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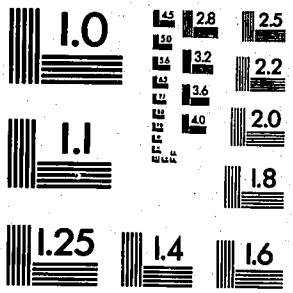

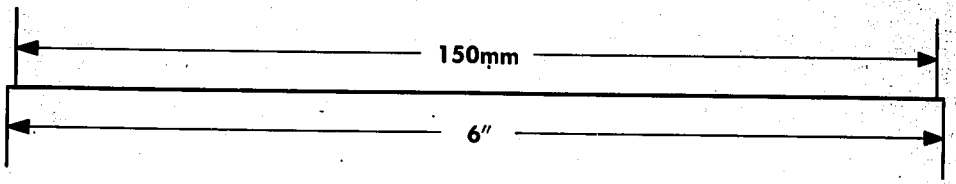

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Use of Urine Samples to Assess and Control Exposures to 4,4′-Methylene Dianiline in the Aerospace Industry

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4,4′-Methylene dianiline (4,4′-MDA) is a suspected human carcinogen. The Occupational Safety and Health Administration (OSHA) is presently preparing to promulgate a standard for human exposure in the workplace. The objectives of this paper are to present the rationale for the collection of urine samples that can be used to supplement environmental monitoring and to describe three circumstances in which urine monitoring was used. Biological monitoring is useful when determining exposure to 4,4′-MDA because 1) it is readily absorbed through the skin, 2) there are poor warning properties if skin contact occurs, 3) skin exposure is hard to measure directly, and 4) personal protective clothing and gloves are often inadequate in preventing all skin exposure.

Sampling surveys were conducted at three aerospace manufacturing facilities. These sites represent a variety of process operations where 4,4′-MDA is used. The analysis of urine samples permitted the identification of exposed workers when air sample results were substantially below the proposed OSHA permissible exposure limit. Additionally, corrective actions taken to reduce exposure could be objectively assessed by comparing the urine results before and after the changes were made. The primary corrective actions applied in two of the sites were the replacement of latex gloves with laminate gloves that are more impervious and the initiation of better work practices. Such simple changes were responsible for lowering urine concentrations from hundreds of parts per billion to under 10 ppb.

Introduction

4,4′-Methylenedianiline (4,4′-MDA) is used in conjunction with epoxy and polyimide resins to make a variety of end products. The use of 4,4′-MDA for parts manufacturing is expanding rapidly, particularly in the aerospace industry. These parts are strong, lightweight, and resistant to heat. Additional uses are in the manufacture of corrosion-resistant pipe, coatings, castings, and electrical circuit boards. In 1987, it was estimated that there were more than 4000 workers in the United States potentially exposed to known uses of 4,4′-MDA, with an additional undetermined number likely to be exposed in less defined occupations.[1]

Exposure to 4,4′-MDA has previously been associated with toxic liver damage, nausea, irritation of mucous membranes, and contact sensitization.[2–4] In 1982, the bioassay results from a National Toxicology Program study[5] of 4,4′-MDA supported earlier bioassay findings that 4,4′-MDA is a carcinogen in rats and mice. The International Agency for Research on Cancer (IARC) concluded that there is sufficient evidence that 4,4′-MDA is an animal carcinogen.[6] There are two reports of studies suggesting an increased incidence of cancer in workers.[7,8] These reports on workers were not reviewed by the IARC working group and they were not able to make a determination of the carcinogenicity of 4,4′-MDA in humans. The National Institute for Occupational Safety and Health (NIOSH) has reviewed the available information on 4,4′-MDA and concluded that 4,4′-MDA is a potential occupational carcinogen. NIOSH has furthermore concluded that occupational exposures to 4,4′-MDA should be controlled to the lowest feasible limit.[9,10] In July 1987, the Occupational Safety and Health Administration (OSHA) published the recommendations of a mediated rulemaking advisory committee for a health and safety standard for 4,4′-MDA.[1] As a part of those recommendations, it was proposed that

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Mention of company or product names in this report does not imply endorsement by the National Institute for Occupational Safety and Health.

OSHA limit airborne exposure to 81 μg/m³ (10 ppb) over an 8-hour workday and limit airborne exposure to 810 μg/m³ (100 ppb) as a short-term exposure. Currently, OSHA is completing a final rule on 4,4′-MDA that will describe acceptable exposure criteria for the workplace.

This report describes exposures to 4,4′-MDA among aerospace workers at three different locations and illustrates how urine sampling has been used as an additional method for assessing exposures. This report also indicates how having comprehensive assessment information is critical to adequately controlling exposure.

Routes of Entry, Metabolism, and Elimination

The primary routes of occupational exposure to chemicals are typically via inhalation and skin contact. Because 4,4′-MDA is a high-molecular-weight compound (MW = 198) with a melting point of 92°C and a low vapor pressure of approximately 1.5×10^{-7} mm Hg at 25°C, airborne exposures at room temperature generally will occur as airborne particulate rather than as a vapor. However, many industrial operations require elevated temperatures to partially cure or totally cure 4,4′-MDA-containing resin systems. Elevated process temperatures will increase the vapor pressure of 4,4′-MDA which will enhance volatilization and may produce significant airborne concentrations that may be subsequently inhaled or deposited onto surfaces as condensed particulate. Vapor production can occur even when 4,4′-MDA has been first mixed with a resin.

