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pp' – METHYLENE DIANILINE (MDA) AS AN OCCUPATIONAL HEALTH PROBLEM A SUGGESTED TIME-WEIGHTED AVERAGE EXPOSURE LEVEL AND MEDICAL PROGRAM

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ABSTRACT

The use of p,p'-Methylene dianiline, (MDA), or 4,4'-diaminodiphenyl-methane (DDM) in a single industrial establishment resulted in eleven cases of acute episodes of jaundice during a nine-year period, (1967–1976). The company mixed pre-ground MDA with silica sand (95%). The MDA was used as an epoxy hardener (5%). Studies were conducted to define the circumstances involved. Standard medical and industrial hygiene investigations were carried out to determine the degree of exposure, routes of absorption and clinical conditions of the workers exposed.

Results indicated that the length of exposure ranged from one day to three weeks. Skin absorption was found to be the major route of entry into the body. Jaundice was definitely related to the degree of exposure. No medical supervision was in effect before this study. A medical program to include a pre-placement and periodic examination has been suggested to detect changes in liver function tests.

Based on the findings of the authors and those of McGill, a time-weighted average exposure level of 0.04 mg/m^3 has been recommended.

p,p'-Methylene dianiline (MDA) also known as 4,4'-diaminodiphenylmethane (DDM) has been associated with hepatotoxic effects in humans since 1965. Kopelman and coworkers[2,3] reported 84 cases of hepatocellular damage evidenced by elevated serum glutamic oxalo-acetic-acid-transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) activities. Occupational exposure to MDA has resulted in hepatotoxic episodes of workers who work with MDA.

McGill and Motto[4] described 13 cases of hepatitis which developed between 1966 and 1972, among workers who worked intensively with molten MDA material over a period of a few days. Williams and coworkers[8] described six cases of hepatitis occurring over an 18-month period, among 300 workers who used epoxy resins containing MDA. One other case of hepatitis, possibly associated

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with occupational exposure to MDA was reported to the U.S. Environmental Protection Agency[5]. Gohlke and Schmidt[1] showed that MDA produces liver lesions in intragastrically fed rats, and Pludis and coworkers[6] demonstrated liver degeneration and spleen lesions in rats fed MDA. The latter study reported an LD_{50} of 830 mg/kg while a dose of 83 mg/kg was injurious to the liver and spleen of the rat. Schoental[7] reported induced hepatomata and kidney tumors in one rat of 16, adenocarcinoma of the uterus in another and liver lesions in most of the animals.

Between 1967 and 1976 eleven cases of MDA poisoning occurred at a small industrial establishment in Southern Ontario.

MATERIALS AND METHODS

The plant in question started using methylene dianiline (MDA) (4,4'-diaminodiphenylmethane) as an epoxy hardener in September 1966. The solid phase of the epoxy system was composed of silica sand (95), MDA (5%) and a trace of silica flour. This particular company received the MDA, which had been previously ground and screened, from their parent company in the United States. The only procedures that the employees in the Ontario Plant were exposed to were the blending and packaging operations.

Blending was carried out in two blenders each of 1 000 kg capacity. These blenders were housed in a room approximately 6 m × 6 m with a sloping roof of 7 m average height. In the centre of the roof, there was a 91 cm diameter exhaust fan which was used during the entire blending procedure. This room was equipped with a 3 m × 2.5 m sliding corrugated steel door which was shut during blending to help contain MDA which might escape.

The two blenders were approximately 3.6 m off of the floor, with the ingredients lifted to the blenders by means of a fork lift truck. The materials were mixed for approximately 20 minutes and then packaged in 30 kg packages each containing 24 kg of powder (MDA, sand etc.) in a plastic bag lined pail with 42 kg of resin in a separate container.

Five to seven workers were employed in the manufacturing area at any one time. Up to 1976, there were no special precautions taken except the wearing of respirators to reduce the silica exposure during the addition of silica sand and flour. In 1976, the company began providing workers performing MDA operations with coveralls, gauntlets, shoe covers, head and neck covers as well as positive pressure air line breathing apparatus. In addition, local exhaust ventilation was provided at the blender. Despite these changes, some workers were still affected.

Area air samples were taken in 1976 with midget impingers over a 15 minute sampling period at an airflow rate of 3 liters/minute. The collection medium was an aqueous solution of 0.4N acetic and hydrochloric acids. The resulting solutions were analyzed for methylene dianiline.

This analysis was carried out by diazotizing the sample with a sodium nitrite sodium bromide solution. The excess nitrite is driven off with sulfuric acid, and the pH adjusted with sodium carbonate. The diazo compound is coupled with 1-N-naphthylethylene to form a red blue colour which is read on spectrophotometer at 550 nm in 50 mm quartz cells against a reagent blank. The limit of the detection of the method used, per 15 liters of sampled air is 0.0066 mg/m^3.

Area air samples were taken before the blending was done, during blending and at the packaging station at various positions close to the operator.

The medical files of the affected persons were reviewed and the biochemical changes followed up.

RESULTS

Table 1 shows the results of air sampling for MDA.

TABLE 1
Air sampling for MDA.

Sample	Location	MDA (mg/m^3 of air)
1.	Platform, (dumping silica) 2 blender	0.04
2.	Platform, (dumping MDA) 2 blender	3.11
3.	2 blender, mixing (blender floor during mixing)	0.48
4.	Platform, (dumping MDA) 1 blender	0.20
5.	Packaging, 2 by operator	0.68
6.	Packaging, 2 behind operator	0.53

Sample 1

The sample was taken on the elevated loading platform behind the operator while he added silica sand to the blender. The value of 0.04 mg/m^3 represents a background level in the rooms. No MDA had been used for one week in this room during that period. This shows the need to clean all pipes etc. to remove residual MDA which has built up in this area. However, this level of exposure was not sufficient to produce toxic symptoms.

