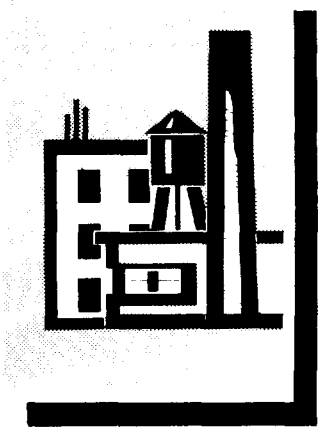
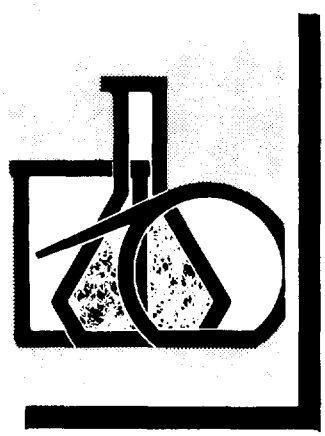
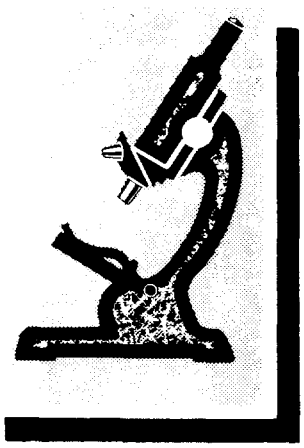
NIOSH

SPECIAL HAZARD REVIEW with CONTROL RECOMMENDATIONS







4,4'-METHYLENEBIS (2-CHLOROANILINE)

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

SPECIAL HAZARD REVIEW

WITH

CONTROL RECOMMENDATIONS

FOR

4,4'-METHYLENEBIS(2-CHLOROANILINE)

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NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH

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PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and safety of workers exposed to an ever-increasing number of potential hazards in their workplace. Pursuant to the fulfillment of this need, the National Institute for Occupational Safety and Health (NIOSH) has developed a reporting strategy intended to assist employers in providing personal protection for employees from exposure to carcinogenic, mutagenic, and teratogenic substances. This strategy involves the development of Special Occupational Hazard Reviews which serve to support and complement the other major criteria documentation activities of the Institute. It is the intent of a Special Occupational Hazard Review to document, from a health standpoint, the problems associated with a given industrial chemical or process. While Special Occupational Hazard Reviews are not intended to supplant the more comprehensive NIOSH Criteria Documents nor the less comprehensive NIOSH Current Intelligence Bulletins, they are nevertheless prepared in such a way as to be amenable to full regulatory usage if so desired. Dissemination of Special Occupational Hazard Reviews may be accomplished through appropriate trade associations, unions, industries, and members of the scientific community.

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CONTENTS

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The Division of Criteria Documentation and Standards Development (DCDSD), National Institute for Occupational Safety and Health, had primary responsibility for the development of this Special Hazard Review for 4,4'-Methylenebis(2-chloroaniline). Jack L. Arthur, M.En, of this Division had program responsibility. Personnel from other NIOSH Divisions who assisted in the development of this report include: David H. Groth, M.D., Division of Biomedical and Behavioral Science; Elva Elesh, M.D., Division of Surveillance, Hazard Evaluation, and Field Studies; Alexander W. Teass, Ph.D., Division of Physical Science and Engineering.