Because 4,4′-MDA is an aromatic amine, it is not surprising that it is appreciably absorbed through the skin.[11–13] When a known amount of ^{14}C 4,4′-MDA was placed on the skin of rats, guinea pigs, and rhesus monkeys and left occluded for 24 hours (followed by thorough washing of the treated area), the absorption of the dose was quite extensive — amounting to 54, 30, and 21 percent, respectively.[12] In addition, an initially rapid and irreversible binding of the applied dose also appeared to occur when a dilute solution of 4,4′-MDA in ethanol (a solvent mix occurring in some aerospace applications) was placed on the skin of the above animal species and its removal was attempted by washing. After the topical dose was allowed to dry for 5 minutes, the area was scrubbed repeatedly with soap and water or with acetone, soap, and water. Using guinea pigs, and after just 5 minutes of exposure, 15 percent of the dose was unrecoverable after washing with soap, and water, while 26 percent was unrecoverable after washing with acetone, soap and water.[12] This information suggests the importance of preventing all skin contact and the ineffectiveness that simple washing would have if contact occurred. It is also clear that skin absorption is hastened in the presence of organic solvents.

The skin absorption rate, as calculated from the guinea pig data obtained in the above study[12] and corroborated by another unpublished experimental animal study,[13] indicates that the transdermal flux rate is between 1.5 and 2.0 percent of the dose per hour. A more practical means of expressing transdermal flux is to present it as mass penetrating a given surface area per unit of time. Analysis of the above data from the guinea pig experiments provides a steady-state transdermal penetration rate of 1.5 μg/cm²/hr, while the initial penetration rate is at least equal to 4 μg/cm²/hr. For purposes of comparison, a single human thumb has a surface area of about 15 cm²; a hand, about 500 cm²; and the whole body, about 20,000 cm².[14]

The inhaled air concentration can be measured, but air samples alone cannot determine the proportion of the airborne material that is retained in the respiratory system. The relatively rapid dermal absorption of 4,4′-MDA would suggest that any material which is deposited in any area of the respiratory system would eventually be absorbed. For lack of precise information on the absorption rate of 4,4′-MDA from inhaled particles and vapors, the U.S. Environmental Protection Agency, as well as OSHA, assumed 50 percent absorption from the lung in their risk analyses.[1] Specific studies to determine the rate and extent of pulmonary absorption have not been performed, and the effect of 4,4′-MDA contained in a resinous dust matrix is not known. However, absorption might be higher than the 50 percent estimate because studies[15–17] have found that, in general, a high proportion of inhaled airborne aerosols are retained in the respiratory tract and the bioavailability of related amines (e.g., aniline vapor) is about 90 percent.

Accidental ingestion of 4,4′-MDA is less likely to occur but can be significant if poor work practices are allowed and food or cigarettes are handled with contaminated hands. Considering that OSHA is limiting an inhalation dose to less than 400 μg/day (81 μg/m³ × 1.2 m³/hr × 8 hrs/day × 50% absorbed) and there are over 57,000 μg 4,4′-MDA in a mass the size of a drop of water, inconspicuous but toxicologically significant quantities of 4,4′-MDA could contact the skin and conceivably be a significant source of exposure.

The uptake, metabolism, distribution and elimination of 4,4′-MDA in humans has not been well studied. Because 4,4′-MDA is now recognized as a potential human carcinogen, a controlled experimen-

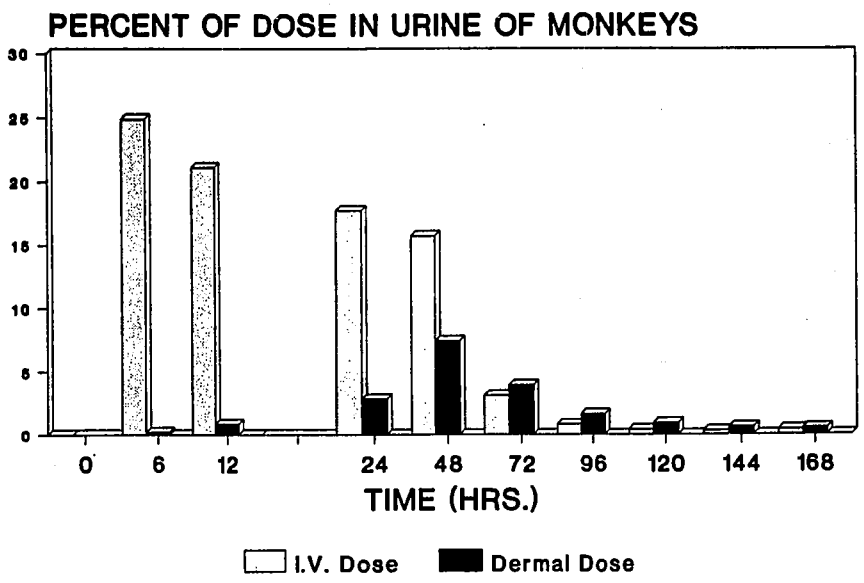

FIGURE 1. Elimination of ^{14}C 4,4'-MDA after dosing of rhesus monkeys by two routes. Data from U.S. Environmental Protection Agency Report 560/5-86-011, "Dermal Absorption of ^{14}C Labeled 4,4'-MDA in Rats, Guinea Pigs, and Rhesus Monkeys."

tal dosing study of humans is not ethically possible. Instead, animal experiments and studies of potentially exposed workers must be relied upon to study the excretion of this compound.