Sample 2

This was taken in the same place as#1. The only difference being that MDA was being added.

Sample 3

This sample was taken during the mixing cycle of the blender. Before the sample had been taken there had been a spill from the blender. Sample 3 was not being taken during this time. The local exhaust was on as was the case in samples 1 and 2. Also at the time of the spill, the large 91 cm diameter roof fan was turned on to exhaust excess MDA. This fan was left on for one half hour before sample 3 was taken. It was thought that during this time the ventilation would elimate the excess MDA; however, the result of 0.48 mg/m^3 could reflect some of the contamination of the spill. The sample was taken in the middle of the room.

Sample 4

This sample was taken behind the operator on 1 blender. The lower result obtained on this blender, while dumping MDA, is a result of leaving the roof fan on. This was done for samples 5 and 6 also.

Sample 5

This sample was taken beside the operator during the packaging process.

Sample 6

This sample was taken in the middle of the room. This is an ambient value during the packaging process.

Improper gasketing of equipment accounted for a large proportion of dust during blending. During the industrial hygiene survey, some inadequate local exhaust was present. The flexible exhaust hose (20 cm in diameter) that was placed near the operation when charging and bagging took place was found to have a large hole in it and had to be replaced. Air velocity at the hose was 183 m per minute. MDA could be seen on all the overhead pipes signifying poor housekeeping.

TABLE 2
Frequency of sings and symptoms among 11 ill workers.

Signs or symptoms	Percentage
Jaundice	100
Abdominal pain	100
Nausea or vomiting or both	100
Fever (temperature 39 °C)	18.2
Chills	18.2
Headache	18.2
Sore throat	18.2
Dark urine	54.5
Acholic stools	45.5
Pruritus	18.2
Rashes	9
Anorexia	18.2
Weakness	36
Myalgia or arthralgia or both	9
Anuria	9
Methemoglobinuria	9
Diarrhea	9

During production, each worker was wearing coveralls which were changed twice a day, a hat with a wide brim, impervious gloves and an airline respirator. Good personal hygiene was promoted and the employees were encouraged to shower before leaving the plant.

The coveralls used were found not to be impervious to MDA, and when the process was being used, considerable MDA went through the coveralls. Armpits were reported stained with the material in affected persons due to the cut made in the coverall by the workers to relieve the heat stress of summer days.

Table 2 shows the frequency of the presenting signs and symptoms among the eleven workers. The most common features were severe abdominal pains simulating peptic ulcer, acute cholecystitis, or diaphragmatic pleurisy associated with nausea, vomiting and rapidly developing jaundice. Other symptoms such as fever, chills, headaches, sore throat, were prominent in 20–40% of the cases. Symptoms of jaundice, viz. dark urine, acholic stools, pruritus, rashes, were reported in 9–18% of cases. General symptoms of weakness, anorexia, muscle pains occurred early in the exposure. In one case, due to the negligence of the worker and the excessive exposure, anuria and methemoglobinuria developed. Diarrhea occurred in one case. In all cases, an increase in bilirubin, transaminases and alkaline phosphatase occurred.

Table 3 shows the range of peak values in the eleven workers during the acute illness phase. It was noted that the transaminase returned to normal values before the alkaline phosphatase, which, in fact, kept rising. These biochemical changes supported the suggestion that MDA produces a cholestatic type of jaundice[2,3,4].

TABLE 3
Bilirubin, transaminase and alkaline phosphatase during acute illness in 11 workers.

	Average	Range of peak values
Bilirubin (mg/100 ml)	7	2.1 – 12
Transaminases (units)	178.4	80 – 400
Alkaline phosphatase (K – A)	42.08	8.4 – 120

In one case, investigations were performed to rule out an obstructive aetiology and all tests gave negative results. Other tests, such as Australian antigen, stool culture for viruses and Coombs test, were reported negative in all cases limiting the diagnosis to a toxic hepatocellular jaundice. The duration of jaundice varied from 3–5 weeks. Most of the workers required corticosteroids to clear up the cholestatic phase before recovery.

DISCUSSION

There is a strong evidence that MDA was the sole aetiological factor in the episodic occurrence of jaundice over the years in this plant.

The main route of entry of MDA to the affected persons was skin absorption, as demonstrated by staining of the armpits. The severity of jaundice was related to the degree of skin contact as was the case in the worker who handled MDA with bare hands.

Exposure to 0.04 mg/m^3 was found to be safe in our study. Exposed workers did not develop toxic symptoms. McGill and Motto showed levels of exposure to MDA as low as 0.0051 ppm which corresponds to 0.0412 mg/m^3 in their study. Based on our study and that of McGill and Motto, a time-weighted average exposure of 0.04 mg/m^3 has been recommended.

A medical supervision program is recommended to include a preplacement evaluation of the medical history, past history of hepatitis or jaundice, past exposure to potential hepatotoxic agents, alcohol and drugs. A preplacement medical examination to detect any liver pathology is essential. It is recommended that persons with evidence of past or present abnormalities of the liver be excluded from exposure.

A base-line liver function profile is to be maintained for hired applicants. The suggested liver profile includes transaminase, alkaline phosphatase and bilirubin. Results of urinalysis are also requested.

The periodic medical examination would include all items covered in the preplacement examination. This could be done annually or twice a year depending on the degree of exposure. Test for hepatic cell injury are recommended to be done at shorter intervals and correlated with personal air sampling results, if available.

Removal from exposure is indicated when tests are abnormal, and the worker is not to resume work until all the tests are within normal limits.

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