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I. INTRODUCTION

4,4'-Methylenebis(2-chloroaniline), more commonly referred to as MOCA, a registered trade name of the DuPont Company, has the formula C13H12C12N2. It has a molecular weight of 267.16. A yellow to light gray-tan, nearly odorless, crystalline solid, 4,4'-Methylenebis(2-chloroaniline) has a specific gravity of 1.44 at 24 C and a melting range of 100-110 C. Its vapor pressure is very low, i.e., less than 0.00001 mmHg at 25 C, and 0.000036 mmHg at 100 C. It is only slightly soluble in water, but is soluble in alcohol, ether, ketones, esters, organic solvents (e.g., trichloroethylene and toluene), and in lipids. 4,4'-Methylenebis(2-chloroaniline) is a weak base having the general chemical characteristics of primary aromatic amines. Synonyms for this compound include: 4,4'-methylene-bis(2-benzenamine); diamino-3-chlorophenylmethane; bisamine; di-(4-amino-3-chlorophenyl)methane; 4,4'-diamino-3,3'-dichlorodiphenylmethane; 3,3'-dichloro-4,4'-diaminodiphenylmethane; methylenebis(ortho-chloroaniline); and p,p'-methylenebis(ortho-chloroaniline). Common or trade names include: 4,4'-Methylenebis(2-chloroaniline); DACPM; MBOCA; MOCA; MCA; Curaline M; Curene 442; and Cyanaset (1,2).

It is commercially important as a curing agent for diisocyanate-based polymers (polyurethanes) and epoxy resin systems used in the manufacture of certain products, particularly integral-skin polyurethane semi-rigid foam as used for crash padding, and solid urethane rubber moldings such as gear blanks and industrial tires. 4,4'-Methylenebis(2-chloroaniline) is used to vary the hardness,

flexibility, and impact strength of these products. The first U.S. commercial production of 4,4'-Methylenebis(2-chloroaniline) is believed to have begun in 1956, using a process based on the reaction of formaldehyde and ortho-chloroaniline. Commercial-grade 4,4'-Methylenebis(2-chloroaniline) is available in the form of pellets or granules, and in a premixed compound with polyhydric alcohols (polyols). During the melting of solid 4,4'-Methylenebis(2-chloroaniline), when temperatures of about 200 C are used, the release of irritant and toxic vapors (primarily ortho-chloroaniline) may occur (1,2).

NIOSH estimated through a national survey that in the early 1970's approximately 55,000 U.S. workers were potentially exposed to 4,4'-Methylenebis(2-chloroaniline) (3). The majority of these workers were employed in small-to-medium sized establishments where occupational health services may not have been readily available.

Based on information presented by NIOSH (Appendix I), 4,4'-Methylenebis(2-chloroaniline) was one of 14 substances for which the Occupational Safety and Health Administration (OSHA) promulgated an emergency temporary standard on May 3, 1973. Final, individual standards for these substances were promulgated by OSHA on January 29, 1974. (4) On December 17, 1974, the standard for 4,4'-Methylenebis(2-chloroaniline) was remanded for procedural reasons by the 3rd Circuit Court of the U.S. Court of Appeals (Synthetic Organic Chemicals Manufacturer's Association vs. Brennen 506.F2d 385 1974). Subsequent to the court decision, the standard was deleted from the Code of Federal Regulations. Even though not enforceable as a Federal

standard, several states, including California, continued to enforce the standard under state law. The California Department of Health has recently held hearings to consider promulgation of environmental exposure limits for 4,4'-Methylenebis(2-chloroaniline).

In 1972, the American Conference of Governmental Industrial Hygienists (ACGIH) included 4,4'-Methylenebis(2-chloroanaline) as an experimental carcinogen in Appendix A of its Threshold Limit Values booklet (5) without a recommended environmental limit. The experimental carcinogen designation was applied by the ACGIH to industrial substances found to be of high potency for inducing tumors under experimental conditions in animals. In 1975, the ACGIH revised their designation for experimental carcinogens to be "Occupational Substances Suspected of Oncogenic Potential for Workers" and assigned 4,4'-Methylenebis(2-chloroaniline) a threshold limit value of 0.02 ppm with a skin notation. The documentation for this TLV was apparently not based on a consideration of the carcinogenic potential of this chemical but was established with the belief that this limit was "sufficiently low as to prevent systemic poisioning, provided skin contact is avoided." (6). The documentation included a warning that worker exposure by all routes should be reduced to a minimum in light of the warning of the potency for the chemical to induce tumors in animals (7). In 1974, the International Agency for Research on Cancer reviewed the information concerning 4,4'-Methylenebis(2-chloroaniline)'s potential carcinogenicity (1).

