheating prior to molding

Textile workers
- Drying continuous webs
- Drying impregnated or coated yarns
- Drying rayon cake packages
- Drying slasher coatings
- Drying wound packages

III. Manufacturers of Instruments for Measurement of Radiofrequency Energy in the Near Field*

Mention of company name or product does not constitute endorsement by the National Institute for Occupational Safety and Health or the Occupational Safety and Health Administration.

General Microwave Corp.
Farmingdale, Long Island, New York

For electric field only:
High sensitivity isotropic radiation hazard meter, Model 4

Instruments for Industry, Inc.
Farmingdale, Long Island, New York

For electric field only:
Electric field radiation hazard monitor, Model RHM-2

Narda Corporation
Plainview, Long Island, New York

For electric and magnetic fields:
Electric field strength probe, Model 8644
Magnetic field strength probes, Model 8635 or 8633
Readout meters, Model 8619 or Model 1816

*This list is complete and accurate to the best knowledge of NIOSH: however, there may be other manufacturers of comparable equipment of which the Institute is not aware.

IV. Supporting Technical Information

A. ELECTROMAGNETIC RADIATION

Radiofrequency energy (or RF radiation) is part of the electromagnetic energy spectrum. With regard to the energy emitted from a RF sealer or heater, electromagnetic radiation may be considered as a series of waves of energy propagated through space and composed of oscillating electric and magnetic fields. These waves are produced by moving electric charges, and may be of natural origin (e.g. the sun), or may be of human origin (e.g. produced by electronic devices such as diathermy machines, microwave ovens, and television and radio transmitters). The wave of electromagnetic energy is characterized, in part, by:

1) the strengths of the electric and magnetic fields — the intensity of electromagnetic forces

2) the frequency of oscillation — the number of complete oscillations per second of the wave

3) the wavelength — the distance between two consecutive peaks of the wave

Wavelength and frequency are inversely related; as the wavelength increases, the frequency decreases. The energy content of electromagnetic radiation is related to wavelength; waves of longer wavelength (lower frequency) contain less energy per quantum* unit. A graphic representation of the electromagnetic radiation spectrum is presented in Figure 1.

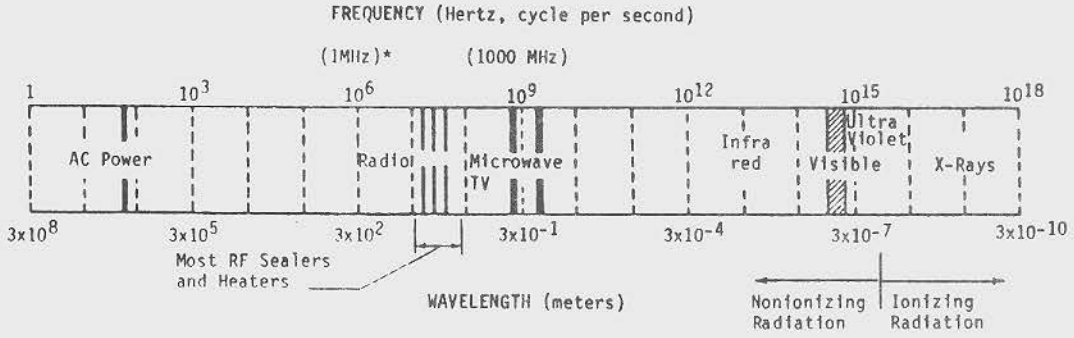

Figure 1 The Electromagnetic Spectrum

Electromagnetic energy emitted from a source propagates through space until it is absorbed, reflected, transmitted and/or diffracted by objects in its path. When

*Electromagnetic energy can also be described as discrete particles (or quanta) of energy.

electromagnetic radiation contains sufficient energy (at frequencies much higher than radiofrequencies), it can ionize atoms of the material absorbing the energy (i.e. dislodge electrons from the atoms of the absorbing material). Radiation of sufficient energy to cause ionization of molecules in biological tissue is often referred to as ionizing radiation, whereas radiation of insufficient energy to cause this effect is referred to as nonionizing radiation. The ionizing and nonionizing regions of the electromagnetic spectrum are shown in Figure 1. While nonionizing radiation absorbed by biological tissue is not capable of ionizing atoms or molecules, it nevertheless may produce changes in the vibrational and rotational energies of the biological molecules, leading to changes in the molecules or dissipation of the energy in the form of heat.

B. RF SEALERS AND HEATERS

RF sealers and heaters generate, by means of electronic circuitry, oscillating fields of electric and magnetic energy. RF sealers generally operate within the band of frequencies from 10 to 70 MHz (a megahertz (MHz) is one million cycles per second), although most of the sealers operate at nominal frequencies from 13 to 40 MHz. A few wood glueing machines operate at frequencies as low as 3 - 6 MHz, and a few RF heaters used for plastics operate at frequencies as high as 300 - 400 MHz. RF electromagnetic energy emitted from an RF sealer or heater is considered nonionizing radiation by virtue of its frequency and quantum energy. Unshielded or improperly shielded RF sealers or heaters can leak stray RF energy. Measurements have been made of electric and magnetic field strengths, in the immediate area of an operator, as great as 2000 volts/meter and 10 amperes/meter, respectively.[1,2] The majority of surveyed RF machines leaked stray energy in excess of 200 volts/meter or 0.5 amperes/meter.[2] Measurements of electric and magnetic field strengths will be discussed below.

C. MEASUREMENTS OF RF ENERGY FIELDS

In the measurement of RF energies, the distances from the RF source at which the measurements are being made must be considered. For purposes of this Bulletin, distances from the RF source can be categorized as being either far field or near field. The far field includes all distances from the RF source greater than approximately ten times the wavelength. Wavelengths corresponding to frequencies used by RF sealers and heaters may range from about one meter to a few hundred meters. The frequency of 27 MHz, which is typical for many RF heaters, is associated with a nominal wavelength of about 11 meters. In the far field, the amount of energy associated with the typical wave can be expressed as a power density (with the units of milliwatts per square centimeter, mW/cm^2). The value of the power density in the far field can be measured with a power density monitor, or can be calculated from measurement of the intensity of either the electric field or the magnetic field alone. The strength of the average electric field is expressed in units of volts/meter with the mean squared value expressed in $volts^2/meter^2$; the strength of the average magnetic field is expressed in units of amperes/meter with the mean squared value expressed in $amperes^2/meter^2$.

The near field comprises distances from the RF source less than about five wavelengths, which includes the immediate vicinity of the RF device where most worker exposures to RF energy occur. In the near field, electromagnetic waves have different characteristics than in the far field. Furthermore, in the occupational setting near a RF sealer or heater, the electromagnetic field generally is not uniform, and the energy field incident upon a worker is complex and depends on many factors. A power density monitor, designed for use in the far field, is likely to give exceedingly inaccurate measurements in the near field. Further, in the near field, as opposed to the far field, there is no simple mathematic equivalency between values of power density and measurements of either electric or magnetic field strength.

In the past, values of far-field power density have been used in various public health guides and recommendations for exposure limits, including those intended for occupational settings. However, a power density value, which can be measured or calculated for far-field conditions, is not appropriate for quantifying near-field exposure of a worker operating an RF sealer or similar device. In the near field, measurements of both the electric *and* the magnetic fields are necessary to properly characterize worker exposure conditions. Instruments are now commercially available to make near-field measurements of the electric and magnetic fields. Users should follow instrument manufacturers' use instructions carefully to avoid damage of sensitive instrument probes. A list of manufacturers of these instruments is presented in Section III of the Appendix.

D. ABSORPTION OF RF ENERGY

When RF energy propagating through space encounters an object, it may be reflected by the object (forced to change direction of travel), transmitted through the object, or absorbed by the object. The extent to which RF energy is reflected, transmitted, and/or absorbed depends on the frequency of the RF energy, and on the shape, size, and dielectric properties of the object as well as its orientation relative to the incident RF energy.

Humans can absorb RF energy at the frequencies used by most RF sealers and heaters. In workers who are not in contact with an electrical ground, the highest absorption rates for whole-body irradiation can occur at frequencies between 60 and 100 MHz with a peak at approximately 80 MHz.[3,4] These frequencies of high absorption rates are very close to the frequencies used by most sealers and heaters. Hence, workers near RF sealers and heaters can absorb considerable amounts of the stray energy emitted from the RF machines. Effects of directly touching an electrical ground plane can lower, by as much as one half, the frequency at which an irradiated body will maximally absorb energy.[3] Contact of the worker with an electrical ground plane can shift the frequency of maximum absorption rate to well within the frequency band of most RF sealers and heaters; this could increase the amount of energy absorbed by the worker and worsen the exposure condition. RF shielding material incorporated into the floor, walls, and ceiling of some RF workrooms could constitute such a ground plane.

E. BIOLOGICAL EFFECTS OF ABSORBED RF ENERGY

Details of some experiments performed in laboratory animals with low intensity RF energy at frequencies commonly used with sealers and heaters are summarized in the following table.

Table 1. Some Reported Biologic Effects in Animals Exposed to RF Energy at Frequencies in the Range of 10 to 70 MHz

Frequency (Wavelength)	Exposure Conditions	Animal	Reported Effects	Reference
50 MHz	0.5-6 volts/meter for 10-12 hrs/day; 180 days	rats and/or rabbits	changes in conditioned reflexes changes in encephalograms decreased blood cholinesterase activity increased urine 17-ketosteroids decreased leukocyte count decreased phagocytic activity	5
(4.3 meters)	150 volts/meter for 60 min/day; 4 months	rats	changes in conditioned reflexes	6
69.7 MHz	12 volts/meter for 1 hr/day; 1.5 months	rats	increases weights of adrenal and pituitary glands	7
69.7 MHz	48 volts/meter for 4 hrs/day; 1.5 months	infant rats	decreased weight of thyroid gland increased weight of adrenal gland	7
14.88 MHz	70 volts/meter	infant rats	decreased weights of thyroid and adrenal glands	7
14.88 MHz	100 volts/meter for 4 hrs/day; 10 months	rats	changes in phagocytic activity	8

V. Recommendations for Hazard Control

Immediate Actions

Control of the emission of RF energy from RF sealers and heaters should rely on the application of properly designed and installed shielding material. The shielding should be placed on or around the equipment so as to minimize occupational exposure due to emissions of stray RF energy. All shielding material should be properly grounded. Shielded conductors should be used for conveying RF current, and path impedance should be minimized by using good conductor materials. Many of these control features are available on RF sealers and heaters being marketed new, and some machines already in use can be retrofitted with some of these features. Older machines may require custom modification to control stray emissions.

The distance between the worker and the source of RF energy emission should be maximized. Examples of means to accomplish this include the use of automatic feeding devices, rotating tables, and remote materials handling.

The RF sealing and heating equipment should be electronically tuned to minimize the stray power emitted.

Whenever possible, equipment should be switched off when not being used. Maintenance and adjustment of the equipment should be performed only while the equipment is not in operation.

After the performance of maintenance or repair, all machine parts, including cabinetry, should be reinstalled so that the equipment is intact and its configuration is unchanged.

Warnings and Information

Access to the vicinity of RF sealers and heaters where there may be stray RF energy should be limited as much as possible to the operator and necessary assistants, maintenance personnel, and industrial hygiene or safety personnel. Use of the RF equipment should be restricted to properly trained personnel.

Areas in which exposures to RF energy have been determined to be appreciable should be posted. Any signs should be of such size as to be recognizable and readable from a distance of three meters. All warning signs must be printed in English and in the predominant languages of non-English-reading workers, and should conform to the design recommended by OSHA.[9]

Areas in which the RF energy is present at levels higher than the permissible exposure limit also should be posted. The warning signs should contain the following additional information: HAZARD--DO NOT ENTER. The sign must be

readable from a distance of three meters. The perimeter of the restricted area should be clearly demarcated with signs visible to all personnel approaching the area.

Medical Monitoring

A medical surveillance program, tailored to the expected degree of employee use of RF equipment and potential for exposure to RF energy, should be developed. The program should include preplacement examination of all new employees and an initital examination of all present employees subject to occupational exposure to RF energy. In an effort to identify possible adverse effects associated with exposure to RF energy, annual examinations should be considered for workers who may be exposed to RF energy on a regular, long-term basis. Work histories should be included in all examinations.

Medical histories and physical examinations should give particular emphasis upon target organs potentially affected by RF energy including the eye (cataracts), the central nervous system, the blood (decreased leukocyte count), the immune defense system, and the reproductive system. Adverse reproductive effects may involve both maternal and paternal exposure. For persons occupationally exposed to RF energy, medical records including health and work histories should be maintained throughout the period of employment and for an extended period after termination of employment.

Exposure Measurements

Areas in the occupational environment where levels of RF energy have been determined to be appreciable should be surveyed at regular intervals. Immediately following a physical or electronic alteration of the equipment or an alteration in the process, a complete survey should also be performed. If measurements taken during a survey indicate that occupational exposure exceeds the permissible exposure limit, a second survey should be made on the next workday. If the limit is still exceeded, the use of RF equipment producing excessive values should be prohibited until appropriate controls have been instituted. The survey data sheets should contain all information pertaining to the survey, and should include the date and time of measurement, the type of monitoring equipment used, the employees' names, and the remedial actions taken, if any. These records should be maintained for an extended period of time.

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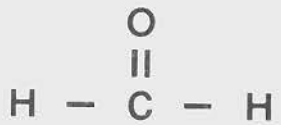
NIOSH

Current Intelligence Bulletin 34

APRIL 15, 1981

FORMALDEHYDE:

EVIDENCE OF CARCINOGENICITY



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

The National Institute for Occupational Safety and Health (NIOSH) Current Intelligence Bulletin is the primary product of the Current Intelligence System. The purpose of the Current Intelligence System is to promptly review, evaluate, and disseminate new information received by NIOSH that may indicate either the existence of an occupational hazard not previously recognized or a greater hazard than generally known. The Current Intelligence System staff within the Division of Criteria Documentation and Standards Development was responsible for the preparation of this Bulletin.

Current Intelligence Bulletins are disseminated to NIOSH staff, other government agencies, and the occupational health community, including labor, industry, academia, and public interest groups. The Bulletins are intended to disseminate new data that may affect prevailing perceptions of occupational hazards. They convey important public health information and recommend voluntary protective measures. Current Intelligence Bulletins do not recommend occupational standards, nor are they intended to have any regulatory significance.

IDENTIFIERS AND SYNONYMS FOR FORMALDEHYDE

Chemical Abstracts Service Registry Number: 50-00-0
NIOSH RTECS Number: LP8925000
Chemical Formula: CH_2O

BFV
Fannoform
Formaldehyde, gas
Formaldehyde, solution
Formalin
Formalith
Formic aldehyde
Formol
Fyde
HCHO
Ivalon
Karsan
Lysoform
Methanal
Methyl aldehyde
Methylene oxide
Morbicid
Oxomethane
Oxymethylene
Paraform
Superlysoform

FORMALDEHYDE: *Evidence of Carcinogenicity*

April 15, 1981

The National Institute for Occupational Safety and Health (NIOSH) recommends that formaldehyde be handled as a potential occupational carcinogen and that appropriate controls be used to reduce worker exposure. These recommendations are based primarily on a Chemical Industry Institute of Toxicology (C I I T) study in which laboratory rats and mice exposed to formaldehyde vapor developed nasal cancer, and are supported by a New York University study where rats exposed to a mixture of formaldehyde and hydrochloric acid vapors developed nasal cancer. Formaldehyde has also been shown to be a mutagen in several short-term laboratory studies. In addition to the carcinogenic potential, other adverse health effects caused by formaldehyde are described. NIOSH requests that producers and distributors of formaldehyde, and of substances and materials containing formaldehyde, give this information to their employees and customers, and that professional and trade associations and unions inform their members.

BACKGROUND

Formaldehyde is a colorless, flammable gas with a strong, pungent odor. It can form explosive mixtures with air and oxygen. As an important industrial chemical of major commercial use, formaldehyde is found throughout the environment. In outdoor air it can originate from many sources such as incinerators, photochemical smog, and engine exhaust. Atmospheric levels of formaldehyde have been reported to range from less than 0.005 ppm to 0.06 ppm near industrial outlets or in areas of heavy smog. Workers who smoke are exposed to additional levels of formaldehyde, since cigarette smoke contains as much as 40 ppm of formaldehyde by volume. Thus, an individual who smokes a pack of cigarettes a day would inhale 0.38 mg,[1,2] whereas occupational exposure to formaldehyde at 3 ppm could result in a daily intake of 29.0 mg.

Production and Uses - Formaldehyde is usually manufactured by reacting methanol vapor and air over a catalyst (chemical initiator). This results in formaldehyde containing trace amounts of methanol and formic acid. Formaldehyde is sold mainly as an aqueous (water-based) solution called formalin, which is 37% to 50% formaldehyde by weight. It is also used in its solid form as paraformaldehyde and s-trioxane.[1] The U.S. produced about 6.4 billion pounds of aqueous formaldehyde

in 1978.[3] Most of this quantity was used domestically. The U.S. consumption of formaldehyde by the year 1983 will likely exceed 7.5 billion pounds. (See appendix for list of major producers of formaldehyde.)

Half of the formaldehyde produced is used to produce synthetic resins such as urea- and phenol-formaldehyde resins. These resins are used primarily as adhesives when making particleboard, fiberboard, and plywood. Urea-formaldehyde concentrates are used in various coating processes, in paper products, and in making foams for thermal insulation. The textile industry uses formaldehyde for producing creaseproof, crushproof, flame resistant, and shrinkproof fabrics. Acetal resins, made from formaldehyde, are used to mold plastic parts for automobiles, home appliances, hardware, and garden and sporting equipment.[4] Formaldehyde is used in some medicines because it modifies and reduces the toxicity of viruses, venoms, and irritating pollens.[5] The use of formaldehyde in embalming fluids is now required by all state laws.[6]

The widespread use of formaldehyde is due to its high reactivity, colorless nature, purity in commercial form, and low cost. In making other chemicals, it can link similar and dissimilar molecules together. In the paper industry, formaldehyde and its derivatives impart wet strength, as well as shrink and grease resistance. Leather and fur can be tanned by formaldehyde. Formaldehyde is used in the photographic industry because it hardens and insolubilizes the gelatin surfaces of film and papers.[5] The table below lists, in alphabetical order, various products made with or containing formaldehyde.[4]

TABLE - Product Uses of Formaldehyde

Adhesives	Insulation, Foam & Some Others
Cosmetics	Intermediate Chemicals
Deodorants	Laminates
Detergents	Leathers, Fur & Hair
Dyes	Lubricants, Synthetic
Embalming Fluids	Paints
Explosives	Paper
Fertilizers	Pharmaceuticals
Fiberboard, Plywood (indoor-outdoor), Particle board	Plastics/moldings (Automobile Appliances, and Sporting Equipment)
Hardware, Garden	Rubber
Filters	Surface Coatings
Food	Textiles
Friction Materials	Urethane Resins
Fuels	Watersoftening Chemicals
Fungicides	

Occupational Exposures - During a 1972-74 survey, NIOSH estimated that 1.6 million workers were exposed to formaldehyde in more than 60 industrial categories. Of these workers, about 57,000 were exposed to formaldehyde 4 hours or more per day. Nearly one-third of the 1.6 million workers (507,200) were engaged in medical and other health services. Another one-third of them (457,200) were in the following industrial categories: chemicals and allied products, printing and publishing, paper and allied products, machinery (except electrical), retail general merchandise, automotive dealers and service stations, eating and drinking places (i.e., busboys, cooks, dishwashers, etc.), and personal services (such as funeral services and crematories, photographic studios, and dry-cleaning plants). Appendix I lists many of the occupational groups exposed to formaldehyde. However, not all workers in each occupational group are exposed to formaldehyde. Therefore it would be prudent for workers in these groups to check their work environment for formaldehyde or products which contain formaldehyde.[7] Appendix II gives ranges of formaldehyde concentrations, by industry, that were found by NIOSH investigators during the past 10 years.

Exposure Standards - The U.S. Department of Labor, Occupational Safety and Health Administration (OSHA) standard for formaldehyde requires an 8-hour time-weighted average (TWA) concentration limit of 3 ppm, a ceiling concentration of 5 ppm, and an acceptable maximum peak above the ceiling concentration of 10 ppm for no more than a total of 30 minutes during an 8-hour shift.[8]

In 1976, NIOSH recommended, based upon the irritant effects of formaldehyde, that employee exposure to formaldehyde in the occupational environment be controlled to a concentration no greater than 1.2 milligrams per cubic meter of air (1 ppm) for any 30-minute sampling period.[9] The carcinogenic potential of formaldehyde was not known at that time, and therefore was not considered in developing the recommendations.

TOXICITY

Carcinogenicity/Mutagenicity - Evidence for the carcinogenicity of formaldehyde was first reported in October 8, 1979. Preliminary data from an ongoing inhalation study of rats and mice, sponsored by the Chemical Industry Institute of Toxicology (C I I T), indicated that for exposures of 15 ppm for 6 hours/day, 5 days/week for 16 months formaldehyde is carcinogenic in rats. Some rats had developed cancer by the 12th month. The study, conducted by Battelle Columbus Laboratories, follows a C I I T protocol using Fischer 344 rats and B6C3F1 mice, exposed in groups of 120 animals of each sex, at each of three exposure levels, plus controls, for 6 hours per day, 5 days per week. The study design calls for groups of animals of both species to be exposed concurrently to either 15, 6, or 2 ppm of formaldehyde vapor.[10]

After 16 months of exposure at 15 ppm, three rats developed squamous cell carcinomas originating in the epithelium of the nasal turbinates. A fourth case of nasal squamous cell carcinoma developed in the group exposed to 6 ppm; however, this cancer appeared to have originated from a different site (i.e., from a layer of

the skin on the nose rather than the nasal turbinates). In a second progress report (January 16, 1980), the C I I T stated that between the 16th and the 18th month of exposure, a sharp increase in the number of cases of nasal cancer had been observed in rats exposed to 15 ppm formaldehyde. A total of 36 rats developed squamous cell carcinomas of the nasal turbinates after 18 months of exposure. Up to the 18th month sacrifice, no similar tumor had been observed in rats exposed to 2 or 6 ppm or in mice exposed to 2, 6 or 15 ppm formaldehyde.[11,12]

The C I I T presented its latest interim report at the Third C I I T Conference on Toxicology (November 20 and 21, 1980).[13] It has shown that after 24 months of exposure to 15 ppm formaldehyde, a total of 93 rats have developed squamous cell carcinomas of the nasal turbinates. Two rats have developed respiratory epithelial carcinomas. Furthermore, two rats exposed to 6 ppm and two mice exposed to 15 ppm formaldehyde have also developed squamous cell carcinomas of the nasal turbinates.

Lesions typical of an enzootic viral infection of the salivary gland, sialodacryoadenitis, were found in rats of all exposure groups at the 12th month necropsy. However, mice did not contract the disease. The possibility that the viral infection contributed to the carcinoma response in the C I I T study cannot be discounted, but it is considered unlikely for the following reasons: 1) mice which were not affected by the viral infection developed the nasal cancer; 2) the signs of infection occurred only for a short period of time during the 11th and 12th month of exposure and the first nasal cancers were detected at the 12th month. Therefore, the nasal cancer had probably already formed by the time of the infection.

Squamous cell carcinoma of the nasal turbinates rarely occurs spontaneously. In two recently completed inhalation studies sponsored by C I I T, involving a total of 1,920 Fischer 344 rats, and in two feeding studies involving 1,680 rats, no similar cancer was observed.[10] At the National Cancer Institute, only two cases of nasal squamous cell carcinoma have been observed in 5,884 unexposed Fischer 344 rats.[14]

The interim data from the C I I T in this study indicate that formaldehyde causes nasal cancer in rats. No factors now apparent would significantly alter the interpretation of the existing results.

Epidemiologic studies conducted to date do not permit a definitive evaluation of the carcinogenic risk of formaldehyde to humans.

Because of the concern of the federal regulatory and research agencies about the exposure of humans to formaldehyde, in January 1980, the Interagency Regulatory Liaison Group (IRLG) reviewed the formaldehyde carcinogenicity data in detail. As a result, the Consumer Product Safety Commission (CPSC) in cooperation with the IRLG agencies, convened a panel of scientists from eight federal agencies under the auspices of the National Toxicology Program to review health data related to formaldehyde. This panel has stated, "It is the conclusion of the Panel that it is prudent to regard formaldehyde as posing a carcinogenic risk to humans."[15]

Most chemicals known to cause cancer are also capable of causing a change in the genetic material within a cell (mutation).[16] Therefore, mutagenicity tests support the results of animal tests to determine carcinogenic potential. Formaldehyde has long been known to be mutagenic. Positive findings of the mutagenicity of formaldehyde have been reported in the following laboratory experimental systems: fruit flies (drosophila), grasshoppers, flowering plants, fungi, and bacteria.[17]

A recent report (October 19, 1979) of the New York University (NYU), Institute of Environmental Medicine supports the C I I T evidence of formaldehyde being a carcinogen in experimental animals.[18] One hundred male Sprague-Dawley rats were exposed to a mixture of formaldehyde and hydrogen chloride (HCl) at concentrations of 14.6 ppm and 10.6 ppm, respectively, for a total of 544 days, 6 hours/day over a period of 814 days. The most important finding was that 25 rats developed squamous cell carcinomas of the nasal cavity, and 2 developed benign papillomas (nonmalignant circumscribed tumor of skin cells) of the nasal cavity. The time from first exposure to death from these cancers ranged from 305 to 705 days (mean: 549 days).

Formaldehyde and HCl can combine in the environment to form the chemical bis (chloromethyl) ether (BCME).[19,20] BCME was first reported to cause cancer in rats by subcutaneous administration in 1969.[21] Since then, inhalation studies have shown that BCME causes lung and nasal cancer in rats.[22,23] The most common type of nasal cancer was esthesioneuroepithelioma (tumor of the nerve tissue) and not squamous cell carcinoma.[22,23]

It is not known if the nasal cancer observed in the NYU mixed exposure study was caused by formaldehyde, HCl, BCME, or a combination of these substances. However, formaldehyde seems the most probable etiologic agent for the following reasons. In the NYU study 27 rats developed nasal tumors, 25 of which were squamous cell carcinomas of the nasal cavity. This type of nasal cancer has been seen infrequently in the BCME inhalation studies and has never been observed to occur spontaneously in the more than 2,000 control animals at NYU over a period of many years.[18] This is the same type of tumor as that produced by formaldehyde in the C I I T study at similar levels of exposure. Second, in the NYU study no rat developed lung cancer as was observed in the BCME inhalation studies. For example, of 40 cancers of the respiratory tract reported in one BCME inhalation study,[23] 14 cancers (13 squamous cell, 1 adenocarcinoma) were from the lung and 26 cancers (17 esthesioneuroepithelioma, 1 squamous cell, and 8 others) were from the nasal cavity.

Other Health Effects - The first signs or symptoms noticed on exposure to formaldehyde at concentrations ranging from 0.1 to 5 ppm are burning of the eyes, tearing (lacrimation), and general irritation to the upper respiratory passages. Higher exposures (10 to 20 ppm) may produce coughing, tightening in the chest, a sense of pressure in the head, and palpitation of the heart.[2,24,25] Exposures at 50 - 100 ppm and above can cause serious injury such as collection of fluid in the lungs (pulmonary edema), inflammation of the lungs (pneumonitis), or death.[9]

In one report, five nurses working near an artificial kidney (hemodialysis) machine developed wheezing and recurrent episodes of productive cough.[26] The

attacks generally occurred in winter and often followed colds. The formaldehyde used to sterilize the machine was found to have caused this respiratory distress.

Dermatitis due to formaldehyde solutions or formaldehyde-containing resins is a well-recognized problem.[27] After a few days of exposure, a worker may develop a sudden inflammatory (eczematous) reaction of the skin of the eyelids, face, neck, scrotum, and flexor surfaces of the arms. An eczematous reaction may also appear on the fingers, back of the hands, wrists, forearms, and parts of the body that are exposed to the rubbing of clothing. This sometimes occurs after years of repeated exposure.

RECOMMENDATION

Formaldehyde has induced a rare form of nasal cancer in both Fischer 344 rats and in B6C3F1 mice as reported in an ongoing study by the C I I T. In a second study by NYU, formaldehyde appears to have induced the same type of cancer in Sprague-Dawley rats. Although humans and animals may differ in their susceptibility to specific chemical compounds, any substance that produces cancer in experimental animals should be considered a cancer risk to humans. Formaldehyde has also demonstrated mutagenic activity in several test systems. Although a substance cannot as yet be designated a potential occupational carcinogen based solely on results of mutagenicity tests, positive results in mutagenicity tests should be used as supporting evidence for identifying a potential occupational carcinogen.

Based on these results, NIOSH recommends that formaldehyde be handled in the workplace as a potential occupational carcinogen. Safe levels of exposure to carcinogens have not been demonstrated, but the probability of developing cancer should be reduced by decreasing exposure. An estimate of the extent of the cancer risk to workers exposed to various levels of formaldehyde at or below the current 3 ppm standard has not yet been determined. In the interim NIOSH recommends that, as a prudent public health measure, engineering controls and stringent work practices be employed to reduce occupational exposure to the lowest feasible limit. The "Guidelines for Minimizing Employee Exposure to Formaldehyde", Appendix IV, should be adapted to specific work situations.

Ronald F. Coene, P.E.
Acting Director

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Occupations Involving Exposure to Formaldehyde

Accountants
Adult Education Teachers
Advertising Agents and Salesmen
Aeronautical and Astronautical Engineers
Agriculture and Biological Technicans
Air Conditioning, Heating, and Refrigeration
Aircraft
Animal Caretakers, Except Farm
Archivists and Curators
Asbestos and Insulation Workers
Assemblers
Automobile Body Repairmen
Automobile Mechanics
Bakers
Bank Tellers
Barbers
Bartenders
Billing Clerk
Biological Scientists
Bookbinders
Bookkeepers
Bookkeeping and Billing Machine Operators
Bootblacks
Bottling and Canning Operatives
Brickmasons and Stonemasons
Bus Drivers
Busboys
Cabinetmakers
Carpenter Apprentices
Carpenters
Carpenters' Helpers
Carpet Installers
Cashiers
Cement and Concrete Finishers
Chambermaids and Maids, Except Private Household
Checkers, Examiners, and Inspectors; Manufacturers
Chemical Technicians
Chemists
Child Care Workers, Except Private Household
Cleaners and Charwomen
Clerical Supervisions, N.E.C.
Clerical Workers - Miscellaneous
Clerical Workers - Not Specified
Clinical Laboratory Technologists and Technicians
Clothing Ironers and Pressers
Compositors and Typesetters
Computer and Peripheral Equipment Operators
Computer Programmers
Computer Specialists, N.E.C.
Construction Laborers, Except Carpenters' Helper
Cooks, Except Private Household
Counter Clerks, Except food
Craftsmen and Kindred Workers, N.E.C.
Cranemen, Derrickmen, and Hoistmen
Credit men
Cutting Operatives, N.E.C.
Decorators and Window Dressers
Dental Assistants
Dental Hygienists
Dental Laboratory Technicians
Dentists
Designers
Dishwashers
Draftsmen
Dressmakers and Seamstresses, Except Factory
Drill Press Operatives
Dry Wall Installers and Lathers
Duplicating Machine Operators
Dyers
Editors and Reporters
Electric Power Linemen and Cablemen
Electrical and Electronic Engineering Technicians
Electrical and Electronic Engineers
Electrician Apprentices
Electricians
Elevator Operators
Embalmers
Engineering and Science Technicians, N.E.C.
Engineers, N.E.C.
Engravers, Exc. Photoengravers
Estimators and Investigators, N.E.C.
Expediters and Production Controllers
File Clerk
Filers, Polishers, Sanders, and Buffers
Food Counter and Fountain Workers
Food Service Workers, N.E.C., Except Private
Foremen, N.E.C.
Fork Lift and Tow Motor Operatives
Freight and Material Handlers
Funeral Directors
Furnacemen, Smeltermen, and Pourers
Furniture and Wood Finishers
Garage Workers and Gas Station Attendants
Gardeners and Groundskeepers, Exc. Farm
Geologists
Glaziers
Graders and Sorters, Manufacturing
Grinding Machine Operatives
Guards and Watchmen
Hairdressers and Cosmetologists
Health Administrators
Health Aides, Except Nursing
Health Record Technologists and Technicians
Health Technologists and Technicians, N.E.C.
Heat Treaters, Annealers, and Temperers
Heavy Equipment Mechanics, Including Diesel
Household Appliance and Accessory Installers
Housekeepers, Except Private Household
Industrial Engineering Technicians
Industrial Engineers
Inspectors, N.E.C.
Insurance Adjusters, Examiners, and Investigators
Insurance Agents, Brokers, and Underwriters
Janitors and Sextons
Jewelers and Watchmakers
Job and Die Setters, Metal
Key Punch Operators
Laborers - Miscellaneous
Laborers - Not Specified
Lathe and Milling Machine Operatives
Laundry and Dry Cleaning Operatives, N.E.C.
Librarians
Loom Fixers
Machine Operatives - Miscellaneous Specified
Machine Operatives - Not Specified
Machinists
Mail Handlers, Except Post Office
Managers and Administrators, N.E.C.
Meat Cutters and Butchers, Except Manufacturing
Meat Cutters and Butchers, Manufacturing
Mechanic, Exc. Auto, Apprentices
Mechanical Engineers
Mechanics and Repairmen - Miscellaneous
Mechanics and Repairmen - Not Specified
Metal Platers
Millwrights
Mine Operatives, N.E.C.
Mixing Operatives
Molders, Metal
Motion Picture Projectionists
Nursing Aides, Orderlies, and Attendants
Office Machine Operators, N.E.C.
Office Managers, N.E.C.
Officers, Pilots, and Pursers; Ship
Oilers and Greasers, Exc. Auto
Operations and Systems Researchers and Analysers
Operatives - Miscellaneous
Operatives - Not Specified
Opticians, and Lens Grinders and Polishers
Packers and Wrappers, Except Meat and Produce
Painters and Sculptors
Painters, Construction and Maintenance
Painters, Manufactured Articles
Pattern and Model Makers, Except Paper
Payroll and Timekeeping Clerks
Personal Service, N.E.C. - Attendants
Personnel and Labor Relations Workers
Pharmacists
Photoengravers and Lithographers
Photographers
Photographic Process Workers
Physicians, Medical and Osteopathic
Plumbers and Pipe Fitters
Podiatrists
Practical Nurses
Precision Machine Operatives, N.E.C.
Pressmen and Plate Printers, Printing
Pressman Apprentices
Punch and Stamping Press Operatives
Purchasing Agents and Buyers, N.E.C.
Radio and Television
Radiologic Technologists and Technicians
Receptionists
Recreation and Amusement - Attendants
Recreation Workers
Registered Nurses
Research Workers, not specified
Restaurant, Cafeteria, and Bar Managers
Riveters and Fasteners
Sailors and Deckhands
Sales Managers and Department Heads, Retail Trade
Sales Managers, Except Retail Trade
Salesmen and Sales Clerks, N.E.C.
Sawyers
Secretaries, N.E.C.
Sheetmetal Workers and Tinsmiths
Shipping and Receiving Clerks
Shoe Repairmen
Shoemaking Machine Operatives
Sign Painters and Letterers
Social Workers
Solders
Specified Craft Apprentices, N.E.C.
Spinners, Twisters, and Winders
Stationary Engineers
Stationary Firemen
Statistical Clerks
Statisticians
Stenographers
Stock Clerks and Storekeepers
Stock Handlers
Tailors
Teachers, Except College and University, N.E.C.
Technicians, N.E.C.
Telephone Installers and Repairmen
Telephone Linemen and Splicers
Telephone Operators
Textile Operatives, N.E.C.
Therapists
Therapy Assistants
Ticket, Station, and Express Agents
Tile Setters
Tool and Die Maker Apprentices
Tool and Die Makers
Truck Drivers
Typists
Upholsterers
Vehicle Washers and Equipment Cleaners
Veterinarians
Waiters
Warehousemen, N.E.C.
Weighers
Welders and Flame-cutters
Winding Operatives, N.E.C.
Writers, Artists, and Entertainers, N.E.C.

This list of occupational groups is primarily a list of specific job titles and therefore a generic classification such as textile workers will be made up of several groups (e.g., foremen, machine operative, clothing ironer, etc.).

N.E.C. - Not elsewhere classified

APPENDIX II

Some Formaldehyde Concentrations, by Industry, from NIOSH Industrial Hygiene Surveys.

Industry	Formaldehyde Level
Fertilizer Production	0.2 - 1.9 ppm
Dyestuffs	<0.1 - 5.8 ppm
Textile Manufacture	<0.1 - 1.4 ppm
Resins (Foundry)	<0.1 - 5.5 ppm
Bronze Foundry	0.12 - 0.8 ppm
Iron Foundry	<0.02 - 18.3 ppm
Treated Paper	0.14 - 0.99 ppm
Hospital Autopsy Room	2.2 - 7.9 ppm
Plywood Industry	1.0 - 2.5 ppm

This information was adapted from a written communication from Richard A. Keenlyside, M.D., Medical Officer, NIOSH to the Deputy Director, NIOSH, November 7, 1980.

The table has been changed to reflect corrections made to the original memorandum (March 1982).

APPENDIX III

List of Major Manufacturers of Formaldehyde

Allied Chemical Corporation
Borden, Inc.
Celanese Corporation
E. I. du Pont de Nemours and Co., Inc.
GAF Corporation
Georgia-Pacific Corporation
Getty Oil, Inc.
Gulf Oil Corporation
Hercules, Inc.
International Minerals and Chemical Corporation
Monsanto Company
Occidental Petroleum Corporation
Reichold Chemicals, Inc.
Tenneco, Inc.
Univar Corporation
Wright Chemical Corporation

APPENDIX IV

GUIDELINES FOR MINIMIZING EMPLOYEE EXPOSURE TO FORMALDEHYDE

NIOSH recommends that formaldehyde be handled in the workplace as a potential occupational carcinogen. Exposure should be limited to as few employees as possible, while minimizing workplace exposure levels. The area in which formaldehyde is used should be restricted to only those employees essential to the process or operation. The guidelines listed below are general in nature and should be adapted to specific work situations as required.

EXPOSURE MONITORING

Initial and routine employee exposure surveys should be made by competent industrial hygiene and engineering personnel. These surveys are necessary to determine the extent of employee exposure and to ensure that controls are effective.

The NIOSH Occupational Exposure Sampling Strategy Manual,[1] may be helpful in developing efficient programs to monitor employee exposure to formaldehyde. The manual discusses determination of the need for exposure measurements and selection of sampling times.

Employee exposure measurements should primarily consist of 8-hour TWA (time-weighted average) exposure estimates calculated from personal or breathing zone samples (air that would most nearly represent that inhaled by the employees). In addition, short term samples should be taken during periods of maximum expected exposure by using all available knowledge of the area, employee work procedures, and processes. Area and source measurements may be useful to identify problem areas, processes, and operations.

CONTROLLING EMPLOYEE EXPOSURE

There are four basic methods of limiting employee exposure to formaldehyde. None of these is a simple industrial hygiene or management decision and careful planning and thought should be used prior to implementation.

o Product Substitution

The substitution of an alternative material with a lower potential health risk is an important method for reducing exposure. However, extreme care must be used when selecting possible substitutes. Alternatives to formaldehyde should be fully evaluated with regard to possible health effects prior to selection.

o Contaminant Controls

The most effective control of airborne concentrations of formaldehyde is at the source of contamination by enclosure of the operation and/or use of local exhaust ventilation. Guidelines for selected processes and operations can be found in the NIOSH Recommended Industrial Ventilation Guidelines:[2]

When enclosing a process or operation, a slight vacuum should be used to create negative pressure so that leakage will result in the flow of external air into the enclosure and minimize contamination of the workplace. This can be accomplished with a well-designed local exhaust ventilation system that physically encloses the process as much as possible, with sufficient capture velocity to keep the contaminant from entering the work atmosphere.

Ventilation equipment should be checked at least every three months to ensure adequate performance. System effectiveness should be checked soon after any change in production, process, or control which might result in significant increases in airborne exposure to formaldehyde.

o Employee Isolation

If feasible, employees may be isolated from direct contact with the work environment by the use of automated equipment operated by personnel observing from a closed control booth or room. The control room is maintained at a greater air pressure than that surrounding the process equipment so that air flow is out of, rather than into, the room. This type of control will not protect those employees that must do process checks, adjustments, maintenance, and related operations. These employees will need to use personal protective equipment.

o Personal Protective Equipment

The use of personal protective equipment, which may include respirators, goggles, gloves, etc., should not be used as the only means to prevent or minimize exposure during routine operations.

However, exposure to formaldehyde can be controlled with the use of this equipment:

— During the time period necessary to install or implement engineering or work practice controls; or

— In work situations in which engineering and work practice controls have proven ineffective; or,

— For maintenance; or

— For operations which require entry into tanks or closed vessels; or

— In emergencies.

Proper maintenance procedures, good housekeeping in the work area, and employee education are all vital aspects of a good control program. Employees should be informed as to the nature of the hazard, its control, and appropriate personal hygiene procedures.

MEDICAL SURVEILLANCE

Effects such as upper respiratory irritation or dermatitis should alert management that unacceptable exposure to formaldehyde is occurring. A medical surveillance program should be made available that can evaluate these effects. In addition, skin protection should be stressed in the workplace to keep the number of new cases of dermatitis to a minimum.

AVAILABILITY OF REFERENCES

(1) From GPO as #017-033-00247-9 for $2.75.
(2) From GPO as #017-033-00136-7 for $3.90.

GPO publications can be ordered from:

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NIOSH

Current Intelligence Bulletin 35

MAY 22, 1981

ETHYLENE OXIDE (EtO)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

The National Institute for Occupational Safety and Health (NIOSH) Current Intelligence Bulletin is the primary product of the Current Intelligence System. The purpose of the Current Intelligence System is to promptly review, evaluate, and disseminate new information received by NIOSH that may indicate either the existence of an occupational hazard not previously recognized or a greater hazard than generally known. The Current Intelligence System staff within the Division of Criteria Documentation and Standards Development was responsible for the preparation of this Bulletin.

Current Intelligence Bulletins are disseminated to NIOSH staff, other government agencies, and the occupational health community, including labor, industry, academia, and public interest groups. The Bulletins are intended to disseminate new data that may affect prevailing perceptions of occupational hazards. They convey important public health information and recommend voluntary protective measures. Current Intelligence Bulletins do not recommend occupational standards, nor are they intended to have any regulatory significance.

Mention of company names or products does not constitute endorsement by NIOSH.

On July 20, 1983, NIOSH testified at the Occupational Safety and Health Administration's informal public hearing on a proposed standard for ethylene oxide. The testimony presented by NIOSH updates the information contained in Current Intelligence Bulletin #35 and recommends, among other things, that the occupational standard for ethylene oxide be:

> A 5ppm ceiling, and that this ceiling concentration not be achieved for more than 10 minutes in any working day, and that an 8-hour time weighted average (TWA) be set lower than 0.1ppm.

Copies of the complete testimony may be obtained from NTIS.
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DHHS (NIOSH) Publication No. 81-130

NIOSH CURRENT INTELLIGENCE BULLETIN: #35

ETHYLENE OXIDE (EtO): Evidence of Carcinogenicity

May 22, 1981

The National Institute for Occupational Safety and Health (NIOSH) recommends that ethylene oxide be regarded in the workplace as a potential occupational carcinogen, and that appropriate controls be used to reduce worker exposure. These recommendations are based primarily on an industry-sponsored study demonstrating that ethylene oxide is carcinogenic in experimental animals. In this study, ethylene oxide was associated with increases in leukemia in female rats and peritoneal mesotheliomas (malignant tumors) in male rats. There has been widespread recognition of the mutagenic potential of ethylene oxide, and recent evidence demonstrates adverse reproductive effects in mammals, which also are of public health concern. In addition, limited epidemiologic investigations at two worksites provide evidence that excess risk of cancer mortality may exist for the ethylene oxide workers studied. Some workers are on occasion exposed to relatively high concentrations of ethylene oxide, particularly where it is used for fumigation and sterilization. On the basis of this information, NIOSH requests that producers, distributors, and users of ethylene oxide, and of substances and materials containing ethylene oxide, give this information to their workers and customers, and that professional and trade associations and unions inform their members.

BACKGROUND

Purpose of Bulletin

The purpose of this bulletin is to disseminate recent information concerning the potential carcinogenic hazard of ethylene oxide (EtO) to workers, and to update the assessment made in the 1977 NIOSH Special Occupational Hazard Review on EtO.[1] This bulletin conveys public health information and recommends voluntary protective measures.

In the 1977 review, NIOSH concluded that occupational exposure to EtO may increase the frequency of mutations in human populations. This conclusion was based on observations of (1) changes in the genetic material of cells in at least 13 biological species following exposure to EtO, and (2) covalent chemical bonding between EtO and deoxyribonucleic acid (DNA), a major constituent of genetic material. While these observations raised concern about the potential carcinogenicity of EtO, there were no epidemiologic studies or long-term carcinogenesis assays available at the time to assess carcinogenic potential for humans.

Additional evidence is now available that suggests the current Occupational Safety and Health Administration (OSHA) standard of 50 parts per million (ppm)

as a time-weighted average (TWA) concentration needs to be reexamined for its adequacy in safeguarding worker health. A recent study demonstrates that EtO induces cancer in experimental animals.[2] A dose-related increase in mononuclear cell leukemia was established in that study; exposures as low as 10 ppm increased the proportion of female rats with the leukemia. Peritoneal mesothelioma was treatment-related in male rats exposed to EtO at 33 and 100 ppm. Also, experiments indicate that EtO exposure to either male or female animals results in adverse effects on reproduction.[3,4]

Other work supports these findings. Epidemiologic investigations of cancer mortality among Swedish workers exposed to EtO suggest an increased risk of leukemia and other cancers.[5,6] Recent information also suggests that EtO is associated with chromosomal abnormalities in peripheral lymphocytes of exposed workers.[7] The environmental measurements reported indicate that these workers were exposed to 8-hour TWA concentrations below the current OSHA standard.

Although this bulletin focuses on new evidence of carcinogenic, mutagenic, and reproductive hazards, EtO has other adverse effects on health. The acute toxic effects of EtO in humans and animals include acute skin, respiratory, and eye irritation; skin sensitization; nausea, vomiting, and diarrhea; and nervous system effects. Nonmalignant chronic effects in humans include anemia and respiratory irritation, with susceptability to secondary respiratory infection. The literature reporting these effects was reviewed in the 1977 NIOSH document.[1] More recently, cases of peripheral neuropathy among exposed workers have been reported.[8]

Production and Use

At room temperature and atmospheric pressure, EtO is a colorless gas; at higher pressures it may be a volatile liquid. Synonyms and identifiers are listed in Appendix III. It has a characteristic ether-like odor with a widely variable threshold of detection in humans; the mean detectable concentration is about 700 ppm (1260 mg/m^3).[9] It is completely miscible with water, alcohol, acetone, benzene, ether, carbon tetrachloride, and most organic solvents. Ethylene oxide is highly reactive and potentially explosive in the presence of alkali metal hydroxides and highly active catalytic surfaces, or when heated. However, it is relatively stable in aqueous solutions, or when diluted with carbon dioxide (CO_2) or halocarbons. In order to reduce explosion hazards, when EtO is used as a fumigant or sterilant it is often in mixtures, such as 10% EtO and 90% CO_2, or 12% EtO and 88% halocarbon.

Ethylene oxide is a major industrial chemical and is one of the 25 chemicals of highest production volume in the United States. Current production capacity in the United States is about 6.1 billion pounds (2.8 Tg) per year. In 1978, the industrial consumption of EtO was about 4.9 billion pounds (2.2 Tg), and the projected consumption for 1983 is about 6.2 billion pounds (2.8 Tg). The chemical is used extensively worldwide, and U.S. production capacity is about 43% of the world capacity.[10]

On a volume basis, EtO is primarily used as an intermediate in the production of several industrial products. The largest consumption of EtO is in the production of ethylene glycol for automotive antifreeze and as an intermediate for polyester fibers, films, and bottles. The second largest consumption is in production of nonionic surface-active agents for industrial applications and for heavy-duty home laundry detergents and dishwashing formulations. Production of glycol ethers (e.g., solvents for surface coatings) and ethanolamines (used in production of soaps, detergents, and textile chemicals) constitute the third and fourth largest uses, respectively.

