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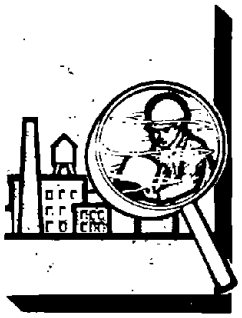
4,4'– METHYLENEDIANILINE (MDA)

(Revised)



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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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.

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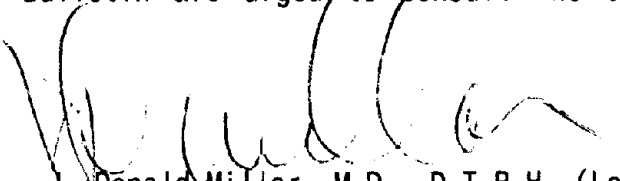
The purpose of this bulletin is to disseminate recent information on the potential carcinogenicity of 4,4'-methylenedianiline (MDA) previously identified by NIOSH in 1976 in CIB No. 8 as 4,4'-diaminodiphenylmethane (DDM). In the CIB, the occupational health community was informed of the hepatotoxicity 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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