In order to illustrate absorption and excretion of 4,4'-MDA, the following animal experimental findings using rats, guinea pigs, and monkeys are summarized below. In separate experiments, radiolabeled 4,4'-MDA was injected intravenously and applied dermally to rhesus monkeys, rats, and guinea pigs.[12] A ^{14}C label was incorporated into both rings of the 4,4'-MDA structure. In order to determine the extent to which dermally applied 4,4'-MDA is absorbed through the skin and excreted in the urine, a 10-mg dose was given to each of three monkeys intravenously or by an occluded dermal application. The monkeys were restrained in a metabolic chair for 24 hours after dosing. The dermal application site was thoroughly washed with soap and water at the end of the dosing period.

The excretion of ^{14}C from the rhesus monkey after administration by both intravenous and dermal routes is portrayed in the histogram in Figure 1. With the intravenous dose, the excretion decreased during successive collection periods, and 62 percent of this dose was eliminated in the first 24 hours. However, a protracted elimination is supported by the continued occurrence of metabolites at 7 days. Ninety-four percent of the intravenous dose was recovered in the urine and feces, with 84 percent of the recovered dose occurring in the urine by 7 days. Because the animals were not sacrificed, the portion of the dose retained was not determined. In comparison, only 68 percent of the dermally applied dose was recovered, of which 19 percent was excreted in the urine and 47 percent was recovered in the skin wash. The data indicate that about 21 percent was absorbed through the skin and 32 percent was retained in the skin. If the 4,4'-MDA retained in the skin is eventually metabolized, then 53 percent of the applied dermal dose would be excreted eventually. Peak urinary excretion occurred 25 to 48 hours after the experiment began, and excretion continued throughout the 7-day urine collection period. When the exposure is through the skin, it is likely that the delay in excretion is slower than the rate of elimination when the exposure is through the respiratory tract because of the delayed rate of absorption (entry) into the body.

Species differences in the excretion of 4,4'-MDA were noted.[12] The total amount of ^{14}C excreted from monkeys and guinea pigs 96 hours after intravenous dosing were similar, being 94.1 and 91.5 percent, respectively. However, proportional differences in the route of excretion were detected. In monkeys, most of the dose (84.3 percent) was excreted in the urine, while in the guinea pig, almost two-thirds (56.5

percent) of the dose was excreted in the feces. When the same doses were applied topically, the proportion excreted in the urine was 16.8 and 10.5 percent, respectively. Such interspecies differences must be recognized when comparing animal data and especially when trying to extrapolate experimental animal data to humans.

Each of the above studies that are related to the excretion of 4,4′-MDA in urine used only radiolabeled material. Therefore, without chemical speciation, it was not possible to know the actual metabolites that were formed.

4,4′-MDA is appreciably acetylated in humans. One study showed that humans excrete up to 15 times more acetylated parent compound than unacetylated parent compound.[18] Strong hydrolysis using 5 *M* sodium hydroxide (NaOH) and heat can hydrolyze both the N-acetyl and N,N′-diacetyl 4,4′-MDA to the parent compound prior to analysis.[19] Analysis of urines from workers who have been exposed to 4,4′-MDA suggests that acetylated metabolites are predominant.[20] The hydrolysis of acetylated metabolites to 4,4′-MDA *in vitro* is advantageous since the ratio of acetylated metabolite to parent compound varies between individuals. Therefore, if this metabolite was not hydrolyzed and only free 4,4′-MDA was determined, the amount of unmetabolized parent compound would be highly dependent on the person from whom the sample was obtained. In addition, there would be less unmetabolized parent compound present to detect.

Description of Facilities

Environmental characterizations of workers' exposures are described here for three facilities involved in manufacturing products for the aerospace industry.

Facility A, making jet engine parts out of preimpregnated graphite fiber fabrics (prepregs) of the type PMR-15, was surveyed only to determine the extent of exposure and, if necessary, to make recommendations to reduce exposure. PMR-15 fabric, containing approximately 35 percent resin, consists of monomeric polyimide ester precursors, 4,4′-MDA, and some methanol. 4,4′-MDA constitutes about 33 percent (w/w) of the resin. Thus, the overall 4,4′-MDA content in PMR-15 is about 12 percent by total weight. At facility A, PMR-15 fabric is first knife cut into specified shapes and kept together as "kits." Other workers layer the fabric over steel molds to create the desired shape. Often, workers will squirt the prepreg with methanol to increase pliability. The molded parts undergo several heating operations. The first heated operation is called "debalking" and acts to pull the layers of prepreg together under vacuum and low heat to form a single piece. Additional layers are added and debalked and when all the layers are in place, the part undergoes an intermediate chemical curing called "imidization" under higher temperatures and vacuum. Employees who remove the imidized part from the molds are called "demold" workers. The final cure is performed in an autoclave at very high temperatures and pressure. Parts taken from the autoclave after this final cure are believed to be chemically inert. Work at this facility is generally continuous for the workers assigned to this area.