Many smaller uses account for the remainder of EtO consumption. Ethylene oxide is used as a pesticide fumigant (including antimicrobial sterilant). Industries and work settings where it is used as a sterilant or fumigant include: health care, diagnosis, and treatment facilities; medical products manufacturing; libraries; museums; research laboratories; beekeeping; spices, seasonings, and black walnut meats fumigation; dairy packaging; cosmetics manufacturing; animal and plant quarantine service at ports of entry; transportation vehicles (e.g., aircraft, buses, and railroad cars) fumigation; and clothing, furs, and furniture fumigation.

Potential for Occupational Exposure

The vast majority of EtO is found in chemical plants where it is produced and used for intermediates. Because EtO is highly explosive and reactive, the process equipment containing it in these plants generally consists of tightly closed and highly automated systems. The equipment is often located outdoors, and workers spend most of their work shift inside or around control rooms, away from the equipment. Samples collected in general process areas of six plants indicated that EtO concentrations were, with few exceptions, less than 1 ppm.[11] The greatest potential for worker exposure probably occurs during the loading or unloading of transport tanks, product sampling procedures, and equipment maintenance and repair.

In contrast to the chemical-manufacturing plants, other industries and activities may use only a very small portion of the total EtO produced, but are responsible for high occupational exposures to many workers. For example, less than 0.24% of the annual U.S. production of EtO is consumed in the health care and medical products industries,[12] and only about 0.02% of the production is used for sterilization in hospitals.[1] Yet, in 1977 NIOSH estimated that approximately 75,000 health care workers employed in sterilization areas were potentially exposed to EtO and that 25,000 others may have been incidentally exposed due to improper engineering and administrative controls.[1] In a limited field survey of hospitals, NIOSH found that EtO concentrations near malfunctioning or improperly-designed equipment may reach transitory levels of hundreds or even a few thousand ppm. Time-weighted average ambient and breathing zone concentrations were generally below the OSHA standard of 50 ppm.

EPIDEMIOLOGIC EVIDENCE FOR CANCER IN HUMANS

In 1979, Hogstedt et al. reported the results of a historical prospective mortality study of workers employed in a Swedish EtO production facility.[5] Individuals in

this investigation were employed as of 1961 and exposed or employed for more than 1 year. These individuals were followed through 1977. The authors required an interval of at least 10 years between initial employment and the beginning of the observation period. Three separate cohorts were studied: 89 persons who worked full time in the EtO production area, with 1,234 person-years of observation; 86 maintenance workers who intermittently worked in the EtO area, with 1,211 person-years of observation; and 66 workers who had never worked in EtO production, with 955 person-years of observation. The followup was complete for each cohort. Diagnoses for malignancies were provided by the Swedish Cancer Registry. The expected numbers of deaths were calculated from Swedish national mortality rates adjusted for age and calendar time-period.

Among the full-time production workers, 23 deaths were observed, compared with 13.5 expected ($p<0.05$). Of the 23 deaths, 9 cancer deaths were observed, compared with 3.4 expected ($p<0.01$). With regard to cause-specific mortality, 2 leukemia deaths were observed, compared with 0.14 expected ($p<0.01$), and 3 stomach cancer deaths were observed, compared with 0.4 expected ($p<0.01$). Twelve circulatory system deaths were observed, compared with 6.3 expected ($p<0.05$). Of the two leukemia cases in the cohort of full-time production workers, one died from chronic lymphatic leukemia and the other from acute myeloid leukemia. In contrast, the cohorts of maintenance workers with intermittent exposure and the workers never exposed to EtO did not demonstrate any statistically significant excess cause of death. However, one leukemia death was observed among the maintenance workers, compared with 0.13 expected deaths. This case was reported to be chronic lymphatic leukemia.

The complex exposure patterns and production changes in the chemical industry make it difficult to assess exposure in this study. However, the authors estimated that concentrations of airborne EtO in the facility during the 1940's were probably below 25 mg/m^3 (14 ppm), with occasional exposures up to the odor threshold of 1,300 mg/m^3 (730 ppm). Concentrations of 10-50 mg/m^3 (6-28 ppm) were estimated for the 1950's and early 1960's, although peaks above the odor threshold still occurred. Random samples in the 1970's showed a range of 1-10 mg/m^3 (0.6-6 ppm), and occasional higher values.

Other potential chemical exposures in the production area included ethylene dichloride, ethylene chlorohydrin, ethylene, and bis-chloromethyl ether, as well as traces of other unspecified chemicals. Although the authors could not attribute the excess cancer to any particular substance, EtO and ethylene dichloride were thought to be suspect because of the amounts of exposure and toxicological reports.

Also in 1979, Hogstedt et al. reported an investigation of leukemia among workers potentially exposed to EtO in a Swedish factory.[6] In this factory, a mixture of 50% EtO and 50% methyl formate had been used since 1968 to sterilize hospital equipment. Between 1972 and 1977, 3 cases of leukemia (2 women, 1 man) occurred among the workforce of 230 persons. It was determined that only 0.2 cases would have been expected for men and women combined, based on the sex-specific Swedish national leukemia incidence rates for 1972. The cases of leukemia were categorized as chronic myeloid leukemia and acute myelogenic leukemia for the women, and as primary macroglobulinemia for the man.

The authors calculated the 8-hour TWA concentration of EtO in the breathing zone of the two women who developed leukemia to be 20 ± 10 ppm. The EtO exposure was not reported for the man who developed leukemia, but it was estimated that, as plant manager, he was exposed to EtO 3 hours per week. This individual also had some occasional contact with benzene in laboratory work.

The significance of these epidemiologic findings is limited by the small number of observed deaths, the uncertainty of worker exposure information, and the inability to attribute the observed mortality to a particular chemical. These epidemiologic investigations cannot be cited as definitive evidence of an excess risk of cancer resulting from EtO exposure, but they should be considered evidence that excess risk of cancer may exist for the EtO workers studied.

EVIDENCE OF CARCINOGENICITY IN EXPERIMENTAL ANIMALS

The final report of an inhalation toxicology study of EtO sponsored by a group of EtO manufacturers was released January 28, 1981.[2] In this chronic inhalation study, male and female rats of the Fischer 344 strain were exposed to EtO vapor at test concentrations of 10, 33, or 100 ppm for 6 hours per day, 5 days per week, for about 2 years. Two other groups of animals served as untreated controls. Initially there were 120 animals of each sex in each of the experimental and control groups.

Postmortem examinations were made of all animals that died or were killed when moribund, and at scheduled intervals at 6, 12, 18, 24, and 25 months. Based on histologic evaluation, the researchers concluded that the incidences of mononuclear cell leukemia and peritoneal mesothelioma were significantly increased because of exposure to EtO. At the end of the experiment, the incidence of mononuclear cell leukemia in female rats was dose-related, increasing linearly with increasing exposure concentrations. A statistically significant increase in mononuclear cell leukemia was observed only in the group of females exposed at 100 ppm. For females exposed at 33 ppm, the cumulative percentage incidence of leukemia was significantly higher than that for one control group and for a combination of both control groups, but not for the second control group. However, the incidence for the females exposed at 33 and 10 ppm did indicate a dose response. The regression analysis of leukemia incidence versus exposure concentration was significant with a correlation coefficient of +0.99, indicating that induction of the leukemia was highly correlated to exposure at each concentration.

Peritoneal mesothelioma was reported to be treatment-related in the male rats exposed at 33 and 100 ppm. Among the males expsoed at 100 ppm, the cummulative percentage developing this tumor was statistically higher than controls beginning with the 21st month of exposure, whereas the incidence of the tumors in males exposed at 33 ppm was not appreciably higher than in controls until the last month of the study. These peritoneal tumors originated on the testicular mesothelium and were confined to the abdominal cavity.

In addition, the researchers reported that analysis (mortality-adjusted trend) indicated EtO exposure was associated with a higher frequency and/or earlier

observation of mononuclear cell leukemia in male rats. The researchers also reported that a significant, positive, mortality-adjusted trend analysis indicated that the normal occurrence of pituitary adenoma in male and female rats was accelerated by exposure to EtO.

Government scientists representing NIOSH, OSHA, and the National Toxicology Program reviewed this study with the investigators and concluded that EtO induced mononuclear cell leukemia in the female rats and peritoneal mesothelioma in male rats.

In 1979, Dunkelberg reported preliminary results of a long-term carcinogenicity assay in mice.[13] Ethylene oxide was administered to female NMRI mice by subcutaneous injection in weekly dosages of 0.1, 0.3, or 1.0 mg per animal. Two control groups were used: one received the vehicle (tricaprylin) only, and the other group received no treatment. The animals had been treated for 91 weeks at the time the results were reported. Dunkelberg reported that tumors (sarcomas) appeared at the injection site in the treated groups, but not in the control groups. The first tumor appeared in the 50th week of treatment. The number of subcutaneous tumors at the injection site appeared to increase with the size of the dose; the number of tumors at sites distant from the injection sites was not significantly greater in the treatment groups than in control groups. Such findings may indicate a chemical's carcinogenic potential, although the relevance of subcutaneous tumors at injection sites to carcinogenicity is often questioned. Dunkelberg has apparently not published a final report.

EVIDENCE OF MUTAGENIC AND REPRODUCTIVE EFFECTS

The ability of a chemical to serve as an alkylating agent and to cause mutations in a variety of biological test systems is widely accepted as an indicator that the chemical may have carcinogenic potential. Both alkylation and mutagenicity have been demonstrated for EtO. Further, effects of a chemical on basic genetic material within the cells of living mammals are relevant for assessing mutagenic and carcinogenic hazards for humans. Evidence of this nature is available for EtO.

Results in Sub-Mammalian Test Systems

EtO is effective as both an alkylating agent and as a mutagen in a wide variety of biological systems. It will bind covalently and irreversibly to mammalian protein,[14] human protein,[15] and mammalian DNA.[16] Several investigators have reported the mutagenic properties of EtO in microbial and plant systems including: viruses,[17,18] Salmonella typhimurium,[19] Escherichia coli,[20] Neurospora crassa,[21] barley,[22,23,24,25] rice,[26] wheat,[27] and Tradescantia paludosa.[28] Studies in Drosophila melanogaster exposed to EtO have revealed an increase in both sex-linked recessive lethal,[29,30] and autosomal deletion mutations[30] in a dose-response relationship. In D. melanogaster, lethal mutations and translocations have been induced in all stages of spermatogenesis.[31]

Results in Humans and Experimental Animals

The capability of EtO to cause gene mutations and transmissible genetic damage in mammalian systems also has been reported. Appelgren et al. demonstrated the ability of EtO to reach the testes of mice following intravenous injection.[32] A whole-body autoradiographic study using ^{14}C-labelled EtO indicated that ^{14}C concentrations in the testicle, epididymis, and other organs were higher than those in the blood when measured 20 minutes to 4 hours after EtO exposure. This radioactivity was still present in the epididymis 24 hours after exposure had ended. Two investigators reported dominant lethal mutations: in mice following intraperitoneal administration of a single dose of EtO at 150 mg/kg of body weight,[33] and in rats following a single inhalation exposure of 1,000 ppm for 4 hours.[34] An unpublished study by Cumming et al.[35] reports a dose-response relationship for unscheduled DNA synthesis (UDS) in the testes of mice exposed to EtO by inhalation. UDS reflects the repair of damaged DNA catalyzed by enzymes. Normally, there should be no DNA synthesis in the testes during sperm maturation. At both 600 and 800 ppm a maximum response indicating DNA damage was observed after 4 hours of exposure. Generoso et al. also studied the effects of EtO on heritable translocations (HT) in the mouse.[33] Male mice were injected intraperitoneally with EtO at doses of 30 or 60 mg/kg of body weight per day. Each male mouse was then allowed to mate with three female mice. The male progeny were studied for sperm translocation heterozygosity. A dose-response relationship was observed; 9.36% (38/406) of the animals had HT in the high dose group, while 1.32% (6/456) had HT in the low dose group. None of the animals (0/822) in the control group had HT.

Appelgren et al., in 1978, reported significantly increased numbers of polychromatic erythrocytes containing micronuclei in mice and rats following intravenous injection of EtO.[36] Fomenko and Strekalova[37] and Strekalova et al.[38] reported increased numbers of chromosomal aberrations in bone marrow cells of rats exposed to EtO by inhalation at concentrations ranging from 1 to 112 mg/m^3 (0.6 to 63 ppm). Tests of statistical significance were not reported in either study. Significant excesses of chromosomal abnormalities in bone marrow cells have been reported in rats exposed to EtO by oral doses of 9 mg/kg of body weight (in aqueous solution),[39] or by inhalation of EtO at 250 ppm for 7 hours per day for 3 days.[19] Chromosomal aberrations have been reported in humans accidentally exposed to high concentrations of EtO.[40] More detailed reviews of the mutagenicity of EtO are available.[1,41,42]

In 1978, a company that uses EtO in manufacturing and distributing health care products began to investigate possible adverse effects of EtO on its workers. The investigation entailed monitoring the work environment for concentrations of EtO at its nine facilities, and medical evaluation of 75 workers who had potential EtO exposure. The medical evaluation included analysis of chromosomal aberrations in lymphocytes for all exposed workers and sperm analysis for the men. Workers were exposed for an average of 2.9 years (range: 0.5-10 years). A group of 37 workers who had no known prior exposure to EtO served as controls for the chromosomal analysis.

The company submitted data from this study to NIOSH in April to September 1980; most of the data have since been published.[7] The submitted data revealed that (1) all nine facilities complied with the OSHA standard of 50 ppm for an 8-hour TWA, but there were instances when the extant NIOSH recommendation[1] for a maximum short-term (15-minute) exposure of 75 ppm had been exceeded; (2) physical examinations showed no unusual findings in exposed persons; (3) there was a statistically significant increase in the number of chromosomal aberrations in peripheral lymphocytes obtained from the blood of workers exposed to EtO, when compared with those not exposed; (4) there were statistically significant increased numbers of sister chromatid exchanges (SCE's) in the peripheral lymphocytes of some workers exposed to EtO, and that this increase was statistically significant for workers who had chromosomal abnormalities characterized by quadriradial and triradial exchanges; and (5) data from sperm analysis were inconclusive.

The incidences of chromosome aberration and sister chromatid exchange were higher among the workers exposed to EtO than in workers who had no known EtO exposure. However, it is difficult to evaluate the significance of the findings because of the manner in which the data were presented and the design of the investigation. A major concern is the failure to select matched control individuals for concurrent cytogenetic testing. Cigarette smoking which may affect the incidence of sister chromatid exchange and chromosome aberration, was not accounted for in this investigation. However, quadriradial chromosomes are rare, and while their significance is not well understood, their occurrence should be viewed with concern.

Systematic field investigations are needed to confirm these findings. However, based on these data and in light of the additional evidence of EtO causing chromosomal breakage in workers and experimental animals, it is probable that cytogenetic effects did occur in the workers exposed at TWA concentrations below the OSHA standard of 50 ppm.

Results of a one-generation reproductive study in rats also have been reported.[3] This study involved exposing male and female rats to EtO vapor for 12 weeks prior to mating. Animals were exposed at concentrations of 10, 33, or 100 ppm for 6 hours per day. Before mating, animals were exposed 5 days per week; during and after mating they were exposed 7 days per week. Two control groups of animals were exposed to room air.

The major treatment-related adverse effect observed was a significant reduction in the number of pups born per litter in the group of highest exposure (100 ppm). There were fewer implantation sites per pregnant female, and the average ratio of the number of fetuses born to the number of implantation sites was smaller in the highest exposure group than any other group. Fewer females in the 100-ppm exposure group than in the control groups became pregnant after two mating periods.

The potential for EtO to cause adverse transplacental effects also has been reported.[4] Female mice were administered EtO intravenously at daily doses of 0, 75, or 150 mg/kg of body weight during one of four periods of gestation (days 4-6,

6-8, 8-10, or 10-12). Maternal animals showed signs of toxicity at the higher dose level when administered in the first, third, and fourth periods, but not in the second period (days 6-8 of gestation). A significant reduction in mean fetal body weight compared with controls was reported for all four treatment periods at the 150-mg/kg level. There was a significant increase in the percentage of malformed fetuses/litter from dams administered EtO at the high dose level during the second and fourth gestational periods. Approximately 19% of the fetuses in each litter from maternal animals that showed no signs of toxicity when given 150 mg/kg in the second period had some type of malformation, mostly in the cervical and thoracic regions of the skeleton.

Chemicals may be considered to be teratogenic if they produce certain malformations in the offspring in the absence of maternal toxicity. In this experiment, EtO administered intravenously to pregnant mice at 150 mg/kg on days 6-8 of gestation caused such a response. However, the investigators cautioned that the case of teratogenicity of EtO is weakened somewhat by the high incidence of maternal mortality they observed with the same dose at other gestational periods.

EXPOSURE STANDARDS AND GUIDES

OSHA's standard for occupational exposure to EtO is 50 ppm (90 mg/m^3) as a time-weighted average (TWA) concentration for an 8-hour work shift.[43] Studies of carcinogenicity were not available when this standard was developed.

In its 1977 review of EtO, NIOSH recommended that occupational exposure be limited to a ceiling concentration of 75 ppm (135 mg/m^3), determined during a 15-minute sampling period. Additionally, NIOSH recommended that the OSHA standard of 50 ppm (90 mg/m^3) as a TWA be observed. NIOSH emphasized that its document did not attempt to address the adequacy of the OSHA standard.[1]

The values recommended by NIOSH in 1977 were the same as the Threshold Limit Values (TLV's) then recommended by the American Conference of Governmental Industrial Hygienists (ACGIH) for Time Weighted Average (TWA) and Short Term Exposure Level (STEL) concentrations, respectively.[44] In 1979, ACGIH published its intent to change its TLV to 10 ppm (20 mg/cu m^3) as a TWA concentration.[45,46]

Reflecting increased concern over the mutagenic and carcinogenic potential of EtO, some manufacturers and commercial users of the chemical are adopting occupational exposure guidelines lower than the OSHA standard. Self-imposed guidelines adopted by companies have been reported to range from 1 to 10 ppm as 8-hour TWA concentrations, with two companies also adopting peak limits of 5 and 15 ppm.[47]

RECOMMENDATIONS

Ethylene oxide has caused statistically significant increases in mononuclear cell leukemia in female Fischer 344 rats. The incidence of this disease in the exposed females increased linearly with dose. Among male Fischer 344 rats in the same

experiment, EtO induced peritoneal mesothelioma which originated in the testicular mesothelium. Although humans and animals may differ in their susceptibility to specific chemical compounds, any substance that produces cancer in experimental animals should also be considered to have carcinogenic potential in humans. The mutagenicity of EtO has been extensively demonstrated in lower biological species and in mammals. Recent experiments in mammals have demonstrated adverse reproductive effects, which are also of public health concern. The widespread recognition of EtO as an effective alkylating agent and mutagen reinforces concern over the carcinogenic potential of EtO. Also, epidemiologic investigators reported excess cancer mortality at two worksites where workers were exposed to EtO. These epidemiologic findings are not by themselves proof of an excess risk of cancer resulting from EtO exposure. However, the causal inference from animal experimental evidence is compatible with the observed excess of cancer among workers exposed to EtO in two separate operations.

Based on these recent findings, NIOSH recommends that EtO be regarded in the workplace as a potential occupational carcinogen. Safe levels of carcinogens have not been demonstrated, but the probability of developing cancer should be reduced by decreasing exposure. The excess cancer risks to workers exposed to EtO at or below the present OSHA standard of 50 ppm as a TWA concentration have not yet been estimated. However, NIOSH believes the present standard needs to be reexamined because its adoption preceded the recognition of the carcinogenic potential of EtO and was established to protect against only acute and nonmalignant chronic effects. As prudent public health policy, NIOSH urges employers, in the interim, to voluntarily assess the conditions under which their workers may be exposed to EtO and take all reasonable steps to reduce exposure to the extent possible. The actions taken by some companies to voluntarily adopt exposure guidelines lower than the present standard are commendable moves in the right direction, however, these exposure guidelines have not been evaluated by NIOSH. The "Guidelines for Minimizing Worker Exposure to Ethylene Oxide," Appendix I, should be adapted to specific work situations.

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APPENDIX I

GUIDELINES FOR MINIMIZING WORKER EXPOSURE TO ETHYLENE OXIDE

NIOSH recommends that ethylene oxide (EtO) be regarded in the workplace as a potential occupational carcinogen. Exposure should be limited to as few workers as possible, and workplace exposure levels should be minimized. Substitutes of lesser hazards should be used where practicable. The area in which EtO is used should be restricted to only those workers essential to the process or operation.

NIOSH recognizes that it may be harder to reduce exposure in the industries and work settings where EtO is used as a sterilant or fumigant than in industrial plants where systems are generally closed and automated. Considerable attention has been directed toward developing control methods for sterilizing and fumigating operations. The recommendations of NIOSH's 1977 Special Occupational Hazard Review with Control Recommendations: Use of Ethylene Oxide as a Sterilant in Medical Facilities are still appropriate and should be implemented whenever applicable.[1] Consult the end of this appendix for the availability of Government publications.

More recent work in this area was presented at a seminar sponsored by the Health Industry Manufacturers Association (HIMA). The proceedings from this seminar contain useful information on monitoring and controlling emissions of EtO from sterilizing systems. This publication discusses in detail work practices and engineering controls that can be incorporated into existing and new sterilizer systems and areas. Engineering controls include installing exhaust ventilation at the sterilizer door, providing a purge or airflush cycle to precede the full opening of the sterilizer door, ensuring that all equipment and piping are leak-free, venting water drains and exhausted air outside the work area and occupied spaces, and providing capture and removal of EtO off-gasing from sterilized items. The proceedings can be obtained by writing to HIMA, 1030 15th Street, N.W., Suite 1100, Washington, D.C. 20005, and requesting information on HIMA Report No. 80-4, The Safe Use of Ethylene Oxide: Proceedings of the Educational Seminar. A companion document, HIMA Report No. 81-1, Monitoring Airborne Ethylene Oxide: Proceedings of the Ethylene Oxide Monitoring Workshop, is in preparation.

The latest in a series of EtO-related activities undertaken by the American Hospital Association is the development of a personnel training manual. The manual, to be published in the summer of 1981, is intended to be used by central service supervisors in the routine training of their staff in the safe use of ethylene oxide as a gas sterilant in health care facilities. The manual will be entitled Ethylene Oxide Use in Hospitals: A Manual for Health Care Personnel. For

information on its availability contact: American Hospital Association, 840 North Lake Shore, Chicago, Illinois 60611.

The U.S. Environmental Protection Agency (EPA) has been supporting an extensive study to identify engineering controls, monitoring devices, and personnel procedures that would reduce exposure to EtO in industries that use it as a pesticide (e.g., as a sterilant or fumigant). This work, performed by the MITRE Corporation under EPA Contract No. 68-01-5944, is nearing completion; and a final report with recommendations should be available in the spring of 1981. For information on the availability of this report contact:

U.S. Environmental Protection Agency
Special Pesticide Review Division (TS-791)
Branch #1
Crystal Mall #2, Room 711-H
1921 Jefferson Davis Highway
Arlington, Virginia 22202

Telephone: (703) 557-7401

The guidelines listed below are more general and have greatest application in industrial settings. However, they should be given consideration for all settings and be adapted to specific work situations as required.

EXPOSURE MONITORING

Initial and routine worker exposure surveys should be made by competent industrial hygiene and engineering personnel. These surveys are necessary to determine the extent of worker exposure and to ensure that controls are operational and effective.

The NIOSH Occupational Exposure Sampling Strategy Manual may be helpful in developing efficient programs to monitor worker exposure to EtO.[48] The manual discusses determination of the need for exposure measurements and selection of sampling times.

Worker exposure measurements should be 8-hour TWA and short-term (15-minute) exposure estimates calculated from personal or breathing zone samples (air most like that inhaled by the workers). Short-term samples should be taken during periods of maximum expected exposure by using all available knowledge of the area, work procedures, and processes. Area and source measurements may be useful to identify problem areas, processes, and operations.

CONTROLLING WORKER EXPOSURE

There are four basic methods of limiting worker exposure to EtO, none of which is a simple industrial hygiene or management decision. Careful planning and thought should be used prior to implementation.

o Product Substitution

The substitution of an alternative material with a lower potential health risk is an important method for reducing exposure. However, extreme care must be used when selecting possible substitutes. Possible health effects and exposure potentials of alternatives to EtO should be fully evaluated prior to selection.

o Contaminant Controls

Airborne concentrations of EtO can be most effectively controlled at the source of contamination by enclosure of the operation and/or use of local exhaust ventilation. Guidelines for selected processes and operations can be found in NIOSH's Recommended Industrial Ventilation Guidelines.[49]

When enclosing a process or operation, a slight vacuum should be used to create negative pressure so that leakage will result in the flow of external air into the enclosure and minimize contamination of the workplace. This can be accomplished with a well-designed local exhaust ventilation system that physically encloses the process as much as possible, with sufficient capture velocity to keep the contaminant from entering the workplace atmosphere. The design of ventilation systems should take into account the flammable, explosive, and reactive characteristics of EtO.

Ventilation equipment should be checked at least every 3 months to ensure adequate performance. System effectiveness should also be checked soon after any change in production, process, or control that might result in significant increases in airborne exposure to EtO.

o Worker Isolation

If feasible, workers may be isolated from direct contact with the work environment by the use of automated equipment operated by personnel observing from a closed control booth or room. The control room is maintained at a greater air pressure than that surrounding the process equipment so that air flow is out of, rather than into, the room. This type of control will not protect those workers that must perform process checks, adjustments, maintenance, and related operations. Special precautions are often necessary to prevent or limit exposure in these situations and frequently involve the use of personal protective equipment.

o Personal Protective Equipment

Personal protective equipment, which may include respirators, goggles, and gloves, should not be used as the only means to prevent or minimize exposure during routine operations. Ethylene oxide can penetrate many materials; care should be exercised in selecting personal protective equipment to insure that the equipment is relatively impermeable to EtO.

However, exposure to EtO can be controlled with the use of this equipment:

- During the time necessary to install or implement engineering or work practice controls; or
- In work situations in which engineering and work practice controls have proven ineffective; or
- For maintenance; or
- For operations that require entry into tanks or closed vessels; or
- In emergencies.

Proper maintenance procedures, good housekeeping in the work area, and worker education are all vital aspects of a good control program. Workers should be informed as to the nature of the hazard, its control, and appropriate personal hygiene procedures.

MEDICAL SURVEILLANCE

A medical surveillance program should, as noted in the 1977 NIOSH review,[1] be made available that can evaluate both the acute and chronic effects of EtO exposure. Effects such as upper respiratory irritation, dermatitis, or other forms of sensitization and irritation should alert management that unacceptable acute exposure to EtO may be occurring. A careful history with emphasis on the reproductive history should be done initially and updated yearly. In addition, an evaluation of chronic effects would require that an examination give particular attention to the hematological, neurological, and reproductive systems. Unusual findings for a worker should prompt medical personnel to consider specific tests (e.g., cytogenetic analysis) for the individual.

AVAILABILITY OF GOVERNMENT PUBLICATIONS

Government publications referenced in this appendix are available from the Government Printing Office (GPO).

Reference 1: From GPO as #017-033-00262-2 for $2.30.
Reference 48: From GPO as #017-033-00247-9 for $2.75.
Reference 49: From GPO as #017-033-00136-7 for $3.90

GPO publications can be ordered from:

Superintendent of Documents
U.S. Government Printing Office
Washington, D.C. 20402

APPENDIX II

MAJOR MANUFACTURERS OF ETHYLENE OXIDE

BASF - Wyandotte Corporation
Calcasieu Chemical Company
Celanese Corporation
Dow Chemical U.S.A.
Northern Petrochemical Company
Olin Corporation
PPG Industries, Inc.
Shell Chemical
Sun-Olin Corporation
Texaco Chemical Company
Union Carbide Corporation

APPENDIX III

IDENTIFIERS AND SYNONYMS FOR ETHYLENE OXIDE AND ETHYLENE OXIDE MIXTURES USED IN GASEOUS STERILIZATION

Chemical Abstracts Service Registry Number: 75-21-8

NIOSH RTECS Number: KX2450000

Chemical Formula: C_2H_4O

Anprolene
Benvicide
Carboxide
Cry-Oxide
Dihydrooxirene
Dimethylene oxide
Epoxyethane
1,2-Epoxyethane
Ethylene oxide
EO
ETO
EtO
Oxacyclopropane
Oxane
Oxidoethane
Oxiran
Oxirane
Oxirene, dihyro-
Oxyfume
Oxyfume 12
Oxyfume Sterilant -20
Pennoxide
Steroxide -12
Steroxide -20
T-gas

The above information was obtained from the NIOSH's computerized Registry of Toxic Effects of Chemical Substances (RTECS), and from the National Library of Medicine's computerized chemical dictionary file CHEMLINE. Registered trademark information is not included in these files. Therefore, some of the above synonyms and identifiers may be trademarked but are not so indicated above.

NIOSH

Current Intelligence Bulletin 36

June 30, 1981

SILICA FLOUR: SILICOSIS
(CRYSTALLINE SILICA)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

The National Institute for Occupational Safety and Health (NIOSH) Current Intelligence Bulletin is the primary product of the Current Intelligence System. The purpose of the Current Intelligence System is to promptly review, evaluate, and disseminate new information received by NIOSH that may indicate either the existence of an occupational hazard not previously recognized or a greater hazard than generally known. The Current Intelligence System staff within the Division of Criteria Documentation and Standards Development was responsible for the preparation of this Bulletin.

Current Intelligence Bulletins are disseminated to NIOSH staff, other government agencies, and the occupational health community, including labor, industry, academia, and public interest groups. The Bulletins are intended to disseminate new data that may affect prevailing perceptions of occupational hazards. They convey important public health information and recommend voluntary protective measures. Current Intelligence Bulletins do not recommend occupational standards, nor are they intended to have any regulatory significance.

DHHS (NIOSH) Publication No. 81-137

CURRENT INTELLIGENCE BULLETIN: #36

SILICA FLOUR: SILICOSIS

June 30, 1981

The National Institute for Occupational Safety and Health (NIOSH) warns producers and users of silica flour that the risk of developing silicosis may be very high for workers exposed to silica flour. NIOSH determined the status of worker health and surveyed airborne silica dust concentrations at two silica flour mills at the request of the Mine Safety and Health Administration (MSHA). Of 61 current and former workers with 1-14 years of exposure to silica dust, 23 (37%) had chest radiographic evidence of silicosis. Of particular concern are the medical evaluations of four of these affected workers who had relatively short-term silica dust exposures (2.5-6 years), indicating rapidly developing silicosis. Usually, about 20 years of exposure to dust containing silica precedes development of silicosis. NIOSH's sampling results agreed with the results from past MSHA inspection samples that showed a large percentage of high silica dust concentrations. On the days of sampling, 61 of 91 samples were above MSHA's exposure limit for silica, and 77 were above NIOSH's recommended exposure limit. In view of the high prevalence of silicosis after relatively short exposures to silica flour in these two mills, and a history of high silica dust exposures in these and 25 other mills, NIOSH believes workers exposed to silica flour are at serious risk of developing silicosis. This concern extends to workers in industries that use silica flour who may also be at increased risk. Therefore, NIOSH recommends control of silica flour exposure and the labelling of products that contain silica flour.

BACKGROUND

Simple, Accelerated, and Acute Silicosis

Silicosis is a debilitating respiratory disease caused by inhalation of fine crystalline silica dust that is retained in the lungs.[1] The amount of dust inhaled, the percentage of free or uncombined silica in the dust, the size of the dust particles, and the length of exposure all affect the onset of silicosis. The inhaled dust deposited in the bronchioles and alveoli reacts within the lung tissue to form silicotic nodules. The nodules appear on chest radiograms as discrete, rounded opacities or shadows. The presence of silicotic nodules and a history of occupational exposure to silica dust are necessary for a positive diagnosis of silicosis. The earliest symptom of silicosis is shortness of breath. As the disease progresses, the silicotic nodules coalesce and form a continuous mass of fibrotic tissue, called progressive massive fibrosis.

Silicosis manifests itself in different ways depending on exposure conditions and individual variations. Researchers have described three forms of the disease. They differ primarily in the length of exposure before the onset of symptoms of the disease and the rate at which the disease then progresses. The common or

simple form of silicosis has been recognized as an occupational disease since antiquity. It may take 20 or more years of exposure before a chest radiogram is positive for silicosis. Usually there is little or no respiratory impairment associated with the early stages of simple silicosis. The silica content of the dust to which workers developing simple silicosis are exposed is often less than 30%.

Accelerated and acute silicosis develop after shorter exposures to respirable silica dust at high concentrations. Accelerated silicosis differs from simple silicosis mainly in the time from first exposure to silica dust until silicotic nodules appear on a chest radiogram. In accelerated silicosis the exposure varies between 5-15 years, the progression of disease development is faster, and often there is progressive massive fibrosis.

Acute silicosis, also termed silicoproteinosis, develops after 1-3 years of exposure and progresses even faster than accelerated silicosis. There is a rapid loss of pulmonary function, invariably followed by death. A distinctive feature in acute silicosis is the presence of a surfactant-like liquid in the alveoli. On a chest radiogram there are few silicotic nodules, and they are rather diffuse.

No effective medical treatment is available for silicosis.

Silica Flour Industries

Silica flour is used industrially as an abrasive cleaner and as an inert filler.[2] Silica flour is found in toothpaste, scouring powder, and metal polish. It is an extender in paint, a wood filler, and a component in road surfacing mixtures. It is also used in some foundry processes. The actual number of workers exposed to silica flour in the United States is not known.

After crystalline silica is mined, it is milled to a fine powder and packaged for shipment. Silica flour is not always labelled as containing crystalline silica, and it may be labelled incorrectly as amorphous silica[3], which is commonly believed to cause little or no fibrosis.[4] More data are appearing which indicate that the fibrogenic potential of amorphous silicas should be reconsidered.[5] A recent report by Groth on the chronic effects of inhaled amorphous silicas in animals identified the fibrogenic potential of certain synthetic amorphous silicas.[6] Thus, workers in industries that use silica flour may be unaware that it is a hazardous material because of either the absence of labelling or the mislabelling of silica flour containers.

Occupational Standards

MSHA's Metal and Nonmetal Mining and Milling standard[7] and the Occupational Safety and Health Administration's standard[8] for respirable crystalline silica (SiO_2) for an 8-hour workshift are expressed by the formula:

$$\frac{10 \text{ mg } SiO_2/m^3}{\% SiO_2 + 2}$$

where: $mg\ SiO_2/m^3$ = milligrams of silica per cubic meter of air
$\% SiO_2$ = the percentage of silica in the respirable dust.

For example, the calculated Federal standard for silica flour that is essentially 100% respirable silica is 0.10 mg/m^3.

In 1974 NIOSH recommended that the exposure limit for respirable crystalline silica be 0.05 mg/m^3 averaged over a work shift of up to 10 hours a day, 40 hours a week.[9] NIOSH recommended that silica sand or other materials containing more than 1% free silica be prohibited as an abrasive substance in abrasive blasting or cleaning operations. NIOSH is now preparing an updated review and evaluation of information on crystalline silica that has become available since the criteria document was completed.[10] New data on sampling and analysis, engineering controls, work practices, and toxic effects reported in humans and animals exposed to crystalline silica are described. The new information tends to support the NIOSH-recommended standard. NIOSH's criteria document[9] and literature update[10] should be consulted for further details.

Other Reports

From numerous reports in the literature, two reports were selected to illustrate the occurrence of rapidly developing silicosis in a worker in a silica flour user industry and the ineffectiveness of some respirator programs.

An Australian worker developed symptoms of silicosis after 2 years of exposure to silica flour in the manufacture of metal polish.[11] The workplace concentration of silica was not measured. The silica used was 99.5% silica ground to 200 gauge. About 60 times a year he opened 24 bags of silica flour, poured the powder into a drum, and then emptied the drum slowly into a mixer. The man died 2.5 years after a diagnosis of acute silicosis was made. The authors commented that the silica flour bags had no warning label.

Many cases of silicosis have been reported in sandblasters. Even though whole-grain sand is of larger average size than silica flour, many silica particles are of respirable size (less than 10 μ in diameter). The efficiency of several types of non-air-supplied and air-supplied protective hoods worn by sandblasters was investigated by Samimi and coworkers.[12] They determined the concentrations of respirable silica in the ambient air and inside workers' hoods during short, moderate, and long periods of sandblasting. About one-third of the workers using non-air-supplied hoods did not wear their respirators under their hoods, and the others wore respirators that were not regularly maintained. Some air-supplied hoods worn with properly-fitted respirators did provide adequate protection during the actual periods of sandblasting. However, the sandblasters were not protected from excessive silica dust in the ambient air when they removed their protective equipment during nonsandblasting periods. The authors concluded that most sandblasters wearing various types of protective equipment, even air-supplied hoods with respirators, were exposed to an average level of silica dust several times greater than the standard. The average exposure duration in fatal silicosis in sandblasters was 10 years.

NIOSH INVESTIGATIONS

At the request of MSHA, NIOSH conducted a study at two silica flour mills in 1979. The purpose of the study was to determine the prevalence of silicosis in this workforce and to measure the levels of silica dust exposures. Both mills had a history of exceeding MSHA's standard for respirable crystalline silica dust.

The results of these investigations have been reported.[3,13,14] The medical evaluation consisted of a chest radiogram, spirometry, and a questionnaire emphasizing occupational history and respiratory symptoms. Of 61 current and former workers with 1-14 years of exposure to silica dust, 16 (26%) had chest radiograms indicating simple silicosis and 7 (11%) had progressive massive fibrosis. The average duration of exposure to silica dust for the 16 workers with simple silicosis was 7.7 years (range: 1-9 years). The 7 workers with progressive massive fibrosis had an average exposure duration of 7.1 years (range: 2.5-14 years). One worker, aged 24, had progressive massive fibrosis after only 2.5 years of silica exposure, another after 4 years, and two others after 6 years.

The silica content of the dust from both mills was determined by X-ray diffraction to be approximately 99% free silica. The mean diameters of the dust particles from air sampled at various mill operations were 2.3 - 5.2 μ, which are within the respirable range. Analysis of air samples from both mills on the days of sampling showed that 61 of the 91 dust samples were above MSHA's standard for crystalline silica; 77 were above NIOSH's recommended standard. Some samples were several hundred times over the NIOSH recommendation.

NIOSH considered the situations at both mills at the time of study to be extremely dangerous. There was a significant health hazard present; continued worker exposure at the concentrations measured would cause irreversible harm and shorten life expectancy. Although respiratory protection programs were on record at both facilities, they were ineffective.[14]

NIOSH also reviewed MSHA silica dust sampling results from the 2 mills and 25 other silica flour mills for 1974-79.[14] Altogether, 170 inspections were made, representing 1,350 workers. Of 1,142 samples analyzed for respirable silica, 608 (53%) exceeded MSHA's standard. Only one workplace had no samples in excess of the MSHA standard. There was no significant decline in the number of samples in excess of the standard over the period observed, despite attempts to control the dust at the 26 mills that were not in compliance with the regulation.

NIOSH RECOMMENDATIONS

Worker exposure to silica flour should be controlled to within NIOSH's recommended standard for respirable crystalline silica of 0.05 mg/m^3, averaged over a workshift of up to 10 hours a day, 40 hours a week. Employers and workers should take appropriate actions to reduce silica flour exposure to this limit.

1. Exposure Monitoring

Worker exposure surveys should be made by competent industrial hygiene and engineering personnel. Surveys are necessary to determine the extent of worker exposure and the effectiveness of engineering controls.

A detailed analytical method for free silica (quartz) is in the NIOSH Manual of Analytical Methods, 2nd Ed., Vol. 5, 1979 as method # 259.[15] This method is a revision of the previous NIOSH method.

2. Engineering Controls

The most effective control of airborne concentrations of silica flour is at the source of contamination by enclosure of the operation and/or use of local exhaust ventilation. Guidelines for selected processes and operations can be found in NIOSH's Recommended Industrial Ventilation Guidelines[16] and in the American Conference of Governmental Industrial Hygienist's Industrial Ventilation - A Manual of Recommended Practice.[17]

When enclosing a process or operation, a slight vacuum should be used to create negative pressure so that leakage will result in the flow of external air into the enclosure and minimize contamination of the workplace. This can be accomplished with a well-designed local exhaust ventilation system that physically encloses the process as much as possible, with sufficient capture velocity to keep the contaminant from entering the work atmosphere.

Ventilation equipment should be checked at least every 3 months to ensure adequate performance. System effectiveness should be checked soon after any change in production, process, or control which might result in significant increases in airborne exposure to silica flour.

3. Medical Surveillance

Preplacement and annual medical examinations should be made available to all workers who manufacture, use, or handle silica flour or materials containing silica flour. These examinations should include at least:

a. Comprehensive work and medical histories to evaluate exposure and signs and symptoms of respiratory disease;

b. A 14 x 17 inch posteroanterior chest radiogram, preferably interpreted using the 1971 ILO U/C classification (1980 ILO classification when available);[18] and

c. Pulmonary function tests including forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1), with calculation of the FEV_1/FVC ratio.

Workers with radiographic evidence of silicosis should be given the opportunity to transfer to jobs without silica exposure (defined as exposure at concentrations less than half of the NIOSH-recommended standard).

4. Work Practices

Work practices involve both the design of work procedures and the actions of workers. The following work practices are recommended:

a. Work procedures should be developed so they do not produce dust;

b. Work clothes should be vacuumed before removal;

c. General housekeeping duties should be intensified so that there is no dust accumulation on machinery, beams, corners, and other surfaces. Such accumulations often contain respirable particles which can become airborne when disturbed. Dustless methods of cleaning such as vacuuming or wetting down should be used. Dry sweeping or blowing with compressed air should be avoided; and

d. Emphasis should also be given to cleanup of spills, preventive maintenance, and timely repair of equipment.

5. Personal Protective Equipment

Personal protective equipment is not recommended as a primary means of control. Exposure of workers to airborne silica flour should not be controlled with the use of respirators except:

a. During installation and implementation of engineering or work practice controls;

b. In work situations in which engineering and work practice controls are technically not feasible;

c. During major overhaul and repair of equipment, if exposure to silica flour is possible;

d. In operations that require entry into tanks or closed vessels; or

e. In emergencies.

A list of Respirator Use Conditions from the NIOSH/OSHA Pocket Guide to Chemical Hazards can be found in the Appendix.[19] Only respirators jointly approved by NIOSH and MSHA should be used. Equipment meeting these criteria may be found in the NIOSH Certified Equipment List.[20]

6. Worker Education

Worker education is a vital aspect of a good control program. Workers should be informed of the hazardous nature of silica flour, the results of workplace monitoring and medical tests, and the correct useage and maintenance of respirators.

7. Labelling of Silica Flour Containers

Packaged silica flour should be labelled correctly, and health warnings should be placed on each container to alert users and handlers as well as producers to the hazards of silica flour.

Ronald F. Coene, P.E.
Acting Director

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APPENDIX

Respirator Use Conditions[19]

NIOSH has recommended respirator use for silica concentrations at 5, 10, 50, and 500 times the standard, defined as a permissible exposure limit (PEL) (see the Occupational Standards section of this bulletin). The degree of respiratory protection for exposure situations is dependent on the type of device that is selected. In the listing below, the first choice (1), offers minimal adequate protection; (2) offers greater protection, etc.

NIOSH recommends respirator use as follows:

5 X PEL mg/m^3:	(1)	Dust mask
10 X PEL mg/m^3:	(1)	Dust mask, except single-use and quarter-mask respirators
	(2)	Fume or high-efficiency particulate respirator
	(3)	Supplied-air respirator
	(4)	Self-contained breathing apparatus
50 X PEL mg/m^3:	(1)	High-efficiency particulate respirator with a full facepiece
	(2)	Supplied-air respirator with a full facepiece, helmet, or hood
	(3)	Self-contained breathing apparatus with a full facepiece
500 X PEL mg/m^3:	(1)	Powered air-purifying respirator with a high-efficiency particulate filter
	(2)	Type C supplied-air respirator operated in pressure-demand or other positive pressure or continuous-flow mode

NIOSH

Current Intelligence Bulletin 37

October 26,1981

ETHYLENE DIBROMIDE (EDB)
(Revised)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

The National Institute for Occupational Safety and Health (NIOSH) Current Intelligence Bulletin is the primary product of the Current Intelligence System. The purpose of the Current Intelligence System is to promptly review, evaluate, and disseminate new information received by NIOSH that may indicate either the existence of an occupational hazard not previously recognized or a greater hazard than generally known. The Document Development Branch staff within the Division of Standards Development and Technology Transfer prepared this Bulletin.

Current Intelligence Bulletins are disseminated to NIOSH staff, other government agencies, and the occupational health community, including academia, industry, labor, and public interest groups. The Bulletins are intended to disseminate new data that may affect prevailing perceptions of occupational hazards. They convey important public health information and recommend voluntary protective measures. Current Intelligence Bulletins do not recommend occupational standards, nor do they have any regulatory status.

DHHS (NIOSH) Publication No. 82-105

NIOSH CURRENT INTELLIGENCE BULLETIN: #37

ETHYLENE DIBROMIDE (EDB)
REVISED

October 26, 1981

The National Institute for Occupational Safety and Health (NIOSH) reaffirms its 1977 recommendation that ethylene dibromide (EDB) be treated as a potential occupational carcinogen in the workplace. This includes a ceiling limit of 0.13 ppm (1.0 mg/m^3) as determined over any 15-minute sampling period and use of appropriate controls to reduce worker exposure. Recent animal studies involved exposure to ethylene dibromide by skin application, oral administration, and inhalation. Statistically significant increases in tumors of the respiratory tract, mammary gland, spleen, and nasal cavity were observed. Inhalation studies with rats and mice at ethylene dibromide concentrations below the current Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) of 20 ppm demonstrated a carcinogenic risk. In addition, the new animal bioassay studies reaffirm the increased toxic effects reported in 1978 when EDB is administered with disulfiram, a widely-used drug in alcoholism control programs. This increased interaction may not necessarily be restricted to disulfiram, but may occur with similarly structured compounds such as Thiram®, a fungicide and seed disinfectant.

BACKGROUND

Purpose of Bulletin

This Bulletin is being released because of the anticipated increased use of EDB as a fruit fumigant, and to alert workers who may have a potential EDB exposure to recent information about its potential carcinogenic risk. This information reinforces NIOSH's 1977 assessment that EDB is highly toxic and may cause cancer in humans.[1] In the 1977 assessment, NIOSH concluded that persons chronically exposed to EDB may be at increased risk of adverse reproductive and other effects. Evidence from animal experiments indicates that these effects may include sterility, inheritable changes in offspring, teratogenesis, and adverse effects on the liver, kidneys, heart, and other internal organs. Skin contact with EDB was found to produce chemical burns as well as systemic effects from percutaneous absorption.

Production and Use

EDB was first produced on a commercial scale during the mid-1920's. Current U.S. production is estimated at approximately 300 million pounds annually. EDB is used primarily as a scavenger in leaded fuels in combination with ethylene dichloride. These scavengers are used to form volatile lead compounds during combustion, which are more completely removed from the

combustion chamber. This usage is decreasing as the consumption of leaded gasoline declines. EDB is also used as a soil, grain, and fruit fumigant, as an intermediate in the synthesis of dyes and pharmaceuticals, and as a solvent for resins, gums, and waxes. NIOSH estimates that approximately 108,000 U.S. workers are potentially exposed to EDB during its production and use. In addition, an estimated 875,000 workers are potentially exposed to very low levels of EDB while working with leaded gasoline.[2]

Exposure Standards and Guides

OSHA's current standard for occupational exposure to EDB is 20 ppm as a time-weighted average (TWA) concentration for an 8-hour work shift, with an acceptable ceiling concentration of 30 ppm. A maximum peak above the acceptable ceiling concentration for an 8-hour work shift of 50 ppm for not more than 5 minutes is also permitted (29 CFR 1910.1000). This standard was adopted from the American National Standards Institute recommendation (ANSI Z37.31-1970).