Additional information to that which appeared in the above sources is currently available. The following section provides a brief review

of the information available in 1973 (Appendix I), and a more detailed presentation of recent studies along with recommendations for control of workplace exposures to 4,4'-Methylenebis(2-chloroaniline).

II. HAZARD INFORMATION UPDATE

4,4'-Methylenebis(2-chloroaniline) was found to be "moderately toxic" when administered orally in single doses to male rats, with an Approximate Lethal Dose (ALD) of 1,000 mg/kg, (8). The report indicated that 4,4'-Methylenebis(2-chloroaniline) affected the kidneys of the experimental animals, and interfered with the hemopoietic system, as evidenced by the formation of methemoglobin and formation of red blood cells at sites other than the bone marrow. The clinical signs of toxicity at lethal doses included rapid and irregular respiration (eventually becoming labored), pallor, cyanosis, weakness, polyuria, and coma. Repeated sublethal oral doses (200 mg/kg) in the rat produced pallor, slight cyanosis, and a depressed rate of weight gain during treatment.

In a separate report (9) submitted from the same laboratory, the oral LD50 for 4,4'-Methylenebis(2-chloroaniline) (as a 10% solution in acetone (15)/peanut oil (85)) in male rats was reported as 750 mg/kg, with gross pathological changes including congested kidneys, an enlarged spleen, and hemorrhagic serosa of the stomach found in a few select animals.

Single 40 mg/kg doses of 4,4'-Methylenebis(2-chloroaniline) produced marked methemoglobinemia in dogs (10). The methemoglobin level returned nearly to normal 24 hours after the single dose. When administered daily in gradually increasing doses a slight methemoglobinemia and a macrocytic anemia developed, accompanied by fecal excretion of urobilinogen. The study also identified a major metabolite of 4,4'-Methylenebis(2-chloroaniline) in the dog urine,

5-hydroxy-3,3'-dichloro-4,4'-bis-aminodiphenylmethane. Clinical signs noted were weakness, vomiting, pallor and cyanosis.

Skin absorption studies on rabbits showed the ALD by this route to be greater than 5 g/kg, with pallor and weight loss observed (10). Repeated applications of 2.2 g/kg to the skin of rabbits resulted in pallor, cyanosis and hematuria during the 1st week of treatment only. No significant hematologic changes were found. Skin tests with guinea pigs indicated the compound to be mildly irritating, and not to produce allergic contact dermatitis (8).

An interim report of an 18-month feeding study conducted in NIOSH laboratories (11) confirmed the earlier reports reviewed in the 1973 NIOSH Hazard Review (Appendix I) that 4,4'-Methylenebis(2-chloroaniline) caused pulmonary and mammary gland adenocarcinomas, hepatocellular carcinomas, Zymbal gland tumors and hemangiosarcomas in male rats. 4,4'-Methylenebis(2-chloroaniline) was fed in graded doses in two different diets to male rats for 18 months; 250, 500, and 1,000 ppm in protein adequate (27% casein) and 125, 250, 500 ppm in protein deficient (8% casein). Groups of male rats which were fed the same two diets, but without 4,4'-Methylenebis(2-chloroaniline), served as controls. All surviving animals were killed 24 months after initiation of the chemical feeding. All animals that were started on the experiment were necropsied, including those that died during the experiment or were killed in a moribund state, as well as those killed at 24 months. A statistically increased incidence of the following types of tumors were observed in the 4,4'-Methylenebis(2-chloroaniline) treated animals regardless of the protein content of their diet:

adenocarcinoma of the lungs, hepatocellular carcinoma, mammary gland adenocarcinoma, and Zymbal gland tumors. There was a definite dose-response relationship, the larger the dose the greater the incidence of tumors. This interim report demonstrates that the effect of diet alone could not account for the carcinogenic activity of 4,4'-Methylenebis(2-chloroaniline).

The lowest concentration shown to produce all of the above tumor types in the protein adequate group was also the lowest concentration tested in that group, 250 ppm of 4,4'-Methylenebis(2-chloroaniline). The lowest concentration shown to produce pulmonary and mammary gland adenocarcinomas in the protein deficient group was 125 ppm of 4,4'-Methylenebis(2-chloroaniline) in the diet, again the lowest concentration tested in that group. The increased incidence of lung neoplasms in this group was statistically significant (6/100 vs. 0/100). The authors concluded that "In both diet groups the lungs were the most sensitive organs to the induction of neoplasms by 4,4'-Methylenebis(2-chloroaniline)."