Facility B uses Fiberite® preimpregnated graphite fabrics containing a polyimide-type resin, ethanol, and between 4 and 13 percent 4,4′-MDA (w/w). These fabrics are used at Facility B to produce various parts for the military. The operations involve die cutting fabric into specified dimensions, sewing these pieces together, and finally curing the designs in a heated press for several hours. The prepregs are handled without a protective film during the die-cutting operation and thereafter. Work on these parts is generally intermittent, where a few workers may be dedicated exclusively to this product for 1–5 days of a week, followed by other work not involving potential exposure to 4,4′-MDA.

Facility C produces parts for military applications but impregnates its own fabric and thread for lay-up work and wet winding, respectively. 4,4′-MDA is added to two primary resin mixes either as a pure flake or as liquid Uniroyal Tonox® LC. Approximately 50 percent of the latter is 4,4′-MDA, and when it is mixed with resin, approximately 17.5 percent of the resin consists of 4,4′-MDA. This facility is different in that workers are potentially exposed to both raw 4,4′-MDA and to wet resins. Either of these hardeners is used almost daily by a few workers. This facility differs from the other two in that work with B-stage prepregs is not performed.

Experimental Sampling Design

The objective of the sampling strategy at Facility A was to determine the nature and extent of exposure to 4,4′-MDA and to recommend corrective measures if appropriate. At Facility A, environmental air samples were collected for 3 days (Wednesday through Friday). Urine samples were collected "around the clock" at five time intervals during the 3 workdays on which environmental samples were collected. These urine samples were collected upon arising from bed, during lunch break, at end of shift, at dinner, and

before retiring to bed. Samples were again collected Monday morning upon arriving at work after a 2-day weekend. Notes on job activities, work practices, and the use of protective equipment were kept during this period.

The objective of the sampling strategy at Facility B was similar to that at Facility A except that if an unacceptable exposure was found, corrective steps would be initiated and sampling would be repeated until satisfactory results could be obtained. Sample collection at Facility B took place periodically over a period of 7 months. The types of samples included both environmental (air, wipe, glove contamination) and urine. Preliminary sampling had already been initiated at this facility by the site safety and health staff to investigate the extent of exposures. Thereafter, sampling was performed to document the effect of modifying work practices and/or the type of personal protection worn. In all, samples were collected on four occasions.

Sample collection at Facility C was initiated most recently. The sampling strategy was identical to that at Facility B in that it was performed to document the extent of exposure before and after the implementation of changes in personal protection and work practices. Initially, continuous urine sample collection was pursued, including sampling over the weekend to simultaneously investigate the elimination of 4,4'-MDA over time and the effect of the corrective modifications being made. In this facility, sampling and modifications to work practices and to personal protection are still ongoing. Sampling was conducted by the site safety personnel.

Air Samples

All air samples were collected on 37-mm acid-treated glass fiber filters, assembled with a paper O-ring support pad in a three-piece cassette. Sampling was performed open-faced at a sampling flow rate of 2.5 L/min. Each sample was collected in the worker's breathing zone. Most samplers were attached at the beginning of the shift and removed at the end. Analysis was performed using NIOSH Method 5029.[21] The sample filters are eluted from the acid-treated glass fiber filters with 4 ml 0.1 *N* potassium hydroxide in methanol. The alkaline eluent converts all the salts of 4,4'-MDA back to the free amine. This procedure involves the use of a high–performance liquid chromatograph (HPLC) for separation of the analyte while an ultraviolet (UV) detector and electrochemical detector (ECD) are attached in series to monitor each chromatographic run. The UV detector is set at 254 nm wavelength. A direct injection of the eluent is made into the HPLC. Analyte recovery of spiked samples, samples spiked and stored for 1 month, and samples spiked with air drawn through has previously been performed. Recovery ranged from 94.5 percent at 3712 ng/filter to 77.8 percent at 9 ng/filter. Using a linear regression analysis of the calibration curve, the analytical limits of quantitation (LOQ) were 0.14 µg/filter for the UV detector and 0.03 µg/filter for the ECD. The limits of detection (LOD) were 0.04 µg/filter for the UV detector and 0.01 µg/filter for the ECD. The relative standard deviation (RSD) of the results from the two detectors was calculated but is not shown in the results. For sample loadings above 0.4 µg/filter, the RSD was below 5 percent. This method provides a detection limit of about 1 ppt, provided that a 1000-L air sample is collected.

Wipe Samples

Wipe samples of various surfaces were submitted for analysis to determine the extent of surface contamination. Wipe samples were collected using dry 2-in. × 2-in., cotton gauze pads which were rubbed firmly over an area of 100 cm^2, unless otherwise dictated by the size of the object. Samples were immediately placed in 10 ml of 0.1 *N* methanolic potassium hydroxide solution to stabilize the 4,4'-MDA. Analyte recovery and long-term stability studies have shown the extraction efficiency to be greater than 90 percent and stability to be essentially unchanged when the analyte is in solution. After filtering the solutions using a 0.45-micron PTFE filter, the samples were injected into a HPLC system.

Analyses were performed by using an analytical setup similar to that described above for air sample analysis. The chromatographic parameters were an isocratic run of 0.1 *N* sodium acetate in 30 percent acetonitrile/70 percent water at 1 ml/min using a C_{18} column. Some samples contained interferences that eluted with 4,4'-MDA. A gradient program was used to eliminate this problem. The program consisted of 15 percent acetonitrile/70 percent water in 15 minutes, and a 15-minute hold at 30 percent acetonitrile/70 percent water. The solvents contained 0.1 *N* sodium acetate to facilitate the use of the ECD. Based upon calibration curves, the LODs for isocratic analysis were 0.06 µg/ml of sample for the ECD and 0.11 µg/ml for the UV detector. The LOQs for isocratic analysis were 0.19 µg/ml of sample for the ECD and 0.36 µg/ml for the UV detector. Using the gradient program, both detectors gave an LOD of 1 µg/ml and an LOQ of 3 µg/ml.