In 1977, NIOSH recommended that occupational exposure to EDB be limited to a ceiling concentration of 0.13 ppm (1.0 mg/m^3), as determined over any 15-minute sampling period.[1]

In 1978, the American Conference of Governmental Industrial Hygienists (ACGIH) voided their 20-ppm threshold limit value (TLV) recommendation and assigned EDB an A1b classification (Human Carcinogen) without a TLV. After further review of the data in 1980, the ACGIH changed the classification to A2 (Industrial Substances Suspect of Carcinogenic Potential for Man). No TLV for EDB is assigned.[3]

In addition, California's Division of Occupational Safety and Health (Cal/OSHA) has had an Emergency Temporary Standard of 0.13 ppm adopted that became effective September 23, 1981. If this level is not rejected by the California Office of Administrative Law, it will remain in effect for 120 days. This is the same level recommended by NIOSH in 1977.

Extent of Exposures

Most of the environmental data on EDB came from the monitoring of exposures at EDB manufacturing operations, gasoline production and distribution facilities, and fruit fumigation operations.

NIOSH performed an industrial hygiene survey of two manufacturing and two user facilities of EDB. Samples were taken for more than 69 potentially-exposed workers in 17 job classifications. Median EDB exposures by similar job types in the manufacturing processes ranged from 0.010 to 0.5 ppm (35 TWA personal samples), and 0.0002-0.054 ppm in antiknock blending operations (39 TWA personal samples). General area samples collected at breathing zone heights had median TWA levels of 0.2 ppm for 10 samples at process sites, and 0.5 ppm for 3 samples at laboratory sites.

For quality control samples, EDB ceiling levels ranged from 0.04 to 23.4 ppm; for loading and unloading of tank cars, they were 0.09-2.4 ppm.[4]

A NIOSH environmental survey of fruit fumigation operations reported worker exposure (personal samples) to EDB ranging from nondetectable (8 of 29 samples) to 2.92 ppm for a post fumigation fruit loader in the transport truck trailer. Forklift operator exposures ranged from 0.06 to 2.08 ppm. Area samples of airborne EDB concentrations ranged from nondetectable (13 of 33 samples) to 2.96 ppm at the EDB introduction point into the fumigation chamber.

In another survey, conducted at three fruit packing plants, personal and area air samples were collected for the determination of EDB exposures. Of the 14 personal samples collected, EDB was nondetectable in 13 samples, with the other indicating a concentration of 0.14 ppm for a fumigator. Area sample airborne EDB concentrations ranged from nondetectable (16 of 20 samples) up to 0.81 ppm for a sample collected at the door of the fumigation chamber.[6]

TOXICITY

Evidence of Carcinogenicity in Experimental Animals

In 1977, NIOSH reported the preliminary results of a National Cancer Institute (NCI) study that indicated potential carcinogenic effects in rats and mice when EDB was administered by gavage.[7] The completed bioassay was reported in 1978.[8] Under the conditions of this bioassay, EDB was carcinogenic to Osborne-Mendel rats and B6C3F1 mice. Additional animal carcinogenicity bioassays have been conducted since then to assess the carcinogenic potential of EDB by inhalation and skin absorption.

Van Duuren et al. reported in 1979 an increased incidence of skin papillomas, skin carcinomas, and lung tumors in treated male and female noninbred Ha:ICR Swiss mice. The animals received repeated skin applications of EDB 3 times weekly for 40-594 days at 25 or 50 mg/application/mouse. This was the first reported study demonstrating EDB to be carcinogenic by skin application.[9]

The National Toxicology Program (NTP) and NCI recently reported the results of a carcinogenesis bioassay of EDB by the inhalation route.[10] Groups of rats and mice of each sex were exposed to airborne EDB at concentrations of 10 and 40 ppm, levels below and above OSHA's PEL of 20 ppm. Animals were exposed 6 hours/day, 5 days/week for 78-103 weeks.

In this bioassay, EDB was found to be carcinogenic for rats at both the 10- and 40-ppm dosages, causing increased incidences of tumors of the nasal cavity and adenomas of the pituitary gland in males and females, hemangiosarcomas of the circulatory system and mesotheliomas in the tunica vaginalis in males, and fibroadenomas of the mammary gland in females. Likewise, EDB was carcinogenic for mice at both dosages, causing increased

incidences of alveolar/bronchiolar carcinomas in males and females, and fibrosarcomas in the subcutaneous tissue, hemangiosarcomas of the circulatory system, tumors of the nasal cavity, and adenocarcinomas of the mammary gland in females.

Concurrent with the NTP and NCI study, NIOSH sponsored a study on EDB's chronic inhalation toxicity in rats.[11] The study was designed to determine the effects of EDB inhalation at OSHA's current PEL of 20 ppm, with and without disulfiram in the diet. Rats were exposed 7 hours/day, 5 days/week, for 18 months to simulate occupational exposure to EDB.

The results showed a high mortality rate and a statistically significant increase in the incidence of benign and malignant tumors of the spleen, mammary gland, and nasal cavity for rats exposed by inhalation to EDB at 20 ppm and fed the standard rat diet. Rats exposed by inhalation at 20 ppm and fed the diet containing 0.05% disulfiram by weight exhibited a higher mortality rate, as well as an earlier development and a statistically significant increased incidence of tumors of the liver and mesentery compared with those animals exposed to EDB alone.

These data[10,11] demonstrate EDB to be carcinogenic in rats and mice when exposed by inhalation. The data also show that the addition of disulfiram to the diet results in approximately a ten-fold increase in the incidence of hepatocellular carcinomas over exposure to EDB alone. EDB has also been shown to be carcinogenic in mice as a result of percutaneous absorption.[9]

Epidemiologic Evidence of Cancer in Humans

The epidemiologic studies of EDB reported in the literature are inconclusive because they suffer from small cohort size, incomplete or missing exposure data, and insufficient latencies to observe carcinogenic effects.

In 1980, a retrospective mortality study of 161 workers (99 in Plant A and 63 in Plant B) exposed to EDB at two EDB manufacturing plants, was reported. The results indicated an observed increase in deaths due to malignant neoplasms and nonmalignant respiratory disease among the workers from Plant B. However, when the data from both plants were combined, no significant increase in mortality was observed.[12] In another study only one death was observed in a group of 53 workers potentially exposed to EDB in a chemical manufacturing plant. The cause was listed as cancer of the kidney.[13]

In studies of the effect of EDB exposure on sperm production conducted in 1977 and 1978, sperm counts were performed on 59 workers potentially exposed to EDB in a chemical manufacturing plant. The author concluded that exposures to EDB at the levels found for this population (less than 5.0 ppm) had no adverse effect on sperm counts. Neither possible confounding exposures nor the health of the individuals was discussed. No tests were performed to determine sperm motility, penetrance, morphology, or density or to evaluate other sperm function parameters.[13]

In 1979, a retrospective evaluation of the reproductive histories of exposed workers at four EDB manufacturing plants was published. The authors assessed the reproductive histories in terms of the number of live births in 297 wives of workers. The observed number of live births (only 50% of the expected value) was significantly lower than expected at one of the four plants.

However, the employees at this plant had 22 known surgical and nonsurgical sterilizations, the highest rate of the four plants. No significant difference was observed in expected births at the other three plants. No information was given on total conceptions, including spontaneous or induced abortions, among workers' wives.[14]

Evidence of Mutagenicity

A 1979 study reported that gaseous EDB at concentrations ranging from 0.2 to 2 ppm induced significant numbers of sex-linked recessive lethal mutations in Drosophila melanogaster males. Mutation induction was directly proportional to both exposure time and exposure concentration up to 60 ppm-hours, for all cell stages tested. This genetic evidence is in concordance with the irreversible, cumulative nature of EDB toxicity.[15]

RECOMMENDATIONS

The recent experimental data reinforce NIOSH's 1977 conclusion that ethylene dibromide is carcinogenic in animals. Ethylene dibromide has been shown to cause significant increases in tumors of the respiratory tract, mammary gland, spleen, and nasal cavity when administered to animals by skin application, gavage, or inhalation. Furthermore, the data confirm that when disulfiram is administered concurrently with EDB both its toxicity and carcinogenicity are enhanced. As was reported in 1978 by NIOSH, the interaction of EDB and disulfiram warrants a special precaution, and measures should be taken to prevent any individual from being exposed to both substances at the same time.[16] This increased interaction may not necessarily be restricted to disulfiram, but may occur with similarly structured compounds such as Thiram®.

Although humans and animals may differ in their susceptibilities to specific chemical compounds, any substance that produces cancer in experimental animals should be considered a potential human carcinogen.

NIOSH urges employers to voluntarily assess the conditions under which their workers may be exposed to EDB, especially with concurrent exposures to disulfiram or other similarly structured chemicals, such as Thiram®. NIOSH reaffirms its 1977 recommended workplace environmental limit of 0.13 ppm. Employers should regard this level as the upper boundary of exposure and make every effort to maintain the exposure as low as is technically feasible.

J. Donald Millar, M.D.
Assistant Surgeon General
Director

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APPENDIX I

IDENTIFIERS AND SYNONYMS FOR ETHYLENE DIBROMIDE

Chemical Abstracts Service Registry Number 106-93-4
NIOSH RTECS Number KH92750
Chemical Formula $C_2H_4Br_2$

Aadibroom
Bromofume
Celmide
Dibromoethane
1,2-Dibromoethane
sym-Dibromoethane
Dowfume EDB
Dowfume MC-2
Dowfume W-8
Dowfume W-85
Dowfume 40
E-D-BEE
EDB
EDB-85
ENT 15,349
Ethylene Bromide
Ethylene Dibromide
Fumo-Gas
Glycol Dibromide
Iscobrome D
Kopfume
Nefis
Pestmaster
Pestmaster EDB-85
Sanhyuum
Soilbrum-40
Soilbrum-85
Soilfume
Unifume

APPENDIX II

MANUFACTURERS OF ETHYLENE DIBROMIDE

Dow Chemical U.S.A.
2030 Dow Center
Midland, Michigan

Ethyl Corporation
330 South Fourth Street
Richmond, Virginia

Great Lakes Chemical Corp.
P. O. Box 2200
West Lafayette, Indiana

PPG Industries, Inc.
One Gateway Center
Pittsburgh, Pennsylvania

NIOSH

Current Intelligence Bulletin 38

MARCH 29, 1983

VIBRATION SYNDROME

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

The Current Intelligence Bulletin is the primary product of the National Institute for Occupational Safety and Health's (NIOSH) Current Intelligence System. The system promptly reviews, evaluates, and disseminates new information received or developed by NIOSH that may indicate either the existence of an occupational hazard not previously recognized or a hazard greater than is generally perceived. The staff of the Document Development Branch, Division of Standards Development and Technology Transfer and the staff of the Division of Biomedical and Behavioral Science prepared this bulletin.

Current Intelligence Bulletins are disseminated to NIOSH staff, other government agencies, and the occupational safety and health community, including academia, industry, labor, and public interest groups. The bulletins are intended to disseminate new data that may affect prevailing perceptions of occupational hazards. They convey important public health information and recommend voluntary protective measures. Current Intelligence Bulletins do not recommend occupational standards or have any regulatory status.

DHHS (NIOSH) Publication No. 83-110

CURRENT INTELLIGENCE BULLETIN #38

VIBRATION SYNDROME

March 29, 1983

In light of a recently completed, comprehensive study, conducted by the National Institute for Occupational Safety and Health (NIOSH), the Institute concludes that vibrating handtools can cause vibration syndrome, a condition also known as vibration white finger and as Raynaud's phenomenon of occupational origin. Vibration syndrome has adverse circulatory and neural effects in the fingers; the signs and symptoms include numbness, pain, and blanching (turning pale and ashen). Of particular concern is evidence of advanced stages of vibration syndrome after exposures as short as one year. NIOSH recommends that jobs be redesigned to minimize the use of vibrating handtools and that powered handtools be redesigned to minimize vibration. Where jobs cannot be redesigned to eliminate vibrating tools such as pneumatic hammers, gasoline chain saws, and other powered handtools, engineering controls, work practices, and administrative controls should be employed to minimize exposure.

PURPOSE OF BULLETIN

Occupational health and safety professionals, employers, and workers should be alerted to recent information on the potential hazards of vibrating handtools. A comprehensive study recently completed by NIOSH demonstrates the seriousness of vibration syndrome in workers and provides an accurate measure of the prevalence of vibration syndrome. The study suggests that vibration syndrome is severely underreported by workers and health professionals. Workers tend to underreport the syndrome because symptoms are intermittent and occur most frequently under conditions not

present in a doctor's office (e.g., early in the morning or when the hands are cold or wet). In addition, many workers are unfamiliar with the potential seriousness of vibration syndrome. Cases tend to be underreported by physicians because most have not been informed of how to distinguish the symptoms of Raynaud's phenomenon from other medical conditions where blanching or sensory loss occurs. Consequently, many doctors do not perform the appropriate clinical examination and interview to test for vibration syndrome.

Implementation of NIOSH's recommendations should reduce the incidence and severity of vibration syndrome. However, existing data are insufficient to recommend a safe duration and intensity of exposure or specific work practices that will prevent the occurrence of vibration syndrome. Through research, NIOSH is seeking additional information about the relationship between exposure duration and vibration syndrome, as well as effective control technologies to prevent vibration syndrome.

BACKGROUND

Raynaud's phenomenon was first described as "a condition, a local syncope [loss of blood circulation], where persons see one or more fingers becoming white and cold all at once" [1]. In 1 to 3% of the cases, these blanching attacks become progressively more severe over the years, leading to blue and cold fingers; even though the skin may become atrophic, ulcerated, or gangrenous. "Primary" Raynaud's phenomenon, originally described by Dr. Maurice Raynaud, occurs spontaneously in less than 15% of the general population [2]. The ratio of female to male patients is five to one [3]. "Secondary" Raynaud's phenomenon has the same signs and symptoms and progresses through the same stages of severity but may be correlated with a specific cause (i.e., other medical conditions, vinyl chloride, or vibrating handtools). Some medical conditions, particularly fractures, lacerations, costoclavicular syndrome, connective tissue diseases, vascular disorders such as Buerger's disease, generalized atherosclerosis, or a long history of high blood pressure, may result in the same signs and symptoms as primary Raynaud's phenomenon. This CIB is limited to a discussion of Secondary Raynaud's phenomenon resulting from the use of vibrating handtools, referred to as vibration syndrome.

Early stages of vibration syndrome are characterized by tingling or numbness in the fingers. Temporary tingling or numbness during or soon after use of a vibrating handtool is <u>not</u> considered vibration syndrome. To be diagnosed as vibration syndrome, these neurologic symptoms must be more persistent and occur without provocation by immediate exposure to vibration. Other symptoms of vibration syndrome include blanching, pain, and flushing. The symptoms usually appear suddenly, and are precipitated by exposure to cold. With continuing exposure to vibration, the signs and symptoms become more severe and the pathology may become irreversible.

The severity of vibration syndrome can be measured using a grading system developed by Taylor [4]. After a clinical observation and an interview, a worker can be placed into one of the categories in Table 1. Clinical aspects of vibration syndrome are discussed in the Appendix.

Table 1. Stages of Vibration Syndrome

Stage	Condition of Fingers	Work and Social Interference
00	No tingling, numbness, or blanching of fingers	No complaints
0T	Intermittent tingling	No interference with activities
0N	Intermittent numbness	"
TN	Intermittent tingling and numbness	"
01	Blanching of a fingertip with or without tingling and/or numbness	"
02	Blanching of one or more fingers beyond tips, usually during winter	Possible interference with nonwork activities; no interference at work
03	Extensive blanching of fingers; during summer and winter	Definite interference at work, at home, and with social activities; restriction of hobbies
04	Extensive blanching of most fingers; during summer and winter	Occupation usually changed because of severity of signs and symptoms

EXTENT OF EXPOSURE

Based on a 1974 study of occupational exposures to vibration, NIOSH estimates that 1.2 million workers in the United States are potentially exposed to hand-arm vibration (Table 2) [5]. These workers are potentially at risk of developing vibration syndrome.

Table 2. Workers Potentially Exposed to Hand-Arm Vibration

No. of Workers	Industry	Type of Tool
500,000	Construction	Handtools
200,000	Farming	Gasoline chain saws
14,000	Metal working	Handtools
54,000	Steel	Furnace cleaning using powered handtools
30,000	Lumber and wood	Gasoline chain saws
34,000	Furniture manufacturing	Handtools
100,000	Mining	Pneumatic drills
250,000	Truck and auto manufacturing	Handtools
64,000	Foundries	Handtools
Total 1,246,000		

Adapted from reference [5]

EVIDENCE OF HEALTH EFFECTS

Although individual workers reported symptoms of Raynaud's phenomenon and many published studies indicated that occupational exposure to vibration does cause vibration syndrome, there are few medical records of vibration syndrome. In 1979, the Bureau of Labor Statistic's Supplementary Data System contained fewer than 39 cases that might have been vibration syndrome [6]. To resolve the question of whether vibration syndrome is a rare disease or whether the small number of recorded cases is, in fact, due to underreporting NIOSH conducted a recently completed, comprehensive study designed to avoid problems noted in previously published studies [7].

NIOSH studied 385 workers exposed to hand-arm vibration from pneumatic chipping hammers and grinders at two foundries and a shipyard. Workers in the foundries and the shipyard who had never used vibrating handtools comprised the control group. Workers in the exposed groups were in the same work locations as the control workers, and were exposed to vibrating handtools while on the job.

A physician on the research team who had extensive experience in the diagnosis of vibration syndrome examined each worker in the double blind study. Based on clinical observation and interview, each worker was placed in one of the stages shown in Table 1. Neither the worker nor the physician was told if a worker was classified as exposed or control.

In the foundries, 47% of the exposed workers had advanced vibration syndrome (stage 1 or more severe); 19% of the exposed workers in the shipyard were similarly affected. Although no workers in the control group were found to have vibration syndrome, 83% of the exposed workers in the foundries and 64% of the exposed shipyard workers had discernable symptoms. Table 3 displays prevalence of vibration syndrome by stage among the workers.

Table 3. Prevalence of Vibration Syndrome by Stage in Foundry and Shipyard Populations

	Vibration Syndrome Stages	Controls Foundries and Shipyard N=63*	Exposed Workers Foundries N=147*	Exposed Workers Shipyard N=58*
Circulatory Symptoms (or combined symptoms)	03	0%	5%	5%
	02	0%	22%	5%
	01	0%	20%	9%
		Subtotal	47%	Subtotal 19%
Neurological Symptoms Alone	TN	0%	20%	17%
	ON	0%	7%	17%
	OT	0%	9%	11%
		Subtotal	36%	Subtotal 45%
No Symptoms	00	100%	17%	36%
Total		100%	100%	100%

*N = Number of workers

Adapted from Vibration White Finger Disease in U.S. Workers [7]

Workers with medical conditions that might produce signs and symptoms similar to Raynaud's phenomenon were excluded from both the control and exposed groups. Of studies performed in the United States, these prevalence rates are the best available evidence that link Raynaud's phenomenon with exposure to vibration. These data demonstrate the potential seriousness of vibration syndrome in foundries and shipyards and by implication in other workplaces where there are similar tools and operations.

There is a direct relationship between years exposed and severity of vibration syndrome. This relationship in foundry workers is demonstrated in Table 4. Vibration syndrome of stage 1 or greater severity was found in 31% of the workers exposed 1.5 years or less, 41% of the workers exposed 1.5 to 3 years, and 71% of the workers exposed more than 3 years. A similar relationship was observed among shipyard workers (Table 5).

Table 4. Exposure Duration and Severity of Health Effect for Foundry Workers Using Chipping Hammers*

Vibration Syndrome Stage	Exposure Duration (Years) and Prevalence of Symptoms			Percent of Total Workers at a Stage
	Less Than 1.5 N=66**	1.5-3.0 N=29**	More Than 3.0 N=52**	N=147**
02 and 03	11%	24%	50%	27%
01	20%	17%	21%	20%
0T, 0N, and TN	48%	48%	14%	36%
00	21%	11%	15%	17%
Total	100%	100%	100%	100%

*Chi square value 29.8 with p less than .00001
**N = Number of workers

Adapted from Vibration White Finger Disease in U.S. Workers [7]

Table 5. Exposure Duration and Severity of Health Effect for Shipyard Workers Using Chipping Hammers*

Vibration Syndrome Stage	Exposure Duration (Years) and Percent of Workers at a Stage			
	Less Than 5.0 N=22**	5.0-15.0 N=17**	More Than 15.0 N=19**	Percent of Total Workers at a Stage N=58**
TN, 01, 02, and 03	23%	29%	58%	36%
0T and 0N	32%	18%	32%	28%
00	45%	53%	10%	36%
Total	100%	100%	100%	100%

*Chi square value of 9.9 with p=.041
**N = Number of workers

Adapted from Vibration White Finger Disease in U.S. Workers [7]

NIOSH also analyzed the length of time between initial occupational exposure and the onset of symptoms. This is given for each stage in Table 6. The average time for the appearance of blanching, advanced vibration syndrome of stage 1 or greater severity, for foundry workers was 2 years, and for shipyard workers it was 17 years. There is no definitive explanation for this difference. One theory attributes the difference to variations in work practices.

Table 6. Latency Period of Vibration Syndrome for Workers in Foundries and Shipyards

	Foundries		Shipyards	
	Number of Workers	Average Latency (Years)	Number of Workers	Average Latency (Years)
Latency of Tingling for Workers with Stages 0T, TN, 01, 02, 03 (excludes 0N)	94	2	21	9
Latency of Numbness for Workers with Stages 0N, TN, 01, 02, 03 (excludes 0T)	80	2	26	12
Latency of Blanching for Workers with Stages 01, 02, 03	69	2	11	17

Adapted from Vibration Syndrome White Finger Disease in U.S. Workers [7]

Although the symptoms of vibration syndrome have also been associated with smoking and age, these associations were not seen in the study.

The results of the NIOSH study corroborate those of many published studies of Raynaud's phenomenon and vibration. In 1918, Hamilton studied workers who used pneumatic chipping hammers and drills in the limestone quarries of Indiana, and described "spastic anemia of the hands" [8]. Vibration syndrome was described in the 1930's and 1940's by Seyring, who studied workers in iron foundries [9]; by Hunt, who studied riveters who used pneumatic handtools [10]; by Telford et al., who studied workers who used electrically driven high-speed rotating handtools [11]; and by Agate and Druett, who examined casting workers who used grinding wheels [12]. Dart [13] reported vibration syndrome among 112 workers who used pneumatic and electric tools in the U.S. aircraft industry.

In 1960 Pecora et al. concluded that vibration syndrome "may have become an uncommon occupational disease approaching extinction in this country [the United States]" [14]. This finding is inconsistent, however, with those of researchers from many countries that have been published before

and since that report [15,16,17,18,19,20]. This may be due to the fact that Pecora et al. based their conclusions on the results of a questionnaire survey of occupational health physicians, a review of existing occupational health information and the results of an examination of some workers.

Ashe and coworkers reported on a small number of drillers from the hard rock mines of Saskatchewan, Canada, seven of whom were examined in the hospital [15,16]. In these clinical investigations, arteriography and biopsies were performed on the digital arteries of the fingers. In the worst cases, there was extensive damage to the digital artery with narrowing of the blood vessels. This investigation demonstrated that prolonged exposure to vibration could lead to extensive pathological damage to the digital arteries of the fingers.

In the 1960's and 1970's, vibration syndrome was also associated with gasoline-powered chain saws used in forestry work. For example, in Finland, Pyykko [17] found that the vibration of the two-stroke internal combustion engine (transmitted through the handles to the hands) was associated with vibration syndrome in 40% of the lumberjacks studied.

Other studies have been undertaken since the NIOSH study was initiated. In the United States, Taylor et al. [18] examined foundry workers who used pneumatic handtools; in Italy, Bovenzi et al. [19] studied shipyard workers; Kasamatsu et al. [20] studied Japanese chain saw operators; and Harada and Matsumoto [21] examined three groups of workers exposed to different kinds of vibration (rock drillers in a zinc mine, chipping-hammer operators in an iron foundry, and motorcycle mailmen). All studies found significant evidence of vibration syndrome.

The exact point at which vibration syndrome becomes irreversible has not been firmly established. Recently Taylor et al. reported the effect of reduced vibration levels on severity and prevalence of vibration syndrome [22]. After anti-vibration chain saws had been introduced in England, Taylor et al. found that the overall prevalence of vibration syndrome decreased. Vibration syndrome was less prevalent in workers who used only anti-vibration saws than among workers who used other types of saws. In addition, users of anti-vibration saws had an overall decrease in severity of the syndrome. The results of studies such as this have led to the redesign of other tools to reduce the degree of vibration. For example, the ARO 8316® pneumatic scaling hammer and the Vast Hardill VHB-80® pneumatic pavement breaker were specifically designed to reduce both vibration and noise levels.

Despite considerable research, little is known about the physiological basis of vibration syndrome or which specific vibration parameters, such as acceleration, frequency spectrum, or energy transferred to the hand, are the most necessary to control. The progressive stages of vibration syndrome arise from the cumulative effect of vibration-induced trauma to the hands from the regular, prolonged use of vibrating handtools in certain occupations.

Only recently have methods been developed to perform reproducible vibration measurements [23]. In the NIOSH study, acceleration levels were measured in three orthogonal directions [7]. To minimize distortion during measurement of acceleration, the lightest available accelerometers were selected and were tightly mounted to the vibrating tool. For tools with high acceleration rates, such as chippers, the accelerometer was mounted in a fixture which was welded to the chisel. Measuring devices were calibrated before and after each measurement.

Exposure Standards and Guides

The Occupational Safety and Health Administration (OSHA) has not promulgated any standards, nor has NIOSH published recommendations that addressed occupational vibration. Other countries have proposed such standards [24,25]; and the International Organization for Standardization (ISO) has proposed a draft standard for hand-arm vibration (ISO/DIS 5349-1982) [26]. The draft standard specifies methods for measuring and reporting hand-transmitted vibration exposure and attempts to relate these measurements to a limited amount of epidemiological data. The reader is referred to that document. However, due to the difficulty of measuring vibration exposure and the lack of a quantitative relationship between vibration levels and health effects, the ISO draft standard has yet to be accepted in the United States and several other countries. ISO has not yet proposed a final standard to replace the draft standard.

RECOMMENDATIONS

Based on the recent NIOSH study and other published studies, NIOSH concludes that occupational health professionals, workers, and employers should consider the seriousness of vibration syndrome. NIOSH recommends that engineering controls, medical surveillance, work practices, and personal protective equipment be used to help reduce exposure to vibrating handtools and to help identify vibration syndrome in its early stages among workers likely to be at risk.

Engineering Controls

The amount of exposure to vibration in many jobs can be reduced by proper job and production design. Where job redesign is not feasible, direct intervention by means of reducing tool vibration should be attempted.

Recommendation 1 Production lines should be engineered to minimize the need to use vibrating handtools. For example, quality controls on casting could be increased to reduce the average refinishing needed.

Recommendation 2 Tool manufacturers should modify and redesign tools to reduce hand-arm vibration. Tools with reduced vibration levels should be furnished to workers. Purchasers are encouraged to request suppliers to provide evidence that their equipment reduces vibration. More research is needed before a specific standard can be recommended for vibrating handtools. In the meantime, purchasers are encouraged to select tools that minimize vibration. Such information can be obtained from manufacturers' product or technical brochures.

Medical Surveillance and Worker Education

The number of vibration syndrome cases reported is small. Physicians have failed to diagnose the syndrome and workers tend not to report it. All workers who use vibrating handtools are at risk and should be examined for signs and symptoms of vibration syndrome. An examination is recommended because the severity of vibration syndrome appears to be directly related to the cumulative duration of exposure and because health effects can become irreversible.

Recommendation 3 More research is needed in order to specify an optimum surveillance program, but for the present, NIOSH recommends that a medical surveillance program be implemented and that it should be tailored to the degree that workers use vibrating handtools. It should include preplacement examination of all new workers and an initial examination of all present workers who use vibrating handtools. Work histories should be included in all examinations. Work histories should include any prior exposure to vibrating handtools. Medical records, including health and work histories, should be maintained throughout employment and for an extended period after termination of employment.

Recommendation 4 Workers using vibrating handtools and their employers should be informed of the symptoms of vibration syndrome.

Recommendation 5 Workers should see a physician promptly if they experience prolonged symptoms of tingling, numbness, or signs of blanched or blue fingers.

Recommendation 6 Health professionals, particularly occupational health physicians, should be trained in the appropriate clinical examination and interview necessary to diagnose vibration syndrome. (A special NIOSH VWF videotape has been prepared to aid in the diagnosis of vibration syndrome [31]).

Work Practices

Some tools, such as grinders, can cause greater vibration levels to impinge on the hand when wear is uneven or their alignment slips. While insufficient information is available to recommend a safe exposure duration, it is known that the severity of vibration syndrome is related to the extent and duration of continuous exposure to vibration.

Recommendation 7 Vibrating handtools should be carefully maintained according to manufacturers' recommendations.

Recommendation 8 Work schedules with a 10-minute break after each hour of continuous exposure may help reduce the severity of vibration syndrome. Research is needed to determine, however, whether another schedule of rest breaks on job rotation is more appropriate.

Recommendation 9 Workers are advised to:

a. Wear adequate clothing to keep the body temperature stable and normal, since a low body temperature reduces blood flow to the extremities and therefore may trigger an attack of vibration syndrome. Workers are also advised to keep hands warm and dry while on the job. When their hands become wet and chilled, workers should dry them and put on dry warm gloves before additional exposure to vibration. More than one pair of gloves may be required on the job.

b. Let the tool do the work, grasping it as lightly as possible while working safely and maintaining tool control. The tool should rest on the workpiece or support as much as possible. The tighter the tool is held, the greater the vibration transmitted to the worker.

c. Substitute a manual tool or other processes where practical.

Personal Protective Equipment

Many types of gloves help maintain body warmth, and, in addition, some designs may attenuate vibration; however, this may be limited to only some of the higher frequencies found in vibrating handtools. Although gloves alone are not recommended as a method of reducing vibration transferred to the hands, they will help keep hands warm, and thus help reduce the severity of vibration syndrome.

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APPENDIX I

CLINICAL ASPECTS OF VIBRATION SYNDROME

The physiological cause of vibration syndrome is not known [27]. Vibration may directly injure the peripheral nerves, causing numbness of the fingers and hands. Paresthesia of the hands may be secondary to vascular constriction of the blood vessels, causing ischemia of the peripheral nerves. Likewise, the physiological or chemical changes due to vibration in the blood and blood vessels can only be speculated upon at this time [28].

Some medical conditions may result in symptoms similar to vibration syndrome. Table I-1 summarizes these conditions [30].

Table I-1. Differential Diagnosis--Raynaud's Phenomenon

Primary:		
	Raynaud's Disease	
Secondary:		
1.	Connective Tissue Disease	a. Scleroderma b. Systemic Lupus Erythematosus c. Rheumatoid Arthritis d. Dermatomyositis e. Polyarteritis Nodosa f. Mixed Connective Tissue Disease
2.	Trauma	
	i. Direct to Extremities	a. Following injury, fracture or operation b. Vibrating handtools c. Frostbite and immersion syndrome
	ii. To Proximal Vessels by Compression	a. Thoracic outlet syndrome (cervical rib, scalenus anterior muscle) b. Costoclavicular and hyper-abduction syndromes
3.	Occlusive Vascular Disease	a. Thromboangiitis obliterans b. Arteriosclerosis c. Embolism d. Thrombosis
4.	Dysglobulinemia	a. Cold hemagglutination syndrome - Cryoglobulinemia - Macroglobulinemia
5.	Intoxication	a. Acro-osteolysis b. Ergot c. Nicotine d. Vinyl chloride
6.	Neurogenic	a. Poliomyelitis b. Syringomyelia c. Hemiplegia
7.	Vibration	a. Vibration syndrome

Adapted from Vibration White Finger in Industry [30]

Taylor and Pelmear [30] described the clinical manifestations of vibration syndrome. Slight intermittent tingling or numbness, or both intermittent tingling and numbing, of the fingers are usually ignored by the patient because they do not interfere with work or other activities. These are the first symptoms of vibration syndrome. Later, the patient may experience attacks of finger blanching confined at first to a fingertip; however, with additional vibration exposure, attacks may extend to the base of the finger. Cold often provokes attacks but there are other factors involved in the trigger mechanism, such as central body temperature, metabolic rate, vascular tone of the vessels (especially susceptible in the early morning), and emotional state. Attacks usually last 15 to 60 minutes, but in advanced cases may last 1 or 2 hours. Recovery starts with a red flush, a reactive hyperemia, usually seen in the palm, advancing from the wrist towards the fingers. "Due to repeated ischaemic attacks in advanced cases, touch and temperature sensation is impaired. There is a loss of dexterity and an inability to do fine work. With further vibration exposure, the number of blanching attacks is reduced, and is replaced by a dusky, cyanotic appearance of the digits leading to nutritional changes in the finger pulps" [29]. Ultimately, small areas of skin necrosis appear at the fingertips [30]. This condition has been called acrocyanosis. A videotape, titled Vibration Syndrome, is available from NIOSH; it describes the etiology, symptomatology, assessment, and treatment of the syndrome [31].

The severity of the vibration syndrome condition can be measured by using the grading system developed by Taylor [4] (Table 1). Based on a clinical observation and interview, the worker is placed into one of eight categories shown.

Stage 1 and stage 2 attacks occur mainly in the winter and especially during the early morning, either at home or when going to work (i.e when the hands contact the cold steering wheels of vehicles). Workers outside in cold weather, such as forestry workers, are most prone to early morning attacks. Previous studies have shown that as duration of exposure increases, the number of attacks tends to increase [28,32]. During stage 2, workers may report interference with or limitation of activities outside their work (e.g., gardening, fishing, swimming, washing and maintaining an automobile, and woodworking). These activities have one factor in common: in the cold, they are more likely to trigger an attack.

In stage 3, the attacks occur in summer as well as winter. There is interference with work, particularly outdoor work such as forestry and construction; difficulty with fine work such as electronics; and difficulty in picking up small objects. Patients experience difficulty in buttoning and zippering clothing; inability to distinguish between hot and cold objects; and clumsiness of fingers with increasing stiffness of the finger joints and loss of manipulative skills.

In stage 4, the severity of the vibration syndrome and the interference with work, social activities, and hobbies require workers to change their occupation. In the severest forms there are advanced changes in the arteries of the fingers, leading to complete obliteration of the arteries.

Cumulative exposure to vibrating handtools (especially continuous exposure during a workshift) may lead to more severe symptoms. Accordingly, medical surveillance for vibration syndrome should be repeated at shorter intervals for workers with extended exposure to high frequency vibration. More research is needed to specify a surveillance schedule.

NIOSH

Current Intelligence Bulletin 39

MAY 2, 1983

GLYCOL ETHERS

2 – METHOXYETHANOL and
2 – ETHOXYETHANOL

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

The National Institute for Occupational Safety and Health (NIOSH) Current Intelligence Bulletin is the primary product of the Institute's Current Intelligence System. The purpose of this system is to provide prompt review, evaluation, and dissemination of new information received by NIOSH that may indicate either the existence of an occupational hazard not previously recognized or a hazard greater than generally known. This bulletin was prepared by the Document Development Branch of the Division of Standards Development and Technology Transfer, and the Division of Biomedical and Behavioral Science.

Current Intelligence Bulletins are disseminated to NIOSH staff, other government agencies, and the occupational health community, including academia, industry, labor, and public interest groups. The bulletins are intended to disseminate new data that may affect prevailing perceptions of occupational hazards. They convey important public health information and recommend voluntary protective measures. Current Intelligence Bulletins do not recommend occupational standards or have any regulatory status.

DHHS (NIOSH) Publication No. 83-112

CURRENT INTELLIGENCE BULLETIN #39

THE GLYCOL ETHERS, WITH PARTICULAR REFERENCE TO 2-METHOXYETHANOL AND 2-ETHOXYETHANOL: Evidence of Adverse Reproductive Effects

May 2, 1983

The National Institute for Occupational Safety and Health (NIOSH) recommends that 2-methoxyethanol (2ME) and 2-ethoxyethanol (2EE) be regarded in the workplace as having the potential to cause adverse reproductive effects in male and female workers. These recommendations are based on the results of several recent studies that have demonstrated dose-related embryotoxicity and other reproductive effects in several species of animals exposed by different routes of administration. Of particular concern are those studies in which exposure of pregnant animals to concentrations of 2ME or 2EE at or below their respective Occupational Safety and Health Administration (OSHA) Permissible Exposure Limits (PEL's) led to increased incidences of embryonic death, teratogenesis, or growth retardation. Exposure of male animals resulted in testicular atrophy and sterility. In each case the animals had been exposed to 2ME or 2EE at concentrations at or below their respective Occupational Safety and Health Administration (OSHA) Permissible Exposure Limits (PEL's). Therefore, appropriate controls should be instituted to minimize worker exposure to both compounds. NIOSH suggests that producers, distributors, and users of 2ME and 2EE, and of substances and materials containing 2ME and 2EE, give this information to their workers and customers, and that professional and trade associations and unions inform their members.

BACKGROUND

Physical and Chemical Properties

The glycol ethers 2-methoxyethanol (2ME) and 2-ethoxyethanol (2EE) are part of a family of ethylene glycol ethers. At room temperature and atmospheric pressure, 2ME and 2EE are colorless liquids. Both compounds are completely miscible with water and with many organic solvents. Both are highly reactive in the presence of strong oxidizers; 2ME is also highly reactive in the presence of strong bases [1,2]. Identifiers and synonyms for 2ME and 2EE are listed in Appendix II.

Production, Use, and Exposure

The Toxic Substances Control Act (TSCA) Inventory for 1977 reports a wide range of production volumes for 2ME (as many as 161 million pounds) and 2EE (as many as 171 million pounds) [3].

Both 2ME and 2EE are used as solvents in the manufacture of protective coatings such as lacquers, metal coatings, baking enamels, phenolic varnishes, epoxy resin coatings, and alkyd resins [1]. They are also used as solvents for nitrocellulose, printing inks, textile dyes and pigments, and leather finishes. Both are used as anti-icing additives in brake fluids, in aviation fuels, and as antistall agents in gasoline. Both compounds are used in organic synthesis. In particular, a large amount of 2EE is used to manufacture 2-ethoxyethyl acetate (2EEA). 2EE is also used in the formulation of varnish removers, thinners, cleaning products, soaps, detergents, cosmetics, pesticides, pharmaceuticals, and adhesives. In addition to manufacturing operations, exposure to 2ME and 2EE may occur during the use of the many formulated products that contain them.

Based on the National Occupational Hazard Survey (NOHS) conducted by NIOSH between 1972 and 1974, it is estimated that as many as 100,000 workers are potentially exposed to 2ME and that 400,000 workers are potentially exposed to 2EE [4].

EXPOSURE STANDARDS AND GUIDES

OSHA's Permissible Exposure Limit (PEL) for occupational exposure to 2ME is 25 ppm (80 mg/m^3) and its PEL for 2EE is 200 ppm (740 mg/m^3), both as a time-weighted average (TWA) for an 8-hour workshift (29 CFR 1910.1000) [5]. The OSHA standards bear a "Skin" notation, indicating the potential for skin absorption of toxic amounts of 2ME and 2EE. These standards are based primarily on reports of blood, kidney, liver, and central nervous system toxicity caused by 2ME and 2EE in animals and on case reports of human exposure to 2ME. No studies on reproductive effects of 2ME and 2EE were considered when these standards were adopted.

The American Conference of Governmental Industrial Hygienists (ACGIH) has recommended Threshold Limit Values (TLV's) for 2ME and 2EE [6]. The TLV for 2ME as a TWA for an 8-hour workshift is 25 ppm, and the Short Term Exposure Limit (STEL) for up to 15 minutes is 35 ppm. For 2EE, the ACGIH lowered its TLV in 1981 from 100 ppm to 50 ppm, and its STEL from 150 ppm to 100 ppm [7]. The TLV for 2EE was lowered to prevent workers from being exposed to concentrations that had produced significant blood changes in laboratory animals [8]. The ACGIH TLV's also bear a "Skin" notation. In the Notice of Intended Changes (for 1982), TWA's of 5 ppm are proposed for 2ME, 2EE, and their respective acetates; these intended changes are based primarily on testicular effects observed in recent animal studies [9].

In 1982, most manufacturers of 2ME and 2EE adopted company industrial hygiene exposure guides below current OSHA PEL's [10]. For 2ME, the 8-hour TWA exposure limits range from 2-10 ppm. For 2EE, some manufacturers have adopted an 8-hour TWA of 5 ppm.

EFFECTS OF 2-METHOXYETHANOL (2ME)

Human Reproductive Effects

In one study of a small population involved in manufacturing and packaging of 2ME, no clinically significant differences were found between the exposed and comparison groups that could be attributed to the work environment for the fertility parameters studied. Exposures to 2ME were reported to be well below 25 ppm. 2EE and other glycol ethers were also manufactured in these facilities [11].

Animal Studies

Exposure to 2ME caused dose-related adverse reproductive effects in female and male experimental animals. Pregnant mice exposed by gavage and pregnant rats and rabbits exposed by inhalation had increased incidences of embryonic deaths and abnormalities that were statistically significant (henceforth referred to as "significant"). Significantly increased incidences of testicular atrophy (decreased testicular weight) and microscopic testicular changes were observed among male mice given oral doses and male mice, rats, and rabbits exposed by inhalation. Infertility in male rats and abnormal spermhead morphology in mice have also been reported after inhalation of 2ME. Reproductive effects observed from exposure to 2ME are summarized in Table I. Most of the information contained in this Table as well as in Tables II and III is statistically significant. However, nonstatistically significant effects are also included in the tables when they were of the same or similar nature as those observed at higher doses in the same or a similar study. Tables I, II, and III also provide many of the details of the exposure conditions employed in the various studies; such detail is not provided in the text.

Female Animal Studies

Adverse effects in pregnant animals and their offspring after 2ME exposure that have been reported include: significant increases in embryonic deaths, major and minor fetal abnormalities, and maternal deaths and blood effects. Dose dependent embryomortality and gross fetal defects were observed in fetuses of mice exposed by gavage to 2ME at 250 mg/kg on days 7-14 of gestation [12]. Embryonic deaths were significantly increased among pregnant rabbits that inhaled 10 or 50 ppm of 2ME on days 6-18 of gestation. Similar results were reported after exposure at 3 ppm of 2ME, but they were not statistically significant [13]. The authors of that

study noted that the embryonic death rate in the rabbit control group was less than the rate observed in their historical rabbit control groups. The authors also noted that the rate of embryonic death among rabbits exposed at 10 ppm was comparable to the rate in historical controls. Nevertheless, embryonic mortality observed in this study did increase with the exposure concentration. No evidence of teratogenicity and only minimal fetotoxicity was observed in fetuses of rats exposed to 2ME at 50 ppm [13]. However, another study did report fetal defects in rats after exposure at 50 ppm on days 7-15 of gestation [14]. Fetal skeletal variations, which are among the most sensitive indicators of teratogenicity, were obtained at 2ME doses as low as 31 mg/kg/day given to pregnant mice [12]. Male fetuses of pregnant mice exposed on days 6-15 of gestation at 50 ppm of 2ME had a significant increase in the incidence of unilateral testicular hypoplasia (underdevelopment of the testes) [15].

Unilateral testicular hypoplasia is considered a slight fetotoxic effect. Female rats and rabbits exposed to 2ME at 30, 100, or 300 ppm for 3 months had no evidence of gross reproductive or microscopic changes in the ovaries [16]. No reduction of fertility was observed in the rats exposed at 300 ppm [17]. In mice, embryonic deaths and fetal abnormalities occurred at lower 2ME doses than required to significantly lower maternal white blood cell (WBC) counts [12]. A reduced WBC count was one basis for the current OSHA PEL for 2ME.

Male Animal Studies

Significant increases in testicular atrophy, microscopic testicular changes, and blood effects were reported in mature male animals exposed to 2ME. Mice given oral doses of 2ME at 250 mg/kg/day, 5 days/week for 5 weeks had severe testicular atrophy [18]. Testicular atrophy and death occurred among rabbits after 13 weeks inhalation exposure to 2ME at 300 ppm; slight to severe microscopic testicular changes were observed at 30-100 ppm [16]. In the same laboratory, no treatment related microscopic testicular changes were observed in rabbits exposed to 2ME at 3 ppm, 10 ppm or 30 ppm after a similar 13 week inhalation study [19]. Testicular atrophy was observed in rats and mice exposed at 1,000 ppm of 2ME for 9 days [20]. After 13 weeks of exposure at 300 ppm of 2ME, testicular atrophy [16] and infertility were observed in rats [17]. However, fertility was regained in 55% of the rats between weeks 26-32 of the study. Rats exposed for 5 days to 2ME at 500 ppm were temporarily infertile but fertility returned to control levels by week 10 after exposure [21]. Mice similarly exposed to 2ME at 500 ppm developed abnormal spermhead morphology; the fertility of these mice was not tested [21]. The testicular effects found in mice [18] and rabbits [16] occurred at lower doses of 2ME than those that caused significantly lower WBC counts.

TABLE I

REPRODUCTIVE EFFECTS OF 2-METHOXYETHANOL

Sex	Species	Route of Administration & Dose	Effects	Reference
F, pregnant	Mouse	Gavage, 31-1,000 mg/kg, days 7-14 of gestation	Embryonic death (100% at 1,000 mg/kg, 99.7% at 500 mg/kg, 53% at 250 mg/kg); fetal gross defects (250 mg/kg); skeletal malformations (62-250 mg/kg); lower fetal weight (125 & 250 mg/kg); fetal skeletal variations & delayed skeletal ossification (31-250 mg/kg)	12
F, pregnant	Rabbit & Rat	Inhalation, 3-50 ppm, 6 hrs/day, gestation days 6-18 (rabbit) & days 6-15 (rat)	Embryonic death, rabbit (24% at 50 ppm & 11% at 10 ppm); major fetal external, skeletal & visceral abnormalities, lower fetal weight, rabbit (50 ppm); delayed skeletal ossification, rat and rabbit (50 ppm)	13
F, pregnant	Rat	Inhalation, 50-200 ppm, 7 hrs/day, days 7-15 of gestation	Embryonic death (200 ppm); fetal CV & skeletal defects (50 & 100 ppm)	14
F, pregnant	Mouse	Inhalation, 3, 10 or 50 ppm, 6 hrs/day, days 6-15 of gestation	Reduced litter size and fetal unilateral testicular hypoplasia (50 ppm)	15
F	Rabbit & Rat	Inhalation, 30-300 ppm, 6 hrs/day, 5 days/wk, 13 wks	No gross or microscopic changes in reproductive organs; death, rabbit (100 & 300 ppm)	16
F	Rat	Inhalation, 30-300 ppm, 6 hrs/day, 5 days/wk, 13 wks	No reduction of fertility	17
M	Mouse	Oral, 63-2,000 mg/kg, 5 days/wk, 5 wks	Testicular atrophy (250-2,000 mg/kg); death (2,000 mg/kg)	18
M	Rabbit & Rat	Inhalation, 30-300 ppm, 6 hrs/day, 5 days/wk, 13 wks	Testicular atrophy (300 ppm); microscopic testicular changes, rabbit (30-300 ppm), rat (300 ppm); death, rabbit (300 ppm)	16
M	Rabbit	Inhalation, 30-300 ppm, 6 hrs/day, 5 days/wk 13 wks	No increase in gross or microscopic testicular changes	19
M	Rat	Inhalation, 30-300 ppm, 6 hrs/day, 5 days/wk, 13 wks	Infertility (300 ppm)	17
M	Rat & Mouse	Inhalation, 100-1,000 ppm, 6 hrs/day, 9 of 11 days	Testicular atrophy, rats and mice (1,000 ppm); microscopic testicular changes, rats (300 & 1,000 ppm) (No histopathology performed on mouse tissues.)	20
M	Rat	Inhalation, 25 or 500 ppm, 7 hrs/day, 5 days	Temporary infertility (500 ppm)	21
M	Mouse	Inhalation, 25 or 500 ppm, 7 hrs/day, 5 days	Abnormal spermhead morphology (500 ppm)	21

CV = Cardiovascular

Mutagenicity Testing

The mutagenicity of 2ME was tested in Salmonella typhimurium strains TA 1535, TA 1537, TA 98, and TA 100 with and without Aroclor-induced rat liver S-9 supernatant [22]. At the concentrations tested (up to 200 mg/plate), 2ME was not mutagenic.