In comparing the animals that received 500 ppm of 4,4'-Methylenebis(2-chloroaniline) in the protein deficient and protein adequate groups, the investigators concluded that protein deficiency caused an increased incidence of hepatocellular carcinomas. However, there was a lower incidence of mammary gland and lung adenocarcinomas in the protein deficient group as compared to the protein adequate group.

There was an increased incidence of hemangiosarcomas in the protein deficient group, 22% (4/18) in the 500 ppm group vs. 2% (1/49) in the

controls when comparisons were made between only those treated animals alive at the time the hemangiosarcomas were first diagnosed. The Fisher Exact Test yields a P value of 0.0164 (i.e., significant at the 0.05 level). The most current information, as yet unpublished, indicates the lifetime incidence rates to be 8% (4/50) in the treated, protein deficient group, and 1% (1/100) in the controls. The Fisher Exact Test yields a P value of 0.0425 (i.e., significant at the 0.05 level).

Another objective of the study was to determine whether or not the treated animals with tumors had more 4,4'-Methylenebis(2-chloroaniline) in their urine than the treated animals without tumors. The results were not consistent. There were significantly higher levels of 4,4'-Methylenebis(2-chloroaniline) (P less than 0.05) in the urine of animals with tumors in the 500-ppm dosage groups, regardless of diet, than in those animals in the same dosage groups without tumors. In the protein adequate, 500-ppm group, animals with tumors had a mean of 0.79 ppm in the urine after acid hydrolysis, while those without tumors had 0.50 ppm. In the protein deficient, 500-ppm group, the respective values were 2.19 ppm and 1.12 ppm. However, there were no statistically significant differences between similar groups at the other concentrations of 4,4'-Methylenebis(2-chloroaniline) tested. The urine was collected and analyzed 75-76 weeks after initiating the exposures and just before exposure was discontinued.

At the lowest concentration tested, 125 ppm, the mean concentration in the urine before acid hydrolysis was 0.09 ppm, and 0.63 ppm after acid hydrolysis. Although the significance of the observation is not known, it is interesting to note that equal or higher levels of

4,4'-Methylenebis(2-chloroaniline) have been reported in the urine of exposed workers (15, 16).

In work performed at Haskell Laboratory, urinary bladder tumors were produced in dogs given 4,4'-Methylenebis(2-chloroaniline) orally (12). Six female beagle dogs were given an oral dose of 100 mg by capsule, 3 days per week for the first 6 weeks, and then 5 days per week continuously for periods up to 9 years. The dose varied from 8 to 15 mg/kg body weight per day among the dogs. Six untreated female beagle dogs were used as controls. The test was terminated after 9 years of treatment, at which time all animals were killed and necropsied. The average plasma glutamic-pyruvic transaminase activity of the dogs fed 4,4'-Methylenebis(2-chloroaniline) was found to be higher than that of the controls during the 1st and last 2 years on test. During the 8th and 9th years, the urine sediment from the dogs given 4,4'-Methylenebis(2-chloroaniline) contained excessive numbers of erythrocytes, leukocytes, and epithelial cells. Some epithelial cells exhibited abnormalities that suggested neoplasia in the genitourinary tract. One treated animal died after 3.4 years from complications which were not considered by the investigators to be related to the test compound. One treated animal, killed after 8.3 years, had a papillary transitional cell carcinoma of the urinary bladder. The remaining four animals were killed after 9 years. Three of these had papillary transition cell carcinomas of the urinary bladder, and one had both a transitional cell carcinoman and an adenocarcinoma of the urethra. The urethral tumor had metastasized to the liver, but the papillary transitional cell carcinomas found in the other four dogs had

not invaded the muscle layers of the bladder wall, and had not metastasized. Since no urinary bladder tumors were found in the six control dogs, 4,4'-Methylenebis(2-chloroaniline) was judged to be carcinogenic for the urinary bladder of dogs under the conditions employed (P less than 0.025, Fisher's Exact Test, one tail). Three of five treated dogs contained hyperplastic nodules in the liver, with no such nodules in the six control dogs (P greater than 0.05, Fisher's Exact Test, one tail). This was considered by the investigators to be suggestive of an effect of 4,4'-Methylenebis(2-chloroaniline) treatment.