TABLE I. Split Sample Results of Urinalysis for 4,4'-MDA, (in µg/L) — Facility A

Laboratory Spiked Urine Samples Results		Field Urine Samples Results from Facility A	
Spiked Amount	HSE Result[A]	NIOSH[B]	HSE[C]
17	13	ND	1
17	9	ND	5
17	9	ND	2
17	10	ND	3
83	64	ND	2
83	64	ND	1
83	60	ND	10
83	72	ND	3
172	164	ND	2
172	164	ND	9
172	164	ND	14
172	164	(5.5)	20

[A]Analysis was kindly provided by John Cocker, Health and Safety Executive (HSE), England.

[B]The limit of detection (LOD) was reported at 11 ppb, the last value in parentheses was technically below the LOD.

[C]The LOD was reported at 1 ppb.

Bulk Samples

Bulk samples can be analyzed to determine the presence of 4,4'-MDA. To express the result as percent 4,4'-MDA by weight, all samples must first be collected dry and weighed. To minimize the loss of analyte during storage, the samples should be transported cold and stored frozen until analysis. Otherwise, the sample can be initially weighed and immediately placed into the extraction/stabilizing solution (1 ml of 0.1 *N* potassium hydroxide in methanol for each 0.1 g of bulk material).

In the laboratory, the solutions were agitated in a sonic bath for 1 hour. After filtering the solutions using 0.45 micron PTFE filters, the samples were injected into a HPLC system. The chromatographic parameters were an isocratic run of 0.1 *N* sodium acetate in 30 percent acetonitrile/70 percent water at 1 ml/min using a C_{18} column. Identification and quantification used dual detection with a UV detector set at 245 nm in series with an ECD set at 0.85 V. The LOD was 0.00003 percent and the LOQ was 0.0001 percent 4,4'-MDA (w/w).

Glove Samples

Gloves can be collected after use from workers and the amount of 4,4'-MDA inside the glove can be analytically determined. Workers in our studies usually wore the outer synthetic glove over a light cotton glove. Sample collection from the outer gloves was accomplished by first rinsing the inside of the glove with 20 ml of 0.1 *N* potassium hydroxide in methanol. The glove was twisted closed about 1.5 inches below the open end to avoid picking up accidental contamination of the glove when it was removed from the hand. Once the glove was closed off, the solvent was vigorously swished around the inside for about 30 seconds. Permeation studies have indicated that methanol will not completely penetrate latex gloves for about 10 minutes.[22] After the mixing period, the solvent was carefully poured into a small glass scintillation vial. Once the inside of a glove was rinsed out, it was inverted with a freshly gloved hand and an additional 20 ml of solvent was poured into the glove to determine the outside "challenge" concentration.

A sample of the cotton glove worn inside the synthetic glove was obtained at the same time as the glove rinses by cutting off the thumb and other areas of the glove and placing each part with clean tweezers into a glass scintillation vial containing 10 ml of the desorbing solvent. Unused outer and inner gloves were treated as above and were used as negative controls. Analysis was performed in the same manner as the above wipe sample analysis. The LOD for the glove wash samples and cotton thumb samples were 1.2 and 0.6 µg per sample using an ECD.

Urine Samples

Urine samples were collected in addition to the personal environmental samples and were used to

document the extent of personal exposure to 4,4'-MDA through all routes. Most often the collections were timed (time from last to present urine voiding was known). The original volume of each sample was determined by weighing to the nearest gram and was recorded. An aliquot of about 25 ml was transferred to a 30-ml sample bottle. All sample containers were made of high-density polyethylene to withstand freezing, which usually occurred immediately after collection.

Analysis of all urine samples from Facility A were performed at NIOSH by a HPLC method (unpublished).[23] A total of 213 urine samples from workers, plus 10 on-site control urine samples from nonexposed workers, 3 tap water samples, 3 deionized water samples, and 5 "contaminant double" samples (described below) were collected and analyzed for 4,4'-MDA. In addition, blank urine samples, later spiked with pure 4,4'-MDA at 17, 83, and 164 µg/L and used as calibration standards, were also shipped in triplicate to the Occupational Medicine and Hygiene Laboratory, Health and Safety Executive (HSE), London, England, for separate analysis. The HSE uses a procedure requiring gas chromatography and mass spectrometry detection.[19] The "contaminant double" samples consisted of two open sample bottles taped together (used by male workers only). After a urine collection was completed, the open empty bottle was half filled with tap water, capped, shaken, and a sample aliquot taken for analysis. This sample was intended to assess contamination of the urine samples by 4,4'-MDA particles falling from workers bodies and clothing into the urine sample bottles during collection. In all such samples, no 4,4'-MDA was detected in the contaminant double or water samples.