EFFECTS OF 2-ETHOXYETHANOL (2EE)

Human Reproductive Effects

The only known published investigation of reproductive performance in a human population exposed to 2EE is difficult to interpret and is of questionable value because of mixed solvent exposures. Syrovadko and Malsheva evaluated the incidence of gynecological disorders and birth defects in female enameling workers [23]. The two solvent mixtures used were chlorobenzene and 2EE (1:1), and tricresol and "solvent naptha" (1:4). The concentrations of 2EE were reported to have been "low." There was no difference in the incidence of gynecological disorders between the enamelers and administrative workers (a comparison group including some former enamelers), but both groups were said to have 2.6-9.4 times more gynecological disorders than three other comparison groups. Among the disorders detected were inflammations, benign neoplasms, cervical erosions, and menstrual disorders. The rate of birth defects was significantly increased among the offspring of enamelers (10.0% vs 3.9% in plant controls), with heart and foot defects being predominant.

Animal Studies

Exposure of female and male animals to 2EE has caused significant dose-related adverse reproductive effects similar to the effects caused by 2ME. Oral, inhalation, subcutaneous, and dermal treatment of pregnant rats with 2EE caused increased incidences of embryonic death and abnormalities. 2EE inhalation exposure of pregnant rabbits and oral exposure of pregnant rats caused the same effects. The offspring of pregnant rats exposed by inhalation had altered behavior and neurochemical concentrations in the brain. In male mice, rats, and dogs treated orally and in rats treated subcutaneously, testicular atrophy and microscopic testicular changes have been reported. Table II summarizes the reproductive effects observed in animals exposed to 2EE.

Female Animal Studies

Significant increases in embryonic deaths, fetal abnormalities, altered behavioral test results, and changes in brain neurochemical concentrations have been reported after exposure of pregnant animals to 2EE. Embryonic deaths occurred in: rats after 2EE was given orally at 47 mg/kg/day [24]; rabbits that inhaled 2EE at 160 ppm [25]; rats that inhaled 2EE at 765 ppm [25]; and rats that received 1.0 ml/day of 2EE dermally [26,27]. The

resorption rate was 100% in rats receiving 2.0 ml/day [26]. Fetal cardiovascular and skeletal effects were found after inhalation exposure of pregnant rabbits at 160 ppm and pregnant rats at 200 ppm [25]. Rabbit fetuses also had kidney and ventral body wall defects. Skeletal defects were detected in fetuses of rats that received 2EE at 93 mg/kg/day orally or subcutaneously, [24] and 1.0 ml/day dermally [26]. Fetal growth retardation indicated by lower weights and shorter lengths was observed in rats exposed by inhalation [25]. Subtle teratogenic effects were reported in the offspring of pregnant rats exposed during gestation to 2EE at 100 ppm [28]. The changes included altered behavioral test results at different stages of development after birth and differences in brain neurochemical concentrations in newborn and 21-day-old rats; these differences were more pronounced in the offspring exposed earlier in gestation. Maternal toxicity was greater in rabbits that inhaled 615 ppm of 2EE than in rats that inhaled 765 ppm [25]. Rats receiving 2.0 ml/day dermally of 2EE exhibited a temporary lack of muscular coordination immediately after application [26]. Exposure of female rats to 2EE at 650 ppm for three weeks prior to mating had no effect on fertility [25].

Male Animal Studies

Significant increases in testicular atrophy, microscopic testicular changes, and deaths were reported in animals exposed to 2EE. Severe testicular atrophy occurred in mice given 1,000 mg/kg/day orally [18]. Testicular changes were found in rats and dogs given 2EE at 186 mg/kg/day orally and in rats given 372 mg/kg/day subcutaneously [24]. Testicular atrophy and blood effects in 2EE-treated mice were less severe than those in mice given 2ME at the same dosage levels; testicular effects in 2EE-treated mice occurred at a lower dose than the dose causing WBC effects [18].

Mutagenicity Testing

The mutagenicity of 2EE was tested in Salmonella typhimurium strains TA 1535, TA 1537, TA 98, and TA 100 with and without Aroclor-induced rat liver S-9 supernatant [22]. At the concentrations tested (up to 23 mg/plate), 2EE was not mutagenic. The National Toxicology Program reported that 2EE was not mutagenic in Salmonella typhimurium at 10 mg/plate [29]. The same four Salmonella strains were used with and without microsomal fractions prepared from Aroclor-induced rat and hamster liver.

Carcinogenicity Testing

The Department of Health and Human Services' National Toxicology Program is currently testing 2EE for carcinogenicity in male and female rats and mice at 0.5, 1.0, and 2.0 g/kg/day by gavage [29]. Because mortality was high in the 2.0 g/kg groups, survivors were killed after 16 weeks; males had testicular lesions. The final report of this study should be available in 1983.

TABLE II

REPRODUCTIVE EFFECTS OF 2-ETHOXYETHANOL

Sex	Species	Route of Administration & Dose	Effects	Reference
F, pregnant	Rat	Oral, 12-372 mg/kg/day, days 1-21 of gestation	Embryonic death increased (47-372 mg/kg); fetal skeletal defects & lower weight (93-186 mg/kg)	24
F, pregnant	Rat	sc, 23-93 mg/kg/day, days 1-21 of gestation	Fetal skeletal defects & lower weight (93 mg/kg)	24
F, pregnant	Mouse	sc, 47 or 93 mg/kg/day, days 1-18 of gestation	No embryotoxic or teratogenic effects	24
F, pregnant	Rabbit	sc, 23 mg/kg/day, days 7-16 of gestation	No embryotoxic or teratogenic effects	24
F, pregnant	Rabbit	Inhalation, 160 or 615 ppm, 7 hrs/day, days 1-18 of gestation	Embryonic death (100% at 615 ppm & 22% at 160 ppm); fetal CV, renal, and ventral body wall defects and skeletal variations (160 ppm); reduced maternal food consumption (160 & 615 ppm); maternal death (615 ppm)	25
F	Rat	Inhalation before pregnancy, 150 or 650 ppm, 7 hrs/day, 5 days/wk, 3 wks; then inhalation during gestation, 200 or 765 ppm, 7 hrs/day, days 1-19 of gestation	No effect on fertility Embryonic death (100% at 765 ppm); fetal CV & skeletal defects & growth retardation (200 ppm); mild maternal toxicity (765 ppm)	25
F, pregnant	Rat	Inhalation, 100 ppm, 7 hrs/day, days 7-13 or 14-20 of gestation	Altered behavioral test results; altered brain neurochemical concentrations	28
F, pregnant	Rat	Dermal, 1.0 or 2.0 ml/day, days 7-16 of gestation	Embryonic death (100% at 2.0 ml/day & 76% at 1.0 ml/day); fetal CV defects & skeletal variations (1.0 ml/day)	26
M	Rat	Oral, 46-744 mg/kg, daily, 13 wks	Microscopic testicular changes (186 & 744 mg/kg)	24
M	Rat	sc, 93-744 mg/kg, daily, 4 wks	Microscopic testicular changes (372 & 744 mg/kg)	24
M	Dog	Oral, 46-186 mg/kg, daily 13 wks	Microscopic testicular changes (186 mg/kg)	24
M	Mouse	Oral, 500-4,000 mg/kg, 5 days/wk, 5 wks	Testicular atrophy (1,000 & 2,000 mg/kg); death (4,000 mg/kg)	18

CV = cardiovascular
sc = subcutaneous

OTHER ACUTE AND CHRONIC TOXIC EFFECTS OF 2ME AND 2EE

The acute toxic effects of 2ME in humans are irritation of the eyes, nose, and throat; drowsiness; weakness; and shaking [1]. Swallowing of 2ME may be fatal. Prolonged or repeated exposure may cause headache, drowsiness, weakness, fatigue, staggering, personality change, and decreased mental ability. In a 1978 case study report of two workers exposed to 2ME, Ohi and Wegman described clinical evidence of encephalopathy in both, bone marrow depression in one and pancytopenia in the other. Although airborne concentrations (8 ppm) were well below the PEL, both workers had significant skin contact with 2ME. The health status of both workers returned to normal after removal from exposure and treatment [30].

In animals, 2EE has caused liver, kidney and lung damage, and anemia as well as eye irritation.

EFFECTS OF OTHER STRUCTURALLY RELATED GLYCOL ETHERS

Although there is limited experimental information on the reproductive effects of individual compounds structurally related to 2ME and 2EE, much of the information that is available is consistent with the reproductive effects caused by 2ME and 2EE. Table III summarizes the information on the eight structurally related glycol ethers discussed here: 2-methoxyethyl acetate (2MEA), 2-ethoxyethyl acetate (2EEA), 2-butoxyethanol(2BE), 2-phenoxyethanol (2PE), ethylene glycol dimethyl ether (EGdiME), bis(2-methoxyethyl) ether or diethylene glycol dimethyl ether (bis2ME), 2-(2-ethoxyethoxy)ethanol (2EEE), and 1-methoxy-2-propanol or propylene glycol monomethyl ether (1MP). The chemical structure of each compound is given in Appendix III. Seven of these compounds are ethylene glycol ethers, and one is a propylene glycol ether. These compounds share a similar stereochemical configuration. Some were tested only in male animals or only in female animals.

The acetate esters of 2ME and 2EE (2MEA and 2EEA, respectively) have caused male reproductive toxicity made equivalent to that of 2ME and 2EE in male mice. 2EEA appears to have fetoxicity and teratogenicity equivalent to that of 2EE in rats [14,27].

Although additional studies are being conducted by NIOSH and others, the present information is insufficient to fully assess the potential for adverse reproductive effects on humans due to exposure to 2BE, 2PE, EGdiME, bis2ME, 2EEE, or 1MP. Nevertheless, some of this information is provided here so that the reader is alerted to their potential for causing adverse effects.

TABLE III

REPRODUCTIVE EFFECTS OF GLYCOL ETHERS STRUCTURALLY RELATED TO 2-METHOXYETHANOL and 2-ETHOXYETHANOL

Compound	Sex	Species	Route and Dosage	Effects	Reference
2MEA	M	Mouse	Oral, 63-2,000 mg/kg, 5 days/wk, 5 wks	Testicular atrophy (500 - 2,000 mg/kg); death (2,000 mg/kg)	18
2EEA	F, pregnant	Rat	Inhalation, 129-600 ppm, days 7-14 of gestation	Embryonic death (100% at 600 ppm); embryonic death (17% vs 4% controls) fetal CV & skeletal defects (387 ppm)	14*
	F, pregnant	Rat	Dermal, 1.4 ml/day, days 7-16 of gestation	Embryonic death	27*
	M	Mouse	Oral, 500-4,000 mg/kg, 5 days/wk, 5 wks	Testicular atrophy (1,000-4,000 mg/kg); death (4,000 mg/kg)	18
2BE	F, pregnant	Rat	Inhalation, 200 ppm, days 7-14 of gestation	Slight maternal toxicity; no embryonic or teratogenic effects	14*
	F, pregnant	Rat	Dermal, 0.48 or 1.4 ml/day, days 7-16 of gestation	Maternal death (1.4 ml/day); no apparent excess embryonic death (0.48 ml/day)	27*
	M	Mouse	Oral, 500-2,000 mg/kg, 5 days/wk, 5 wks	Microscopic testicular changes in 1 of 5 mice (1,000 mg/kg); death (2,000 mg/kg)	18
2PE	M	Mouse	Oral, 500-2,000 mg/kg, 5 days/wk, 5 wks	Microscopic testicular changes in 1 of 5 mice (1,000 mg/kg); death (2,000 mg/kg)	18
EGdiME	F, pregnant	Mouse	Gavage, 250-490 mg/kg, days 7-10 of gestation	Embryonic death(480 mg/kg); major fetal external and skeletal effects (350 & 490 mg/kg); fetal skeletal variations and growth retardation.	32
bis2ME	M	Rat	Inhalation, 250 or 1,000 ppm, 7 hrs/day, 5 days	Temporary infertility (1,000 ppm)	32
	M	Mouse	Inhalation, 250 or 1,000 ppm, 7 hrs/day, 5 days	Abnormal spermhead morphology (1,000 ppm)	32
2EEE	F, pregnant	Rat	Inhalation, 100 ppm, days 7-15 of gestation	No embryotoxic or teratogenic effects	14*
	F, pregnant	Rat	Dermal, 1.4 ml/day, days 7-16 of gestation	No excess embryonic death	27*
1MP	M	Rat & Mouse	Inhalation, 300-3,000 ppm, 6 hrs/day, 9 of 11 days	No microscopic testicular changes	20

CV = Cardiovascular
*Interim results; final results await skeletal and visceral evaluation

EGdiME orally administered on days 7-10 gestation caused embryonic death and was teratogenic in mice [31]. Preliminary data showed maternal death upon dermal application of 1.4 ml per day of 2BE to rats during gestation [27]. The same preliminary investigation found no significant excess embryonic death upon dermal application of 0.48 ml per day of 2BE or 1.4 ml per day of 2EEE to rats during gestation; final results await skeletal and visceral evaluation [27]. Microscopic evaluation revealed atrophy of the seminiferous tubules in one of five mice orally dosed with 2BE or 2PE [18]. Inhalation exposure to bis2ME caused temporary infertility in rats and abnormal spermhead morphology in mice [32]. No testicular effects were observed following short-term 1MP exposure as were observed from 2ME exposure in the same investigation [20].

CONCLUSIONS AND RECOMMENDATIONS

2ME and 2EE have caused significant increases of adverse reproductive effects in experimental animals of both sexes. 2ME was teratogenic and embryotoxic when administered to pregnant mice, rats, and rabbits. In non-pregnant female animals, 2ME caused no changes in reproductive organs that were discernible either grossly or microscopically. A single study indicated that the fertility of female rats was not affected by 2ME exposure. In male animals, exposure to 2ME resulted in testicular atrophy, histopathological testicular changes, infertility, and abnormal spermhead morphology. 2EE caused similar reproductive effects in animals. 2EE was teratogenic and embryotoxic when administered to pregnant rats and rabbits. In non-pregnant female rats, exposure to 2EE did not affect fertility, but it did produce varying degrees of toxicity in pregnant rabbits and rats. In males, 2EE produced testicular atrophy in mice and microscopic testicular changes in mice, rats, and dogs.

Adverse reproductive effects in both male and female animals have been reported at concentrations that ranged from less than to four times the OSHA PEL for 2ME or 2EE. Of particular concern are the changes observed below the OSHA PEL's. Reproductive effects have been observed in both male and female animals exposed to 2ME at concentrations lower than those causing abnormal blood effects (low WBC counts). Although humans and animals may differ in their susceptibility to specific chemical compounds, any substance that produces adverse reproductive effects in animals should be considered to have the potential to cause similar reproductive effects in humans. This concern is highlighted by the fact that these effects have been observed in several species of animals exposed by various routes. As described above, exposure to 2ME has been associated with encephalopathy and pancytopenia in humans who had significant skin contact with this solvent. A desire to protect workers from such blood disturbances formed the basis, in part, for the current OSHA PEL's.

Based on these recent findings, as well as continued concern for adverse effects after percutaneous absorption, NIOSH recommends that 2ME and 2EE be regarded in the workplace as having the potential to cause adverse

reproductive effects in male and female workers and embryotoxic effects, including teratogenesis, in the offspring of the exposed, pregnant female.

Although there have been animal studies conducted at concentrations at which these effects did not occur, we cannot assume that these are safe concentrations for humans. By decreasing exposure the potential for adverse reproductive and embryotoxic effects will decrease.

Even though reproductive and embryotoxic risks have not been determined for workers exposed to 2ME and 2EE at their respective OSHA PEL's, NIOSH believes that these standards should be reexamined. The adverse reproductive and embryotoxic potentials of 2ME and 2EE were not known when OSHA adopted these standards to protect workers against other acute and chronic effects.

NIOSH urges employers to voluntarily assess how their workers may be exposed to 2ME and 2EE and to reduce exposure to the lowest extent possible. The voluntary lowering of industrial exposure guides for 2ME and 2EE by some chemical manufacturers is commendable. The "Guidelines for Minimizing Worker Exposure to 2-Methoxyethanol and 2-Ethoxyethanol," Appendix I, should be adapted to specific work situations.

As previously discussed, concern also extends to structurally related glycol ethers that have not been tested adequately to assess fully their potential for causing reproductive effects. Preliminary test results of some structurally related glycol ethers indicate that they also have the potential for causing adverse reproductive effects similar to 2ME and 2EE. In light of these findings, NIOSH recommends similar cautions be exercised to reduce worker exposure to these structurally related glycol ethers until adequate testing demonstrates their safety.

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APPENDIX I

GUIDELINES FOR MINIMIZING WORKER EXPOSURE TO
2-METHOXYETHANOL AND 2-ETHOXYETHANOL

NIOSH recommends that 2-methoxyethanol (2ME) and 2-ethoxyethanol (2EE) be regarded in the workplace as having the potential to cause adverse reproductive effects, including teratogenesis. Exposure should be limited to only those workers essential to the process or operation, and workplace exposure levels should be minimized. Less hazardous solvents should be substituted where practicable. Because there have been several studies that reported reproductive effects as a result of skin absorption, every effort should be made to eliminate skin exposure.

The guidelines listed below are general and have greatest application in industry; however, they should be given consideration for all settings and be adapted to specific situations.

EXPOSURE MONITORING

Initial and routine worker exposure surveys should be made by competent industrial hygiene and engineering personnel. These surveys are necessary to determine the extent of worker exposure and to ensure that controls already in place are operational and effective. NIOSH's Occupational Exposure Sampling Strategy Manual may be helpful in developing efficient programs to monitor worker exposure to 2ME and 2EE [33]. The manual discusses how to determine the need for exposure measurements and select sampling times.

Worker exposures should be estimated by 8-hour TWA and short-term (15-minute) exposures calculated from personal or breathing zone samples. Short-term samples should be taken during periods of maximum expected exposure by using all available knowledge of the work areas, procedures, and processes. Area and source measurements may be useful to identify problem areas, processes, and operations.

Detailed analytical methods for both 2ME and 2EE are in the NIOSH Manual of Analytical Methods, Second Edition. The method for 2ME, #579, is in Volume 2, [34] and the method for 2EE, #S361, is in Volume 5 [35].

CONTROLLING WORKER EXPOSURE

There are four basic methods of limiting worker exposure to 2ME and 2EE, none of which is a simple industrial hygiene or management decision. Careful planning and thought should be used prior to implementation.

Product Substitution

The substitution of an alternative material with a lower potential health risk is an important method for reducing exposure. Extreme care must be used when selecting substitutes. Although the test results for some structurally related glycol ethers reported in this bulletin seem to suggest less hazardous compounds, the testing is not yet sufficient to identify a substitute for 2ME and 2EE. Possible health effects and potential exposures of alternatives to 2ME and 2EE should be fully evaluated prior to selection.

Contaminant Controls

Airborne concentrations of 2ME and 2EE can be most effectively controlled at the source of contamination by enclosure of the operation and use of local exhaust ventilation. Guidelines for selected processes and operations can be found in NIOSH's Recommended Industrial Ventilation Guidelines [36]. When enclosing a process or operation, a slight vacuum should be used to create negative pressure so that leakage will cause external air to flow into the enclosure and minimize contamination of the workplace. This can be accomplished with a well-designed local exhaust ventilation system that physically encloses the process as much as possible, with sufficient capture velocity to keep the contaminant from entering the workplace atmosphere. The design of ventilation systems should take into account the reactive characteristics of 2ME and 2EE.

Ventilation equipment should be checked at least every three months to ensure adequate performance. System effectiveness should also be checked soon after any change in production, process, or control that might result in significant increases in airborne exposure to 2ME and 2EE.

Worker Isolation

If feasible, workers may be isolated from direct contact with the work environment by the use of automated equipment operated from a closed control booth or room. The control room should be maintained at a greater air pressure than that surrounding the process equipment so that air flows out of, rather than into, the room. This type of control will not protect workers who must perform process checks, adjustments, maintenance, and related operations. Therefore, special precautions are often necessary to prevent or limit worker exposure in these situations and frequently involve the use of personal protective equipment.

Personal Protective Equipment

Personal protective equipment, which may include goggles, gloves, coveralls, footwear, and respirators, should not be the only means of preventing or minimizing exposure during routine operations. Since 2ME and 2EE can penetrate the skin, personal protective clothing and equipment should be selected that is impermeable to 2ME and 2EE.

APPENDIX II

IDENTIFIERS AND SYNONYMS FOR 2-METHOXYETHANOL AND 2-ETHOXYETHANOL

1. 2-Methoxyethanol

Chemical Abstracts Service Registry Number: 109-86-4
NIOSH RTECS Number: KL57750
Structural Formula: $CH_3-O-CH_2-CH_2-OH$
Empirical Formula: $C_3H_8O_2$

Dowanol EM
Ethylene glycol methyl ether
Ethylene glycol monomethyl ether
Glycolmethyl ether
Glycol monomethyl ether
MECS
Methoxyhydroxyethane
Methyl Cellosolve
Methyl glycol
Methyl oxitol
Monomethyl ether of ethylene glycol
Poly-solv EM

2. 2-Ethoxyethanol

Chemical Abstracts Service Registry Number: 110-80-5
NIOSH RTECS Number: KK80500
Structural Formula: $CH_3-CH_2-O-CH_2-CH_2-OH$
Empirical Formula: $C_4H_{10}O_2$

Cellosolve
Cellosolve solvent
Dowanol EE
Ethyl cellosolve
Ethylene glycol ethyl ether
Ethylene glycol monoethyl ether
Glycol ethyl ether
Glycol monoethyl ether
Hydroxy ether
NCI-C54853
Oxitol
Poly-solv EE

This information was obtained from the NIOSH's computerized Registery of Toxic Effects of Chemical Substances (RTECS) [37]. Registered trademark information is not included in this file. Therefore, some of the above synonyms and identifiers have trademarks but are not so indicated.

APPENDIX III

STRUCTURALLY RELATED GLYCOL ETHERS

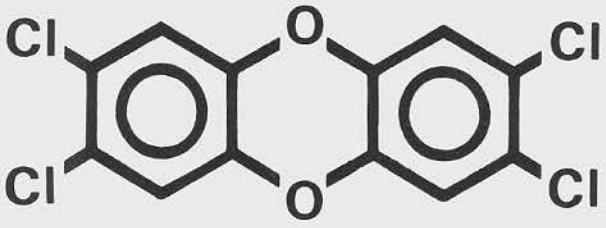
2MEA	=	2-Methoxyethyl acetate	$(CH_3-O-CH_2-CH_2-O-\overset{\overset{O}{\|}}{C}-CH_3)$
2EEA	=	2-Ethoxyethyl acetate	$(CH_3-CH_2-O-CH_2-CH_2-O-\overset{\overset{O}{\|}}{C}-CH_3)$
2BE	=	2-Butoxyethanol	$(CH_3-CH_2-CH_2-CH_2-O-CH_2-CH_2-OH)$
2PE	=	2-Phenoxyethanol	$(C_6H_5-O-CH_2-CH_2-OH)$
EGdiME	=	Ethylene glycol dimethyl ether	$(CH_3-O-CH_2-CH_2-O-CH_3)$
bis2ME	=	bis(2-methoxyethyl)ether	$(CH_3-O-CH_2-CH_2-O-CH_2-CH_2-O-CH_3)$
2EEE	=	2-(2-Ethoxyethoxy)ethanol	$(CH_3-CH_2-O-CH_2-CH_2-O-CH_2-CH_2-OH)$
1MP	=	1-Methoxy-2-propanol or propylene glycol monomethyl ether	$(CH_3-O-CH_2-\underset{\underset{CH_3}{\|}}{CH}-OH)$

NIOSH

Current Intelligence Bulletin 40

January 23, 1984

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD, "dioxin")



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

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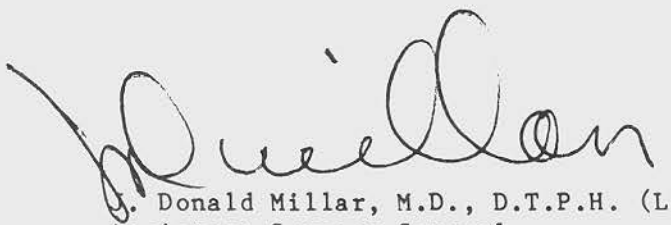
DHHS (NIOSH) Publication No. 84-104

FOREWORD

Current Intelligence Bulletins are reports issued by the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control, Atlanta, Georgia, for the purpose of disseminating new scientific information about occupational hazards. A Current Intelligence Bulletin may draw attention to a hazard previously unrecognized or may report new data suggesting that a known hazard is either more or less dangerous than was previously thought.

Current Intelligence Bulletins are prepared by the staff of the Division of Standards Development and Technology Transfer, NIOSH, (Robert A. Taft Laboratories, 4676 Columbia Parkway, Cincinnati, Ohio, 45226) and are distributed to representatives of organized labor, industry, public health agencies, academic institutions, and public interest groups as well as to those federal agencies, such as the Department of Labor, which have responsibilities for protecting the health of workers. It is our intention that anyone with the need to know should have ready access to the information contained in these documents; we welcome suggestions concerning their content, style, and distribution.

Because of the recent attention given to human exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, "dioxin") contaminated materials and published reports on the toxicity of TCDD, NIOSH staff consider it necessary to present a review of the pertinent data and a summary of findings related to the human hazard potential of TCDD. Because of the compression in this bulletin of the voluminous literature on TCDD, it is suggested that readers wanting to know more of the details of the reported studies consult the appended references.



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CURRENT INTELLIGENCE BULLETIN #40

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD, "DIOXIN")

January 23, 1984

ABSTRACT

In animals, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, "dioxin") causes various systemic effects at a wide range of exposure concentrations, including tumorigenesis, immunological dysfunction, and teratogenesis. Studies of humans exposed to TCDD-contaminated materials suggest that TCDD is the cause of observed chloracne, metabolic disorders (porphyria), and other systemic problems and are suggestive of TCDD's ability to cause cancer.

TCDD occurs as a contaminant of materials such as 2,4,5-trichlorophenol (TCP), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), and 2-(2,4,5-trichlorophenoxy)propionic acid (silvex). Occupational exposure may occur through contact with these materials during use or from the past contamination of worksites.

The National Institute for Occupational Safety and Health (NIOSH) recommends that TCDD be regarded as a potential occupational carcinogen, that occupational exposure to TCDD be controlled to the fullest extent feasible, and that decontamination measures be used for TCDD-contaminated work environments. This recommendation is based on a number of reliable studies demonstrating TCDD carcinogenicity in rats and mice.

BACKGROUND

Physical and Chemical Properties of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)

TCDD is one of a family of isomers known chemically as dibenzo-p-dioxins. The chemical and physical properties are summarized in Table I. TCDD is a colorless crystalline solid at room temperature. It is sparingly soluble in most organic solvents and essentially insoluble in water. TCDD is stable to heat, acids, and alkali and will decompose when exposed to ultraviolet light, including sunlight [1].

TABLE I

CHEMICAL AND PHYSICAL PROPERTIES OF TCDD [2,3]

CAS Registry No.:	1746-01-6	
Empirical formula		$C_{12}H_4Cl_4O_2$
Percent by weight	C	44.7
	O	9.95
	H	1.25
	Cl	44.1
Molecular weight		322
Vapor Pressure mm Hg at 25°C		1.7×10^{-6}
Melting point, °C		305
Decomposition temperature, °C		>700
Solubilities, g/liter		
o-Dichlorobenzene		1.4
Chlorobenzene		0.72
Benzene		0.57
Chloroform		0.37
n-Octanol		0.05
Methanol		0.01
Acetone		0.11
Water		2×10^{-7}

Formation and Use of TCDD

TCDD forms as a stable by-product or contaminant during the production of TCP. Run-away reactions at high temperature, in which excess TCDD was produced, have occurred at TCP production sites in the United States and elsewhere [4]. Normally, TCDD persists as a contaminant in TCP in relatively small, variable amounts (0.07-6.2 mg/kg) [5]. TCP has been utilized primarily as a feedstock for production of the phenoxy herbicides 2,4,5-T and silvex, resulting in the contamination of these products with TCDD. Production of 2,4,5-T and silvex ceased in the United States in 1979. However, stockpiles of both products are still being distributed and

used. TCP also is used in the production of hexachlorophene, a bactericide and fungicide.

The combustion of 2,4,5-T can result in its conversion to small amounts (0.6 ppt TCDD/1 ppm 2,4,5-T burned) of TCDD. Also, the burning or heating of commercial and purified chlorophenates and pyrolysis of polychlorinated biphenyls (PCBs) contaminated with trichlorobenzenes have resulted in the production of TCDD [6,7]. The formation of TCDD from trace chemical reactions in fires has been postulated but has not been verified [8,9].

Existing Regulations and Guides

No occupational exposure standard exists for TCDD. The United States Environmental Protection Agency (U.S. EPA) temporarily suspended or banned most uses of 2,4,5-T and silvex in 1979, although their use was allowed on sugarcane, orchards and for miscellaneous non-crop uses [10]. On October 18, 1983 EPA published its intent to cancel registration of pesticide products containing 2,4,5-T and silvex and to prohibit the transfer, distribution, sale or importation of any unregistered pesticide product containing 2,4,5-T or silvex or their derivatives [11].

Nature of Occupational Exposure to TCDD

It is not possible to estimate accurately the number of U.S. workers currently at risk of exposure to TCDD. Occupational exposure to TCDD may occur during production of TCP; in decontamination of worksites from prior production or use of TCP, 2,4,5-T, or silvex; from waste materials (such as reclaimed oil) contaminated with TCDD; or from cleanup after fires in transformers containing polychlorinated aromatics.

Dust or soil particles contaminated with TCDD can remain airborne or accumulate on indoor or outdoor work surfaces and may present a potential exposure hazard. Exposure to TCDD as a vapor will normally be negligible because of its low vapor pressure. Contact with TCDD-contaminated liquids is possible through the handling of drums or tanks containing the liquid or through dispersion of the liquid.

TOXICITY

Results of Studies of TCDD in Animals

Acute and Chronic Toxicity

There is wide variation in the dosage of TCDD required to cause death among animal species (oral LD_{50} 0.6-5,000 μg TCDD/kg body weight (bw)) [12,13]. Progressive weight loss with death several weeks later is reported to characterize the response in experimental animals after administration of a lethal dosage of TCDD [12,14,15]. Animals given single or repeated oral dosages of TCDD of 0.1 to 25 μg/kg bw demonstrated increased liver weights and lipid accumulation, thymic atrophy, and histopathological changes in liver and thymus [12,16-18].

TCDD is reported to be at least three times more potent than any other known compound in stimulating production of aminolevulinic acid synthetase (ALA), the rate-limiting enzyme in porphyrin and heme synthesis [19,20]. Varied effects on hematological functions have been reported in rats and mice dosed with TCDD: increased numbers of erythrocytes and leucocytes, increased hemoglobin concentration, decreased blood platelets in rats [21,22], and decreased hemoglobin concentration in mice [23].

Effects on Reproductive Function

TCDD administered at dosages of 0.125-3.0 μg TCDD/g bw to mice and rats induced fetotoxicity that included cleft palates and kidney anomalies [24-26], intestinal hemorrhages and excessive tissue/organ fluid (edema), and prenatal mortality [27,28].

Impairment of reproduction has been reported for rats ingesting 0.01 μg TCDD/kg bw/day. Significant decreased fertility, litter size, number of pups alive at birth, postnatal survival, and postnatal body weight of pups were evident in two successive generations delivered from male and female rats that ingested TCDD 90 days prior to first mating, during pregnancies, and for the durations of time between pregnancies [29]. No significant dose-related reproductive effects were observed in male mice treated with up to 2.4 μg TCDD/kg bw/day and mated with untreated female mice [30,31].

Immunological Effects

TCDD induced immunological function alterations, expressed by decreased thymus-to-body weight ratios, in nursing newborn rats exposed through dosing of the lactating mother [32]. Other reports have shown that pre- and post-natal maternal dosing of rats and mice with TCDD caused thymic atrophy

and suppression of cellular immunity in the offspring [33]. TCDD administered intraperitoneally or orally to mice induced a strong immunosuppressive effect on antibody production and cell-acquired immune responses [34].

Mutagenic Effects

Results of mutagenicity tests are inconclusive. In two studies TCDD was mutagenic in Salmonella typhimurium TA 1532 without activation [35,36]. In another study, which used a more sensitive mutant strain, Salmonella typhimurium TA 1537, TCDD was not a mutagen [37]. There is weak evidence of chromosomal aberrations in bone marrow of rats given dosages of 0.25 to 4 µg TCDD/kg bw [38,39].

Carcinogenic Effects

Male rats fed dosages of 0.001 µg TCDD/kg bw/week for 78 weeks and sacrificed at week 95 of the study showed a variety of neoplastic tumors (ear duct carcinoma; lymphocytic leukemia; kidney adenocarcinoma; malignant peritoneal histiocytoma; skin angiosarcoma; hard palate, tongue and nasal turbinate carcinoma) [40]. Female rats that had ingested TCDD for two years at a dosage of 0.1 µg/kg bw/day developed carcinomas of the liver and squamous cell carcinomas of the lung, hard palate, nasal turbinates, or tongue [41]. Male and female rats orally dosed with 0.5 µg TCDD/kg bw/week for two years demonstrated neoplastic nodules of the liver and thyroid adenomas [42].

Male mice fed dosages of TCDD of 0.05 or 0.5 µg/kg/week for two years developed liver cancer; female mice fed 0.2 or 2.0 µg/kg/week for the same duration developed liver cancer and thyroid follicular cell adenomas [42]. TCDD applied to the skin of female mice for two years (0.005 µg/kg bw/application; 3 days/week) resulted in a significantly higher incidence ($p=0.007$) of skin cancers (fibrosarcomas) when compared to untreated controls. An increase in the same tumor type, although not statistically significant ($p=0.084$), was also observed in the male mice that received a maximum dosage of 0.001 µg TCDD per application [43].

Human Health Effects

The only information on the health effects in humans from exposure to TCDD is from clinical or epidemiological studies of populations who were occupationally and non-occupationally exposed to 2,4,5-T and TCP contaminated with TCDD. Because of the coincidental exposure to 2,4,5-T and TCP and to other herbicides as well as to TCDD, it is not possible to

attribute the observed health effects solely to TCDD exposure. To date, no studies of humans include a quantitation of exposure to TCDD.

Chloracne and Other Systemic Effects

Chloracne is a chronic and sometimes disfiguring skin eruption caused by exposure to halogenated aromatic compounds including TCDD. Chloracne is possibly a result of systemic effects of these compounds, although it also may occur as a contact dermatitis [44,45].

There are numerous cases of chloracne reported following accidental exposure to chlorinated aromatic chemicals which were probably contaminated with TCDD [46-48]. The most notable recent exposure occurred in Seveso, Italy in 1976 [49]. In most incidences of chloracne, there are a variety of signs and symptoms (ranging from gastrointestinal disturbances to metabolic disorders) which accompany the appearance of the skin eruptions and persist for varying lengths of time [50-54].

Reproductive Effects In Humans

Reproductive effects resulting from possible human exposure to TCDD are inconclusive. Data on male workers who applied agricultural sprays of 2,4,5-T or who produced TCDD-contaminated materials are consistent with the animal data which suggest no reproductive effects in males from TCDD exposure [55-57]. To date, no study of reproductive effects in women or in offspring of males or females with defined exposure to TCDD has been reported.

Studies of birth defects in populations that may have been exposed non-occupationally to TCDD have been conducted in Australia where a correlation was observed between 2,4,5-T use and seasonal variation in the rate of spinal cord and spine formation defects; no causal association could be drawn [58]. In a similar study in Hungary, an increased incidence of congenital malformations including spine formation defects could not be correlated with increased use of 2,4,5-T [59]. A study based on incomplete fetal tissue samples from the Seveso, Italy population found no mutagenic, teratogenic, or fetotoxic effects in 30 interrupted pregnancies and four spontaneous abortions in women believed to have been exposed to TCDD [60]. A U.S. EPA study found a positive relationship between spontaneous abortions and 2,4,5-T use in the Alsea, Oregon area [61]. The study, however, has been severely criticized because of its numerous limitations: inaccurate comparisons of the study and control areas; inaccuracies in the collection of data on spontaneous abortions; incomplete and inaccurate data on 2,4,5-T usage; and failure to recognize that the rate of spontaneous abortions was not greater than would be expected [62].

Studies of Mortality and Carcinogenesis in Humans

Findings have been inconclusive in many mortality studies of workers with occupational exposure to TCDD-contaminated materials because of the small size of the study population and concomitant exposures to other substances.

No excess mortality or tumor incidence was observed among Swedish railroad workers exposed to unknown amounts of 2,4-D, 2,4,5-T, and other herbicides but believed to have been exposed primarily to phenoxy acid herbicides for at least 45 days [63]. In a subsequent analysis of mortality in this group of workers, 45 deaths (49 expected) were observed in the total population. A significant excess of tumors also was observed among those believed to be exposed primarily to Amitrol® (3-amino-1,2,4-triazole), a suspect carcinogen, as well as to phenoxy herbicides. Two cases of stomach cancer (0.33 expected) were observed among those exposed primarily to phenoxy herbicides [64].

Among Swedish forestry workers exposed to phenoxy herbicide preparations, supervisors, who had more extensive exposure to herbicides than the other forest workers, had a nonsignificant excess of deaths from all cancers. Mortality associated with the presence of tumors was, however, lower than expected for the total group of exposed workers [65].

In a group of 74 workers involved in an accident during TCP production in Germany, 21 deaths occurred during the following 27 years. Seven (7) malignant neoplasms vs. 4.2 expected and a significant excess of stomach cancer (3 observed vs. 0.61 expected) were observed [66].

Several case control studies of cancer patients have yielded data on the carcinogenicity of phenoxyacetic herbicides. Two studies were conducted in Sweden following a clinical observation of patients with soft tissue sarcoma who had previous occupational exposure to the herbicides [67]. The first study of 52 cases of soft tissue sarcoma concluded that the sarcoma cases were 5.3 times more likely than the 206 controls to have had occupational exposure to phenoxyacetic acids (primarily 2,4,5-T and 2,4-D) [68]. The second study of 110 cases of soft tissue sarcomas indicated that this population was 6.8 times more likely to have had exposure to phenoxyacetic acids than the 219 controls [69]. In neither study was it possible to demonstrate the relative risk related to exposure to TCDD-contaminated 2,4,5-T because of the presence of impurities such as chlorinated dibenzodioxins and dibenzofurans which were part of the phenoxyacetic herbicides.

In other reports from Sweden, 11 of 17 patients with malignant lymphoma reported occupational exposures to phenoxyacetic acids or chlorophenols

[70]; a case control study with 169 malignant lymphoma cases found a significantly higher occupational exposure to phenoxyacetic acids (primarily 2,4,5-T, and 2,4-D) associated with the sarcoma cases than did the 338 controls. Analysis by individual herbicide exposure was not possible [71].

Two additional studies conducted in Sweden for colon cancer and nasal and nasopharyngeal cancer did not demonstrate an elevated risk for occupational exposure to phenoxyacetic acids [72,73].

Among four small groups of U.S. production workers exposed to TCP and 2,4,5-T a total of 105 deaths were observed [74-76]. In these, three deaths were attributed to soft tissue sarcoma (43 times the number expected for this age group of U.S. white males) [77]. Later, four additional cases were reported to have soft tissue sarcomas [78-81]. However, a detailed review of work records and expert review of pathological tissue specimens have shown only two of the seven cases with both confirmed exposure to TCP or 2,4,5-T and diagnosis of soft tissue sarcoma [82].

Summary of Toxicity in Animals and Humans

TCDD causes a variety of systemic and immunological effects in animals with wide variation among species in the dosage required to cause death. Studies using rats and mice have demonstrated that TCDD is an animal teratogen and carcinogen. Results of tests for mutagenicity are inconclusive.

Humans exposed to materials reported to be contaminated with TCDD have developed chloracne and other signs of systemic poisoning. Soft tissue sarcoma has been observed in excess among workers exposed to phenoxy herbicides. These data are inconclusive regarding TCDD toxicity in humans because the populations studied had mixed exposures making causal relationships between exposure and effect unclear. The data are, however, suggestive of an association between exposure to phenoxyacetic herbicides contaminated with TCDD and excess lymphoma and stomach cancer. Attempts to associate reproductive effects with TCDD exposure are inconclusive because of the inadequately defined populations studied and the difficulties of defining exposure.

RECOMMENDATIONS

There are several classifications for identifying a substance as a carcinogen. Such classifications have been developed by the U.S. National Institute of Environmental Health Sciences, National Toxicology Program [83], the International Agency for Research on Cancer [84], and OSHA [85]. NIOSH considers the OSHA classification the most appropriate for use in identifying carcinogens in the workplace. This classification is outlined

in 29 CFR 1990.103.* Since TCDD has been shown to carcinogenic in experimental studies with rats and mice, and studies are suggestive of an association between human exposure to TCDD-contaminated materials and carcinogenicity, NIOSH recommends that TCDD be considered as a potential occupational carcinogen and exposure to TCDD in all occupational settings should be controlled to the fullest extent feasible. While observations to date do not confirm a causal relationship between TCDD exposure and soft tissue sarcoma, they suggest a need for continued investigations.

Because of the variety of situations likely to be encountered in TCDD-contaminated worksites, it is not possible to offer in this bulletin detailed procedures for assessing exposures or decontamination. Based on NIOSH hazard evaluations of TCDD-contaminated sites, the following general guidelines are recommended until more specific procedures can be developed [86,87].

Assessment of Exposure

Workers may be exposed to TCDD derived from a variety of sources: the production of TCP, residues from prior production or use of 2,4,5-T or silvex, waste materials contaminated by TCDD, or contamination resulting from transformer fires. The first step in assessing workplace contamination should be environmental sampling to determine the presence of TCDD contamination, keeping in mind the possible routes of exposure, with later sampling conducted to define the quantity of TCDD in the environment. The assessment may include sampling of soil and settled dust for TCDD, air sampling for TCDD-contaminated particles, and wipe sampling of surfaces [86,87].

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*"'Potential occupational carcinogen' means any substance, or combination or mixture of substances, which causes an increased incidence of benign and/or malignant neoplasms, or a substantial decrease in the latency period between exposure and onset of neoplasms in humans or in one or more experimental mammalian species as the result of any oral, respiratory or dermal exposure, or any other exposure which results in the induction of tumors at a site other than the site of administration. This definition also includes any substance which is metabolized into one or more potential occupational carcinogens by mammals."

Decontamination and Worker Protection Programs

In general, decontamination procedures must provide an organized process in which levels of contamination are reduced. This requires containment, collection, and disposal of contaminated solutions and residues generated during the cleanup. Separate facilities should be provided for decontamination of large equipment.

Each stage of decontamination, such as gross decontamination and repetitive wash/rinse cycles, should be conducted separately, either by using different locations or by spacing in time. Personnel decontamination locations used should be physically separated to prevent cross-contact and should be arranged in order of decreasing level of contamination. Separate entry/exit routes and locations should be provided for workers when it is necessary to isolate them from different contamination areas containing incompatible waste. Entry and exit points to these areas should be well marked and controlled. Access to the decontamination area should be separate from the path between the contaminated and clean areas. Dressing stations for entry should be separate from re-dressing areas for exit.

Protective Clothing and Equipment

All workers who may be exposed to TCDD should be equipped with adequate chemical protective clothing and equipment to ensure their protection. In the selection of protective clothing, consideration should be given to the utilization of disposable apparel due to the uncertainty of decontamination of clothing.

The protective apparel should consist of both outer and inner garments. The outer garments should consist of a zippered coverall with attached hood and draw string or elastic sleeves, gloves and closure boots. If exposure is to particulate or dust, the coveralls should be made of a non-woven fabric such as spunbonded polyethylene, Tyvek®. In cases of exposure to liquids, the coveralls, gloves and boots should be made of chemically resistant materials such as disposable laminates, e.g., Saranax® coated Tyvek®, or synthetic elastomers such as butyl, nitrile or neoprene rubber. The inner garments should consist of cotton coveralls, undershirts, undershorts, gloves, and socks and should be disposed of after use. The effectiveness of the protective clothing should be evaluated under simulated use conditions, regardless of the type of clothing used. All disposable clothing should be placed in marked and approved containers and disposed of appropriately. All reusable clothing and equipment should be thoroughly cleaned and checked for residual contamination before reuse or storage.

Respiratory Protection

The use of respiratory protection requires that a respiratory protection program be instituted according to the requirements of 29 CFR 1910.134 [88] and that the respirators have been approved by the Mine Safety and Health Administration (MSHA) and by NIOSH. This program should include training on proper fit testing and use and procedures for respirator maintenance, inspection, cleaning and evaluation.

For situations where TCDD contamination is low (e.g., exposure to dust contaminated with low levels of TCDD), air purifying respirators should provide sufficient protection until the extent and characterization of the exposure can be determined. Where quantities of materials highly contaminated with TCDD have been released and have contaminated an area (e.g., production accidents), all workers who may be exposed to TCDD should wear respirators that consist of a self-contained breathing apparatus with a full facepiece operated in pressure-demand or other positive pressure mode. An alternate method utilizes a combination Type C supplied air respirator, with full facepiece, operated in pressure-demand mode and equipped with auxiliary positive pressure self-contained air supply.

Post-Decontamination Testing

The adequacy of the decontamination effort should be determined by conducting follow-up sampling and analysis of the contaminated areas and protective equipment. This testing should be conducted as each area is decontaminated and after the entire facility has been cleaned.

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NIOSH

Current Intelligence Bulletin 41

February 9, 1984

1,3 - Butadiene

$$CH_2=CH-CH=CH_2$$

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

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ERRATA FOR CIB 41

Page 5, paragraph 1--line 9; change 8,000 ppm to 1,250 ppm

The sentence should read:
"Exposed female mice also had a statistically significant increase of granulomatous tumors of the ovary at exposures of 625 and 1,250 ppm and mammary gland carcinomas at a concentration of 1,250 ppm when compared with the controls.

FOREWORD

Current Intelligence Bulletins are reports issued by the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control, Atlanta, Georgia, for the purpose of disseminating new scientific information about occupational hazards. A Current Intelligence Bulletin may draw attention to a hazard previously unrecognized or may report new data suggesting that a known hazard is either more or less dangerous than was previously thought.

Current Intelligence Bulletins are prepared by the staff of the Division of Standards Development and Technology Transfer, NIOSH, (Robert A. Taft Laboratories, 4676 Columbia Parkway, Cincinnati, Ohio, 45226) and are distributed to representatives of organized labor, industry, public health agencies, academic institutions, and public interest groups as well as to those federal agencies, such as the Department of Labor, which have responsibilities for protecting the health of workers. It is our intention that anyone with the need to know should have ready access to the information contained in these documents; we welcome suggestions concerning their content, style, and distribution.

It is recommended that 1,3-butadiene be regarded as a potential occupational carcinogen, teratogen, and as a possible reproductive hazard. Consequently, appropriate engineering and work practice controls should be used to reduce worker exposure. These recommendations are based on long-term animal studies which demonstrated carcinogenicity, teratogenicity and adverse effects upon the testes and ovaries.

On the basis of this information, it is recommended that producers and users of 1,3-butadiene disseminate this information to their workers and customers and that professional and trade associations and unions inform their members of the potential hazards of working with 1,3-butadiene.