4,4'-Methylenebis(2-chloroaniline) has also been shown to be mutagenic in in vitro experiments. McCann et al, (13) reported 2.7 revertants per nmol (1050 revertants/plate) in the "Ames" test which utilizes Salmonella typhimurium as the test organism.

In approximately 22 years of industrial experience with the manufacture of 4,4'-Methylenebis(2-chloroaniline), DuPont has found no evidence of a carcinogenic effect in its workers (14). This is the only documentation of 4,4'-Methylenebis(2-chloroaniline)'s carcinogenic potential based on human experience which was found in the literature. It is noted in the report that the group studied was small, and that the length of time for which the workers were exposed to 4,4'-Methylenebis(2-chloroaniline) was too short to "permit statistically significant conclusions."

III. SUMMARY AND CONCLUSIONS

From the toxicologic information presented in APPENDIX I and the preceding information update, a profile of 4,4'-Methylenebis(2-chloroaniline)'s potentially hazardous properties can be developed. 4,4'-Methylenebis(2-chloroaniline) possesses the general toxicity characteristics of aromatic amines, and may, if introduced into the human body, produce cyanosis from methemoglobin formation (2). From an occupational health standpoint, there is greater concern for 4,4'-Methylenebis(2-chloroaniline)'s carcinogenic potential, evidence for which comes primarily from animal bioassays as well as in vitro mutagenicity studies. Results reported by five independent groups of investigators clearly demonstrate 4,4'-Methylenebis(2-chloroaniline) to be oncogenic in the rat, mouse, and dog. Ingestion of daily doses of 4,4'-Methylenebis(2-chloroaniline) by mice and rats has resulted in the appearance of cancers of the liver, kidneys, lungs, skin, and mammary glands (11, Appendix I). Subcutaneous injection of 4,4'-Methylenebis(2-chloroaniline) in rats produced liver and lung cancer in both sexes (Appendix I). Urinary bladder cancer was produced in female beagle dogs fed doses of 4,4'-Methylenebis(2-chloroaniline) which varied from 8 to 15 mg/kg body weight per day for up to 9 years (12). Further, 4,4'-Methylenebis(2-chloroaniline) is mutagenic in in vitro tests utilizing Salmonella bacteria (13).

Based on positive oncogenic results in three animal test species, NIOSH recommends that 4,4'-Methylenebis(2-chloroaniline) be treated as a potential occupational carcinogen. Because a significant route of

entry into the body is by skin absorption (1, 7, 15), efforts must be made to prevent skin contact with 4,4'-Methylenebis(2-chloroaniline), whenever possible. The use of protective clothing made of butyl rubber, neoprene, or spunbonded olefin has been shown to assist in the reduction of worker exposure through skin contact (14, 17).

Although research information is not yet available to demonstrate a quantitative relationship between skin absorption of 4,4'-Methylenebis(2-chloroaniline) and urinary levels in workers, industrial experience indicates that urinary monitoring is necessary as an adjunct to the monitoring of airborne 4,4'-Methylenebis(2-chloroaniline) in order to detect worker exposure as a result of absorption through the skin (15). The finding of 4,4'-Methylenebis(2-chloroaniline) in the urine demonstrates that exposure has occurred and can indicate work situations which need additional control efforts. Likewise, monitoring of workplace surfaces can identify where contamination problems exist and where the potential for workplace exposure is greatest. Details of one company's method of analysis for 4,4'-Methylenebis(2-chloroaniline) in urine are given in Appendix III. Detailed procedures for monitoring work surfaces for 4,4'-Methylenebis(2-chloroaniline) contamination are presented in reference 18 and in Appendix IV.