The LOD and LOQ for the procedure used at NIOSH were defined as the quantity of 4,4'-MDA that produces a signal-to-noise ratio of 3:1 and 10:1, respectively. The LOD and LOQ were estimated from chromatogram of a 17-µg/L 4,4'-MDA standard in urine matrix and the urine blank baseline instrumental noise. The LOD and LOQ were estimated as 11 and 33 µg/L, respectively. The recovery efficiency from the urine matrix averaged 51 percent with a range of 31–87 percent, as calculated from quality assurance samples spiked at 17, 83, and 164 µg/L. The average recovery did not vary significantly between concentrations but did vary with the source of the urine (i.e., a matrix effect).

Sample reliability for the samples collected at Facility A are uncertain. Based on the results of concurrent analysis by NIOSH and HSE (Table I), many more samples could have contained detectable 4,4'-MDA if a lower detection limit had been possible. Furthermore, these data suggest that the NIOSH results may have been understating the actual concentrations by up to fourfold (assuming the HSE results are correct).

Samples collected at facilities B and C were analyzed by HSE and by Pacific Toxicology Laboratories, Inc. (PTLI), Los Angeles, California. The HSE analysis is performed on a gas chromatograph with mass spectrometry detection (GC-MS). Recovery efficiency has been reported at greater than 85 percent and the LOD and LOQ during recent analyses was 1 and 5 µg/L, respectively.[24] PTLI analyzed samples by both an HPLC method with ECD and a GC-MS method which is similar to the HSE method. The LOD and LOQ reported by PTLI for both methods is comparable to the HSE.[25] Blank urine samples with known amounts of pure 4,4'-MDA and worker field samples were periodically split for analysis by both laboratories to determine comparability of results. The results of these samples are reported in Table II. The results indicate a lack of strict comparability between the two laboratories. Results received from the HSE laboratory are lower than those received from PTLI. Detailed review of the procedures used at each laboratory have not revealed the cause of this discrepancy and possibly the difference might be due to sample integrity during long overseas shipments. Table II also indicates the acceptable comparability of HPLC versus GC-MS analysis.

In all cases, the creatinine concentration was determined in the urine samples by the laboratory performing the analysis for 4,4'-MDA. Creatinine, along with urine flow rate, were used to assess the validity of each sample as determined by expected ranges. Creatinine adjustment of the 4,4'-MDA concentrations (i.e., µg 4,4'-MDA/g creatinine) was also assessed by comparing this means of expression to other means of expressing the raw data, such as simple concentration and rate.

Results and Discussion

Facility A

Previous urine sampling had been initiated at this site by the company and had been analyzed by a local analytical laboratory. End-of-shift samples were typically between 20 and 50 µg/L. First-morning voids on Mondays were between 6 and 15 µg/L. Further documentation of the extent of exposure and recommendations for reducing exposure were sought.

During the survey of Facility A, a total of 46 personal air samples, 23 surface wipe samples, 16 glove assessment samples, 223 workers' urines, and

TABLE II-A. Split Sample Results for Urinalysis of 4,4'-MDA, Fourth Survey — Facility B

Sample Number	Laboratory Spiked Amount (µg/L)	Amount Found After Analysis			Ratio Between Laboratories (PTLI/HSE)
		HSE[A] (GC-MS)	PTLI[B]		
			GC-MS	HPLC[C]	
1	15	8	16	17	2.13
2	15	9	17	17	1.89
3	15	8	16	18	2.25
4	15	9	17	17	1.89
5	31.5	12	22	25	2.00
					2.03 ± 0.16

[A]Health and Safety Executive (HSE) analysis on gas chromatograph with mass spectrometry detection (GC-MS).

[B]PTLI = Pacific Technology Laboratories, Inc.

[C]HPLC = High-performance liquid chromatography.

various samples of other types were collected primarily during a 3-day period. These results have been described more fully elsewhere.[26] The air, surface, glove, and urine sample results are summarized below.

Table III shows the full-shift personal air monitoring results for five job activities that were surveyed at Facility A. Clearly, the most highly exposed jobs to airborne 4,4'-MDA were among the lay-up and kit-cutter employees. However, the highest, single measurement was only 8.6 µg/m^3 (1.1 ppb). The geometric mean exposures for the lay-up and kit-cutter employees were 0.96 µg/m^3 (0.1 ppb) and 0.3 µg/m^3 (0.04 ppb), respectively. The practical LOD for these air samples was at least 0.004 ppb.

The glove sample results are presented in Table IV. These samples were collected from workers who used them for periods ranging from 30 minutes to 6.25 hours (it was the company policy that gloves be disposed of after 2 hours). The outer glove was a 17-mil synthetic latex glove and was usually worn over a thin cotton glove. Except for the demold workers, each glove sample from the other jobs contained appreciable 4,4'-MDA outside the latex glove, generally on the order of several milligrams. The inside glove rinse results suggest that the gloves did provide protection from 4,4'-MDA because these samples generally contained less than the LOD or, at most, only a fraction of that found outside the glove. The exception were samples of gloves worn by two workers for over 6 hours. In almost all cases, the cotton glove liners appeared to be much more likely to contain 4,4'-MDA than the rinses of the inside of the latex glove and might have a better affinity or storage

TABLE II-B. Split Sample Results for Urinalysis of 4,4'-MDA, Second Survey — Facility C

Sample Number	HSE Result[A] (GC-MS)	PTLI Result[B]		Ratio Between Laboratories (PTLI/HSE)
		GC-MS	HPLC[C]	
16	28	39	52	1.4
33	9	9	12	1
70	55	72	79	1.3
78	190	242	240	1.3
150	140	189	174	1.35
				1.3 ± 0.16

[A]Health and Safety Executive (HSE) analyses utilizing gas chromatograph with mass spectrometry detection (GC-MS).