It is also recommended that the present Occupational Safety and Health Administration (OSHA) standard of 1,000 ppm for exposure to 1,3-butadiene be reexamined. The excess risk of cancer to workers exposed to specific airborne concentrations of 1,3-butadiene has not yet been determined, but the probability of developing cancer would be decreased by reducing exposure.

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CURRENT INTELLIGENCE BULLETIN #41

1,3-BUTADIENE

FEBRUARY 9, 1984

ABSTRACT

Inhalation exposure of rats and mice to 1,3-butadiene induced a carcinogenic response at multiple sites. Mammary fibroadenomas/carcinomas, uterine sarcomas, Leydig cell adenomas of the testes, thyroid follicular cell adenomas, exocrine tumors of the pancreas, and Zymbal gland carcinomas were identified in rats exposed at concentrations of 1,000 or 8,000 ppm of 1,3-butadiene. Mice exposed to 625 or 1,250 ppm of 1,3-butadiene developed a high incidence of malignant lymphomas; an increased incidence of other tumors, including hemangiosarcoma; and testicular and ovarian atrophy.

The offspring of pregnant rats exposed to 1,3-butadiene at 8,000 ppm had major skeletal defects. In addition, fetal toxicity was observed when pregnant dams were exposed at 200 ppm, 1,000 ppm, and 8,000 ppm.

Epidemiological studies of workers employed in facilities producing styrene-butadiene rubber indicated an increased, but not statistically significant, risk of mortality from neoplasms of the lymphatic and hematopoietic tissues and from leukemia.

Based on these data, the National Institute for Occupational Safety and Health (NIOSH) recommends that 1,3-butadiene be regarded as a potential occupational carcinogen and teratogen and as a possible reproductive hazard.

BACKGROUND

Physical and Chemical Properties

1,3-Butadiene is a colorless, noncorrosive, flammable gas. It is slightly soluble in water, more soluble in methanol and ethanol, and readily soluble in common organic solvents such as cyclohexane. Additional chemical and physical properties are listed in Table 1.

Table 1. Chemical and Physical Properties [1-3]

Chemical Identity: 1,3-Butadiene

CAS Registry No.: 106-99-0

Synonyms: Biethylene, bivinyl, butadiene, buta-1,3-diene, alpha-gamma-butadiene, divinyl, erythrene, NCI-C50602, pyrrolylene, vinylethylene

Molecular Weight: 54.10

Molecular Formula: C_4H_6

Structural Formula: CH_2:CHCH:CH_2

Boiling point	-4.41°C (at 760 mmHg)
Freezing point:	-108.9°C
Heat of vaporization, J/g (cal/g), 25°C	389 (93)
Explosive limits, vol % butadiene in air	
lower	2.0
upper	11.5
Vapor pressure	2 atm at 15.3°C 5 atm at 47.0°C
Recognition (Odor) Threshold	1.3 ppm

Production, Use, and Potential for Occupational Exposure

In the United States (U.S.), approximately 78% (3,240 million pounds) of all 1,3-butadiene is produced as a coproduct in the manufacture of ethylene, and 22% (910 million pounds) is produced by dehydrogenation of n-butene and n-butane [4].

Styrene-butadiene rubber (SBR) and polybutadiene rubber (BR) account for the two largest uses of 1,3-butadiene in the U.S., approximately 2,880 million pounds (primarily in the tire industry); polychloroprene (neoprene) rubber

production ranks third, 320 million pounds. Other uses are in styrene-butadiene copolymer latexes used as carpet backing and paper coating materials; in acrylonitrile-butadiene-styrene (ABS) resins used to make high impact resistant pipes and parts for automobiles and appliances; and in the production of nitrile rubber, adiponitrile/hexamethylenediamine for nylon, polybutadiene polymers, thermoplastic elastomers, and methyl methacrylate-butadiene-styrene and nitrile resins. As an intermediate, 1,3-butadiene is used in the production of various chemicals such as 1,4-hexadiene, 1,5-cyclooctadiene, and fungicides such as tetrahydrophthalic anhydride [4].

Approximately 65,000 workers (Table 2) are potentially exposed to 1,3-butadiene as estimated from data compiled from the National Institute for Occupational Safety and Health (NIOSH) National Occupational Hazard Survey (NOHS) [5].

Table 2. Number of Workers Potentially Exposed by Industry

SIC* Code	Description	Workers Potentially Exposed
26	Paper and allied products	1,221
28	Chemical and allied products	44,980
29	Petroleum and coal products	84
30	Rubber and plastics products, NEC	9,086
33	Primary metal industries	55
34	Fabricated metal products	96
35	Machinery, except electrical	1,210
36	Electrical equipment and supplies	121
37	Transportation equipment	145
38	Instruments and related products	175
39	Miscellaneous manufacturing industries	2,244
73	Miscellaneous business services	5,339
80	Medical and other health services	493

*Standard Industrial Classification Code

Health Hazard Evaluation surveys conducted by NIOSH at six facilities indicated that exposures to 1,3-butadiene in those facilities were significantly below the OSHA standard of 1,000 ppm. The range of reported exposures was 0.06 ppm to 39 ppm. The types of facilities surveyed included those which manufactured helmets and visors, synthetic rubber, rubber tires and tubes, automotive weather stripping, braided hoses, and plastic components for aircraft [6-11].

EXPOSURE STANDARDS AND GUIDES

Based on the 1968 Threshold Limit Value (TLV®) of the American Conference of Governmental Industrial Hygienists [12], the Occupational Safety and Health Administration (OSHA) promulgated a standard for occupational exposure to 1,3-butadiene of 1,000 ppm (2,200 mg/m^3) determined as an 8-hour time-weighted average (TWA) concentration [13]. The TLV® of 1,000 ppm was based on the absence of significant progressive injury to rats and guinea pigs exposed at 600, 2,300, or 6,700 ppm of 1,3-butadiene during an 8-month daily exposure period and only mild irritation experienced by human subjects exposed at 8,000 ppm [12].

The ACGIH included 1,3-butadiene in their Notice of Intended Changes for the 1983-84 Threshold Limit Values, based upon reported animal carcinogenicity data. The Intended Change identified 1,3-butadiene as an industrial substance suspect of carcinogenic potential for man. No numerical TLV® was assigned [14].

TOXICITY

Results of Animal Studies

Acute -- Inhalation exposure studies with 1,3-butadiene have shown the lethal concentration for 50 percent (LC_{50}) of the mice and rats tested to be 122,000 ppm and 129,000 ppm, respectively, [15]; an LC_{100} of 250,000 ppm was reported for rabbits exposed to 1,3-butadiene [16]. Toxic effects of exposure in the animals progressed from light anesthesia, to running movements and tremors, to deep anesthesia and death.

Subchronic -- Except for moderately increased salivation at 4,000 and 8,000 ppm concentrations, exposure of rats on a daily basis for 3 months at 1,3-butadiene concentrations of 1,000, 2,000, 4,000, or 8,000 ppm produced no effects in the animals related to the exposures [16]. Rats and guinea pigs exposed daily for 8 months at a 6,700 ppm concentration of 1,3-butadiene experienced a slightly reduced body-weight gain compared to controls. No significant effects were noted in animals exposed at concentrations of 600 or 2,300 ppm [17].

Chronic -- In a chronic inhalation study, rats exposed for two years, 6 hours per day, 5 days per week at 1,3-butadiene concentrations of 1,000 or 8,000 ppm developed tumors at multiple sites. Occurrences of mammary fibroadenomas/carcinomas, thyroid follicular cell adenomas, and uterine stromal sarcomas in female rats exposed at both concentrations were statistically significant when compared with the controls. Male rats had

significant increases in the incidence of testicular Leydig cell adenomas at 1,000 ppm and 8,000 ppm exposures and for pancreatic exocrine tumors at 8,000 ppm when compared with the controls [18].

Mice exposed at 1,3-butadiene concentrations of 625 or 1,250 ppm, 6 hours per day, 5 days per week for 61 weeks developed cancer at multiple sites. A statistically significant increase of tumors in exposed male and female mice compared to the controls included hemangiosarcomas of the heart, malignant lymphomas, papillomas of the stomach, and alveolar/bronchiolar adenomas and carcinomas of the lungs. Exposed female mice also had a statistically significant increase of granulomatous tumors of the ovary at exposures of 625 and 1,250 ppm and mammary gland carcinomas at a concentration of 8,000 ppm when compared with the controls. In addition, 1,3-butadiene was associated with the induction and early onset of non-neoplastic changes in both sexes of mice. These non-neoplastic changes included atrophy of the ovaries, testes, and nasal olfactory epithelium; hyperplasia and metaplasia of the respiratory epithelium; and liver necrosis [19].

Teratogenicity and Reproductive Effects -- An inhalation study of pregnant Sprague-Dawley rats exposed at 200, 1,000, or 8,000 ppm of 1,3-butadiene for 6 hours per day on days 6-15 of gestation produced dose-related maternal and fetal toxicity when compared to an unexposed group of controls. Depressed body weight gain among dams was observed at all concentrations, and fetal growth was significantly retarded among rats exposed at the 8,000 ppm. Fetal deaths, though not statistically significant, were higher for all exposed groups, and at 8,000 ppm, a statistically significant increase in major skeletal abnormalities was recorded (skull, spine, sternum, long bones and ribs) [20].

Mutagenicity -- 1,3-Butadiene was not found to be a direct-acting mutagen, but in the presence of a liver microsomal activating system, it was transformed into mutagenic metabolites [21].

HUMAN HEALTH EFFECTS

Acute Effects

Occupational exposure at 2,000, 4,000 or 8,000 ppm concentrations of 1,3-butadiene is reported to cause irritation of the skin, eyes, nose, and throat. Coughing, drowsiness, and fatigue have also been reported at higher, but not specified, exposure concentrations. These physiological responses dissipated upon removal of the workers from the area where 1,3-butadiene had accumulated [17,22,23]. Dermatitis and frostbite may result from exposure to liquid and evaporating 1,3-butadiene [24].

Epidemiology Studies

A retrospective cohort study was conducted at two SBR production facilities in the U.S. The combined cohorts consisted of 2,756 white males who had an average length of employment of approximately 10 years. No historical exposure data were available. Environmental sampling conducted at the time of the study characterized the most likely chemical exposures to be 1,3-butadiene, styrene, and benzene. Average exposure concentrations of 1,3-butadiene in the two facilities were 1.24 ppm (range, 0.11-4.17 ppm) and 13.5 ppm (range, 0.34-174 ppm). No statistically significant excesses in total or cause-specific mortality were observed for the total worker populations of either facility. However, a subgroup of workers from one cohort had a non-statistically significant excess mortality for cause-specific categories of the lymphatic and hematopoietic tissues [25].

Eight facilities that produced SBR in the U.S. and Canada provided data for another retrospective study [26]. The study covered a period of 36 years and included a total worker population of 13,920 black and white males. No significant excesses in cause-specific mortality were observed; however, some cancers (digestive system, kidney, lymph nodes, and larynx) occurred at a higher rate in white males compared with the general population, and the black male population had a non-statistically significant elevated risk of arteriosclerotic disease. The small number of workers in the cohorts from the 8 facilities studied and the relatively short latency periods of workers exposed inhibited the capability to identify statistically significant increases in risk of mortality or cause-specific disease. Also, environmental data were insufficient to characterize and quantify the workers' chemical exposures.

RECOMMENDATIONS

There are several classifications for identifying a substance as a carcinogen. Such classifications have been developed by the National Toxicology Program [19], the International Agency for Research on Cancer [27], and OSHA [28]. NIOSH considers the OSHA classification the most appropriate for use in identifying carcinogens in the workplace. This classification is outlined in 29 CFR 1990.103* [28]. Since exposure to

*"'Potential occupational carcinogen' means any substance, or combination or mixture of substances, which causes an increased incidence of benign and/or malignant neoplasms, or a substantial decrease in the latency period between exposure and onset of neoplasms in humans or in one or more experimental mammalian species as the result of any oral, respiratory or dermal exposure, or any other exposure which results in the induction of tumors at a site other than the site of administration. This definition also includes any substance which is metabolized into one or more potential occupational carcinogens by mammals."

1,3-butadiene has been shown to produce malignant tumors in rats and mice, it meets the OSHA criteria; therefore, NIOSH recommends that 1,3-butadiene be considered a potential occupational carcinogen. In addition, there is a possible reproductive hazard to workers exposed to 1,3-butadiene based on maternal and fetal toxicity observed in 1,3-butadiene exposed rats; an indication of teratogenicity in exposed rats; and suggestion of testicular and ovarian atrophy in mice exposed to 1,3-butadiene.

NIOSH also recommends that the present OSHA standard of 1,000 ppm TWA for 1,3-butadiene be reexamined, based on the health effects in animals exposed at concentrations of 1,3-butadiene at or below the standard. In addition, the excess risk of cancer to workers exposed to specific airborne concentrations of 1,3-butadiene has not yet been determined, but the probability of developing cancer would be decreased by reducing exposure. As prudent public health policy, employers should voluntarily assess the conditions under which workers may be exposed to 1,3-butadiene and to the fullest extent possible take all reasonable precautions to reduce exposure.

Guidelines recommended in the Appendix for minimizing worker exposure to 1,3-butadiene are general in nature and should be adapted to specific work situations as required.

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APPENDIX

GUIDELINES FOR MINIMIZING EMPLOYEE EXPOSURE TO 1,3-BUTADIENE

It is recommended that 1,3-butadiene be regarded as a potential occupational carcinogen and teratogen and as a possible reproductive hazard. These recommendations are based on long-term animal studies which demonstrated carcinogenicity, teratogenicity and adverse effects upon the testes and ovaries. Consequently, appropriate engineering and work practice controls should be used to reduce worker exposure to the fullest extent feasible. The area in which 1,3-butadiene is used should be restricted to only those employees essential to the process or operation. The guidelines listed below are general in nature and should be adapted to specific work situations as required.

EXPOSURE MONITORING

Initial and routine worker exposure surveys should be made by competent industrial hygiene and engineering personnel. These surveys are necessary to determine the extent of worker exposure and to ensure that controls already in place are operational and effective. NIOSH's Occupational Exposure Sampling Strategy Manual may be helpful in developing efficient programs to monitor worker exposure to 1,3-butadiene [29]. The manual discusses how to determine the need for exposure measurements and select sampling times.

Worker exposures should be estimated by 8-hour TWA and short-term (15-minute) exposures calculated from personal or breathing zone samples. Short-term samples should be taken during periods of maximum expected exposure by using all available knowledge of the work areas, procedures, and processes. Area and source measurements may be useful in identifying problem areas, processes, and operations.

A detailed analytical method for 1,3-butadiene is in the NIOSH Manual of Analytical Methods, Second Edition [30].

CONTROLLING WORKER EXPOSURE

There are four basic methods of limiting worker exposure to 1,3-butadiene, none of which is a simple industrial hygiene or management decision. Careful planning and thought should be used prior to implementation.

Product Substitution

Substitution, when feasible, of an alternative material with a lower potential health risk is an important method for reducing exposure. Extreme care must be used when selecting substitutes. Possible health effects from potential exposure to alternatives for 1,3-butadiene should be fully evaluated prior to selection.

Contaminant Controls

Airborne concentrations of 1,3-butadiene can be most effectively controlled at the source of contamination by enclosure of the operation and use of local exhaust ventilation. Guidelines for selected processes and operations can be found in NIOSH's Recommended Industrial Ventilation Guidelines [31]. When a process or operation is being enclosed, a slight vacuum should be used to create negative pressure so that leakage will cause external air to flow into the enclosure and minimize contamination of the workplace. This can be accomplished with a well-designed local exhaust ventilation system that physically encloses the process as much as possible with sufficient capture velocity to keep the contaminant from entering the workplace atmosphere. The design of ventilation systems should take into account the reactive characteristics of 1,3-butadiene.

Ventilation equipment should be checked at least every three months to ensure adequate performance. System effectiveness should also be checked soon after any change in production, process, or control that might result in significant increases in airborne exposure to 1,3-butadiene.

Worker Isolation

If feasible, workers may be isolated from direct contact with the work environment by the use of automated equipment operated from a closed control booth or room. The control room should be maintained at a greater air pressure than that surrounding the process equipment so that air flows out of, rather than into, the room. This type of control will not protect workers who must perform process checks, adjustments, maintenance, assembly-line tasks, and related operations. Therefore, special precautions are often necessary to prevent or limit worker exposure in these situations and frequently involve the use of personal protective equipment.

Personal Protective Equipment

Personal protective equipment, which may include goggles, gloves, coveralls, footwear, and respirators, should not be the only means of preventing or

minimizing exposure during routine operations. Since 1,3-butadiene is a skin irritant and can produce frostbite, personal protective clothing and equipment should be selected that is appropriate for the potential exposures.

The use of respiratory protection requires that a respiratory protection program be instituted according to the requirements of 29 CFR 1910.134 [32] and that the respirators have been approved by the Mine Safety and Health Administration (MSHA) and by NIOSH. This program should include training on proper fit testing and use and procedures for respirator maintenance, inspection, cleaning and evaluation.

MEDICAL SURVEILLANCE

A medical surveillance program should be made available that can evaluate both the acute and chronic effects of 1,3-butadiene exposure. Effects such as upper respiratory irritation, dermatitis, and irritation should alert management that unacceptable acute exposure to 1,3-butadiene may be occurring. A careful history should be taken initially and updated yearly. Unusual medical findings for a worker should prompt medical personnel to consider specific tests for the individual.

NIOSH

Current Intelligence Bulletin 42

September 27, 1984

Cadmium (Cd)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

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FOREWORD

Current Intelligence Bulletins are reports issued by the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control, Atlanta, Georgia, for the purpose of disseminating new scientific information about occupational hazards. A Current Intelligence Bulletin may draw attention to a hazard previously unrecognized or may report new data suggesting that a known hazard is either more or less dangerous than was previously thought.

Current Intelligence Bulletins are prepared by the staff of the Division of Standards Development and Technology Transfer, NIOSH, (Robert A. Taft Laboratories, 4676 Columbia Parkway, Cincinnati, Ohio 45226) and are distributed to representatives of organized labor, industry, public health agencies, academic institutions, and public interest groups as well as to those federal agencies, such as the Department of Labor, which have responsibilities for protecting the health of workers. It is our intention that anyone with the need to know should have ready access to the information contained in these documents; we welcome suggestions concerning their content, style, and distribution.

The purpose of this bulletin is to disseminate recent information concerning the potential carcinogenic hazard to workers of cadmium (Cd). In 1976, NIOSH published Criteria for a Recommended Standard....Occupational Exposure to Cadmium, recommending a permissible exposure limit of 40 micrograms of cadmium per cubic meter of air (40 $\mu g/m^3$) which was viewed as necessary to prevent chronic renal damage in exposed workers. Epidemiological and toxicological data suggesting an association between cadmium exposure and cancer were cited in that document, but the evidence for carcinogenicity was considered to be inconclusive at that time. Based on subsequent epidemiological and toxicological studies, NIOSH now recommends that cadmium and its compounds be regarded as potential occupational carcinogens.

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CURRENT INTELLIGENCE BULLETIN #42

CADMIUM

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ABSTRACT

A recent epidemiological study has demonstrated a statistically significant excess of lung cancer mortality among workers exposed to cadmium oxide (CdO). A chronic inhalation exposure study with rats provides toxicological evidence that exposure to cadmium chloride ($CdCl_2$) aerosol can cause a dose-dependent incidence of malignant lung tumors. Based primarily on these data, the National Institute for Occupational Safety and Health (NIOSH) recommends that cadmium and its compounds be regarded as potential occupational carcinogens and that appropriate controls be used to reduce worker exposure.

BACKGROUND

Exposure Standards, Recommendations, and Guides

Based on the 1970 recommended cadmium (Cd) standard of the American National Standards Institute (ANSI) [1], the Occupational Safety and Health Administration (OSHA) promulgated a standard for cadmium which set permissible exposure limits for cadmium fume (as Cd) of 100 micrograms of cadmium per cubic meter of air ($\mu g/m^3$) determined as an 8-hour time-weighted average (TWA) concentration and a ceiling concentration of 300 $\mu g/m^3$ and for cadmium dust (as Cd) of 200 $\mu g/m^3$ (as an 8-hour TWA) with a ceiling concentration of 600 $\mu g/m^3$ [2].

In 1976, the National Institute for Occupational Safety and Health (NIOSH) recommended that exposures to any form of cadmium at concentrations greater

than 40 $\mu g/m^3$ (determined as a TWA for up to a 10-hour workday, 40-hour workweek) or at a ceiling concentration greater than 200 $\mu g/m^3$ for any 15-minute period not be permitted [3].

The 1984-85 American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV®) for cadmium dust and salts (as Cd) is 50 $\mu g/m^3$ for an 8-hour TWA, with a 15-minute Short Term Exposure Limit (STEL) of 200 $\mu g/m^3$; for cadmium oxide (CdO) fume, 50 $\mu g/m^3$ (as Cd) as a ceiling; and for cadmium oxide production, an 8-hour TWA of 50 $\mu g/m^3$ (as Cd) [4].

OSHA, NIOSH, and ACGIH have aimed their standards or recommendations for permissible occupational exposures to cadmium toward prevention of such critical health effects as chronic renal damage and acute pulmonary toxicity [2-4].

Production, Use, and Potential for Occupational Exposure

Cadmium is found primarily as cadmium sulfide (less than 1%) in ores containing zinc, lead, and copper. Cadmium-containing precipitates from ore smelting are processed electrolytically to produce cadmium metal. Because of its low boiling point (767°C) and a high vapor pressure relative to the metals with which it is found, cadmium volatilizes readily during smelting and then condenses to form fine airborne particles that react almost immediately with oxygen to form respirable cadmium oxide fume [5].

Approximately 4,000 metric tons of cadmium are used yearly in the United States, of which about half is used for plating other metals and half is used in pigments, batteries, stabilizers for plastics, metallurgy, nuclear reactor neutron-absorbing rods, and semiconductors and as a catalyst [6].

Based on data from the National Occupational Hazard Survey, NIOSH estimates that approximately 1,500,000 workers may be potentially exposed to cadmium, of which approximately 100,000 are identified with exposure to specific cadmium compounds or with industries that utilize cadmium [7]. Sources of potential worker exposure to cadmium include ore smelting operations, mist from cadmium-containing electroplating baths, calcination (drying) of cadmium pigments, and handling of powdered cadmium oxide in production of cadmium soaps that are used to stabilize plastics [5].

CARCINOGENICITY

Epidemiological and toxicological data suggesting an association between cadmium exposure and cancer were included in the 1976 NIOSH document Criteria for a Recommended Standard....Occupational Exposure to Cadmium [3]. In that document, several toxicological studies showed that injection of cadmium metal

or its salts (oxide, chloride, sulfide, and sulfate) into laboratory rats produced local sarcomas and Leydig cell (interstitial cell) testicular tumors, but oral ingestion studies with rats and mice did not demonstrate an increased incidence of malignant tumors. Two epidemiological studies of a single cohort of battery plant workers exposed to airborne cadmium reported an association between cadmium exposure and prostatic cancer [8,9]. In a study of 292 cadmium production workers who had a minimum of 2 years of employment between 1940 and 1969, a statistically significant excess of deaths from all malignancies and from lung cancer was observed in the entire cohort. In addition, a statistically significant excess of deaths from prostate cancer was detected among workers who lived for at least 20 years after the date of first working in a cadmium production facility. Some of these workers had been hired prior to 1926, when arsenic (a known human lung carcinogen) was produced in the plant [10].

NIOSH considered the body of toxicological and epidemiological evidence for carcinogenicity to be inconclusive and recommended against basing a standard on potential human carcinogenicity. However, the criteria document stated, "This recommendation should be reconsidered if additional data on these points that warrant such reconsideration are developed" [3].

Recent Epidemiological Evidence

A recent epidemiological study provides more persuasive evidence for the carcinogenicity of cadmium oxide. Subsequent to the 1976 report of a study of workers in a cadmium production facility [10], the cohort was expanded from the original 292 workers to 602 white males who had worked at least six months between 1940-1969 in the cadmium production area of the cadmium smelting plant [11]. This expanded cohort was followed through 1978. Of the 602 workers, 345 had two or more years of total employment, including some for whom records were not available at the time of the earlier study; the remaining 257 were short-term workers employed for 6 months to 2 years. Mortality from cancer of the respiratory tract was significantly greater in the entire cohort than would have been expected from rates in the general U.S. population (20 observed vs. 12.15 expected, standardized mortality ratio [SMR]=165, 95% confidence interval [CI]=101-254). All respiratory cancer deaths were due to cancer of the lung, trachea, or bronchus. Within the subset of cadmium production workers employed at least two years, the SMR for lung cancer was 265 (20 observed vs. 7.60 expected, 95% CI=162-409) and a significant excess was seen among those hired both before (4 observed vs. 0.56 expected, SMR=714, 95% CI=195-1829) and after (16 observed vs. 7.00 expected, SMR=229, 95% CI=131-371) the cessation of arsenic smelting.

In this study, lung cancer mortality was also found to increase with increasing cumulative exposure to cadmium. Using categories based on a 40 year TWA at a given exposure concentration, SMR's were 53 at $\leq$40 $\mu g/m^3$, 152 at 41-200 $\mu g/m^3$, and 280 at >200 $\mu g/m^3$; the 95% CI

at >200 $\mu g/m^3$ was 113-577. A regression slope calculated for directly standardized rate ratios (SRR) was 7.33×10^{-7} ($p=0.0001$) with elevated lung cancer mortality at 41-200 $\mu g/m^3$ and >200 $\mu g/m^3$. The investigators stated that data provided by the company on smoking and on exposure to residual arsenic did not appear to account for the observed excess of lung cancer mortality.

The findings of other recent epidemiological studies [12-15] are compatible with these results and provide limited additional epidemiological evidence for excess lung cancer mortality. A study of 3,025 nickel-cadmium battery workers potentially exposed to cadmium oxide dust for at least one month between 1923 and 1975 with vital status determined through January 1981 showed significantly increased numbers of deaths from respiratory cancer (89 observed vs. 70.2 expected, SMR=127, $p<0.05$) [12]. However, the possible contribution of nickel hydroxide and oxy-acetylene welding fume exposures to lung cancer mortality was not assessed.

A study of 6,995 cadmium-exposed workers from 17 facilities engaged in primary cadmium production and production of alloys, cadmium soap, and pigments demonstrated no statistically significant tumor excess, but lung cancer mortality was slightly above that expected (199 observed vs. 185.6 expected) [13,14]. The study had limited power to detect elevated lung cancer because only 210 workers (3% of the cohort) were classified as "ever highly exposed," which was defined by the researchers as having had a job title for at least one year that was judged likely to lead to cadmium in urine concentrations of over 20 µg/liter following chronic exposure [14]. In a preliminary report on workers in two cadmium-copper alloy plants, no excess lung cancer mortality was detected in production workers (10 observed vs. 13.4 expected), but a statistically significant excess of lung cancer deaths (36 observed vs. 26.08 expected, SMR=138, $p<0.05$) was observed among workers in one of the two plants who worked in proximity to the cadmium-copper process and had potential exposure to arsenic [15].

Recent Experimental Evidence

A recent toxicological study provides persuasive evidence for the carcinogenicity of cadmium chloride [16]. Rats exposed to cadmium chloride aerosols by inhalation at concentrations of 12.5, 25, and 50 $\mu g/m^3$ for 23 hours daily, 7 days per week for 18 months and observed for an additional 13 months developed primary lung carcinomas in 25 of 35 (71.4%) rats in the 50 $\mu g/m^3$ exposed group, 20 of 38 (52.6%) in the 25 $\mu g/m^3$ group, 6 of 39 (15.4%) in rats exposed at 12.5 $\mu g/m^3$, and 0 of 38 in unexposed controls. Lung cadmium concentrations at necropsy were 10.4 ± 4.2, 4.7 ± 1.5, 5.6 ± 1.0, and <0.03 µg/g wet weight in the four groups, respectively. This study was the first lifetime study of animals exposed by inhalation to a cadmium-containing compound.

Data from two recent toxicological studies contribute information of importance to the biological evaluation of the carcinogenic potential of cadmium. Unexpected (but not statistically significant) cases of lung carcinoma were observed following administration of cadmium oxide to rats by a single inhalation exposure [17] and by multiple intratracheal injections [18].

A recent study in rats chronically exposed through oral ingestion of cadmium chloride dissolved in drinking water did not demonstrate an increased incidence of malignant tumors [19]. However, because the total doses delivered and terminal tissue concentrations of cadmium were not measured, the applicability of these data to an assessment of carcinogenicity is uncertain.

RESEARCH NEEDS

Research is necessary to further assess the carcinogenicity of cadmium in animals and to ascertain the mechanisms by which cadmium causes these effects. Testing of other cadmium compounds and studying the relationship of calcium, zinc, and other metal ions to the potential carcinogenicity of cadmium are of particular importance. Recent data on pulmonary uptake of cadmium compounds [20-23] and on the effects of solubility, particle charge, and crystallinity of cadmium compounds [24-26] suggest the need to better characterize the extent of workers' biological exposure to cadmium in various work settings. In vitro studies should focus on factors that affect cell uptake and intracellular activity of cadmium.

RECOMMENDATIONS

There are several classifications for identifying a substance as a carcinogen. Such classifications have been developed by the National Toxicology Program [27], the International Agency for Research on Cancer [28], and OSHA in its "Identification, Classification, and Regulation of Potential Occupational Carcinogens" 29 CFR 1990 [29], also known as "The OSHA Cancer Policy" [30]. NIOSH considers the OSHA classification the most appropriate for use in identifying potential occupational carcinogens* [31]. Cadmium chloride has been shown to be carcinogenic in an experimental animal study; an

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*"'Potential occupational carcinogen' means any substance, or combination or mixture of substances, which causes an increased incidence of benign and/or malignant neoplasms, or a substantial decrease in the latency period between exposure and onset of neoplasms in humans or in one or more experimental mammalian species as the result of any oral, respiratory or dermal exposure, or any other exposure which results in the induction of tumors at a site other than the site of administration. This definition also includes any substance which is metabolized into one or more potential occupational carcinogens by mammals" (29 CRF 1990.103).

epidemiological study has demonstrated excess lung cancer mortality among workers exposed to cadmium oxide. Based on these data, and given that no studies have been performed to assess the potential hazards from long-term exposure to other cadmium-containing compounds, NIOSH recommends that cadmium and its compounds be considered as potential occupational carcinogens.

The excess risk of cancer in workers exposed to cadmium at specific airborne concentrations has not yet been fully characterized; nonetheless the risk of developing cancer would be reduced by decreasing exposure. NIOSH recommends that the present OSHA standard for cadmium be reexamined, based on new evidence which supports the conclusion that cadmium and its compounds are potential carcinogens and supplements other data on health effects supporting previous NIOSH recommendations [3]. As prudent public health policy, NIOSH urges employers to assess the conditions under which their workers may be exposed to cadmium and take all reasonable precautions to reduce these exposures to the fullest extent feasible.

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NIOSH

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Monohalomethanes

Methyl Chloride CH_3Cl
Methyl Bromide CH_3Br
Methyl Iodide CH_3I

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FOREWORD

Current Intelligence Bulletins are reports issued by the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control, Atlanta, Georgia, for the purpose of disseminating new scientific information about occupational hazards. A Current Intelligence Bulletin may draw attention to a hazard previously unrecognized or may report new data suggesting that a known hazard is either more or less dangerous than was previously thought.

Current Intelligence Bulletins are prepared by the staff of the Division of Standards Development and Technology Transfer, NIOSH (Robert A. Taft Laboratories, 4676 Columbia Parkway, Cincinnati, Ohio 45226) and are distributed to representatives of organized labor, industry, public health agencies, academic institutions, and public interest groups as well as to those federal agencies, such as the Department of Labor, which have responsibilities for protecting the health of workers. It is our intention that anyone with the need to know should have ready access to the information contained in these documents; we welcome suggestions concerning their content, style, and distribution.

It is recommended that methyl chloride, methyl bromide, and methyl iodide be regarded as potential occupational carcinogens. Additionally, it is recommended that methyl chloride be considered a possible teratogen. These recommendations are based upon animal studies which have demonstrated the carcinogenic potential of these compounds and in the case of methyl chloride, teratogenic effects as well. Consequently, appropriate engineering and work practice controls should be used to reduce worker exposure. The excess risk of cancer to workers or the induction of a teratogenic response in the children of workers exposed to specific airborne concentrations of these compounds has not yet been determined, but the probability of developing these adverse effects would be decreased by reducing exposure.

On the basis of this information, it is recommended that producers and users of methyl chloride, methyl bromide, and methyl iodide disseminate this information to their workers and customers and that professional and trade associations and unions inform their members of the potential hazards of working with these compounds.

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CURRENT INTELLIGENCE BULLETIN #43

MONOHALOMETHANES:

Methyl Chloride, Methyl Bromide, Methyl Iodide

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ABSTRACT

The monohalomethanes (methyl chloride, methyl bromide, and methyl iodide) are alkylating agents and thus have generated concern as to their potential for inducing mutations and cancer. All three compounds were found to be direct-acting mutagens in the Ames assay. In experimental studies in either rats or mice using various routes of administration, these three compounds have also demonstrated the ability to produce cancer. Methyl chloride produced a teratogenic effect (heart defects) in the offspring of pregnant mice exposed by inhalation at 500 and 750 ppm.

Based on these data, the National Institute for Occupational Safety and Health (NIOSH) recommends that methyl chloride, methyl bromide, and methyl iodide be considered as potential occupational carcinogens and that methyl chloride be considered a potential occupational teratogen.

BACKGROUND

Physical and Chemical Properties

The three chemicals addressed in this document are commonly called the monohalogenated derivatives of methane (monohalomethanes): chloromethane, bromomethane, and iodomethane. Fluoromethane is not included since there are no data on the extent of exposure in the workplace and little to no information on toxic effects in animals or humans. These derivatives are represented by the general formula CH_3X, where X represents chlorine, bromine, or iodine. Some of the physical and chemical properties of these compounds are summarized in Table 1. In this document, these compounds are referred to by their common names: methyl chloride, methyl bromide, and methyl iodide.

TABLE 1. CHEMICAL AND PHYSICAL PROPERTIES OF THE MONOHALOMETHANES [1-4]

Chemical Identity	Methyl Chloride	Methyl Bromide	Methyl Iodide
CAS[a] Registry No.	74-87-3	74-83-9	74-88-4
RTECS[b] Accession No.	PA6300000	PA4900000	PA9450000
Empirical Formula	CH_3Cl	CH_3Br	CH_3I
Formula Weight	50.49	94.95	141.95
Physical Form	Gas	Gas	Liquid
Boiling Point, °C	-24.2	3.5	42.5
Freezing Point, °C	-97.7	-93.7	-66.1
Vapor Pressure	5 atm at 22.0°C	2 atm at 23.3°C	0.5 atm at 25.3°C
Color	Colorless	Colorless	Colorless, turns brown when exposed to light
Odor	Faint, sweet odor which is not noticeable at dangerous concentrations	Chloroformlike odor at high concentrations	Pungent
Specific Gravity	0.973 (-10°C)	1.736 (-10°C)	2.279 (20°C)
Flammability	Flammable, forms explosive mixture with air at 8-17%	Nonflammable in air, burns in oxygen	Nonflammable

[a]Chemical Abstract Service
[b]Registry of Toxic Effects of Chemical Substances

Production, Use, and Potential for Occupational Exposure

Commercially, methyl chloride, methyl bromide, and methyl iodide have been used as methylating agents, laboratory reagents, refrigerants, aerosol propellants, pesticides, fumigants, fire-extinguishing agents, anesthetics, degreasers, blowing agents for plastic foams, and chemical intermediates.

Relatively little data concerning environmental concentrations of these monohalomethanes in the workplace have been reported. Because of their high volatility, they are frequently contained in closed systems. Health Hazard Evaluation surveys and other field studies conducted by the National Institute for Occupational Safety and Health (NIOSH) have found that workplace environmental concentrations of these monohalomethanes were generally quite low. Methyl chloride concentrations ranged from not detectable to 300 parts per million (ppm) [5-8]; methyl bromide from not detectable to 30 ppm [9-12]; and methyl iodide from not detectable to 6 ppm [12,13]. Possible exposures during the production of these monohalomethanes may develop from leaks in connecting or flexible joints, pump seals, sight glasses, and quality control sampling sites [14].

Approximately 146,000 U.S. workers are potentially exposed to these monohalomethanes (Table 2). This estimate is based on data collected during the National Occupational Hazard Survey (NOHS) conducted by NIOSH during 1972-1974 [15].

Methyl Chloride

In the United States, methyl chloride is produced primarily by the hydrochlorination of methanol [2,4,16]. Although the primary use of methyl chloride is in the manufacture of silicones, this process is a closed system operation with minimal worker exposure. The manufacture of tetramethyl lead and triptane (2,2,3-trimethyl butane), both antiknock fuel additives [2], is the next largest use of methyl chloride. Other uses of methyl chloride include the production of butyl rubber; di-, tri-, and tetra-halogenated methanes; methyl cellulose; quaternary ammonium compounds; methyl mercaptan; methionine; and fungicides and pesticides (primarily methyl arsenate herbicides) [16]. A former high volume use of methyl chloride as a refrigerant and propellant has declined significantly in recent years with the substitution of chlorofluorinated alkane derivatives (chlorinated fluorocarbons). In 1981, approximately 362 million pounds of methyl chloride were produced in the United States, and domestic consumption is projected to expand by approximately 6.5% per year through the mid-1980's [16]. Approximately 41,000 U.S. workers (Table 2) are potentially exposed to methyl chloride [15].

Methyl Bromide

Methyl bromide is produced by direct bromination of methane and by the hydrobromination of methanol [2]. In the United States, methyl bromide is

TABLE 2. NUMBER OF WORKERS POTENTIALLY EXPOSED TO THE MONOHALOMETHANES BY INDUSTRY [15]

SIC* Code	Description	Number of Workers Potentially Exposed		
		Methyl Chloride	Methyl Bromide	Methyl Iodide
07	Agriculture Services and Hunting	647	5,922	-
13	Oil and Gas Extraction	24	129	-
15	General Building Contractors	1,301	934	-
16	Heavy Construction Contractors	405	-	-
17	Special Trade Contractors	1,143	1,936	-
20	Food and Kindred Products	2,720	4,356	-
21	Tobacco Manufacturers	90	108	-
22	Textile Mill Products	8	237	-
23	Apparel and Other Textile Products	-	52	-
24	Lumber and Wood Products	112	471	-
26	Paper and Allied Products	-	1,270	-
27	Printing and Publishing	212	80	-
28	Chemicals and Allied Products	980	4,859	394
29	Petroleum and Coal Products	16	11	-
30	Rubber and Plastics Products, NEC	-	89	-
31	Leather and Leather Products	85	38	-
33	Primary Metal Industries	1,223	44	-
34	Fabricated Metal Products	238	65	-
35	Machinery, Except Electrical	1,292	357	-
36	Electrical Equipment and Supplies	451	345	-
37	Transportation Equipment	1,660	643	-
38	Instruments and Related Products	453	174	-
39	Miscellaneous Manufacturing Industries	418	34	-
41	Local and Interurban Passenger Transit	73	27	-
44	Water Transportation	93	1,047	-
45	Transportation by Air	1,115	11,496	-
48	Communication	424	-	-
49	Electric, Gas, and Sanitary Service	-	10,069	-
50	Wholesale Trade	486	4,713	-
53	Retail General Merchandise	402	1,356	-
54	Food Stores	-	1,481	-
55	Automotive Dealers & Service Stations	14,734	-	-
58	Eating and Drinking Places	-	17,958	-
65	Real Estate	-	4,665	-
73	Miscellaneous Business Services	8,960	12,600	20
78	Motion Pictures	-	597	-
79	Amusement and Recreation Services	342	4,147	-
80	Medical and Other Health Services	431	12,015	-
89	Miscellaneous Services	-	354	-
	TOTALS	40,538	104,679	414

*Standard Industrial Classification Code

used primarily as a soil and spore fumigant [17]. Methyl bromide is also used as a disinfectant, rodenticide, methylating agent, and wool degreaser and in ionization chambers [2,18,19].

Most of the exposure data available on methyl bromide come as a result of the uses of methyl bromide as an agricultural fumigant. These include use as a nematocide, fungicide, herbicide, and insecticide [17]. Methyl bromide is applied into the soil under plastic sheets or used in space fumigation under tarpaulins. It is also applied to a variety of agricultural commodities in specially designed fumigation chambers. Worker exposure may result from leaks in the plastic sheets or the tarpaulin or from failure to allow adequate time for the methyl bromide to dissipate following fumigation.

In 1979, the latest year for which any production quantities are available, between 60 and 80 million pounds of methyl bromide were domestically produced for use as a pesticide; however, approximately 50% of this amount was exported to other nations [20]. Approximately 105,000 U.S. workers (Table 2) are potentially exposed to methyl bromide [15].

Methyl Iodide

Methyl iodide is produced on a limited commercial scale by any of the following methods: 1) the reaction of methanol and iodine in the presence of phosphorous; 2) the reduction of an aqueous solution of iodine with bisulfate ion to yield hydriodic acid, which reacts with dimethyl sulfate to form methyl iodide; or 3) the reaction of hydrogen gas, elemental iodine, and aqueous methanol [2], which is similar to the production method of methyl chloride and methyl bromide. Methyl iodide is used primarily as a methylating agent [2] with approximately 400 U.S. workers (Table 2) potentially exposed [15].

EXPOSURE STANDARDS AND GUIDES

The current Occupational Safety and Health Administration (OSHA) permissible exposure limits (PEL's) (29 CFR 1910.1000) for occupational exposure to these monohalomethanes are as follows [21]:

Methyl Chloride	100 ppm, 8-hr time-weighted average (TWA) concentration
	200 ppm, acceptable ceiling concentration
	300 ppm, acceptable maximum peak for 5 minutes in any 3-hr period above the acceptable ceiling for an 8-hr shift
Methyl Bromide	20 ppm (80 mg/m^3), ceiling concentration; Skin
Methyl Iodide	5 ppm (28 mg/m^3), 8-hr TWA; Skin

The OSHA PEL's for occupational exposure to methyl chloride and methyl iodide are intended to protect against the neurotoxic effects of these compounds. For methyl bromide, the OSHA PEL is intended to protect against the development of pulmonary edema as well as neurotoxic effects. The PEL for methyl chloride is based upon ANSI Z37.18-1969 as developed by the American National Standards Institute (ANSI) [22], while the PEL's for methyl bromide and methyl iodide are based upon the 1968 Threshold Limit Values (TLV®'s) of the American Conference of Governmental Industrial Hygienists (ACGIH) [23]. At the present time, NIOSH has no recommended exposure limit for the monohalomethanes.

ACGIH in its 1984-85 edition of TLV's makes the following recommendations [24]:

Methyl Chloride	50 ppm (105 mg/m^3), 8-hr TWA; 100 ppm (205 mg/m^3), 15-minute TWA Short Term Exposure Limit (STEL)
Methyl Bromide	5 ppm (20 mg/m^3), 8-hr TWA; 15 ppm (60 mg/m^3), 15-minute STEL; Skin
Methyl Iodide	2 ppm (10 mg/m^3), 8-hr TWA; 5 ppm (30 mg/m^3), 15-minute STEL; A2; Skin

The ACGIH has included methyl iodide in its list of suspected carcinogens, designated as Appendix A2 in the TLV listing [24].

The "Skin" notation for methyl bromide and methyl iodide in both the OSHA PEL's and the ACGIH TLV's refers to the potential contribution to the overall exposure by the cutaneous route by either airborne or direct skin contact with the substance.

TOXICITY

Results of Animal Studies

Acute Effects

It has been reported that under similar testing conditions, the acute lethal concentrations capable of killing 50% of rats (LC_{50}) exposed by inhalation for 30 minutes to methyl chloride, methyl bromide, or methyl iodide were 72,000 ppm, 2,800 ppm and 1,750 ppm, respectively [25]. These data suggest that by this route of exposure methyl chloride is 26 times less toxic than methyl bromide and 41 times less toxic than methyl iodide.

Target organs have been reported to be the liver, kidneys, spleen, or brain in mice, rats, and guinea pigs exposed to methyl chloride [26], methyl bromide [27,28], or methyl iodide [29].

Mutagenic Effects

Methyl chloride, methyl bromide, and methyl iodide were mutagenic for Salmonella typhimurium bacterial strains TA1535 and TA100 [30-32]. Because strain TA100 carries the same gene base-pair mutation as strain TA1535 and because both of these strains are sensitive to direct-acting, alkylating agents, a common mode of action for the three methylating agents is implied. An independent analysis of these data indicated that the relative mutagenic potencies of methyl chloride, methyl bromide, and methyl iodide were approximately in the ratios of 1:40:10 [33]. In addition, methyl bromide was found to be mutagenic in Escherichia coli bacteria [34], and methyl iodide was reported to be a direct-acting mutagen for mouse lymphoma L5178Y/TK+/-cells [35].

Carcinogenic and Other Chronic Effects

In a 2-year methyl chloride inhalation study [26], male and female mice were exposed at concentrations of 0, 50, 225, or 1,000 ppm for six hours per day, five days per week. A statistically significant increase in both malignant and nonmalignant renal tumors occurred in only male mice exposed at the 1,000 ppm concentration. These tumors included cortical adenomas and adenocarcinomas, papillary cystadenomas and cystadenocarcinomas, plus tubular cystadenomas. In addition, 1,000 ppm of methyl chloride induced a functional limb muscle impairment and brain lesions in male and female mice, the latter being characterized by degeneration and atrophy of the granular layer of the cerebellum. Also, the male and female mice exposed at 1,000 ppm exhibited atrophy of the spleen.

Rats exposed to methyl chloride under the same experimental conditions, concentrations, and duration did not exhibit induction of cancer or the other lesions observed in the exposed mice [26].

In a 90-day study [36], methyl bromide dissolved in arachis oil was administered by gastric gavage at levels of 0, 0.4, 2, 10, or 50 milligrams of methyl bromide per kilogram of body weight (mg/kg) five days per week to groups of 10 male and 10 female Wistar rats. Squamous cell carcinomas of the forestomach developed in a total of 13 of the 20 male and female rats treated with the 50 mg/kg dose. A dose-related incidence of hyperplasia was also noted in the rats at all levels except at 0 and 0.4 mg/kg [36].

Methyl bromide is currently being studied in two laboratories [37]. The National Institute for Public Health in the Netherlands is exposing rats by inhalation five days per week for their natural lifetimes at concentrations of 0, 3, 30, or 90 ppm. Final necropsies will be completed in 1985. The U.S. National Toxicology Program plans to begin a 2-year carcinogenicity study in late 1984 with mice exposed to methyl bromide [37].

In a study designed to test the carcinogenic potential of methyl iodide in mice susceptible to the induction of lung tumors [38], doses of 0, 0.36, 0.9 or 1.8 mg/kg were administered by intraperitoneal injection (IP) three

days per week for eight weeks. Among the mice given the highest dose (1.8 mg/kg), 9 of 20 animals died. The surviving 11 mice were killed 24 weeks after the first injection. Five of these 11 mice had developed lung tumors (statistically significant at $p<0.05$). Because of the early deaths of 45% of the mice, the experiment may not have demonstrated statistically convincing evidence of the carcinogenicity of methyl iodide.

In another study of methyl iodide [39], groups of 16 and 8 rats were given weekly subcutaneous injections (SC) of 10 mg/kg and 20 mg/kg of body weight, respectively, for approximately one year. Four of the rats in the 10 mg/kg group and two of the rats in the 20 mg/kg group died prematurely of pneumonia. Of the animals that survived, 9 of 12 in the 10 mg/kg group and 6 of 6 in the 20 mg/kg group developed sarcomas at the site of injection. In addition, two sarcomas at distant sites (a paravertebral osteogenic sarcoma and a differentiated sarcoma of the uterus) were identified in the 10 mg/kg group. The authors also reported that multiple metastases were seen in the lungs and lymph nodes. In a second part of this study, 14 rats were administered a single SC injection of 50 mg/kg methyl iodide and were observed for their lifetimes. Four of the rats developed local sarcomas between 446 and 654 days after the administration of the test material; two other rats developed differentiated sarcomas at distant sites (colon and vagina).

Teratogenicity and Reproductive Effects

Methyl chloride was reported to be teratogenic to the offspring of pregnant mice exposed by inhalation at concentrations of 0, 100, 250, 500, 750, or 1,500 ppm on days 6-18 of gestation. Exposure at the 1,500 ppm concentration was terminated early due to morbidity and death of the treated dams. A statistically significant number of fetal heart malformations was observed in the offspring exposed *in utero* at the 500 or 750 ppm concentrations. These malformations consisted of reduction in size or absence of the atrioventricular valves and attendant structures (chordae tendineae and papillary muscles). Exposure concentrations at 250 and 100 ppm were not teratogenic [40,41].

Rats exposed to methyl chloride [40] and rats and rabbits exposed to methyl bromide in another study [42] showed no teratogenic effects. No teratology studies employing methyl iodide were found in the literature reviewed.

In addition to the previously described teratogenic effects, degeneration and atrophy of the seminiferous tubules were induced in male rats exposed by inhalation to methyl chloride at a concentration of 1,000 ppm [26]. These effects were absent in rats exposed at 0, 50, and 225 ppm concentrations. Mice similarly exposed to methyl chloride exhibited no adverse reproductive effects [26].

No studies on reproductive effects from exposure to methyl bromide or methyl iodide have been reported.

Human Health Effects

Most of the available information related to the toxic effects on humans exposed to methyl chloride, methyl bromide, methyl iodide is derived from accidental exposures to relatively high concentrations.

Symptoms of acute exposure to these compounds are relatively similar, consisting of headache, nausea, vomiting, drowsiness, dizziness, giddiness, diarrhea, confusion, ataxia, slurred speech, paralysis, convulsions, delirium, coma, and death [43-47]. The lungs, liver, kidney, and brain appear to be the primary target organs in cases of severe poisoning.

Liquid methyl bromide and methyl iodide have been reported to cause burning and blistering upon contact with the skin [48,49] and conjunctivitis when splashed into the eyes [19].

No human studies to evaluate the possible mutagenic, carcinogenic, or teratogenic effects from exposure to these compounds are currently available.

CONCLUSIONS

The chemicals discussed in this bulletin, methyl chloride, methyl bromide, and methyl iodide, are alkylating agents that have been shown to induce cancer in rats and mice.

The studies which indicated the potential for these compounds to induce cancer in experimental animals are not without their shortcomings. The strains of animals used, the doses and routes selected for administration of the test compounds, and the fact that there was no coordinated study designed to test these compounds as a class impose limitations on the interpretation of the results. However, in NIOSH's judgement the collective data of these studies are sufficient to indicate the potential for carcinogenicity of these substances.

Also, methyl chloride induced degeneration and atrophy of the seminiferous tubules in treated male rats. It has also demonstrated teratogenicity in mice but not rats. No teratogenic effects were found in rats and rabbits exposed to methyl bromide.

RECOMMENDATIONS

There are several classifications for identifying a substance as a carcinogen. Such classifications have been developed by the National Toxicology Program [50], the International Agency for Research on Cancer [51], and OSHA in its "Identification, Classification, and Regulation of Potential Occupational Carcinogens" 29 CFR 1990 [52], also known as "The OSHA Cancer Policy" [53]. NIOSH considers the OSHA classification the most

appropriate for use in identifying potential occupational carcinogens* [54]. All three of the monohalomethanes discussed in this document have been shown to produce malignant neoplasms in experimental studies in either rats or mice. Methyl chloride has been tested in mice and found to be a teratogen. Based on this evidence, NIOSH recommends that methyl chloride, methyl bromide, and methyl iodide be considered as potential occupational carcinogens and that methyl chloride be considered a potential occupational teratogen.

The excess risk of cancer to workers or the induction of a teratogenic response in the children of workers exposed to specific airborne concentrations of these compounds has not yet been determined, but the probability of developing these adverse effects would be decreased by reducing exposure. As prudent public health policy, employers should voluntarily assess the conditions under which workers may be exposed to these monohalomethanes and take all reasonable precautions to reduce exposures to the fullest extent feasible.

NIOSH is particularly concerned that the occupational exposure to methyl bromide may increase as a result of using this compound as a substitute fumigant for the recently restricted use of the fumigant ethylene dibromide (EDB) [55]. Chronic toxicology studies of methyl bromide are currently being conducted [37], and NIOSH recommends that the results of these studies be thoroughly evaluated before significantly expanding the use of methyl bromide.

Guidelines recommended in the Appendix for minimizing worker exposure to these monohalomethanes are general in nature and should be adapted to specific work situations as required.

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*"'Potential occupational carcinogen' means any substance, or combination or mixture of substances, which causes an increased incidence of benign and/or malignant neoplasms, or a substantial decrease in the latency period between exposure and onset of neoplasms in humans or in one or more experimental mammalian species as the result of any oral, respiratory or dermal exposure, or any other exposure which results in the induction of tumors at a site other than the site of administration. This definition also includes any substance which is metabolized into one or more potential occupational carcinogens by mammals" (29 CRF 1990.103).

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APPENDIX

GUIDELINES FOR MINIMIZING WORKER EXPOSURE TO THE MONOHALOMETHANES

It is recommended that methyl chloride, methyl bromide, and methyl iodide be regarded as potential occupational carcinogens and that methyl chloride be considered a potential occupational teratogen. This recommendation is based on the ability of these compounds to induce cancer in experimental animals and the ability of methyl chloride to induce teratogenicity in exposed mice. Consequently, appropriate engineering and work practice controls should be used to reduce worker exposure to the fullest extent feasible. The areas in which these monohalomethanes are produced or used should be restricted to only those workers who are essential to the process or operation. The guidelines and recommendations which follow are general in nature and should be adapted to specific situations as required.

EXPOSURE MONITORING

Initial and periodic worker exposure surveys should be made by qualified industrial hygiene and engineering personnel. These surveys are necessary to determine the extent of worker exposure and to ensure that controls already in place are operational and effective. NIOSH's Occupational Exposure Sampling Strategy Manual may be helpful in developing appropriate strategies to monitor worker exposure to these monohalomethanes [56]. The manual discusses how to determine the need for exposure measurements and to select sampling times.

Worker exposures should be estimated by 8-hour TWA and short-term (15-minute) exposures calculated from personal or breathing zone samples. Short-term samples should be taken during periods of maximum expected exposure by using all available knowledge of the work areas, procedures, and processes. Area and source measurements may be useful in identifying problem areas, processes, and operations.

Detailed descriptions of sampling and analysis techniques for methyl chloride, methyl bromide, and methyl iodide may be found in the NIOSH Manual of Analytical Methods, Second Edition [57].

CONTROLLING WORKER EXPOSURE

Proper maintenance procedures, good housekeeping in the work area, and worker education are all vital aspects of a good control program. Workers should be informed of the materials to which they are exposed, the nature of their hazard, the methods for their control, and appropriate personal hygiene procedures. There are four basic methods of limiting worker

exposure to these monohalomethanes, none of which is a simple industrial hygiene or management decision. Careful planning and thought should be used prior to implementation.

Product Substitution

When feasible, substitution of an alternative material with a lower potential health risk is an important method for reducing exposure. Extreme care must be used when selecting substitutes. Possible health effects from potential exposure to alternatives for these monohalomethanes should be fully evaluated prior to selection.

Contaminant Controls

Engineering controls should be used to eliminate the potential for monohalomethane exposure in the workplace and to prevent fires and explosions. Achieving and maintaining reduced concentrations of airborne monohalomethanes in the workplace depend upon the implementation of engineering control measures, such as properly constructed and maintained closed system operations and ventilation, with appropriate safety designs.

Closed system operations provide the most effective means for minimizing worker exposures to these monohalomethanes. Closed system equipment should be used for manufacturing, storing, and processing these monohalomethanes because of their volatility. Where closed systems cannot be employed or do not effectively control monohalomethane emissions, local exhaust ventilation should be provided to direct vapors and gases away from workers and to prevent the recirculation of contaminated exhaust air. Exhaust ventilation systems for quality control laboratories or laboratories where samples are prepared for analyses should be designed to adequately capture and contain monohalomethane vapors or gases. Special consideration should be given to the releasing of these compounds from pressurized sampling containers. Guidance for designing local exhaust ventilation systems can be found in Recommended Industrial Ventilation Guidelines [58], Industrial Ventilation--A Manual of Recommended Practice [59], and Fundamentals Governing the Design and Operation of Local Exhaust Systems, ANSI Z92-1971 [60].

Ventilation equipment should be checked at least every three months to ensure adequate performance. System effectiveness should also be checked when there are any changes in production, process, or control that might result in significant increases in airborne exposure to these monohalomethanes.

Worker Isolation

If feasible, workers may be isolated from direct contact with the work environment by the use of automated equipment operated from a closed control booth or room. The control room should be maintained at a greater air

pressure than that surrounding the process equipment so that air flows out of, rather than into, the room. This type of control will not protect workers who must perform process checks, adjustments, maintenance, assembly-line tasks, and related operations. Therefore, special precautions are often necessary to prevent or limit worker exposure in these situations and frequently involve the use of personal protective equipment.

Personal Protective Equipment

In a liquid state, all of the monohalomethanes discussed in this document may be injurious to both the skin and eyes upon direct contact. Liquefied methyl chloride and bromide are injurious to the skin because of rapid evaporation and the subsequent cooling effect which produces localized "burns" or "frostbite." Liquid methyl bromide has reportedly produced skin lesions and itching after skin contact and has resulted in conjunctivitis when accidentally splashed into the eyes [61]. Other similar cases have been attributed to penetration of clothing by liquid methyl bromide [19,48,62].

In one report on methyl iodide [29], it was noted that a soaked cloth pad applied to the forearm produced severe persistent lesions. These lesions were described as resembling those caused by mustard gas. These reports emphasize the importance of avoiding direct skin or eye contact with any liquid form of these monohalomethanes [29,63]. This may be accomplished through the proper use of monohalomethane-resistant gloves, aprons, boots, or entire worksuits, depending on the nature and extent of the hazard. Faceshields or chemical safety goggles should be used wherever the potential for splashing exists.

The use of respiratory protection requires that a respiratory protection program be instituted which at a minimum meets the requirements of 29 CFR 1910.134 [64]. In addition to selection of respirators approved by the Mine Safety and Health Administration (MSHA) and NIOSH, a complete respiratory protection program should include at least regular training of personnel, maintenance, inspection, quantitative fit testing, and cleaning of equipment. The program should be evaluated regularly.

It must be stressed that the use of respiratory protection is the least preferred method of controlling worker exposures and should not be used as the only means of preventing or minimizing exposures during routine operations. However, NIOSH recognizes that respirators may be required to provide protection under certain situations (e.g., implementation of engineering controls, certain short-duration situations, emergencies, etc.). NIOSH maintains that only the most reliable respirators should be used to protect workers from exposure to workplace carcinogens. Such

respirators consist of supplied-air, full facepiece, positive pressure respirators where odor warning and filter sorbent properties are not considered. Specifically, the following respirators are recommended for those situations.

- A self-contained breathing apparatus with a full facepiece operated in pressure-demand or other positive pressure mode or

- A combination respirator that includes a type C supplied-air respirator with a full facepiece operated in pressure-demand or other positive pressure or continuous flow mode and an auxiliary self-contained breathing apparatus operated in pressure-demand or other positive pressure mode.

MEDICAL SURVEILLANCE

A medical surveillance program should be available that can evaluate both the acute and chronic effects of exposure to these monohalomethanes. The physician responsible should be provided with an estimate of the worker's potential exposure to these monohalomethanes, including any available workplace sampling results and a description of any protective devices or equipment the worker may be required to use. A thorough medical and work history should be taken initially and updated periodically. As part of this medical surveillance program, workers who are or may be exposed to these monohalomethanes should have preplacement and periodic evaluations focusing on a history of previous exposure to these and other toxic agents. The examining physician should direct particular attention to the hepatic, renal, respiratory, and central nervous systems, as these are most likely to be affected by these monohalomethanes.

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Dinitrotoluenes (DNT)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

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FOREWORD

Current Intelligence Bulletins (CIB's) are reports issued by the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control, Atlanta, Georgia, for the purpose of disseminating new scientific information about occupational hazards. A CIB may draw attention to a hazard previously unrecognized or may report new data suggesting that a known hazard is either more or less dangerous than was previously thought.

CIB's are prepared by the staff of the Division of Standards Development and Technology Transfer, NIOSH (Robert A. Taft Laboratories, 4676 Columbia Parkway, Cincinnati, Ohio 45226) and are distributed to representatives of organized labor, industry, public health agencies, academia, and public interest groups as well as to those federal agencies, such as the Department of Labor, which have responsibilities for protecting the health of workers. It is our intention that anyone with the need to know should have ready access to the information contained in these documents; we welcome suggestions concerning their content, style, and distribution.

This CIB describes the results of research indicating the potential for various technical grade mixtures of dinitrotoluene isomers (TDNT) and the 2,6- isomer of dinitrotoluene (2,6-DNT) to induce cancer and adverse reproductive effects in animals exposed to these substances. Although there is limited evidence indicating that 2,4-dinitrotoluene (2,4-DNT) poses a risk to human health, the existing animal and *in vitro* data are suggestive of such a potential. NIOSH estimates that 1,300 workers are potentially exposed to the isomers of dinitrotoluene (DNT) during the manufacture of TDNT; in the production of munitions; and in the synthesis of toluenediamine (TDA), an intermediate in the production of polyurethane.

NIOSH recommends that TDNT and the 2,6- isomer of DNT be regarded as potential human carcinogens in the workplace and possible inducers of adverse reproductive effects. The excess risk of cancer and of adverse reproductive effects in workers exposed to specific concentrations of TDNT or 2,6-DNT and the potential of the other DNT isomers to induce these adverse health effects have not yet been precisely determined, but the probability of developing such effects would be decreased by reducing exposure.

It is also recommended that producers and users of TDNT or the isomers of DNT disseminate this information to their workers and customers, that professional and trade associations and unions inform their members of the potential hazards of working with DNT, and that appropriate engineering controls and work practices be used to reduce worker exposure to the fullest feasible extent.

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CURRENT INTELLIGENCE BULLETIN #44

DINITROTOLUENE

JULY 1985

ABSTRACT

Rats which over a 1-year period ingested diets containing a technical grade mixture of dinitrotoluenes (TDNT), primarily composed of the 2,4- and the 2,6- isomers, or which were fed only 2,6-dinitrotoluene (2,6-DNT) developed cancers of the liver. The liver cancers consisted of hepatocellular carcinomas and in some cases cholangiocarcinomas. Two-year TDNT ingestion studies in rats produced subcutaneous fibromas and fibrosarcomas, mammary fibroadenomas, and the liver cancers. Male mice fed TDNT for 2 years developed papillary and cortical carcinomas of the kidney and nonmalignant kidney tumors diagnosed as papillary and cortical adenomas. Rats fed 2,4-dinitrotoluene (2,4-DNT) throughout a 2-year carcinogenicity study developed statistically significant incidences of subcutaneous fibromas and mammary fibroadenomas and low incidences of hepatocellular carcinomas and subcutaneous fibrosarcomas which were not statistically significant. Feeding or oral administration of TDNT or 2,6-DNT for up to 2 years induced decreased spermatogenesis, aspermatogenesis, or testicular atrophy in dogs, rats, or mice. Nonfunctioning ovaries were found in mice fed TDNT for 2 years.

Based on these data, the National Institute for Occupational Safety and Health (NIOSH) recommends that TDNT and 2,6-DNT be regarded as potential human carcinogens in the workplace and possible inducers of adverse reproductive effects. Although there is limited evidence indicating that 2,4-DNT poses a risk to human health, the existing animal and *in vitro* data are suggestive of such a potential. The potential of the other DNT isomers to induce adverse health effects has not been determined, but the probability of developing such effects would be decreased by reducing exposure. Therefore, NIOSH recommends that occupational exposures to TDNT and the isomers of DNT be controlled to the fullest feasible extent.

BACKGROUND

Physical and Chemical Properties

The six isomers of dinitrotoluene (DNT)*, 2,3-; 2,4-; 2,5-; 2,6-; 3,4-; and 3,5-DNT, are stable, yellow, crystalline solids at room temperature [1]. When heated, technical grade dinitrotoluene (TDNT)* forms a combustible, oily liquid [2]. The TDNT used in the synthetic organic chemicals industry is composed of approximately 76% 2,4-dinitrotoluene (2,4-DNT)*, 19% 2,6-dinitrotoluene (2,6-DNT)*, and 5% of the other four isomers. Chemical and physical properties of 2,4- and 2,6-DNT are listed in Table 1.

Production, Use, and Potential for Occupational Exposure

DNT is produced by a two-step nitration of toluene in a closed system process [3]. DNT is used in the manufacture of dyes, munitions, and explosives, but its major use today (99%) is in the synthesis of toluenediamine (TDA)*, an organic intermediate in the production of polyurethane [4,5]. In 1982, approximately 720 million pounds of DNT were produced in the United States [6].

It is estimated that up to 1,300 workers are exposed to various forms of DNT, of which an estimated 750-800 workers are potentially exposed to TDNT in its manufacture and use in the production of TDA [3,5] and an additional 500 workers are potentially exposed to 2,4-DNT in the production of munitions and explosives [7]. Based on a projected increase in demand for TDA, annual TDNT production through 1989 is expected to increase approximately 1-4% [5] with a potential increase in the number of workers exposed to TDNT. Anticipated increases in the production of munitions and explosives may contribute to an increase in employment and a potential for an increase in occupational exposure to 2,4-DNT.

EXPOSURE LIMITS

The Occupational Safety and Health Administration (OSHA) promulgated its permissible exposure limit (PEL) of 1.5 milligrams of DNT per cubic meter of air (mg/m^3) for occupational exposure to DNT determined as an 8-hour time-weighted average (TWA) concentration [8] based on the 1968 Threshold Limit Value (TLV®) of the American Conference of Governmental Industrial Hygienists (ACGIH) [9]. The TLV, which has remained unchanged at 1.5 mg/m^3 through 1984 [10], was based on the prevention of hematologic effects in exposed humans and by analogy with the TLV's adopted

*Abbreviations:
- DNT -- dinitrotoluene
- TDNT -- technical grade dinitrotoluene
- 2,4-DNT -- 2,4-dinitrotoluene
- 2,6-DNT -- 2,6-dinitrotoluene
- TDA -- toluenediamine

TABLE 1. CHEMICAL AND PHYSICAL PROPERTIES OF 2,4- and 2,6-DINITROTOLUENE ISOMERS [1,11]

Chemical Identity:	2,4-Dinitrotoluene	2,6-Dinitrotoluene
CAS[a] Registry No.	121-14-2	606-20-2
RTECS[b] Accession No.	XT1575000	XT1925000
Synonyms	2,4-Dinitrotoluol 1-Methyl-2,4-dinitrobenzene	2,6-Dinitrotoluol 1-Methyl-2,6-dinitrobenzene
Molecular Weight	182.14	182.14
Empirical Formula	$C_7H_6N_2O_4$	$C_7H_6N_2O_4$
Boiling Point (at 760 mmHg)	Decomposes at 300°C (572°F)	Decomposes at 260°C (500°F)
Melting Point	71°C (160°F)	66°C (151°F)
Specific Gravity	1.321 (71°C, 160°F)	1.283 (111°C, 232°F)
Solubility		
water	Insoluble	Not available
alcohol	Soluble	Soluble
ether	Soluble	Not available
acetone	Very soluble	Not available
benzene	Soluble	Not available

[a]Chemical Abstract Service
[b]Registry of Toxic Effects of Chemical Substances

for nitro- and dinitro-benzenes [12], rather than on the prevention of cancer. Both the OSHA PEL and the ACGIH TLV include a "Skin" notation which refers to the potential contribution to the overall exposure by the cutaneous route by either airborne or direct contact with DNT. At the present time, the National Institute for Occupational Safety and Health (NIOSH) has no recommended exposure limit (REL) for DNT.

TOXICITY

Results of Animal Studies

Acute Effects

Oral administration of 2,4-DNT (98% purity) or 2,6-DNT (purity >99%) has shown the lethal dose in milligrams per kilogram of body weight (mg/kg) for 50 percent (LD_{50}) of the rats and mice tested to be as follows:

ORAL LD50 VALUES (mg/kg body weight)

	RAT		MOUSE	
	Male	Female	Male	Female
2,4-DNT	568	650	1954	1340
2,6-DNT	535	795	621	807

Signs of DNT toxicity included muscular incoordination, cyanosis, central nervous system depression, and respiratory depression followed by death. Both 2,4- and 2,6-DNT were found to be nonirritating to the eyes and mildly irritating to the skin of rabbits [13].

Metabolism

TDNT, 2,4-, and 2,6-DNT are believed to be metabolized by a three stage process. Following absorption from the site of administration, TDNT, 2,4-, or 2,6-DNT undergoes initial metabolism in the rat liver to dinitrobenzyl alcohol glucuronide (DNBAG) [14,15], which is excreted in the bile and subsequently transferred to the intestine where it is further metabolically altered by intestinal bacteria to aminonitrobenzyl alcohol [16,17]. These bacteria are present in the gastrointestinal flora of rodents and humans [18]. Aminonitrobenzyl alcohol is thought to be reabsorbed and returned to the liver where it is further metabolized to an unidentified but mutagenically active metabolite(s) or its precursor(s) which is capable of covalent binding and genotoxicity [17]. The binding of the genotoxic metabolite(s) to liver DNA, RNA, and protein has been shown to be two to five times greater following administration of 2,6-DNT than with 2,4-DNT. This greater binding capacity indicates a greater genotoxic potential for the 2,6- isomer when compared to the 2,4- isomer [19].

Mutagenic Effects

The six isomers of DNT have been shown to be weakly mutagenic in bacterial assays using several strains of Salmonella typhimurium including TA98 and TA100, nitro-reductase active bacteria [20,21,22]. The DNT isomers, when tested in strain TA100NR3 which lacked nitro-reductase activity, demonstrated no mutagenic response [21].

In vitro assays were performed to test the ability of isolated mammalian cells in culture to produce a mutagenic metabolite of DNT. In Chinese hamster ovary cell assays, TDNT and the six individual DNT isomers showed no mutagenic activity either with or without metabolic activation [16,23,24]. In an assay using metabolically competent rat liver cells, there was no observed increase in DNA repair of liver cell damage when TDNT or the six individual DNT isomers were used [25]. This indicates that the unidentified toxic DNT metabolite(s) or precursor(s) is probably not produced in the liver alone and that subsequent metabolism in the gastrointestinal tract and then the liver appears necessary for the production of the ultimate active mutagenic agent(s) [16,17].

A liver cell DNA repair assay which measures genotoxicity expressed as DNA repair was conducted to establish the role of nitro-reductase active gastrointestinal bacteria in DNT-induced genotoxicity. Rats with normal gastrointestinal bacteria and germfree rats which lacked such bacteria were administered a single 100 mg/kg dose of TDNT by gavage. The rats with normal gastrointestinal bacteria showed an increase in DNA repair of genotoxic liver cell damage, while germfree rats showed no increase [26].

These mutagenicity test results indicate that the mutagenic potential of TDNT and the DNT isomers depends on metabolism in the intestinal tract presumably by nitro-reductase active bacteria and subsequent metabolism in the liver for the formation of the active mutagenic metabolite(s) or its precursor(s).

In another study, TDNT, 2,4-DNT, or 2,6-DNT was administered by gavage to rats in a liver cell DNA repair assay to measure genotoxicity expressed as DNA repair [27]. Results of this study indicated that TDNT and 2,6-DNT were potent inducers of DNA repair; whereas 2,4-DNT produced only a weak response. This research indicates that most of the genotoxic activity of TDNT is probably attributable to 2,6-DNT.

Carcinogenic Effects

Studies of the cancer initiation or promotion potential of DNT, expressed as increased numbers of liver cell alterations, have been reported. These alterations may be precursors of hepatocellular neoplastic nodules [28]. TDNT and the 2,6-DNT isomer demonstrated a cancer initiating activity in rats; whereas the other five DNT isomers had no detectable initiating activity [29]. In a cancer promotion study using TDNT, 2,4-DNT, or 2,6-DNT, all three compounds demonstrated a cancer promoting activity by inducing liver cell alterations [28]. No promotion studies have been reported for the other DNT isomers.

Chronic 2-year carcinogenicity feeding studies with TDNT induced liver (hepatocellular) carcinomas, bile duct (cholangio-) carcinomas, or subcutaneous fibrosarcomas in rats and renal carcinomas in mice [30,31]. Rats fed 2,6-DNT (99.9% purity) for 1 year developed hepatocellular carcinomas [32]. Feeding 2,4-DNT (approximate purity 99% [33]) to rats for 2 years induced statistically significant incidences of subcutaneous fibromas and mammary fibroadenomas and low incidences of hepatocellular carcinomas and subcutaneous fibrosarcomas which were not statistically significant [34].

In a 2-year study [30] with male and female rats, three diets containing TDNT composed of 76% 2,4-DNT and 19% 2,6-DNT were ingested at daily dosages of approximately 35, 14, or 3.5 milligrams per kilogram of body weight per day (mg/kg/day). Hepatocellular carcinomas were found in 10 of 10 male and 4 of 10 female animals in the 35 mg/kg/day dosage group that were killed at week 52 of the study. No hepatocellular carcinomas were observed in control animals. Because of the high incidence of hepatocellular carcinomas, the remaining rats in the 35 mg/kg/day group were killed at week 55. Of the 40 rats examined at this time, 20 of 20 males and 11 of 20 females had hepatocellular carcinomas. Cholangiocarcinomas also were found in 5 of these high dose male rats killed at weeks 52 and 55 but not in the females. At the end of the 2-year study, autopsied male and female rats fed 14 mg/kg/day of TDNT had an increased incidence over controls of hepatocellular carcinomas, cholangiocarcinomas, mammary fibroadenomas, and subcutaneous fibromas and fibrosarcomas. Rats fed 3.5 mg/kg/day of TDNT had an increased incidence of hepatocellular carcinomas and subcutaneous fibromas in males when compared to controls.

In subsequent 1-year ingestion studies [32] intended to confirm the results of the 55 week study cited above [30], groups of male rats were fed TDNT composed of 76% 2,4-DNT and 19% 2,6-DNT at a dosage of 35 mg/kg/day or only the 2,6-DNT (99.9% purity) isomer at dosages of 14 or 7 mg/kg/day. Regardless of dosage, all groups of animals fed TDNT or 2,6-DNT developed hepatocellular carcinomas. Rats fed a diet containing only the 2,4-DNT (99.9% purity) for 1 year at a dosage of 35 mg/kg/day did not develop hepatocellular carcinomas [32].

In another 2-year rat feeding study [31], TDNT containing 98% 2,4-DNT and 1.7% 2,6-DNT induced increases over controls in the incidence of hepatocellular carcinomas in male rats fed 34.5 mg/kg/day and female rats fed 45.3 mg/kg/day of the TDNT. At the same dosages, treatment-related increases in the incidence of subcutaneous fibromas in the male rats and mammary fibroadenomas in the females, as compared with controls, also occurred. In addition, an increased incidence of subcutaneous fibrosarcomas was found in the male rats when compared to controls, but the importance of this response was not discussed. The authors concluded that the tumors noted in their study were induced by 2,4-DNT; however, the possible role played by the 2,6- isomer that was present in the TDNT in producing these tumors was not addressed.

In another study, male mice fed TDNT of the same composition (98% 2,4-DNT, 1.7% 2,6-DNT) at dosages of 96.9 or 13.3 mg/kg/day for 24 months developed papillary and cortical carcinomas of the kidney and nonmalignant kidney tumors diagnosed as papillary and cortical adenomas [31]. The possible role of the 2,6- isomer in the observed tumorigenicity was not discussed.

A 2-year carcinogenicity study with rats that ingested a diet containing 2,4-DNT (approximate purity 99%) for 18 months followed by a 6-month observation period on untreated diet has been reported [34]. Dietary intake of approximately 14 mg/kg/day of the 2,4-DNT induced a statistically significant incidence of subcutaneous fibromas ($p=0.003$) in males and mammary fibroadenomas ($p=0.016$) in the females, when compared to controls. Ingestion of approximately 5.7 mg/kg/day of the 2,4-DNT induced a statistically significant incidence of only subcutaneous fibromas ($p=0.008$) in male rats. A low incidence of hepatocellular carcinomas and subcutaneous fibrosarcomas, although not statistically significant, was also observed at both dosages, but only in the male rats. The importance of these reported cancers was not discussed in the report; however, these tumor incidences exceeded not only those in the study control group but also those of the National Toxicology Program's historical control data for such tumors identified in 13 other studies initiated in the same reporting laboratory from 1977 through 1979 [35]. In addition, the tumor types present and the target tissues affected in this study [34] were the same as those reported for TDNT [30,31] and the 2,6-DNT isomer [32]. These data indicate that 2,4-DNT may also have the capacity for inducing a tumorigenic response. However, the possible presence of other DNT isomers, particularly the 2,6-isomer, in the compound administered in this study and their potential for playing a role in the observed tumorigenicity was not discussed and cannot be discounted.

Unlike rats which did show the tumorigenic response, mice fed 2,4-DNT (approximate purity 99%) at dosages of approximately 14 or 5.7 mg/kg/day for 18 months followed by a 3-month observation period on untreated diet showed no treatment-related increases in tumors [34].

All of the cited animal carcinogenicity studies have used the oral route of administration for TDNT, 2,4-DNT, or 2,6-DNT. Although the primary routes of worker exposure are through inhalation or dermal contact, studies using oral administration are relevant since DNT absorbed from any site of administration is ultimately transferred to the liver for the initial stage of metabolism. In addition, TDNT and 2,6-DNT have induced malignant tumors of the liver, bile duct, kidneys, or subcutaneous tissue, all of which were distant from the site of administration. No carcinogenicity studies have been reported for the 2,3-; 2,5-; 3,4-; or 3,5-DNT isomers.

Reproductive Effects

In short-term or chronic studies, feeding or oral administration of TDNT or 2,6-DNT induced testicular atrophy, decreased spermatogenesis, or aspermatogenesis in treated rats, mice, and dogs when compared to their respective controls [16,23,31]. Nonfunctioning ovaries were found in mice chronically fed TDNT [31].

In studies with 2,6-DNT (purity >99%), ingestion of 144.7 mg/kg/day by groups of rats for 4 or 13 weeks resulted in decreased spermatogenesis or aspermatogenesis and testicular atrophy in all treated animals. Mice fed 2,6-DNT at 288.8 mg/kg/day for 4 weeks showed aspermatogenesis and testicular atrophy. Oral administration of 2,6-DNT to dogs for 8 weeks at 100 mg/kg/day resulted in decreased spermatogenesis and testicular atrophy [23].

In a series of studies [16,31], rats, mice, and dogs were fed or orally administered TDNT (98% 2,4-DNT, 1.7% 2,6-DNT) for periods as long as 2 years. Groups of rats fed TDNT at 265.6 or 92.8 mg/kg/day for 13 weeks developed decreased spermatogenesis or aspermatogenesis and testicular atrophy in all treated animals [16]. Ingestion of TDNT by rats for 2 years at a dosage of 34.5 mg/kg/day caused decreased spermatogenesis and testicular atrophy in treated animals. Mice fed TDNT for 2 years at dosages of 885 mg/kg/day or 96.9 mg/kg/day developed decreased spermatogenesis and testicular atrophy. Nonfunctioning ovaries were found in mice fed TDNT at 911 mg/kg/day for 2 years [31]. Oral administration of TDNT at 25 mg/kg/day to dogs for 4 or 13 weeks caused decreased spermatogenesis [16].

A three-generation reproductive study in rats fed TDNT (98% 2,4-DNT, 1.7% 2,6-DNT) in the diet at dosages as high as 45 mg/kg/day produced no treatment-related effects in any of the offspring [31]. No embryotoxic or teratogenic effects were observed in offspring of pregnant rats dosed by gavage with up to 100 mg/kg/day of TDNT (76% 2,4-DNT, 19% 2,6-DNT) on days 7 through 20 of gestation [36].

Human Health Effects

In humans, the acute toxic effects of exposure to DNT are caused by the chemical's ability to produce methemoglobin, which decreases the oxygen carrying capacity of the blood [37]. The clinical manifestation of methemoglobinemia is cyanosis, which may be accompanied by headache, irritability, dizziness, weakness, nausea, vomiting, dyspnea, drowsiness, unconsciousness, and possibly death. Repeated or prolonged exposure may cause anemia [38].

Studies of reproductive effects resulting from human exposure to TDNT are equivocal. A NIOSH Health Hazard Evaluation (HHE) [39] conducted in a chemical plant which used TDNT in the production of TDA included the determination of workers' exposure to TDNT from analysis of 7 personal and 3 area samples. Concentrations of TDNT ranged from not detected to 0.42 mg/m^3 (one area sample). Concentrations of TDA determined from 14 samples ranged from not detected to 0.39 mg/m^3. Medical evaluation of nine workers potentially exposed to TDNT and TDA in this plant found decreased sperm counts and a reduction in the number of large morphologic sperm forms. An excess of spontaneous abortions, although not statistically significant, was also reported for the wives of the exposed workers. Another HHE of 20 male TDNT-exposed workers [40] indicated no statistically significant differences in the rates of fertility or spontaneous abortions between the wives of exposed and unexposed workers. A subsequent HHE [41]

of male TDNT-exposed workers found no statistically significant differences between exposed and unexposed workers in sperm counts, sperm morphology, fertility, and the rates of spontaneous abortions in their wives. However, the evaluation of male TDA-exposed workers in the same plant showed a statistically significant ($p<0.05$) increase in the number of spontaneous abortions in their wives. Seven area samples analyzed for DNT indicated concentrations in the work areas that ranged from 0.026 to 0.89 mg/m^3. TDA concentrations in area samples from this plant ranged from not detected to 0.687 mg/m^3.

An epidemiologic study to assess reproductive effects in 84 male workers exposed to TDNT and TDA indicated no significant differences between the exposed and 119 unexposed workers in any of the reproductive parameters examined. This assessment included fertility, sperm counts, and sperm morphology for the workers and spontaneous abortions in their wives [42]. In another study to evaluate the fertility of 579 workers employed at three chemical plants producing TDNT and TDA, no statistically significant differences between exposed and unexposed workers were noted [43].

Epidemiologic studies for carcinogenicity in DNT-exposed workers have not been reported.

CONCLUSIONS

The research data presented in this bulletin have focused on the mutagenic, carcinogenic, and adverse reproductive effects produced in animals exposed to TDNT or the DNT isomers.

TDNT and the six isomers of DNT have been shown to be mutagens using *in vitro* assay methods. When these compounds were tested as tumor initiators, only TDNT and 2,6-DNT were active. However, in tumor promotion studies using TDNT, 2,6-DNT, or 2,4-DNT, all three compounds were promotors. These data indicate that 2,4-DNT acts as a promotor only, while TDNT and 2,6-DNT can act as both initiators and promotors.

Animal studies indicate a potential for carcinogenicity from exposure to TDNT or 2,6-DNT. The liver, bile duct, mammary glands, kidneys, and subcutaneous tissue are the primary sites identified with carcinogenic or tumorigenic responses. Studies on the metabolism of DNT indicate that the carcinogenic potential appears to be dependent upon a three-stage metabolic activation of the compound. Although the primary routes of worker exposure are through inhalation and dermal contact rather than the oral route used in animal studies, DNT absorbed from any site of administration is transferred to the liver for the initial stage of metabolism. The DNT metabolite produced in this initial stage of metabolism is thought to undergo gastrointestinal bacterial nitro-reduction with subsequent further activation in the liver to a genotoxic metabolite(s).

A 2,4-DNT carcinogenicity experiment has demonstrated that this isomer may have a tumorigenic capacity in animals. In addition, the types of tumors produced and the target tissues affected in this experiment are the same as those identified in the TDNT or 2,6-DNT studies. Data adequate to permit evaluation of the carcinogenic potential from exposure to the 2,3-; 2,5-; 3,4-; and 3,5-DNT isomers are not available.

Epidemiologic studies of carcinogenicity in humans exposed to TDNT or the DNT isomers have not been reported.

Data from animal studies using TDNT or 2,6-DNT which show reduced spermatogenesis, aspermatogenesis, or testicular atrophy in exposed dogs, rats, and mice and nonfunctioning ovaries in TDNT-exposed mice indicate a potential for adverse reproductive effects from exposure to these compounds. No animal reproductive data have been published for the other DNT isomers. Results from studies of reproductive effects from human exposure to TDNT are equivocal.

The studies which indicate the potential for these compounds to induce cancer and adverse reproductive effects in experimental animals are not without their shortcomings. The strains of animals used, the route and doses selected for administration of the test compounds, and the short duration of several studies impose limitations on the interpretation of the results. However, NIOSH believes that the collective toxicologic data on metabolism, mutagenicity, carcinogenicity, and reproductive effects provide sufficient evidence to warrant concern for adverse health effects from occupational exposure to TDNT or 2,6-DNT. Although there is limited evidence indicating that 2,4-DNT poses a risk to human health, the existing animal and in vitro data are suggestive of such a potential.

RECOMMENDATIONS

There are several classifications for identifying a substance as a carcinogen. Such classifications have been developed by the National Toxicology Program (NTP) [44], the International Agency for Research on Cancer (IARC) [45], and OSHA in its "Identification, Classification, and Regulation of Potential Occupational Carcinogens" 29 CFR 1990 [46], also known as "The OSHA Cancer Policy" [47]. NIOSH considers the OSHA classification the most appropriate for use in identifying potential occupational carcinogens* [48]. Since exposure to TDNT or 2,6-DNT has been

*"'Potential occupational carcinogen' means any substance, or combination or mixture of substances, which causes an increased incidence of benign and/or malignant neoplasms, or a substantial decrease in the latency period between exposure and onset of neoplasms in humans or in one or more experimental mammalian species as the result of any oral, respiratory or dermal exposure, or any other exposure which results in the induction of tumors at a site other than the site of administration. This definition also includes any substance which is metabolized into one or more potential occupational carcinogens by mammals" (29 CFR 1990.103).

shown to produce malignant tumors in rats and mice, they meet the OSHA criteria. Therefore, NIOSH recommends that the technical grade mixtures of DNT (TDNT) and the 2,6- isomer of DNT be considered potential human carcinogens in the workplace. In addition, a reproductive hazard may exist for workers exposed to TDNT or 2,6-DNT. Testicular atrophy, decreased spermatogenesis, or aspermatogenesis seen in three species of experimental animals exposed to TDNT or 2,6-DNT and nonfunctioning ovaries in mice exposed to TDNT form the basis for this concern.

The excess risk of cancer and of adverse reproductive effects in workers exposed to specific airborne concentrations of TDNT or 2,6-DNT and the potential of the other DNT isomers to induce these adverse health effects have not yet been precisely determined. However, the probability of developing such effects would be decreased by reducing exposure. As prudent public health policy, employers should voluntarily assess the conditions under which workers may be exposed to TDNT or the isomers of DNT and take all reasonable precautions to reduce exposure to the fullest feasible extent.

Research is needed to definitively clarify the sequence of events and the role of gastrointestinal bacteria in the reported metabolic pathway for DNT and the associated mutagenic and carcinogenic effects. In addition, animal and epidemiologic research is necessary to further assess the carcinogenic, mutagenic, and adverse reproductive effects observed in animals exposed to TDNT or a specific DNT isomer and the potential for similar effects in workers exposed to TDNT or a DNT isomer. Such studies should use pure isomers of DNT as well as a technical grade mixture.

Guidelines recommended in the Appendix for minimizing worker exposure to DNT are general in nature and should be adapted to specific work situations as required.

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APPENDIX

GUIDELINES FOR MINIMIZING WORKER EXPOSURE TO DINITROTOLUENE

It is recommended that the technical grade mixtures of dinitrotoluene (TDNT) and the 2,6- isomer of dinitrotoluene (2,6-DNT) be regarded as potential human carcinogens in the workplace and possible inducers of adverse reproductive effects. These recommendations are based on animal studies which demonstrated carcinogenicity and adverse reproductive effects. Although there is limited evidence indicating that the 2,4- isomer of dinitrotoluene (2,4-DNT) poses a risk to human health, the existing animal and in vitro data are suggestive of such a potential. Consequently, appropriate engineering and work-practice controls should be used to reduce worker exposure to TDNT and all the isomers of dinitrotoluene (DNT) to the fullest feasible extent. The area in which TDNT or the isomers of DNT are used should be restricted to only those workers essential to the process or operation. The guidelines below are general in nature and should be adapted to specific work situations as required.

EXPOSURE MONITORING

Initial and periodic worker exposure surveys should be made by qualified industrial hygiene personnel. These surveys are necessary to determine the extent of worker exposure and to ensure that controls already in place are operational and effective. The NIOSH Occupational Exposure Sampling Strategy Manual may be helpful in developing efficient programs to monitor worker exposure to DNT [49]. The manual discusses how to determine the need for exposure measurements and how to select sampling times.

Worker exposures should be estimated by 8-hour or other full shift TWA and short-term (15-minute) exposures calculated from personal or breathing zone samples. Short-term samples should be taken during periods of maximum expected exposure by using all available knowledge of the work areas, procedures, and processes. Area and personal measurements may be useful in identifying sources of exposure at processes and operations.

A detailed analytical method for DNT is in the NIOSH Manual of Analytical Methods, Second Edition [50].

CONTROLLING WORKER EXPOSURE

Proper maintenance procedures and worker education are all vital aspects of a good control program. Workers should be informed of the materials to which they are exposed, the nature of their hazard, the methods for their control, and appropriate personal hygiene procedures. There are three basic methods of limiting worker exposure to DNT. Careful planning and thought should precede implementation.

Contaminant Controls

Engineering controls should be used to eliminate the potential for DNT exposure in the workplace and to prevent fires and explosions. Achieving and maintaining reduced concentrations of airborne DNT in the workplace depend upon the implementation of engineering control measures, such as properly constructed and maintained closed system operations and ventilation, with appropriate safety designs.

Closed system operations provide the most effective means for minimizing worker exposures to DNT. Closed system equipment should be used for manufacturing, storing, and processing DNT. Where closed systems cannot be employed or do not effectively control DNT emissions, local exhaust ventilation should be provided to direct dust, vapors, and gases away from workers and to prevent the recirculation of contaminated exhaust air. Exhaust ventilation systems for quality control laboratories or laboratories where samples are prepared for analyses should be designed to adequately capture and contain DNT dust, vapors, or gases. Special consideration should be given to the releasing of these compounds from pressurized sampling containers. Guidance for designing local exhaust ventilation systems can be found in Recommended Industrial Ventilation Guidelines [51], Industrial Ventilation--A Manual of Recommended Practice [52], and Fundamentals Governing the Design and Operation of Local Exhaust Systems, ANSI Z9.2-1979 [53].

Ventilation equipment should be checked at least every 3 months to ensure adequate performance. System effectiveness should also be checked when there are any changes in production, process, or control that might result in significant increases in airborne exposure to DNT.

Worker Isolation

If feasible, workers may be isolated from direct contact with the work environment by the use of automated equipment operated from a closed control booth or room. The control room should be maintained at a greater air pressure than that surrounding the process equipment so that air flows out of, rather than into, the room. This type of control will not protect workers who must perform process checks, adjustments, maintenance, and related operations. Therefore, special precautions are often necessary to prevent or limit worker exposure in these situations and frequently involve the use of personal protective equipment.

Personal Protective Equipment

Workers should prevent direct skin contact with DNT by wearing fully encapsulating protective clothing made of butyl rubber, which has proven to be an effective barrier against DNT [54,55]. Any clothing that becomes contaminated with DNT should be removed and discarded or cleaned before

re-use. Areas of the body which come in contact with DNT should be thoroughly washed with soap and water. As a general hygienic measure, facilities (e.g., change rooms, showers, etc.) for personal cleanliness should be provided.

The use of respiratory protection requires that a respiratory protection program be instituted which at a minimum meets the requirements of 29 CFR 1910.134 [56]. In addition to selection of respirators approved by the Mine Safety and Health Administration (MSHA) and by NIOSH, a complete respiratory protection program should include at least regular training of personnel, fit testing, periodic environmental monitoring, and maintenance, inspection, and cleaning of equipment. The program should be evaluated regularly.

It must be stressed that the use of respiratory protection is the least preferred method of controlling worker exposures and should not be used as the only means of preventing or minimizing exposures during routine operations. However, NIOSH recognizes that respirators may be required to provide protection under certain situations such as implementation of engineering controls, certain short-duration maintenance procedures, and emergencies. NIOSH maintains that only the most protective respirators should be used to protect workers from exposure to workplace carcinogens. Therefore, the following respirators are recommended for these situations:

- A self-contained breathing apparatus with a full facepiece operated in pressure-demand or other positive pressure mode or

- A combination respirator that includes a supplied-air respirator with a full facepiece operated in pressure-demand or other positive pressure mode and an auxiliary self-contained breathing apparatus operated in pressure-demand or other positive pressure mode.

MEDICAL SURVEILLANCE

A medical surveillance program should be made available that can evaluate both the acute and chronic effects of DNT exposure. The physician responsible should be provided with information concerning the adverse effects from exposure to DNT and an estimate of the worker's potential exposure to DNT, including any available workplace sampling results and a description of any protective devices or equipment the worker may be required to use. A medical and work history should be taken initially and updated periodically. As part of this medical surveillance program, workers who are or may be exposed to DNT should have preplacement and periodic evaluations focusing on the history of previous exposure to DNT and other toxic agents. The examining physician should direct particular attention to the urinary, respiratory, and nervous systems; blood; liver; and skin as these are the most likely targets of exposure to DNT.

NIOSH

Current Intelligence Bulletin 45

February 24, 1986

Polychlorinated Biphenyls (PCB's): Potential Health Hazards from Electrical Equipment Fires or Failures

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

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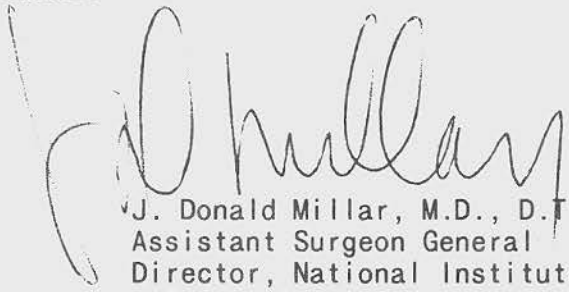
FOREWORD

Current Intelligence Bulletins (CIB's) are reports issued by the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control, Atlanta, Georgia, for the purpose of disseminating new scientific information about occupational hazards. A CIB may draw attention to a hazard previously unrecognized or may report new data suggesting that a known hazard is either more or less dangerous than was previously thought.

CIB's are prepared by the staff of the Division of Standards Development and Technology Transfer, NIOSH (Robert A. Taft Laboratories, 4676 Columbia Parkway, Cincinnati, Ohio 45226) and are distributed to representatives of organized labor, industry, public health agencies, academia, and public interest groups as well as to those federal agencies, such as the Department of Labor, which have responsibilities for protecting the health of workers. It is our intention that anyone with the need to know should have ready access to the information contained in these documents; we welcome suggestions concerning their content, style, and distribution.

Because of the recent attention given to human exposure to polychlorinated biphenyls (PCB's), polychlorinated dibenzofurans (PCDF's), polychlorinated dibenzo-p-dioxins (PCDD's), and related compounds resulting from electrical equipment fires or failures, we think it necessary to present a review of the pertinent data and a summary of findings related to the potential human health hazards of these compounds. Because the voluminous literature on PCB's, PCDF's, and PCDD's has been compressed in this bulletin, it is suggested that readers wanting additional details of the reported studies consult the appended references.