[B]PTLI = Pacific Technology Laboratories, Inc.

[C]HPLC = High-performance liquid chromatography.

TABLE III. Air Sample Concentration of 4,4'-MDA by Job Title, Summary Statistics — Facility A

Job or Area	N	Minimum	Maximum	Arithmetic Mean	Standard Error	Geometric Mean	Geometric Stand. Dev.	Confidence Intervals Lower	Confidence Intervals Upper
				Concentration ($\mu g/m^3$)					
Lay Up	26	0.05	8.57	1.93	0.41	0.96	3.97	0.56	1.65
Demold/Debag	6	0.02	0.32	0.09	0.05	0.03	6.31	< 0.01	0.22
Kit Cut	8	0.07	0.80	0.41	0.10	0.31	2.50	0.14	0.66
Supervisor EASP	3	0.04	0.08	0.06	0.01	0.06	1.36	0.03	0.12
Production Control	3	0.06	3.20	1.05	1.05	0.24	9.55	0.06	64.76
				Concentration (ppb)					
Lay Up	26	0.01	1.06	0.24	0.05	0.12	0.49	0.07	0.20
Demold/Debag	6	< 0.01	0.04	0.01	< 0.01	< 0.01	0.78	< 0.01	0.03
Kit Cut	8	0.01	0.10	0.05	0.01	0.04	0.31	0.02	0.08
Supervisor EASP	3	0.01	0.01	< 0.01	< 0.01	0.01	0.17	< 0.01	0.02
Production Control	3	0.01	0.40	0.14	0.13	0.03	1.18	< 0.01	8.00

Note: The two groups of data above are from the same samples but expressed in units of $\mu g/m^3$ or ppb.

TABLE IV. Glove Sample Results for 4,4'-MDA — Plant A

Date Collected	Sample Number	Worker Number	Job	Duration Worn (hr)	Glove Results (µg/sample) Outside[A]	Inside[B]	Thumb[C]
4-19-69	1	16	Demold	1	–	ND[D]	–
	4	15	Demold	1	ND	ND	ND
	2	2	Kit cut	0.5	64	ND	[0.7]
	3	3	Kit cut	0.5	–	ND	6.1
	5	7	Lay up	1.25	2,675	7.9	7.2
	6	6	Lay up	1.25	–	ND	16
	7	4	Lay up	2.25	18,929	86	104
	8	5	Lay up	2.25	7,725	8.1	22
4-20-89	11	12	Demold	1.5	ND	ND	ND
	12	14	Demold	1.5	17	ND	ND
	10	3	Kit cut	1.5	1,112	[3.0]	12
	9	6	Lay up	0.75	14,622	ND	20
	13	21	Lay up	2.5	5,520	ND	66
	14	10	Lay up	1.75	6,120	ND	not worn
4-21-89	15	9	Lay up	6.25	7,691	40	49
	16	5	Lay up	6.25	9,488	147	not worn
Blank Glove Samples							
	17	–	–	–	ND	ND	ND
	18	–	–	–	ND	ND	ND

[A]Outside of glove was rinsed with 20 ml 0.1 *N* methanolic potassium hydroxide (KOH). Limit of detection = 1.2 µg/sample.

[B]Inside of glove was rinsed with 20 ml 0.1 *N* methanolic KOH. Limit of detection for glove-wash samples was 1.2 µg/sample, and the limit of quantitation was 1.9 µg/sample.

[C]Thumb of cotton glove insert was cut off glove and placed in 10 ml of 0.1 *N* methanolic KOH. Limit of detection = 0.6 µg/sample, and the limit of quantitation was 1.9 µg/sample.

[D]ND = not detected.

capacity for this compound. Extrapolation from the amount of 4,4'-MDA found in the thumb of the cotton liner to the entire contact surface of the hand (assuming equal distribution of contamination) indicates that the hands might be exposed to up to 2 mg of amine. Obviously, this would be a crude estimate of skin contact since the amount found inside the glove is not static but is likely being removed through skin absorption.

The results of surface wipe samples are tabulated in Table V. Surface contamination by 4,4'-MDA was detected throughout the prepreg work area. Of particular importance were the concentrations found in settled dust, on top of wood workbenches, and on the mold edges used for laying up fabricated pieces. The latter two surfaces were commonly observed to be touched without gloves.

Because glove permeation is a function of both outside concentration and duration of exposure, regression analysis of the product of these two factors was performed with the cotton thumb concentration as the dependent variable (Figure 2). Applying a log transformation of this data, r^2 equalled 0.94, meaning that the two factors could well explain most of the variation in the data. Additional data points would be needed to fully explore the strength of this relationship but the data indicate the need to limit the duration of glove use.