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CURRENT INTELLIGENCE BULLETIN #45

POLYCHLORINATED BIPHENYLS (PCB's): POTENTIAL HEALTH HAZARDS FROM ELECTRICAL EQUIPMENT FIRES OR FAILURES

FEBRUARY 24, 1986

ABSTRACT

Numerous fire-related incidents involving electrical equipment containing polychlorinated biphenyls (PCB's) have resulted in widespread contamination of buildings with PCB's and, in some cases, with polychlorinated dibenzofurans (PCDF's) and polychlorinated dibenzo-p-dioxins (PCDD's), including 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Emergency response personnel, maintenance or cleanup workers, or building occupants may be exposed to the compounds by inhalation, ingestion, or skin contact.

In experimental animal studies, exposure to PCB's, PCDF's, or PCDD's has resulted in various effects, including decreased body weights, hepatic lesions, thymic atrophy, and adverse reproductive effects, at a wide range of exposure concentrations. In addition, PCB's and TCDD have been shown to be carcinogenic in rats and mice. Humans exposed to PCB's, PCDF's, or PCDD's have developed chloracne, gastrointestinal disturbances, elevated serum enzyme and triglyceride levels, and numbness of the extremities. Epidemiologic studies of humans exposed to PCB's or PCDD's including TCDD are suggestive of an association between exposure to these compounds and increased incidences of cancer.

Based on existing evidence, the National Institute for Occupational Safety and Health (NIOSH) continues to recommend that PCB's and TCDD be regarded as potential human carcinogens in the workplace. Existing evidence also suggests that PCDF's may pose a risk to human health. Therefore, NIOSH recommends that occupational exposure to PCB's, PCDF's, and PCDD's resulting from electrical equipment fires or failures be controlled to the lowest feasible limit, and that workers involved in decontamination activities use all necessary protective measures to prevent exposure.

BACKGROUND

Physical and Chemical Properties of Polychlorinated Biphenyls (PCB's)

Polychlorinated biphenyls (PCB's)* comprise a class of nonpolar chlorinated hydrocarbons with a biphenyl nucleus in which any or all of the hydrogen atoms have been replaced by chlorine [1]. Commercial PCB's are mixtures of isomers of chlorinated biphenyls exhibiting varying degrees of chlorination. Although there are 209 possible positional chlorobiphenyl isomers, only 100 individual isomers are likely to occur at significant concentrations in commercial PCB mixtures [2].

In pure form, the individual chlorobiphenyl isomers are colorless crystals, but the commercial mixtures are liquid due to depression of the melting points through interaction of the individual isomers [3]. The physical and chemical properties of the individual isomers vary widely according to the degree and to the position of chlorination. The PCB compounds have low solubilities in water (0.007 to 5.9 milligrams per liter) [3] and low vapor pressures (10^{-6} to 10^{-3} millimeters of mercury at 20°C) [1]. PCB's are soluble in most of the common organic solvents, oils, and fats. The compounds are stable to acids and alkali and are resistant to oxidation but are subject to photodechlorination when exposed to sunlight (spectral region above 290 nanometers) [1].

Use of PCB's in Electrical Equipment

Commercial products containing PCB's were widely distributed between 1957 and 1977, when large quantities of PCB's were manufactured in the United States and marketed under the trade name Aroclor®. The Aroclor products were designated by numbers such as 1221, 1242, 1248, 1254, and 1260, with the last two digits representing the approximate percent by weight of chlorine in the mixtures. Aroclor 1016, however, contained 41% chlorine [1].

Properties of PCB's such as thermal stability, nonflammability, and dielectric capability resulted in their use in electrical capacitors and transformers. Electrical capacitors (small and large) contained nearly 100% PCB's [4]. Small capacitors containing 0.1-0.6 pound of PCB's were commonly used in household appliances such as television sets, air conditioners, and fluorescent light fixtures, and have been estimated to have service lives of at least 10 years [5]. Based on Environmental Protection Agency (EPA) estimates that 10% of the small PCB capacitors (<3 pounds of dielectric fluid) are removed from service annually [4], approximately 350 million of

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***Abbreviations used for chemical compounds are:**

PCB -- polychlorinated biphenyl
PCDF -- polychlorinated dibenzofuran
PCDD -- polychlorinated dibenzo-p-dioxin
TCDF -- 2,3,7,8-tetrachlorodibenzofuran
TCDD -- 2,3,7,8-tetrachlorodibenzo-p-dioxin
CDF -- chlorodibenzofuran
CDD -- chlorodibenzo-p-dioxin

the capacitors were still in use in 1984. Large capacitors, with a PCB content of more than 3 pounds, have been used in electrical substations, within buildings, and on utility poles. The latest available information indicates that there were approximately 3.3 million large PCB capacitors in service in 1981 [4].

In transformers containing PCB's, the dielectric fluid generally consists of 60-70% PCB's [4] and up to 40% chlorinated benzenes [6]. Trade names of PCB askarels (the generic term used to refer to a broad class of nonflammable, synthetic, chlorinated hydrocarbon insulating liquids) formulated in the United States include Pyranol®, Inerteen®, and Noflamol® [7]. The volume of fluid in transformers ranges from 40 to 1,500 gallons [8]. PCB transformers have been used mainly in or near buildings where the proximity of electrical equipment to people and/or property warranted the use of a fire-resistant dielectric fluid. According to EPA estimates, at the end of 1984 there were approximately 107,000 PCB transformers in use or in storage for reuse [9], including approximately 77,600 PCB transformers used in or near commercial buildings (e.g., office buildings, shopping centers, hospitals, and schools) [10].

In 1976, the United States Congress enacted the Toxic Substances Control Act (TSCA) (Public Law 94-469), which gave the EPA authority to control the production and use of chemicals in the United States. Under Section 6(e) of TSCA the manufacture, processing, distribution in commerce, and use of PCB's after January 1, 1978 was prohibited; however, the EPA may, by rule, allow a particular use of PCB's to continue. In 1982, the EPA issued a final rule on the use of PCB's in electrical equipment. This rule permits the use of certain electrical equipment containing PCB's (e.g., small capacitors, large capacitors, and transformers) to continue under specified conditions for their remaining useful service lives [4]. In 1985, the EPA issued a final rule on the use of PCB's in electrical transformers. The use of high secondary voltage network PCB transformers in or near commercial buildings (approximately 7,400 transformers) after October 1, 1990, is prohibited. Low secondary voltage network and high secondary voltage radial PCB transformers in or near commercial buildings (approximately 70,200 transformers) must be equipped with enhanced electrical protection devices by October 1, 1990, to avoid overheating from sustained electrical faults [10].

Potential for Exposure to PCB's and Related Compounds Following Electrical Equipment Fire or Failure

Fire-related incidents are defined as incidents involving electrical equipment containing PCB's in which sufficient heat from any source causes the release of PCB's from the equipment casing. In soot-producing incidents an actual fire occurs in or near the PCB-containing electrical equipment eventually resulting in exposure of the PCB's to extremely high temperatures and in the formation and distribution of a black, carbonaceous material. PCB's have been identified in soot following numerous electrical equipment fires [11-17]. Polychlorinated dibenzofurans (PCDF's) [11-15,17-20] and

polychlorinated dibenzo-p-dioxins (PCDD's) [12-15,17-20] have also been identified following this type of fire-related incident. Laboratory studies have confirmed that PCDF's and PCDD's are formed from the pyrolysis of PCB's [21-24] or chlorobenzenes [25] at temperatures ranging from 500° to 700°C (932° to 1292°F).

In addition to PCDD's and PCDF's, other polychlorinated hydrocarbons have been identified in soot from electrical equipment fires. Polychlorinated biphenylenes [13,26], polychlorinated pyrenes [26], and polychlorinated diphenyl ethers [18] have been detected in soot samples collected following capacitor or transformer fires.

Fire-related incidents in which soot is not produced have occurred from the release of PCB's through the pressure relief valves of overheated transformers [27-31]. The pressurized release of hot PCB vapors can entrain considerable quantities of liquid PCB's forming a fine aerosol. Documented safety valve releases of PCB's from transformers demonstrate that the aerosol can be distributed to areas beyond the transformer vault by convective air currents [27,28,30,31]. Although PCB's manufactured in the United States contained up to 2 micrograms of PCDF's per gram of PCB's (μg/g) [32], recent evidence indicates that additional PCDF's may be formed as a result of the sustained high temperatures in non-soot-producing incidents [31].

Air, soot, and surface values for PCB's, PCDF's, PCDD's, 2,3,7,8-tetrachlorodibenzofuran (TCDF), and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) measured following fire-related incidents in the United States are presented in Table 1.

An example of each type of fire-related incident involving PCB transformers is described in the Appendix.

Exposure Limits

The Occupational Safety and Health Administration (OSHA) promulgated its permissible exposure limits (PEL) of 1 milligram per cubic meter of air (mg/m^3) for chlorodiphenyl products containing 42% chlorine and 0.5 mg/m^3 for chlorodiphenyl products containing 54% chlorine determined as 8-hour time-weighted average (TWA) concentrations [35] based on the 1968 Threshold Limit Values (TLVs®) of the American Conference of Governmental Industrial Hygienists (ACGIH) [36]. The TLVs, which have remained unchanged at 1 mg/m^3 (42%) and 0.5 mg/m^3 (54%) through 1985 [37], are based on the prevention of liver injury in exposed workers [38]. The ACGIH Short Term Exposure Limits (STEL) for chlorodiphenyls are 2 mg/m^3 and 1 mg/m^3 for 42% and 54% chlorine products, respectively. The OSHA PEL and the ACGIH TLV and STEL values include a "Skin" notation which refers to the potential contribution to overall exposure by the cutaneous route, including the mucous membranes and eyes, by either airborne or direct skin contact with PCB's [37].

TABLE 1. CONCENTRATIONS OF PCB's AND RELATED COMPOUNDS FOLLOWING FIRE-RELATED INCIDENTS IN THE UNITED STATES[a]

DATE	LOCATION	ELECT EQUIP	SAMPLING DATE	AIR ($\mu g/m^3$)[b] PCB	SOOT ($\mu g/g$) PCB	SOOT ($\mu g/g$) TCDF	SOOT ($\mu g/g$) PCDF	SOOT ($\mu g/g$) TCDD	SOOT ($\mu g/g$) PCDD	SURFACE ($\mu g/100 cm^2$)[c] PCB	SURFACE ($\mu g/100 cm^2$)[c] TCDF	SURFACE ($\mu g/100 cm^2$)[c] PCDF	SURFACE ($\mu g/100 cm^2$)[c] TCDD	SURFACE ($\mu g/100 cm^2$)[c] PCDD	REF
FIRES															
12/80	Cincinnati, OH	Cap	03/81	ND[d]	--	--	--	--	--	7,200	ND	ND	ND	ND	33
02/81	Binghamton, NY	Tran	02/81	80	200,000	12	2,160	0.6	19.9	--	--	--	--	--	13
10/81	Boston, MA	Tran	12/81	--	114,000	3	162	ND	ND	--	--	--	--	--	11
04/82	Miami, FL	Tran	04/82	--	--	ND	1.89	ND	ND	860	--	--	--	--	18
04/82	Tulsa, OK	Tran	04/85	0.5	11	0.007	0.11	ND	0.16	1,100	8.5[e]	81.6[e]	ND	1,408[e]	15
06/82	Jersey City, NJ	Caps	--	2.3	--	--	--	--	--	22	ND	0.14	ND	0.09	20
05/83	San Francisco, CA	Tran	05/83	1,500	86,000	6.3	28.9[f]	0.059	0.32[f]	--	29[e]	101.5[e]	--	--	17
09/83	Chicago, IL	Tran	09/83	58	39,100	--	--	--	--	3,263	0.41	12.2	ND	0.05	12
12/83	Tulsa, OK	Tran	01/84	--	--	--	--	--	--	1,607	--	--	--	--	34
03/84	Columbus, OH	Caps	04/84	--	6,415	3.2	46.4	0.016	4.1	--	--	--	--	--	19
05/84	Miami, FL	Tran	06/84	--	50,000	0.27	98.5	0.004	2.3	--	--	--	--	--	14
PRESSURIZED RELEASES					FLUID ($\mu g/g$)										
--/74	Wappingers Falls, NY	Tran	02/84	--	117,000	--	0.97	--	ND	92	--	--	--	--	30
06/82	Washington, DC	Tran	06/84	--	--	<.074[h]	<7.02[h]	ND	<1.3[h]	320,000	ND	<114[h]	ND	ND	28
06/82	Maplewood, MN	Tran	06/82	90	--	--	ND	--	ND	5,000	--	--	--	--	27
12/83	Syracuse, NY	Tran	12/83	1.1	--	--	--	--	--	7.3	0.02[i]	0.17[fi]	ND	--	29
06/85	Santa Fe, NM	Tran	06/85	41.9	870,000	1.6	44.2	ND	ND	280,000	0.41	3.99	ND	0.19	31

[a] Values represent the highest measurements reported
[b] Micrograms per cubic meter($\mu g/m^3$)
[c] Micrograms per 100 square centimeters ($\mu g/100\ cm^2$)
[d] None detected, ND
[e] Values expressed as nanograms per square meter (ng/m^2)
[f] Values represent total tetrachlorinated forms only
[h] Values represent results obtained in the presence of interfering chemicals
[i] Values reported as µg per wipe sample (area undefined)

Note: Cap = Capacitor
Caps = Capacitors
Tran = Transformer

The National Institute for Occupational Safety and Health (NIOSH) recommends that exposure to PCB's in the workplace be limited at or below the minimum reliable detectable concentration of 1 $\mu g/m^3$ (using the recommended sampling and analytical methods) determined as a TWA for up to a 10-hour workday, 40-hour workweek. The NIOSH recommended exposure limit (REL) was based on the findings of adverse reproductive effects in experimental animals, on the conclusion that PCB's are carcinogens in rats and mice and, therefore, potential human carcinogens in the workplace, and on the conclusion that human and animal studies have not demonstrated a level of exposure to PCB's that will not subject the worker to possible liver injury [39].

TOXICITY

Results of Animal Studies

Effects of PCB's, PCDF's, and PCDD's

In general, the toxic responses observed in animals treated with PCB's, PCDF's, or PCDD's are similar, but the potencies of individual compounds vary according to the degree and position of chlorination. The tetra-, penta-, and hexa-chlorinated isomer groups exhibit greater toxicity than the other chlorinated forms [40-42]. Dibenzofuran and dibenzo-p-dioxin compounds with chlorine at positions 2, 3, 7, and 8 are particularly toxic [43-45]. The lethal doses in milligrams per kilogram of body weight (mg/kg) for 50% (LD_{50}) of the animals tested by the single oral administration of PCB's, TCDF, or TCDD in four animal species are presented in Table 2.

TABLE 2. ACUTE ORAL TOXICITY OF PCB's, TCDF, AND TCDD

	Single-Dose LD_{50} (mg/kg)		
	PCB's	TCDF	TCDD
Guinea pig	NR[a]	>.005 [46]	.0006 [47]
		<.010 [46]	.002 [43]
Monkey	NR	1.000 [46]	<.070 [48]
Rat	1,010 [49]	>1.000 [50]	.047 [48]
Mouse	1,900 [51]	>6.000 [50]	.114 [52]
			.284 [43]

[a]Not reported, NR

Mice, rats, guinea pigs, and monkeys displayed progressive weight loss with death occurring up to several weeks after administration of a single lethal dose of PCB's, TCDF, or TCDD. Few other overt signs of toxicity were observed in mice, rats, and guinea pigs. Monkeys exhibited facial edema, loss of eyelashes and fingernails, and acneform skin eruptions [46,48].

Prominent histopathologic findings included: hepatic lesions in mice [43] and rats [53], hyperplasia of the urinary tract epithelial tissues and lymphoid hypoplasia in monkeys [46,48], and thymic atrophy in all four animal species.

Adverse reproductive effects in experimental animals have been observed in response to PCB's (rats, rabbits, monkeys, dogs, and pigs) [39], TCDD (mice and rats) [54], and TCDF (mice) [55,56]. Rats and mice exposed to PCB's [39] or TCDD [54] have developed liver cancers. No studies regarding the carcinogenicity of PCDF's in animals have been reported.

Effects of Soot Containing PCB's, PCDF's, and PCDD's

A composite sample of soot collected following a transformer fire in Binghamton, New York in 1981, contained 5,000 μg PCB's/g, 48 μg TCDF/g, and 1.2 μg TCDD/g. Single oral administration to guinea pigs of the soot in aqueous methyl cellulose or of a benzene extract of the soot in the same aqueous vehicle produced LD_{50} values of 410 and 327 mg/kg, respectively. Single oral administration of TCDD in aqueous methyl cellulose or in corn oil produced LD_{50} values of 19 and 2.5 μg/kg, respectively. Animals surviving for 42 days after administration of the soot showed dose-related evidence of decreased weight gain and kidney weight, thymic atrophy, increased serum triglycerides, goblet cell hyperplasia of pancreatic interlobular ducts, and metaplasia of salivary gland interlobular duct epithelium. In rabbits, dermal application of the saline-moistened soot or of a benzene extract of the soot at a dose comparable to 500 mg soot/kg body weight for 24 hours produced hypertrophy of centrilobular hepatocytes in 50% of the rabbits at the end of the 65-day observation period. No signs of overt toxicity were observed in the rabbits, except dermal inflammatory reactions noted in rabbits treated with the soot extract [57]. The dermal LD_{50} of TCDD in rabbits is 275 μg/kg [47], while the dermal minimum lethal dose of PCB's (as Aroclor 1260) is from 1.26 to 2.00 grams/kg [58]. Because the measured amounts of TCDF and TCDD in the soot were low, other congeners may have contributed to the toxic effects observed in guinea pigs and rabbits [16,57].

In a subchronic toxicity study, the total soot contained in food that was consumed in 90 days by guinea pigs was 1.2, 22, 55, or 275 mg soot/kg body weight. A fifth group of guinea pigs was terminated after 32 days (total consumption of 400 mg soot/kg body weight) because mortality had reached 35%. The intensities of the toxic responses were dose-related, but no signs of toxicity were detected in guinea pigs with a total consumption of 1.2 mg soot/kg body weight [59].

Human Health Effects

Several cases of chloracne, hyperpigmentation, gastrointestinal disturbances, elevated serum enzyme and triglyceride levels, and numbness of the extremities have been reported among people exposed to PCB's [39,60,61]

or PCDD's [54,62]. Comparative human and animal studies indicate that PCDF's were the main causative agents of similar symptoms reported in individuals who ingested cooking oils contaminated with PCB's and PCDF's [63].

There is suggestive evidence of associations between increased incidences of cancer and exposure to PCB's [64], to PCB's containing significant PCDF's [65,66], and to phenoxyacetic herbicides contaminated with PCDD's including TCDD [67,68]. However, definite causal relationships between exposure and carcinogenic effects in humans remain unclear due to the inadequately defined populations studied and the influences of mixed exposures.

The firefighters and other workers involved in the Binghamton transformer fire cleanup have been followed through a medical surveillance program. Medical evaluation of these workers approximately one year after the fire showed slight increases in serum PCB levels but no observable adverse health effects from this exposure [69]. Selected workers from this study group have been found to have elevated adipose tissue levels of PCDF's and PCDD's [70] and associated histologic changes in the liver [71]. Further monitoring of this population is in progress.

RECOMMENDATIONS

There are several classifications for identifying a substance as a carcinogen. Such classifications have been developed by the National Toxicology Program (NTP) [72], the International Agency for Research on Cancer (IARC) [73], and OSHA in its "Identification, Classification, and Regulation of Potential Occupational Carcinogens" 29 CFR 1990 [74], also known as "The OSHA Cancer Policy." NIOSH considers the OSHA classification the most appropriate for use in identifying potential occupational carcinogens* [74]. Because exposure to PCB's or TCDD has been shown to produce malignant tumors in rats and mice, they meet the OSHA criteria. Therefore, NIOSH continues to recommend that PCB's and TCDD be considered as potential human carcinogens in the workplace. Limited evidence from animal and human studies suggests that PCDF's may also pose a risk to human health. As prudent public health policy, NIOSH recommends that occupational exposure to PCB's, PCDF's, and PCDD's resulting from electrical equipment fires or failures be controlled to the lowest feasible limit.

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*"'Potential occupational carcinogen' means any substance, or combination or mixture of substances, which causes an increased incidence of benign and/or malignant neoplasms, or a substantial decrease in the latency period between exposure and onset of neoplasms in humans or in one or more experimental mammalian species as the result of any oral, respiratory or dermal exposure, or any other exposure which results in the induction of tumors at a site other than the site of administration. This definition also includes any substance which is metabolized into one or more potential occupational carcinogens by mammals" (29 CFR 1990.103).

As a result of fire-related incidents involving PCB-containing electrical equipment, emergency response personnel, maintenance and cleanup workers, and building occupants may be at risk of exposure to PCB's, PCDF's, and PCDD's. The following recommendations are intended to minimize worker exposure to these compounds and reflect experiences NIOSH personnel and others have gained in responding to such incidents. These recommendations focus primarily on PCB transformer fires, although many of the recommendations apply to other types of fire-related incidents involving PCB's.

Recognition of Potential Hazard

Emergency response personnel should be informed of the presence of PCB-containing electrical equipment and of the potential health hazards associated with exposure to emissions from such equipment. All workers should understand that exposure can occur through inhalation, ingestion, and skin absorption (by direct contact or by contact with contaminated surfaces, clothing, and equipment) and recognize that exposure to some of these compounds may result in long term health effects.

Required registration of PCB transformers with local fire departments [10] is intended to assure early recognition of the potential hazards when a fire-related incident occurs. The registration for each transformer should include: building location; location of transformer(s) within or near the building; transformer serial number, manufacturer, and kilovolt/amperage rating; and total volume and generic composition of the dielectric fluids. This information should be readily accessible to those persons responsible for the health and safety of emergency response personnel and others who may come into contact with PCB transformers.

To assist in the identification of PCB transformers the effective use of signs and labeling should be instituted. While labeling of PCB transformers is required (using the mark "M_L") [10], additional signs and labels should be placed in areas near the location of a PCB transformer(s).

The number of emergency response personnel or cleanup workers entering a potentially contaminated area(s), (e.g., interior of the building or transformer vault) should be limited. This action would minimize the number of workers exposed and would reduce the amount of protective clothing and equipment potentially contaminated.

Assessment of Exposure

Contamination assessment is necessary to determine the extent and relative degrees of contamination of an area following a fire-related incident. NIOSH's Occupational Exposure Sampling Strategy Manual is useful in developing appropriate strategies to monitor worker exposure to PCB's and related pyrolysis products [75]. Air and surface wipe samples should be collected in all areas potentially contaminated by the incident. Air sampling should include both the particulate and vapor phase. Wipe samples

should be taken on both vertical and horizontal surfaces. Additional samples may include residual fluid in the transformer, fluid deposited in the vault, or soot. Air and surface wipe samples should be analyzed for PCB's, tetra- through octa-chloro homologs of PCDF and PCDD, and the respective 2,3,7,8-tetrachloro isomers. Detailed descriptions of sampling and analytical techniques for PCB's may be found in the NIOSH Manual of Analytical Methods [76,77]. Sampling procedures and sensitive methods for the analyses of PCDF's and PCDD's have been developed by the New York State Department of Health [16,78].

Personal Protective Clothing

All workers who may be exposed to PCB's, PCDF's, and PCDD's should be equipped with chemical protective clothing to ensure their protection. In the selection of protective clothing, consideration should be given to the utilization of disposable apparel because of the uncertainty of decontamination of reusable clothing.

Outer protective garments should consist of a zippered coverall with attached hood and draw string, elastic cuffs, gloves, and closure boots. If exposure to soot is anticipated, workers should wear outer coveralls made of a nonwoven fabric such as spunbonded Tyvek® to exclude particulates. If exposure to liquids or to both soot and liquids is anticipated, or if the form of the contaminants is unknown, the outer coveralls should be made of chemically resistant materials such as Saranax®-coated Tyvek or Viton®-coated neoprene. Gloves and boots should be made of neoprene, nitrile, butyl rubber, or Viton which have been shown to be resistant to permeation by PCB's [79,80]. For personal comfort workers may wear inner garments consisting of cotton coveralls, undershirts, undershorts, gloves, and socks. Inner garments should be disposed of after use because small amounts of contaminants may be transferred in removing outer garments [79]. All disposable clothing should be placed in approved containers and disposed of according to EPA disposal procedures [4].

Respiratory Protection

The use of respiratory protection for those involved in cleanup operations requires that a respiratory protection program be instituted which, at a minimum, meets the requirements of 29 CFR 1910.134 [81] and that the respirators selected be approved by the Mine Safety and Health Administration (MSHA) and by NIOSH. The respiratory protection program should include training of workers regarding the proper use, fit testing, inspection, maintenance, and cleaning of respirators. The program should be evaluated regularly.

Where a risk of exposure to airborne contaminants exists, such as when visible quantities of soot are to be removed, workers should wear a self-contained breathing apparatus with a full facepiece operated in pressure-demand or other positive pressure mode. Alternatively, a combination supplied air respirator, with full facepiece, operated in

pressure-demand or other positive pressure mode and equipped with auxiliary positive pressure self-contained air supply can be used. When cleanup operations have advanced to a point where airborne PCB's can no longer be detected, air-purifying full facepiece respirators equipped with a high efficiency particulate air filter and organic vapor cartridge should be used, as a precaution, until final decontamination is completed [82].

Decontamination and Worker Protection Programs

In general, decontamination procedures must provide an organized process in which the extent and degree of contamination are systematically reduced. This should include procedures that take into account containment, collection, and disposal of contaminated solutions and residues generated during the incident and cleanup. Separate facilities should be provided for decontamination of large equipment. The EPA's Guide for Decontaminating Buildings, Structures, and Equipment at Superfund Sites provides information for developing a decontamination strategy [83].

Each stage of decontamination, such as gross decontamination and repetitive wash/rinse cycles, should be conducted separately, either by using different locations or by spacing in time. Personnel decontamination locations should be physically separated from the contaminated area(s) to prevent cross-contact and should be arranged in order of decreasing level of contamination. Separate entry/exit routes and locations should be well marked and controlled. Access to the decontamination area should be separate from the path between the contaminated and clean areas. Dressing stations for entry should be separate from redressing areas for exit.

All reusable clothing and equipment should be grouped according to perceived degree of contamination (i.e., high, moderate, or low) and thoroughly cleaned. Decisions concerning decontamination end points are often based on the lack of visible contamination; however, the absence of observable surface contamination does not necessarily indicate the absence of contaminants absorbed into the material. Reusable clothing and equipment should, therefore, be analyzed for residual contamination before reuse or storage.

Soot from transformer fires is typically black, friable, carbonaceous material. Preliminary cleanup of the areas visibly contaminated with soot should involve dry vacuuming of both horizontal and vertical surfaces with a vacuum cleaning system equipped with a high efficiency particulate (HEPA) filter.

Final cleanup methods should include washing surfaces with alkaline [27] or nonionic [84] synthetic detergents in water. The addition of a caustic agent, such as trisodium phosphate, may help to remove grease deposits, floor waxes, and furniture polishes. Waxed and polished surfaces tend to absorb contaminants from the air. Cleaning with organic solvents is useful for nonporous electrical and mechanical equipment where contact with water-based cleaning fluids may damage the equipment. Organic solvents,

such as kerosene, mineral spirits, and trichlorotrifluoroethane, may carry contaminants deeper into porous materials and should not be used on these surfaces. Complete decontamination of porous surfaces, such as concrete and masonry surfaces in vaults, may not be possible; therefore, application of an elastomeric, abrasion- and flame-resistant sealant may be required.

Post-Decontamination Testing

The adequacy of the decontamination effort should be determined by followup sampling and analysis of the contaminated areas and reusable protective equipment. This testing should be conducted as each area is decontaminated and again after the entire facility has been cleaned. Decontamination guidelines for the cleanup of specific buildings following fires involving PCB transformers [83,85] have been proposed by the New York State Department of Health [86], the New Mexico Expert Advisory Panel [87], the California Department of Health Services [88], and the San Francisco Department of Health [89].

Medical Surveillance

A medical surveillance program should be established to prevent (or to attempt to detect at an early stage) adverse health effects in workers resulting from exposure to PCB's or related compounds. Medical and work histories, including previous exposure to PCB's or other toxic agents, should be taken for each worker prior to job placement and updated periodically. The physician responsible should be provided with information concerning the adverse health effects from exposure to PCB's and related compounds and an estimate of the worker's potential exposure, including any available workplace sampling results and a description of all protective clothing or equipment the worker may be required to use.

The examining physician should direct particular attention to the skin, liver, and nervous system as these are the most likely targets of exposure to PCB's and related compounds. Blood determinations which reflect liver function may be useful. Measurement of blood PCB's may also be useful but should not be interpreted as a sensitive indicator of acute exposure. Adipose tissue levels of PCB's, PCDF's, and PCDD's are indicative of total body burden, but these tissue samples are not routinely available. Further studies of exposed populations will permit more definitive medical monitoring recommendations.

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APPENDIX

REPORTS OF FIRE-RELATED INCIDENTS INVOLVING PCB TRANSFORMERS

Fire in a Multi-Story Office Building in Binghamton, New York

On February 5, 1981, an electrical fire occurred in the switchgear adjacent to a PCB transformer in the basement mechanical room of the Binghamton State Office Building. The transformer contained 1,060 gallons of askarel consisting of Aroclor 1254 (65%) and a mixture of tri- and tetra-chlorinated benzenes (35%). A ceramic bushing on the transformer cracked during the fire, resulting in the release of approximately 180 gallons of askarel onto the floor near the fire. The smoke was distributed by convection throughout the building through an open vertical shaft that extended from the mechanical room to the top of the building. The shaft contained the duct for the exhaust air from the restrooms on all the floors. The shaft and ducts were not airtight and allowed smoke and soot to contaminate the work areas of the building, air-conditioning ducts, false ceiling areas, and elevator shafts [13].

Analyses of the soot revealed significant concentrations of PCB's, PCDF's, TCDF, PCDD's, TCDD, and polychlorinated biphenylenes [13,16,90]. Based on analyses of dry surface wipe samples, horizontal surfaces showed higher levels of contamination than vertical surfaces [17]. In soot samples obtained from 11 floors of the building, the absolute amounts of the tetra- through octa-chlorodibenzofuran (CDF) isomer groups varied from sample to sample, but the relative proportions with respect to the amount of PCB in the soot were consistent. The ratio of PCDF to PCB averaged 0.067 $\pm$ 0.026 ($\pm$ one standard deviation) [16].

Air samples collected on the seventh floor after cleanup of most of the surface soot deposits contained 292 picograms of total tetra-CDF per cubic meter of air (pg/m^3) including 26 pg TCDF/m^3 and 5 pg total tetra-chlorodibenzo-p-dioxin (CDD)/m^3 including 3 pg TCDD/m^3 [16].

The cleanup of the Binghamton building has been complex and costly. The building remains closed to normal use pending complete cleaning and renovation. Criteria for reoccupancy are being considered by the New York State Department of Health Expert Advisory Panel based on toxicity studies in guinea pigs using the soot from the building, on chemical analyses of the soot, and on published toxicologic studies of TCDD [86].

Electrical Malfunction in an Office Building in Santa Fe, New Mexico

On June 17, 1985, an electrical malfunction occurred in a transformer located in the basement transformer vault in the main building of the New Mexico State Highway Department Office Building. The transformer contained 245 gallons of askarel consisting of Aroclor 1260 (87%) and a mixture of tri- and tetra-chlorinated benzenes (13%). The electrical malfunction caused the transformer to overheat resulting in the release of vaporized askarel through the safety valve which continued until the unit was de-energized (approximately 65 minutes after initial detection). There was

no fire, but charred (blistered) paint on the transformer casing indicated that the temperature of the casing may have approached 316°C (600°F).

The emission products were distributed throughout the 2-story building by convective air currents and by mechanical transfer via the heating, ventilating, and air conditioning systems. Because the emitted vapor condensed as it reached cooler temperatures, the askarel apparently "rained" in the heavily contaminated rooms adjacent to and above the basement transformer vault.

Air, fluid, and surface wipe samples were collected within 7 days of the incident. Airborne concentrations of PCB's in the main building were 41.94 $\mu g/m^3$ inside the vault, 0.34-25.87 $\mu g/m^3$ in other basement areas, 1.00-19.45 $\mu g/m^3$ in first floor areas, and 0.73-5.96 $\mu g/m^3$ in second floor areas. PCDF's were detected at concentrations ranging from 10.4 to 501.6 pg/m^3 including 0.9-56.2 pg $TCDF/m^3$. Airborne PCDD's ranged from 7.1 to 21.0 pg/m^3 but TCDD was not detected.

The surface concentrations of PCB's were as high as 280,000 $\mu g/100\ cm^2$ in basement areas, 98,000 $\mu g/100\ cm^2$ in first floor areas, and 190 $\mu g/100\ cm^2$ in second floor areas. PCDF's, TCDF, and PCDD's were present in surface wipe samples from areas of the basement and first floor, but TCDD was not detected. Surface wipe samples from second floor areas were not submitted for measurement of the pyrolysis products [31].

The New Mexico PCB Expert Advisory Panel convened on July 16, 1985, to propose air and surface cleanup guidelines for the building. The guidelines were based on the potential risk of cancer resulting from exposure to PCB's, PCDF's, and PCDD's. Animal studies on the carcinogenicity of TCDD were used to estimate the potential cancer risks. It was also necessary to make certain judgments and assumptions regarding the toxicity of the related compounds and the potential for exposure to occupants of the building. The guidelines are intended to maintain the risk of developing cancer below one in one million for a person spending the rest of his/her working lifetime in the building. The Panel recommended cleanup levels of 2 pg TCDD equivalents/m^3 of air and 1 ng TCDD equivalents/m^2 of surface area. Values for other PCDF and PCDD isomer groups can be converted to TCDD equivalents using the following conversion factors:

TO CONVERT VALUES TO TCDD EQUIVALENTS

PCDF's	Factor	PCDD's	Factor
TCDF	0.33	TCDD	1.0
Other tetra-CDF's	0.0	Other tetra-CDD's	0.0
Penta-CDF's	0.17	Penta-CDD's	0.5
Hexa-CDF's	0.005	Hexa-CDD's	0.02
Hepta-CDF's	0.0005	Hepta-CDD's	0.0
Octa-CDF's	0.0	Octa-CDD's	0.0

Concentrations of these compounds can be converted to TCDD equivalents by multiplying the measured values by the appropriate conversion factor. The TCDD equivalents can then be summed and compared to the guideline values. The Panel did not establish cleanup guidelines for PCB's on surfaces [87].

NIOSH

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METHYLENE CHLORIDE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

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FOREWORD

Current Intelligence Bulletins (CIB's) are issued by the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control, Atlanta, Georgia, for the purpose of disseminating new scientific information about occupational hazards. A CIB may draw attention to a hazard previously unrecognized or may report new data suggesting that a known hazard is either more or less dangerous than was previously thought.

CIB's are prepared by the staff of the Division of Standards Development and Technology Transfer, NIOSH (Robert A. Taft Laboratories, 4676 Columbia Parkway, Cincinnati, Ohio 45226) and are distributed to representatives of organized labor, industry, public health agencies, academia, and public interest groups as well as to those federal agencies, such as the Department of Labor, which have responsibilities for protecting the health of workers. It is our intention that anyone with the need to know should have ready access to the information contained in these documents; we welcome suggestions concerning their content, style, and distribution.

NIOSH estimates that 1 million workers are potentially exposed to methylene chloride during its manufacture and use; as a solvent, aerosol propellant or fumigant, and as a blowing agent in flexible urethane foams. In 1976, NIOSH published a document entitled Criteria for a Recommended Standard....Occupational Exposure to Methylene Chloride. In that criteria document, NIOSH recommended a 10-hour time-weighted average (TWA) occupational exposure limit of 75 parts per million (ppm) in order to prevent interference by methylene chloride with delivery of oxygen to tissues, and impairment in functions of the central nervous system (CNS). Since 1976, the carcinogenicity of methylene chloride has been documented in several studies of chronic effects in animals. On the basis of carcinogenic and tumorigenic responses in rats and mice, and in accordance with the Cancer Policy of the Occupational Safety and Health Administration (OSHA) ("Identification, Classification, and Regulation of Potential Occupational Carcinogens," 29 CFR 1990), NIOSH recommends that methylene chloride be regarded as a "potential occupational carcinogen." Although the potential for methylene chloride-induced cancer in humans has not been determined, the probability of a population of exposed workers developing cancer could be decreased by reducing exposure. Therefore, NIOSH recommends that occupational exposure to methylene chloride be controlled to the lowest feasible limit.

It is also recommended that producers and users of methylene chloride disseminate this information to their workers and customers, that professional and trade associations and unions inform their members of the potential hazards of working with methylene chloride, and that appropriate engineering controls and work practices be used to reduce the exposure of workers to the lowest feasible extent.

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CURRENT INTELLIGENCE BULLETIN #46

METHYLENE CHLORIDE

APRIL 18, 1986

ABSTRACT

B6C3F$_1$ mice exposed to methylene chloride in air developed cancers (alveolar/bronchiolar carcinomas) and tumors (alveolar/bronchiolar adenomas) of the lung, and cancers (hepatocellular carcinomas) of the liver. Fischer 344/N rats exposed to methylene chloride in air developed tumors (fibromas and fibroadenomas) of the mammary gland. Sprague-Dawley rats exposed to methylene chloride in air developed cancers (sarcomas) of the salivary glands and tumors (fibromas and fibroadenomas) of the mammary glands. Though existing epidemiologic data derived from workers exposed to methylene chloride are inconclusive, the observation of cancers and tumors in both rats and mice treated with methylene chloride meets the criteria established in the Occupational Safety and Health Administration (OSHA) Cancer Policy for considering methylene chloride a "potential occupational carcinogen." Therefore, the National Institute for Occupational Safety and Health (NIOSH) recommends that worker exposure to methylene chloride be controlled to the lowest feasible limit.

BACKGROUND

Physical and Chemical Properties

Methylene chloride is a colorless, volatile, nonflammable liquid with a penetrating, ether-like odor that is detectable at about 200 parts per million (ppm) in air [1,2]. The chemical and physical properties of methylene chloride are listed in Table 1.

TABLE 1.--Chemical and physical properties of methylene chloride

Chemical identity	Methylene chloride
CAS[a] registry no.	75-09-2
RTECS[b] accession no.	PA8050000
Synonyms	DCM, dichloromethane, methane dichloride, methylene bichloride, methylene dichloride
Molecular weight	84.93
Empirical formula	CH_2Cl_2
Melting point	-96.7°C (-142°F)
Boiling point (at 760 mm Hg)	40.1°C (104.2°F)
Vapor density (air=1)	2.93
Concentration in saturated air (25°C)	550,000 ppm
Specific Gravity (20°C)	1.326
Solubility:	
Water	Slight
Ethyl alcohol	Soluble
Ethyl ether	Soluble
Acetone	Soluble
Carbon disulfide	Soluble

[a]Chemical Abstract Service
[b]Registry of Toxic Effects of Chemical Substances

Production, Use, and Potential for Occupational Exposure

In 1984, approximately 628 million pounds of methylene chloride [3] were produced and imported by the United States. Methylene chloride is widely used in paint removers, degreasing agents, and aerosol propellants; as a blowing agent in flexible urethane foams; as a process solvent in the manufacture of pharmaceuticals and food products, including the

decaffeination of coffee; and as a fumigant for grains and fruits [1,4]. An estimated 1 million workers are potentially exposed to methylene chloride or to products that contain this chemical [4].

EXPOSURE LIMITS

The current Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (PEL) for methylene chloride (29 CFR 1910.1000 Table Z-2) is an 8-hour time-weighted average (TWA) concentration of 500 parts per million (ppm), with a ceiling concentration of 1000 ppm, and a maximum peak concentration of 2000 ppm for no more than 5 minutes within any 2 hours [5]. The PEL for methylene chloride was adopted in 1971, without rulemaking, under the authority of section 6(a) of the Occupational Safety and Health Act of 1970. The OSHA standard was derived from a standard recommended by the American National Standards Institute (ANSI).

In 1976, the National Institute for Occupational Safety and Health (NIOSH) Recommended Exposure Limit (REL) for methylene chloride was 75 ppm, 261 milligrams per cubic meter (mg/m^3), as a TWA for up to a 10-hour workday, 40-hour workweek with a 500 ppm (1740 mg/m^3) peak exposure concentration as determined over any 15-minute sampling period during the workday. This REL was based on the need to prevent significant interference with the delivery of oxygen to the tissues of the body and abnormalities in functions of the central nervous system (CNS) as a result of the production of carboxyhemoglobin attendant to metabolism of methylene chloride. The toxicities of methylene chloride and carbon monoxide (CO) are additive [6]. Because of this additive effect, provisions for calculating a reduced REL for methylene chloride in the presence of CO were included in the NIOSH document entitled Criteria for a Recommended Standard....Occupational Exposure to Methylene Chloride [6]. When concentrations of CO exceed 9 ppm in the workplace, either the concentration of methylene chloride or the concentration of CO should be reduced. The 9 ppm value is that included in the air quality standard of the Environmental Protection Agency (EPA) and was derived from data which indicated that typical background concentrations of CO in environments, in the United States, were generally less than 10 ppm and frequently greater than 5 ppm [7].

The 8-hour TWA Threshold Limit Value (TLV®) recommended by the American Conference of Governmental Industrial Hygienists (ACGIH) is 100 ppm (348 mg/m^3) with a 500 ppm Short Term Exposure Limit (STEL) [8]. This TLV is based on experimental data obtained from male, non-smoking subjects at rest. The ACGIH stated that the blood of workers who were exposed at 100 ppm of methylene chloride would have carboxyhemoglobin levels below 5% in their blood [9]. In addition, the TLV documentation indicates that the concentration of methylene chloride in air should be lowered in the presence of CO, according to the appropriate equation for mixtures. The ACGIH further cautioned that: "concurrent exposures to other sources of carbon monoxide or physical activity will require assessment of the overall exposure and adjustment for the combined effect" [9].

TOXICITY

Carcinogenic Effects

A study sponsored by the National Coffee Association (NCA) was designed to evaluate the oncogenic potential of methylene chloride administered to Fischer 344/N rats in their drinking water. There were 85 rats of each sex for each exposure group; 141 rats of each sex served as controls. Based on historical data for water consumption, the investigators designed the study so that the amount of methylene chloride ingested would be approximately 0, 5, 50, 125, or 250 milligrams of pure methylene chloride per kilogram of body weight per day (mg/kg/day) during the 2-year study [10]. In a second study, similarly treated $B6C3F_1$ mice consumed about 0, 60, 125, 185, or 250 mg/kg/day [11]. A total of 125 males and 100 females served as controls. The number of animals in the exposed groups varied. There were 200 males and 100 females at 60 mg/kg/day, 100 males and 50 females each at 125 mg/kg/day and 185 mg/kg/day, and 125 males and 50 females at 250 mg/kg/day. The actual delivered doses in each study were generally within 10% of the target doses. The data obtained from the rats indicated that methylene chloride-dosed females had an increased incidence of neoplastic nodules and/or hepatocellular carcinomas. The incidence of the neoplasms was significant with respect to matched controls; however, the incidence of tumors was stated, by the investigators, to be within the range of tumor incidence rates among control animals from previous studies that had been conducted in the investigators' laboratory. No carcinogenic response was indicated in any of the treated groups of mice. Under the conditions of their study, the investigators concluded that treatment with methylene chloride for up to 104 weeks did not induce a carcinogenic response.

In an inhalation study [12] sponsored by an industry group subsequently named the Halogenated Solvents Industry Alliance (HSIA), a total of 1,032 male and female Sprague-Dawley rats (129 of each sex at each exposure concentration) and a total of 866 male and female Golden Syrian hamsters (107 to 109 of each sex at each exposure concentration) were exposed at concentrations of 0, 500, 1500, or 3500 parts per million (ppm) of methylene chloride (99.5% pure) for 6 hours per day, 5 days per week for 2 years. The authors stated that "approximately" 95 rats and hamsters of each sex at each exposure concentration were used for studies of chronic toxicity and carcinogenicity. The remainder of the animals of each species, sex, and exposure group were used in hematologic and cytogenetic studies (rats at 6 months only) and killed after either 6, 12, 15, or 18 months of exposures. Groups of 4 rats and 4 hamsters of each sex, from each exposure group, were used to obtain blood for carboxyhemoglobin determinations after 6, 11, 18, 21, or 22 (hamsters only) months of exposures [12].

There were no unusual or statistically significant hematologic or cytogenetic effects observed among either rats or hamsters of either sex at any exposure concentration [12]. However, the mean percent of carboxyhemoglobin in the blood was increased and statistically significant

for each species and sex at each exposure concentration at each time examined (6, 11, 18, and 21 months) as compared to control animals. The increase did not appear to be dose- or time-related since the carboxyhemoglobin concentration did not vary with the concentration or duration of exposure to methylene chloride.

Although female rats, at all three exposure concentrations, had dose-related increases in the total number of benign mammary gland tumors (adenomas, fibromas, and fibroadenomas) per tumor-bearing rat, as compared to the tumor-bearing controls, the number of rats with tumors in each exposure group did not increase. An increased incidence of the mammary gland tumors was also reported for the male rats exposed at 3500 ppm, but the increase was less pronounced than that for the females. The male rats exposed to 3500 ppm of methylene chloride also had a statistically significant increase in the incidence of salivary gland cancer (sarcomas) compared with controls. A similar response, though not statistically significant, was reported among male rats exposed at 1500 ppm. The investigators suggested that a salivary gland viral disease (sialodacryoadenitis) in the rats, combined with the methylene chloride exposures, may have been associated with the development of this tumorigenic response; however, the sarcomas were not identified in the similarly infected female rats exposed to methylene chloride. Male and female hamsters exposed under similar experimental conditions as those used for studies on the Sprague-Dawley rats showed no evidence of a carcinogenic response [12].

A subsequent HSIA-sponsored inhalation study [13] was performed with male and female Sprague-Dawley rats at methylene chloride concentrations of 0, 50, 200, or 500 ppm, 6 hours per day, 5 days per week for 2 years. This study was designed to investigate further the responses observed at the higher exposure concentrations used in the previous study [12]. A slight increase, but not statistically significant, occurred for mammary fibromas and fibroadenomas per female rat exposed at 500 ppm of methylene chloride as compared to control rats. No increased incidence of salivary gland tumors (sarcomas) was observed in any exposure or control group.

As in the earlier study [12], the percent of carboxyhemoglobin in the blood was elevated in rats of each sex, at each exposure concentration, and at each time examined (6, 12, 15, 18, and 24 months). However, unlike the data obtained from the first study which used higher doses, the carboxyhemoglobin response obtained in this study [13], indicated to the investigators, that the metabolism of methylene chloride is dose-related and saturable.

Data from two additional studies of the animal carcinogenicity of methylene chloride are available from a 1985 National Toxicology Program (NTP) technical report [14]. Groups of Fischer 344/N rats and $B6C3F_1$ mice were exposed to methylene chloride (maximum purity, 99%) by inhalation for 2 years, 6 hours per day, 5 days per week at concentrations of 0, 1000, 2000, or 4000 ppm and 0, 2000, or 4000 ppm, respectively. There was a statistically significant increase in the number of benign mammary gland tumors (fibroadenomas) in male rats exposed at 4000 ppm and in the female

rats exposed at 1000, 2000, or 4000 ppm, when compared to controls. Based on these findings, the NTP stated that "...there was some evidence of carcinogenicity of dichloromethane for male F344/N rats as shown by an increased incidence of neoplasms of the mammary gland. There was clear evidence of carcinogenicity of dichloromethane for female F344/N rats as shown by increased incidences of neoplasms of the mammary gland."

In the study of $B6C3F_1$ mice, a statistically significant increase in lung cancers (alveolar/bronchiolar carcinomas) and benign lung tumors (alveolar/bronchiolar adenomas) over controls was reported among males and females exposed at concentrations of 2000 or 4000 ppm. A statistically significant increase was also reported for cancers (hepatocellular carcinomas) of the liver in male mice exposed at 4000 ppm and in female mice exposed at 2000 or 4000 ppm. The NTP concluded "...that there was clear evidence of the carcinogenicity of dichloromethane for male and female $B6C3F_1$ mice as shown by increased incidences of alveolar/bronchiolar neoplasms and of hepatocellular neoplasms" [15].

The studies which indicate the potential of methylene chloride to induce cancers or tumors in experimental animals appear well conducted and without major shortcomings. A possible exception to this pattern is suggested by the report of sialodacryoadenitis among male rats exposed at 1500 ppm methylene chloride in the HSIA study. Otherwise, there were no indications of toxicity that would be expected to interfere with findings of carcinogenicity in these studies.

Epidemiologic Studies

The results of a proportionate mortality study of all deaths, occurring from 1956 through 1976, among active, disabled, or retired males who worked in areas of a plant which manufactured photographic products were published in 1978 [16]. Methylene chloride was used as a primary solvent in the plant studied. The environmental exposures varied from 0 to 350 ppm with a general decline in mean exposure concentrations from 118.8 ppm in 1966 to 40.3 ppm in 1975. The typical patterns of exposure encountered by these workers is unclear. Deaths of all other male workers at the plant were used as a comparison population. Although this proportionate mortality study did not demonstrate any significant excess mortality for any of the disease categories, the study design was limited by: (1) evaluation of only those who died while employed or who were disabled or retired workers, (2) the interrelated nature of the proportionate mortality categories, and (3) the necessary but unverified assumption of equal proportions of cause-specific mortality in the exposed and comparison populations except for the effects of exposure.

These same investigators [16] reported the results of a cohort mortality study of 751 hourly, male workers employed at this plant, in 1964, in the methylene chloride exposure areas, of which 252 had a minimum of 20-years work exposure. This cohort included a greater proportion of long-term

workers than was typical of cohort studies and did not include the mortality of exposed workers who terminated employment before 1964. Two comparison populations were used for this study; one included male hourly workers in the same plant, the other from the general male population of New York State, excluding New York City. Two updates of the original report have been published [17,18]. Each update covered an additional 4 years of mortality experience. The original report and subsequent updates cover a total of 20 years of follow-up (1964-1984). The hypertensive disease category (International Classification of Diseases, 8th Revision, 400-404) was reported as significant (4 observed vs. 1 expected on other Kodak Park workers) in the original report, but this category was not considered in the subsequent updates. No other excesses were reported as statistically significant in the three reports. A non-significant excess of cancer of the pancreas was observed in the total cohort (8 observed vs. 3.0 expected in the New York State and 2.6 expected in the in-plant comparison populations). However, it is noteworthy that this excess was associated with a significance level of less than 5% but greater than 1%, with the latter value being the statistical criteria used for non-hypothesized risk categories [19]. It is also noteworthy that this study had only a 35% statistical power to detect an association at this level of significance [20]. The conclusions from this study are limited by: (1) a narrow cohort definition, (2) limited documentation of exposure, (3) unclear standardization of coding between revisions of the International Classification of Diseases, (4) lack of follow-up on the small number of terminated, non-vested workers, and (5) low statistical power to detect modest increases in less common site-specific cancers.

A second study [21,22] described the mortality experience of two cohorts of workers involved in the manufacture of synthetic fibers: (1) 1,271 workers exposed to methylene chloride and acetone and (2) a reference group exposed only to acetone. Both groups were exposed to these substances for at least 3 months between 1954, when methylene chloride was first used, and 1977, when the study ended. Methylene chloride exposure concentrations ranged from 5 to 900 ppm [21]. Although exposure categories were defined as low, moderate, or high, the observed mortality was not analyzed according to these categories. The cause of death due to malignant neoplasms did not exceed the expected number of deaths based on the U.S. death rates. However, the small number of workers exposed and the relatively short latency period for most of the workers precludes the capability of definitively evaluating an occupational carcinogenic effect in the exposed cohort. When the methylene chloride-acetone exposed cohort mortality experience was compared using a summary statistical analysis to the acetone reference cohort mortality experience, statistically significant differences were observed for deaths from diseases of the circulatory system and from ischemic heart disease [22]. The interpretation of this study is limited by: (1) low statistical power to detect increases in overall malignant neoplasms and site-specific cancers, (2) absence of analysis for qualitative exposure categories, (3) loss to vital status follow-up for 18% of the cohort members, and (4) too brief of a follow-up to detect occupationally related cancer.

CONCLUSIONS

The research data presented in this Current Intelligence Bulletin (CIB) have focused on the carcinogenic effects observed in animals or workers exposed to methylene chloride. The lung, liver, and salivary and mammary glands are the primary sites of carcinogenic or tumorigenic responses in methylene chloride-treated mice and rats. One epidemiologic study, of a small worker population, provides limited evidence that methylene chloride exposure may be related to the increased risk of pancreatic cancer.

As stated earlier, the studies which indicate the potential for methylene chloride to induce cancers or tumors in experimental animals are without major shortcomings. The strains of animals used and the route and doses selected for administration of methylene chloride impose no limitations on the interpretation of the results. Therefore, NIOSH believes that the collective carcinogenicity data provide sufficient evidence to warrant concern about the potential consequences of occupational exposure to methylene chloride.

It is of interest that the studies funded by the Halogenated Solvents Industry Alliance (HSIA) [12,13] found that the concentration of carboxyhemoglobin in the blood of experimental animals was dose related over the exposure range of 0 to 500 ppm and was elevated, but not dose related over the range of 500 to 3500 ppm, indicating to the investigators that metabolic saturation had occurred. These results may explain, in part, why neoplasms were found only among those animals exposed at concentrations in excess of 500 ppm in the HSIA studies. However, these data provide no insight concerning the potential for tumor development among animals that may have been exposed at the lower doses for periods greater than 2 years. This cannot be supported by results from the National Toxicology Program (NTP) study [14] because the animals were exposed at concentrations of 1000 ppm and higher, and because carboxyhemoglobin concentrations were not determined. Some data on the dose-related increase of carboxyhemoglobin were previously described in the 1976 NIOSH criteria document on methylene chloride [6]; in that document, carboxyhemoglobin concentrations were reported to increase with exposure concentration and time over a range of concentrations of 50 to 1000 ppm following exposures of 1 to 7.5 hours per day, 5 days per week. These latter data indicate that the pathway to produce carboxyhemoglobin had not been saturated at methylene chloride exposure concentrations as high as 1000 ppm.

RECOMMENDATIONS

Several methods for identifying a substance as a carcinogen have been proposed. Such classifications have been developed by the National Toxicology Program (NTP) [15], the International Agency for Research on Cancer (IARC) [23], and the Occupational Safety and Health Administration (OSHA) in its "Identification, Classification, and Regulation of Potential Occupational Carcinogens" (29 CFR 1990) [24], also known as "The OSHA Cancer

Policy." Since the OSHA Cancer Policy specifically addresses occupational exposures, NIOSH considers that policy to be the most appropriate for use in identifying a substance as a potential occupational carcinogen.

In its Cancer Policy, OSHA provides criteria that must be applied in order to identify, classify, and regulate a substance as a potential occupational carcinogen. In 29 CFR 1990.112(b), the Policy states: "A substance shall be identified and regulated as a Category II Potential Carcinogen if, upon scientific evaluation, the Secretary determines that; (ii) the substance meets the criteria set forth in 1990.112(a) in a single mammalian species without evidence of concordance." In 1990.112(a) concordance is defined as: "Positive results from independent testing in the same or other species, positive results in short-term tests, or induction of tumors at implantation sites."

Provisions for the use of human and animal data are provided in 1990.143 of the OSHA Cancer Policy. In 1990.143(f), the Policy accepts data obtained following oral, respiratory, or dermal exposure; in 1990.143(g) the Policy allows the use of "high" dose exposures; and in 1990.143(i), the Policy allows the use of either benign or malignant tumors to establish a qualitative inference of carcinogenicity.

The data obtained by the NTP from studies with methylene chloride using rats [14] demonstrate exposure and dose-related increases in benign mammary tumors in males and females, respectively, and exposure-related malignant tumors of the lung and liver in male and female mice. These data in conjunction with the data obtained by the HSIA [12] are sufficient to classify methylene chloride as an OSHA Category I potential carcinogen as described in 1990.112(a).

Although additional support for this classification is not provided by the epidemiologic studies conducted to date [16-18,21,22], such concordance is not required by the OSHA Cancer Policy.

Because methylene chloride has been shown to induce increased numbers of benign and malignant neoplasms in rats and mice, it meets the criteria provided in the OSHA Cancer Policy for classifying a substance as a potential occupational carcinogen; therefore, NIOSH recommends that methylene chloride be considered a potential human carcinogen in the workplace.

The finding of an excess of pancreatic cancers (non-statistically significant) in a small cohort of methylene chloride-exposed workers is also of concern.

The excess risk of cancer to workers exposed to specific airborne concentrations of methylene chloride has not yet been determined, but the

probability of developing such an adverse effect would be decreased by reducing exposure. As prudent public health policy, employers should voluntarily assess the conditions under which workers may be exposed to methylene chloride and take all reasonable precautions to reduce exposures to the lowest feasible limit.

Indications of the carcinogenicity of methylene chloride are not the only concern NIOSH has regarding worker exposure to this widely used solvent. NIOSH's original recommendation concerning exposure to methylene chloride was based, in part, on findings of impaired delivery of oxygen to tissues. At that time, NIOSH described methylene chloride-exposed workers who experienced chest pains, heart palpitations, and rapid pulse. The report of excess mortality from ischemic heart disease in one methylene chloride-exposed cohort [22] appears to be consistent with earlier findings reported by NIOSH. Those findings are not conclusive and require additional verification. Nevertheless, by controlling methylene chloride exposures to the lowest feasible limit, employers can ensure that the concentration of carboxyhemoglobin in the blood does not exceed acceptable levels as described in the 1976 NIOSH criteria document [6].

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APPENDIX

GUIDELINES FOR MINIMIZING WORKER EXPOSURE TO METHYLENE CHLORIDE

Based on the conclusions described in this Current Intelligence Bulletin (CIB), NIOSH recommends that employers, workers, and health care professionals take the following actions to reduce the long-term risk of cancer and the possible risk of adverse effects on the cardiovascular system as a result of methylene chloride exposure.

I. Employers should:

A. Control worker exposure to the lowest feasible limit through effective engineering controls, good work practices, and proper maintenance procedures.

B. Provide appropriate exhaust ventilation or control exposure by enclosed processes.

C. Provide isolation of workers by the use of remote control rooms and utilization of automated equipment.

D. Provide appropriate personal protective clothing and equipment to minimize contact with the skin and eyes, and require workers to change clothing that has become contaminated with methylene chloride.

E. Provide clothing change rooms, showers, and eating areas free from methylene chloride or other chemical exposure. Eating and smoking should not be permitted in areas where methylene chloride is manufactured, stored, or used.

F. Provide suitable and effective respiratory protective equipment (Table 2); provide fit testing and training on the proper use of respirators and provide for regular maintenance, inspection, and cleaning of respirators.

G. Provide routine personal air monitoring for workers potentially exposed to methylene chloride and inform them of the results of analysis. Monitoring for carbon monoxide (CO) should also be conducted.

H. Provide a medical monitoring program that will detect methylene chloride-induced health effects (Table 3). Provide physicians or other health care personnel with all toxicologic information, industrial hygiene sampling data, and a listing of protective devices or equipment the worker may be required to use when a potential for exposure to methylene chloride exists. Conduct medical evaluations to determine the worker's physical fitness for using respiratory protective equipment.

TABLE 2.--Respirator selection for methylene chloride

Conditions of use	Recommended respirator
For any condition requiring the use of respirators except as noted below	Self-contained breathing apparatus equipped with a full facepiece and operated in a pressure-demand or other positive pressure mode or Supplied-air respirator equipped with a full facepiece and operated in a pressure-demand or other positive pressure mode in combination with an auxiliary self-contained breathing apparatus operated in pressure-demand or other positive pressure mode
Firefighting situation	Self-contained breathing apparatus with a full facepiece and operated in a pressure-demand or other positive pressure mode
Escape situations	Any air-purifying respirator equipped with a full facepiece (gas mask) and an organic vapor canister; or any appropriate escape-type self-contained breathing apparatus

TABLE 3.--Signs and symptoms of methylene chloride exposure

Eye or skin irritation
Dizziness
Incoordination
Nausea
Tingling or numbness of extremities
Irritability
Lethargy
Stupor

I. When possible, replace methylene chloride with a chemical that has been shown not to cause cancer or other adverse health effects in animals or in humans.

J. Provide a worker education program which is designed to inform the worker about the potential health risks from exposure to methylene chloride, the proper use of personal protective equipment or clothing, smoking cessation programs, and proper work practice procedures.

K. Provide all workers who are or who may be exposed to methylene chloride with a copy of this CIB pointing out the list of adverse symptoms and health effects associated with exposure to methylene chloride (Table 3).

II. Workers should:

A. Make appropriate use of personal protective equipment and respirators provided by the employer.

B. Avoid contact with methylene chloride and immediately change clothing that has become contaminated with the chemical.

C. Immediately and thoroughly wash with soap and water all areas of the body that come into contact with methylene chloride.

D. Report any health signs and symptoms of exposure to methylene chloride to the responsible health professional. If a private physician is used, see that the physician receives a copy of this CIB.

III. Physicians and other health care professionals should:

A. Be familiar with the signs and symptoms that are suggestive of exposure of workers to methylene chloride (Table 3).

B. Maintain complete medical, chemical exposure, and occupational history information for each worker.

C. Perform periodic medical examinations, giving particular attention to the respiratory, cardiovascular, and nervous systems and to the liver, pancreas, blood, and skin, as these are the primary targets of exposure to methylene chloride.

NIOSH

Current Intelligence Bulletin 47

July 25, 1986

4,4'– METHYLENEDIANILINE (MDA)

(Revised)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

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Mention of the name of any company or product does not constitute endorsement by the National Institute for Occupational Safety and Health.

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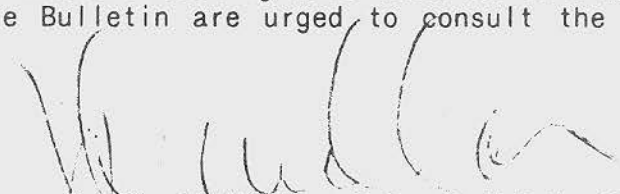
FOREWORD

Current Intelligence Bulletins (CIB's) are reports issued by the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control, Atlanta, Georgia, for the purpose of disseminating new scientific information about occupational hazards. A CIB may draw attention to a hazard previously unrecognized or may report new data suggesting that a known hazard is either more or less dangerous than was previously thought.

CIB's are prepared by the staff of the Division of Standards Development and Technology Transfer, NIOSH (Robert A. Taft Laboratories, 4676 Columbia Parkway, Cincinnati, Ohio 45226) and are distributed to representatives of academia, industry, organized labor, public health agencies, and public interest groups, as well as to those federal agencies, such as the Department of Labor, which have responsibilities for protecting the health of workers. It is our intention that anyone with the need to know should have ready access to the information contained in these documents; we welcome suggestions concerning their content, style, and distribution.

The purpose of this bulletin is to disseminate recent information on the potential carcinogenicity of 4,4'-methylenedianiline (MDA) previously identified by NIOSH in 1976 in CIB No. 8 as 4,4'-diaminodiphenylmethane (DDM). In the CIB, the occupational health community was informed of the hepatotoxicity of DDM in animals and humans and of limited evidence regarding the potential carcinogenicity of DDM in animals. Since 1976, animal studies have confirmed the carcinogenic potential of MDA. In accordance with the Cancer Policy of the Occupational Safety and Health Administration (OSHA) ("Identification, Classification, and Regulation of Potential Occupational Carcinogens," 29 CFR 1990), on the basis of findings of carcinogenic and tumorigenic responses in rats and mice, NIOSH recommends that MDA be regarded as a potential occupational carcinogen. While estimates of the excess risk of cancer in exposed workers have not been determined, it is logical to assume that reducing exposure to MDA in the workplace would reduce the potential risk.

It is recommended that producers and users of MDA disseminate this information to their workers and customers, that professional and trade associations and unions inform their members of the potential hazards of MDA, and that appropriate engineering controls and work practices be used to minimize exposure of workers. Readers seeking more detailed information on the studies referenced in the Bulletin are urged to consult the original publications.



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CURRENT INTELLIGENCE BULLETIN #-47

4,4'-METHYLENEDIANILINE (MDA) (REVISED)

July 25, 1986

ABSTRACT

Wistar rats receiving a single injection of 2,2'-dihydroxy-N-nitrosodipropylamine (a tumor initiator) followed by 4,4'-methylenedianiline (MDA) in the diet for 19 weeks, developed thyroid follicular cell carcinomas and follicular cell and papillary adenomas. Fischer 344/N rats and $B6C3F_1$ mice receiving MDA as 4,4'-methylenedianiline dihydrochloride ad libitum in drinking water for 2 years developed thyroid follicular cell carcinomas and adenomas, C-cell adenomas of the thyroid, hepatocellular carcinomas and adenomas, alveolar bronchiolar adenomas, malignant lymphomas, and benign tumors of the adrenal gland. Workers with airborne and dermal exposure to powdered MDA have developed toxic hepatitis. In addition, increased incidences of cancers of the bladder and large intestine and of lymphosarcoma and reticulosarcoma have been reported in workers with potential exposure to MDA.

The observation of cancers and tumors in both rats and mice treated with MDA meets the criteria established in the Cancer Policy of the Occupational Safety and Health Administration for considering MDA a potential human carcinogen in the workplace. Although there is limited evidence indicating that MDA presents a carcinogenic risk to humans, the probability of developing such effects would be decreased by reducing exposure to the compound in the workplace. Therefore, the National Institute for Occupational Safety and Health (NIOSH) recommends that occupational exposures to MDA be controlled to the lowest feasible limit.

BACKGROUND

Physical and Chemical Properties

In pure form, 4,4'-methylenedianiline (MDA) is a light brown, crystalline solid with a faint amine-like odor. MDA is slightly soluble in water and readily soluble in alcohol, benzene, and ether. It is structurally similar to benzidine and 4,4'-methylenebis (2-chloroaniline) (MOCA or MBOCA). Additional chemical and physical properties are listed in Table 1.

Table 1.--Chemical and physical properties
[Dean 1979; Newman et al. 1981;
Windholz et al. 1983; Lewis and Sweet 1985]

Chemical identity:	4,4'-methylenedianiline (MDA)
CAS[1] registry no.	101-77-9
RTECS[2] accession no.	BY5425000
Synonyms	4-(4-aminobenzyl)aniline, bis(p-aminophenyl)methane, DADPM, DAPM, DDM, diaminodiphenylmethane, p,p'-diaminodiphenylmethane, 4,4'-diaminodiphenylmethane, di-(4-aminophenyl)methane, methylenebis(aniline), methylenedianiline
Molecular weight	198.26
Empirical formula	$C_{13}H_{14}N_2$
Melting point	92°C (198°F)
Boiling point (at 768 mmHG)	399°C (750°F)
Vapor pressure (calculated)	1.5×10^{-7} torr at 25°C (77°F)

[1]Chemical Abstract Service (CAS)
[2]Registry of Toxic Effects of Chemical Substances (RTECS)

Production, Use, and Potential for Occupational Exposure

MDA is produced by the condensation of aniline with formaldehyde in the presence of an acid catalyst [NIOSH 1976, 1984b]. In 1982, annual production was 200-400 million pounds [EPA 1983b]. Approximately 99% of MDA is used in the production of methylene diphenyl diisocyanate (MDI) or polymeric MDI (PMDI), which are used to produce rigid or semirigid polyurethanes. The remaining 1% of MDA is purified and used to make products such as protective coatings, a hardening agent for epoxy resins,

anti-corrosive materials, printed circuit parts, dyestuff intermediates [EPA 1983a], filament wound pipe [NIOSH 1984a], and wire coatings [EPA 1985].

The National Institute for Occupational Safety and Health (NIOSH) estimates that 9,000 U.S. workers may be exposed to MDA [Sundin 1972-74].

EXPOSURE LIMITS

The Occupational Safety and Health Administration (OSHA) has not established a permissible exposure limit (PEL) for MDA. The American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV®) for MDA is 0.1 part of MDA per million parts of air (ppm) or 0.8 milligram of MDA per cubic meter of air (mg/m^3) determined as an 8-hour, time-weighted average (TWA) concentration. The ACGIH short-term exposure limit (STEL) for MDA is 0.5 ppm (4 mg/m^3). The ACGIH TLV and STEL values include a "Skin" notation which refers to the potential contribution to the overall exposure by the cutaneous route, including the mucous membranes and eyes, by either airborne or direct contact with MDA [ACGIH 1985]. The TLV is based on the prevention of hepatitis in workers exposed to MDA [ACGIH 1980]. In their Notice of Intended Changes (for 1985-86), the ACGIH has proposed that the STEL be deleted. Additionally, an "A2" designation has been proposed. The "A2" designation refers to a substance suspected of having carcinogenic potential in man [ACGIH 1985]. NIOSH has not established a recommended exposure limit (REL) for MDA. In a recent risk assessment, the United States Environmental Protection Agency (EPA) classified MDA as a probable human carcinogen [Hirzy et al. 1985] and has referred regulatory responsibility for MDA to OSHA under Section 9(a) of the Toxic Substance Control Act [EPA 1985].

TOXICITY

Results of Animal Studies

Acute Toxicity

The acute toxicity of MDA has been reported in several animal species by various routes of administration. The lethal dose of MDA for 50% of the animals tested (LD_{50}) was: Oral administration to Wistar rats, 347 mg per kilogram of body weight (mg/kg bw) [Marhold 1972]; subcutaneous administration to Wistar rats, 200 mg/kg bw [Steinhoff 1970]; and intraperitoneal (IP) administration to BALB/cCR mice, 74 mg/kg bw [Lopatka et al. 1976]. The lowest dose to have caused death (LDLo) by oral administration to beagle dogs was 300 mg/kg bw [Deichmann et al. 1978].

Mutagenic Effects

MDA was found to be mutagenically active when tested in Salmonella typhimurium strains TA98 and TA100 following metabolic activation [Darby et al. 1978; Parodi et al. 1981; Rao et al. 1982], but was inactive in strains TA1535 and TA1537, with or without metabolic activation [Darby et al. 1978; Rao et al. 1982]. A significant increase in sister chromatid

exchanges ($p<0.001$) in femoral bone marrow have been reported in Swiss mice injected with MDA when compared to vehicle-treated controls [Parodi et al. 1983].

Carcinogenic and Other Chronic Effects

In a chronic study, capsules containing 70 mg of MDA were administered orally 3 times per week to nine female beagle dogs over periods of approximately 4-7 years; the total doses of MDA ranged from 4.0 to 6.26 grams (g)/kg bw. A variety of histopathologic changes were observed in tissues from all of the dogs, particularly in the livers. However, no neoplastic lesions of the liver or urinary bladder were observed. No data for untreated, control dogs were reported [Deichmann et al. 1978].

Bile duct proliferation, oval cell infiltration, and fibrosis were observed in the livers of 16 male Wistar rats fed a diet containing 1,000 ppm MDA for 32-40 weeks [Fukushima et al. 1979]. Bile duct proliferation and spongiosis hepatitis were observed in the livers of 3 of 8 male Spraque-Dawley rats fed ad libitum a diet containing 800 ppm MDA for 48 weeks [Ito et al. 1984]. No neoplastic lesions were observed in the MDA-treated rats in either study. The actual dose of MDA received by the rats in these studies was not reported.

In another study, 80-day-old male albino rats of unknown strain (120 per group) were given 8 or 20 mg MDA/kg bw in peanut oil by gavage 5 days per week for 16 weeks. For control purposes, rats (120 per group) were given peanut oil or were untreated. Ten rats from each group were killed and examined at 10 days, 6 weeks, and 16 weeks for MDA-induced pathology. The remaining rats were examined upon natural death. The average lifespan of all rats treated with MDA was 11.3 months, while that of the animals in the control groups was 12.5 months. The average lifespan for all animals was short, due to pulmonary disorders and otogenic inflammation extending into the meninges. Hepatocellular effects including reduced glycogen concentrations, and increased mitoses and numbers of multinucleated hepatocytes were observed in rats treated with 8 mg MDA/kg bw. In addition to these effects, the livers of the rats treated with 20 mg MDA/kg bw had hyperplastic nodules and "adenoma-like" bile duct proliferations. There was also evidence of "cirrhosis-like" regeneration processes. Statistical analyses of these data were not reported [Gohlke 1978].

In Current Intelligence Bulletin (CIB) No. 8 published in 1976, NIOSH summarized three studies of the carcinogenic effects of MDA in rats [NIOSH 1976]. In one study MDA was administered subcutaneously to 50 Wistar rats (25 of each sex). A two-fold increase of malignant and benign tumors (types unspecified) was observed in the MDA-treated rats when compared with controls treated with saline. Hepatomas have been observed in two studies following MDA administration to rats by gavage: Single occurrences of other tumors, including an adenocarcinoma of the uterus, were also reported. No

conclusions could be drawn from these studies regarding the carcinogenicity of MDA due to their short duration, limited numbers of animals studied, and lack of control animals or historical control data.

In 1976, a 2-year study of the carcinogenic effects of chronic ingestion of MDA in drinking water was performed for the National Toxicology Program (NTP) [Weisburger et al. 1981; NTP 1983]. Drinking water containing either 150 or 300 ppm MDA (as the dihydrochloride salt, >98% pure) was administered ad libitum to groups of Fischer 344/N rats and $B6C3F_1$ mice (50 of each sex) for 103 weeks. Control animals (50 rats and 50 mice of each sex) received drinking water adjusted to the pH of the 300 ppm dose. Based on the water consumed by the animals, the average daily intake of MDA by the animals expressed in mg/kg bw (± one standard deviation) is provided in Table 2.

Table 2.--Average daily MDA intake (mg/kg bw)

	Rat		Mouse	
MDA in drinking water	Male	Female	Male	Female
150 ppm	9 ± 2	10 ± 2	25 ± 5	19 ± 7
300 ppm	16 ± 3	19 ± 2	57 ± 9	43 ± 10

Surviving animals were killed between weeks 104 and 106 of the study. Neoplastic lesions which occurred in statistically significant numbers are listed in Table 3 and include: Thyroid follicular cell carcinomas and adenomas, and C-cell adenomas; hepatocellular carcinomas and adenomas, and neoplastic nodules of the liver; malignant lymphomas; adrenal pheochromocytomas; and alveolar bronchiolar adenomas. Although not statistically significant, uncommon tumors such as bile duct adenomas, papillomas of the urinary bladder, and granulosa cell tumors of the ovary were also reported; these tumors are of low incidence in historical controls [NTP 1983].

Table 3.--Statistically significant incidences of neoplastic lesions in rats and mice treated with MDA [NTP 1983]

Neoplastic lesions	Control	150 ppm	300 ppm
Thyroid follicular cell carcinoma			
rats-male	0/49	0/47	7/48*
Thyroid follicular cell adenoma			
rats-female	0/47	2/47	17/48***
mice-male	0/47	3/49	16/49***
mice-female	0/50	1/47	13/50***
Thyroid C-cell adenoma			
rats-female	0/47	3/47	6/48*
Hepatocellular carcinoma			
mice-male	10/49	33/50***	29/50***
mice-female	1/50	6/50	11/50**
Hepatocellular adenoma			
mice-female	3/50	9/50*	12/50**
Neoplastic nodules of the liver			
rats-male	1/50	12/50**	25/50***
Malignant lymphomas			
mice-female	13/50	28/50**	29/50***
Adrenal pheochromocytomas			
mice-male	2/48	12/49**	14/49***
Alveolar bronchiolar adenoma			
mice-female	1/50	2/50	6/49*

* Significantly different from controls, $p<0.05$.
** Significantly different from controls, $p<0.01$.
*** Significantly different from controls, $p<0.001$.

In 1984, the results were reported of a study designed to test the cancer promotion potential of MDA following administration of 2,2'-dihydroxy-N-nitrosodipropylamine (DHPN), the initiator, using male Wistar rats [Hiasa et al. 1984]. The rats were placed into four groups of 21 each. Group 1

received a single IP injection of 2.8 g DHPN/kg bw followed for 19 weeks with 1,000 ppm MDA in the diet; Group 2 received 2.8 g DHPN/kg bw IP; Group 3, 1,000 ppm MDA in the diet; and Group 4 (controls), 5 milliliters (mL) of saline/kg bw IP. All the rats were killed after 19 weeks. Thyroid follicular cell carcinomas developed in 9.5% of the DHPN and MDA-treated rats (Group 1). Thyroid follicular cell and papillary adenomas developed in 90% of the DHPN and MDA-treated rats (Group 1) and in 28% of the DHPN-treated rats (Group 2); these incidences were significantly different ($p<0.05$) between Groups 1 and 2. No tumors were reported in Groups 3 or 4. A carcinogenic response was not observed when the initiator or promoter were administered separately (Groups 2 and 3), but was observed when the initiator and promoter were administered sequentially (Group 1). Although the study was of short duration, the authors concluded that DHPN was the initiator and that MDA was the promoter [Hiasa et al. 1984], a postulate substantiated by other studies involving the activity of DHPN as an initiator [Hiasa et al. 1982a; 1982b].

Human Health Effects

In 1976, NIOSH reviewed several studies of the health effects of MDA in workers which described the occurrence of jaundice, bile duct inflammation, suppression of bile excretion, and clinical hepatitis [NIOSH 1976]. In other case studies, it was reported that dermal exposure to MDA resulted in allergic contact dermatitis [Emmett 1976], acute myocardial damage [Brooks et al. 1979], jaundice [Dunn and Guirguis 1979], photosensitivity [LeVine 1983], hepatitis [Bastian 1984], and yellow staining of the skin [Cohen 1985]. Hepatitis and impaired visual acuity have been observed following ingestion of MDA [Roy et al. 1985]. No information is available on the rate of absorption or metabolism of MDA in humans.

In 1982, NIOSH published the results of a Health Hazard Evaluation (HHE) [NIOSH 1982] of workers in the blade and pattern shops of a manufacturer of helicopters and helicopter parts. The purpose of the evaluation was to determine if workers in those shops were at an increased risk of cancer of the bladder and colon. A proportionate mortality ratio (PMR) study was designed to analyze the mortality pattern observed in the deaths of 179 white male workers. These deaths were identified from among "exposed" workers who: Had been employed by the company 10 years or longer and had been assigned at least one month in the area where there was potential exposure to epoxy resins and curing agents, including MDA. The concentrations of MDA in the air for three personal samples were: Below 10 micrograms per cubic meter ($\mu g/m^3$) for a 20 liter (L) sample (the limit of detection), 0.23 mg/m^3, and 0.46 mg/m^3. Causes of death for "exposed" workers were examined and statistically significant excesses of cancer of the bladder (3 observed vs. 0.8 expected, PMR 3.74, $p\leq0.05$), cancer of the large intestine (7 observed vs. 3.1 expected, PMR 2.26, $p\leq0.05$), and lymphosarcoma/reticulosarcoma (3 observed vs. 0.87 expected,

PMR 3.45, $p \leq 0.05$) were detected. In the proportional cancer mortality ratio (PCMR) analysis, only cancer of the bladder remained statistically significant (PCMR 3.41, $p \leq 0.05$). In addition, two more cases of bladder cancer were found in "exposed" living workers [NIOSH 1982].

In this study [NIOSH 1982], there were a number of limitations such as: (1) The concentrations of MDA were determined by using a sampling method which has been shown to be unreliable [Boeniger 1985], and may underestimate historical exposure; (2) the workers in the areas were also potentially exposed to a number of other chemicals such as ethylenediamine, cyclohexanone, methyl isobutyl ketone (MIBK), toluene, and butyl glycidyl ether (BGE); (3) the PMR study design is subject to potential biases because it only includes workers with 10 years or more work experience and lacks information on death cause categories; and (4) the duration of exposure and latency for the bladder cancer cases are shorter than that usually associated with solid tumors resulting from occupational or chemical exposures. However, the study provides support for suspected increased risk of cancer of the bladder and colon associated with exposure to MDA. The study also suggests that an increased risk of lymphosarcoma/reticulosarcoma may be associated with exposure to MDA.

CONCLUSIONS

This bulletin has focused on studies regarding the carcinogenic potential of MDA that have been reported since NIOSH CIB No. 8 was published in 1976. That CIB warned of acute liver toxicity in animals and humans.

More recent animal studies indicate a potential for carcinogenicity from exposure to MDA. The liver, thyroid, adrenal glands, and lymphatic system are the primary sites identified with carcinogenic or tumorigenic responses following oral or IP administration of MDA. The occurrence of uncommon tumors of the bile duct and urinary bladder may also be significant due to their low historical control incidences. In rats, MDA also acted as a promoter of tumor development.

Epidemiologic evidence suggests an association between MDA and bladder cancer, colon cancer, lymphosarcoma, and reticulosarcoma in workers with exposure to MDA and other chemical agents. Although airborne exposures to MDA may occur, dermal contact is considered the major route of occupational exposure.

NIOSH believes that the collective toxicologic data on carcinogenicity provide sufficient evidence to warrant concern for occupational exposure to MDA. Although there is limited evidence indicating that MDA presents a carcinogenic risk to exposed workers, the human data, in view of the positive data in other mammalian species, suggest that such a potential may exist.

RECOMMENDATIONS

There are several classifications for identifying a substance as a carcinogen. Such classifications have been developed by NTP [NTP 1984], the International Agency for Research on Cancer (IARC) [WHO 1979], and OSHA in its "Identification, Classification, and Regulation of Potential Occupational Carcinogens" 29 CFR 1990 [OSHA 1984b], also known as "The OSHA Cancer Policy." NIOSH considers the OSHA classification the most appropriate for use in identifying occupational carcinogens* [OSHA 1984b]. Since exposure to MDA has been shown to produce malignant tumors in rats and mice, it meets the OSHA criteria. Therefore, NIOSH recommends that MDA be considered a potential human carcinogen in the workplace.

The excess risk of cancer to workers exposed to MDA has not yet been determined, but the probability of developing cancer would be decreased by minimizing exposure. As prudent public health policy, employers should assess the conditions under which workers may be exposed to MDA and take reasonable precautions to reduce exposures to the lowest feasible limit.

The guidelines for minimizing worker exposure to MDA, presented in the Appendix, are general in nature and should be adapted to specific work situations as required.

*"'Potential occupational carcinogen' means any substance, or combination or mixture of substances, which causes an increased incidence of benign and/or malignant neoplasms, or a substantial decrease in the latency period between exposure and onset of neoplasms in humans or in one or more experimental mammalian species as the result of any oral, respiratory or dermal exposure, or any other exposure which results in the induction of tumors at a site other than the site of administration. This definition also includes any substance which is metabolized into one or more potential occupational carcinogens by mammals" (29 CFR 1990.103).

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APPENDIX

GUIDELINES FOR MINIMIZING WORKER EXPOSURE TO 4,4'-METHYLENEDIANILINE (MDA)

It is recommended that MDA be regarded as a potential human carcinogen in the workplace. This recommendation is based on the ability of MDA to induce cancer in experimental animals and on limited evidence of its carcinogenic risk to humans. Consequently, appropriate engineering and work practice controls should be used to reduce worker exposure to the lowest feasible limit. The guidelines and recommendations that follow are general in nature and should be adapted to specific situations as required. These first three primary recommendations (product substitution, closed systems and ventilation, and worker isolation) provide protection for the worker from both dermal and inhalation exposure.

EXPOSURE MONITORING

NIOSH recommends that each employer who manufactures, transports, packages, stores, or uses MDA in any capacity determine if a potential exists for any worker to be exposed to the chemical.

In work areas where exposures may occur, an initial survey should be done to determine the extent of any worker's exposure. In general, daily worker time-weighted average exposures should be determined by collecting full-shift samples. When the potential for exposure is periodic, short-term samples may be needed in place of or as part of full-shift sampling. Personal sampling is preferred over area sampling. If personal sampling is not feasible, area sampling can be substituted only if the results can be used to approximate the workers' exposure. Source and general area samples may also be useful in identifying the source of emissions so that effective engineering or work practice controls can be instituted. NIOSH is currently developing a sampling method for MDA [Geraci 1986]. In the past, a number of different methods have been used [NIOSH 1984a, 1984d]. The sampling procedure must include provisions for obtaining sufficient sample volumes to ensure that the presence of small concentrations of MDA are not overlooked.

If the initial survey indicates that no worker is exposed to MDA, no further sampling is recommended unless changes in production, process, controls, work practices, or weather conditions occur that may result in a change in exposure conditions. When workers are found to be working in environments containing measurable concentrations of MDA, periodic sampling at intervals not greater than 6 months is recommended. Periodic sampling should be continued until no measurable concentrations of MDA are noted in two consecutive surveys. Periodic sampling should always be conducted in the work area of workers who are wearing respirators for protection against MDA.

The NIOSH Occupational Exposure Sampling Strategy Manual may be helpful in developing efficient strategies to monitor worker exposure to MDA. The

manual contains information regarding determination of the need for exposure monitoring, the number of samples to be collected, and the selection of appropriate sampling times [Leidel et al. 1977].

In a facility in France, workers were monitored for MDA exposure by measurement of MDA's metabolites in their urine [Vaudine et al. 1982]. NIOSH has developed a protocol for determining MDA and MDA metabolites in the urine of workers [Boeniger 1984].

CONTROLLING WORKER EXPOSURE

Proper maintenance of equipment and worker education are vital aspects of a good control program. Workers should be informed of any materials that may contain or be contaminated with MDA, the nature of the potential hazard, and of methods for minimizing exposure. Every attempt should be made to minimize exposure to MDA by implementing the following practices and controls:

Product Substitution

When feasible, substitution of an alternative material with a lesser potential health risk is often the best and most effective method for reducing or eliminating exposure. However, extreme care must be used when selecting substitutes. Possible adverse health effects from exposure to alternatives for MDA should be evaluated prior to selection.

Closed Systems and Ventilation

Engineering controls should be the principal method for minimizing the potential for MDA exposure in the workplace. Achieving and maintaining reduced concentrations of airborne MDA in the workplace depend upon the incorporation of adequate engineering control measures, such as properly constructed and maintained closed-system operations and ventilation.

Closed-system operations provide the most effective means for minimizing worker exposures to MDA. Closed systems should be used for producing, storing, transferring, packaging, and processing MDA. Where closed systems cannot be employed or do not operate effectively, local exhaust ventilation should be provided to direct particulate or vapors away from workers [NIOSH 1984d]. This contaminated exhaust air should not be recirculated [NIOSH 1984c]. Exhaust-ventilation systems for quality control laboratories or laboratories where samples are prepared for analyses, should be designed to adequately capture and contain MDA particulate or vapors. Guidance for designing local exhaust-ventilation systems can be found in Recommended Industrial Ventilation Guidelines [Hagopian and Bastress 1976], Industrial Ventilation--A Manual of Recommended Practice [ACGIH 1984], and Fundamentals Governing the Design and Operation of Local Exhaust Systems, ANSI Z9.2-1979 [ANSI 1979].

Ventilation equipment should be checked at least every 3 months to ensure adequate performance. System effectiveness should also be checked when there are any changes in production, process, or control that might result in significant increases in airborne exposure to MDA.

Worker Isolation

The areas in which MDA is produced or used should be restricted to only those workers who are essential to the process or operation. If feasible, these workers should be isolated from direct contact with the work environment by the use of automated equipment operated from a closed control booth or room. The control booth or room should be maintained at a greater air pressure than that surrounding the process equipment so that air flows out of, rather than into, the room. This type of control will not protect workers who must enter the general work area to perform process checks, adjustments, maintenance, assembly-line tasks, and related operations. Therefore, special precautions are often necessary to prevent or limit worker exposure in these situations and frequently involve the use of personal protective equipment.

Personal Protective Clothing

All workers who may be exposed to MDA should be equipped with chemical protective clothing to ensure their protection. In the selection of protective clothing, consideration should be given to the utilization of disposable apparel because of the uncertainty of decontamination of reusable clothing.

Outer protective clothing should consist of fully encapsulating protective clothing. Gloves should be made of polyvinyl chloride or natural latex which have been shown to be resistant to permeation by MDA dissolved in methanol [Weeks and Dean 1977]. For personal comfort, workers may wear inner garments consisting of cotton coveralls, undershirts, undershorts, gloves, and socks. Special consideration should be given to disposal of inner garments after use because small amounts of contaminants may be transferred to the inner garments when removing outer protective clothing [Schwope et al. 1985]. The effectiveness of the protective clothing should be evaluated under simulated use conditions, regardless of the type of clothing used. Workers should be informed of the potential for heat stress that may occur when working in an encapsulated suit. Areas of the body which come in contact with MDA should be thoroughly washed with soap and water immediately. As a general hygienic measure, facilities (e.g., change rooms, lockers, shower, etc.) for personal cleanliness should be provided.

Respiratory Protection

The use of respiratory protection requires that a respiratory protection program be instituted which, at a minimum, meets the requirements of 29 CFR 1910.134 [OSHA 1984a]. In addition to selection of respirators

approved by the Mine Safety and Health Administration (MSHA) and NIOSH, a complete respiratory protection program should include at least regular training of personnel, fit testing, periodic environmental monitoring, maintenance, inspection, and cleaning of equipment. The program should be evaluated regularly.

It must be stressed that the use of respiratory protection is the least preferred method of controlling worker exposures and should not be used as the only means of preventing or minimizing exposures during routine operations. However, NIOSH recognizes that respirators may be required to provide protection under certain situations (such as implementation of engineering controls, certain short-duration maintenance procedures, and emergencies). NIOSH maintains that only the most protective respirators should be used to protect workers from exposure to workplace carcinogens. Such respirators include:

- A self-contained breathing apparatus with a full facepiece operated in pressure-demand or other positive-pressure mode
- A supplied-air respirator with a full facepiece operated in pressure-demand or other positive-pressure mode, in combination with an auxiliary self-contained breathing apparatus operated in pressure-demand or other positive-pressure mode

Decontamination Procedures

Decontamination of MDA-contaminated work surfaces may be accomplished by initial dry vacuuming of both horizontal and vertical surfaces with a vacuum cleaning system equipped with a high-efficiency particulate (HEPA) filter. Most of the remaining MDA should be transformed to a water-soluble salt by applying a hydrochloric acid/methanol solution, and should be removed by absorption with a sponge. Any residual MDA should be transformed to its corresponding "Schiff" base with p-dimethylaminobenzaldehyde and removed with a methanol-moistened sponge [Weeks and Dean 1978]. The surface should be thoroughly cleaned with a detergent solution and rinsed with water. All contaminated protective clothing or equipment should be removed and discarded, or if cleaned, analyzed for residual contamination before reuse or storage. Contaminated waste should be collected and placed in sealed containers for disposal in accordance with existing regulations of the U.S. Environmental Protection Agency, and the Department of Transportation. State and local regulations may supersede federal regulations, if they are more restrictive.

MEDICAL SURVEILLANCE

A medical surveillance program should be established to prevent (or to attempt to detect at an early stage) both the acute and chronic adverse health effects in workers resulting from exposure to MDA. Medical and work

histories including previous exposure to MDA or other toxic agents should be taken for each worker prior to job placement and updated periodically. The physician responsible should be provided with information concerning the adverse health effects of MDA exposure and an estimate of the worker's potential for exposure to MDA, including any available workplace sampling results and a description of any protective devices or equipment the worker may be required to use. A smoking cessation program should be provided, because cigarette smoking is a well-established risk factor for bladder cancer [Matanoski and Elliot 1981].

The examining physician should direct particular attention to the skin, liver, urinary, respiratory, and gastrointestinal tracts, and to the endocrine system, as these are most likely to be affected by MDA. A baseline health status can be established as a result of this program. Deviations from the baseline health status should permit early detection of adverse health effects and should prompt medical personnel to consider additional specific tests for the individual [Dunn and Guirguis 1979; Schulte et al. 1986]. Complete medical evaluations of each worker should also be performed upon job transfer or termination. The occurrence of disease or other work-related adverse health effects necessitates immediate evaluation of primary preventative measures (e.g., industrial hygiene monitoring, engineering controls, and personal protective equipment). Medical personnel should ensure that workers and employers be informed about work-related hazards associated with exposure to MDA.

CUMULATIVE LIST OF NIOSH CURRENT INTELLIGENCE BULLETINS

1.	Chloroprene	- January 20, 1975
2.	Trichloroethylene	- June 6, 1975
3.	Ethylene Dibromide	- July 7, 1975
4.	Chrome Pigment	- June 24, 1975 - October 7, 1975 - October 8, 1976
5.	Asbestos - Asbestos Exposure during Servicing of Motor Vehicle Brake and Clutch Assemblies	- August 8, 1975
6.	Hexamethylphosphoric Triamide (HMPA)	- October 24, 1975
7.	Polychlorinated Biphenyls	- November 3, 1975
8.	4,4'-Diaminodiphenylmethane (DDM)	- January 30, 1976
9.	Chloroform	- March 15, 1976
10.	Radon Daughters	- May 11, 1976
11.	Dimethylcarbamoyl Chloride (DMCC) Revised	- July 7, 1976
12.	Diethylcarbamoyl Chloride (DECC)	- July 7, 1976
13.	Explosive Azide Hazard	- August 16, 1976
14.	Inorganic Arsenic - Respiratory Protection	- September 27, 1976
15.	Nitrosamines in Cutting Fluids	- October 6, 1976
16.	Metabolic Precursors of a Known Human Carcinogen, Beta-Naphthylamine	- December 17, 1976
17.	2-Nitropropane	- April 25, 1977
18.	Acrylonitrile	- July 1, 1977
19.	2,4-Diaminoanisole in Hair and Fur Dyes	- January 13, 1978
20.	Tetrachloroethylene (Perchloroethylene)	- January 20, 1978
21.	Trimellitic Anhydride (TMA)	- February 3, 1978
22.	Ethylene Thiourea (ETU)	- April 11, 1978
23.	Ethylene Dibromide and Disulfiram Toxic Interaction	- April 11, 1978
24.	Direct Black 38, Direct Blue 6, and Direct Brown 95 Benzidine Derived Dyes	- April 17, 1978
25.	Ethylene Dichloride (1,2-Dichloroethane)	- April 19, 1978
26.	NIAX® Catalyst ESN	- May 22, 1978
27.	Chloroethanes: Review of Toxicity	- August 21, 1978
28.	Vinyl Halides - Carcinogenicity: Vinyl Bromide, Vinyl Chloride, and Vinylidene Chloride	- September 21, 1978
29.	Glycidyl Ethers	- October 12, 1978
30.	Epichlorohydrin	- October 12, 1978
31.	Adverse Health Effects of Smoking and the Occupational Environment	- February 5, 1979
32.	Arsine (Arsenic Hydride) Poisoning in the Workplace	- August 3, 1979
33.	Radiofrequency (RF) Sealers and Heaters: Potential Health Hazards and Their Prevention	- December 4, 1979
34.	Formaldehyde: Evidence of Carcinogenicity	- April 15, 1981
35.	Ethylene Oxide (EtO): Evidence of Carcinogenicity	- May 22, 1981
36.	Silica Flour: Silicosis	- June 30, 1981
37.	Ethylene Dibromide (EDB) Revised	- October 26, 1981

CUMULATIVE LIST OF NIOSH CURRENT INTELLIGENCE BULLETINS (CONTINUED)

38.	Vibration Syndrome	- March 29, 1983
39.	The Glycol Ethers, with Particular Reference to 2-Methoxyethanol and 2-Ethoxyethanol: Evidence of Adverse Reproductive Effects	- May 2, 1983
40.	2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD, "Dioxin")	- January 23, 1984
41.	1,3-Butadiene	- February 9, 1984
42.	Cadmium	- September 27, 1984
43.	Monohalomethanes: Methyl Chloride, Methyl Bromide, and Methyl Iodide	- September 27, 1984
44.	Dinitrotoluene	- July 4, 1985
45.	Polychlorinated Biphenyls (PCB's): Potential Health Hazards from Electrical Equipment Fires or Failures	- February 24, 1986
46.	Methylene Chloride	- April 18, 1986
47.	4,4'-Methylenedianiline (MDA) Revised	- July 25, 1986

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