The urine data are graphically presented in Figures 3 and 4. Because of the concerns discussed under the Methods section about the accuracy of this data, the urine results from Facility A are presented quali-

TABLE V. Wipe Sample Results for 4,4'-MDA — Facility A, PMR-15 Composites Area

Sample Number	Location/Description	Sampled Area (cm^2)	Result (µg/sample)
S1	Top of bookshelf, PMR Area (14D, 43CE)	100	127
S2	Floor, PMR Area (14D, 39CE)	100	9.3
S3	Plastic covering on PMR roll	100	3.8
S4	PMR worktable top	100	19
S5	PMR worktable top -- new	100	ND
S15	PMR wood worktable top (older, yellow stained)	100	64
S16	PMR wood worktable top (table next to above)	100	39
S18	PMR wood worktable top (some staining)	100	76
S6	Switch box #8150	100	72
S7	Residue above oven doors	100	ND
S8	Hoist control #8150	100	[1.8]
S9	Floor, PMR Area	100	22
S10	Phone handle on wall, PMR Area	–	[0.7]
S13	Metal mold edge after heating in oven to debalk laminates	100	158
S14	same as S13, but yellow powder	100	1186
S17	Top of flammable storage cabinet, dusty	100	179
X51	Face wipe layup worker at end of shift after performing trimming and lay-up work	100	2.3

ND indicates sample response was below the limit of detection (LOD). Results in brackets are between the LOD and the limit of quantitation (LOQ). The LOD was 0.6 µg/sample for the electrochemical detector and 1.1 µg/sample for the ultraviolet detector. The LOQ was 1.9 µg/sample for the electrochemical detector and 3.6 µg/sample for the ultraviolet detector. All samples were contained in 10 ml of 0.1 *N* methanolic potassium hydroxide. All samples were wiped with a dry 2 in. x 2 in. gauze pad.

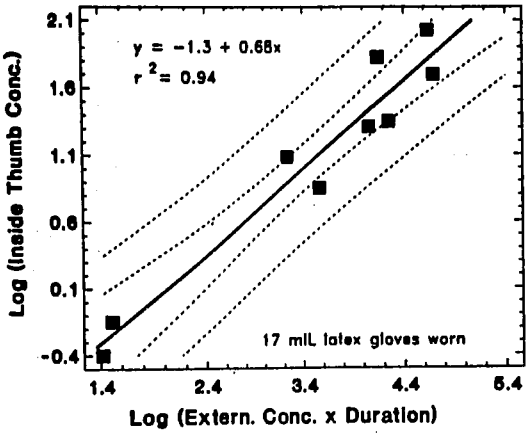

FIGURE 2. Regression of inside cotton thumb concentration of 4,4'-MDA and the external concentration times the duration of the wear. Activities were performed using 17-mil latex rubber gloves.

tatively. Of the 213 workers' urines obtained, only 37 (17 percent) contained detectable amounts of 4,4'-MDA (LOD = 11 µg/L). If a lower detection limit had been available during the analysis of these urine samples, additional samples may have contained otherwise undetected 4,4'-MDA.

The results of the urine analyses indicate that some jobs had a higher potential for exposure than others (Figure 3). Among the lay-up workers, five out of seven were found to excrete 4,4'-MDA during each of the three workdays that they were monitored and the highest urine concentration (123 µg/L) was found among them. Demold workers, on the other hand, were least likely to excrete detectable analyte in their urine. Among the five time periods during which samples were collected, the end-of-shift samples were more likely to contain analyte than any other time period (Figure 4). The next most likely sample to contain detectable analyte was the first morning void. Overall, the urine data corresponded well to each worker's potential for exposure, as measured by the environmental samples and notes taken during the sampling period. Using the personal air concentrations as a surrogate for the intensity of the previous day's work with 4,4'-MDA prepregs and testing it against the next day elimination of 4,4'-MDA in the urine gave a correlation coefficient of 0.75.

Facility B

Initially, monitoring was performed in November 1989 to ascertain the extent of exposure at Facility B. Sampling consisted of air and urine samples. The results of urine samples from two workers, one performing die cutting and the other sewing pregregs together, are presented in Figure 5. Certainly, the die-cutting employee, referred to hereafter as DC, eliminated more 4,4'-MDA in his urine than the worker who was sewing. His postexposure urine sample concentrations were between 50 and 80 µg/L. Additional samples were collected after 2–4 days at home to determine if excretion declined, as it clearly did. 4,4'-MDA was still detectable after 2 days but not after 4 days. Of interest is the rapidity of rise in excretion upon resumption of exposure (see collection on November 30) and the subsequent length of time it took to clear exposure. When handling the prepregs, the die cutter worker wore 6 mil vinyl gloves over a thin cotton (inspectors) glove, along with a Tyvek® coat. The sewing workers typically wore latex or vinyl gloves and Tyvek coats. Gloves were reportedly changed at least every 2 hours. Air concentra-

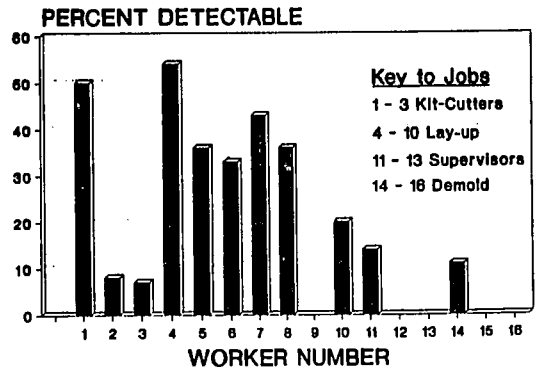

FIGURE 3. Excretion of 4,4'-MDA in each worker tested at Facility A as percent of samples with detectable amounts.

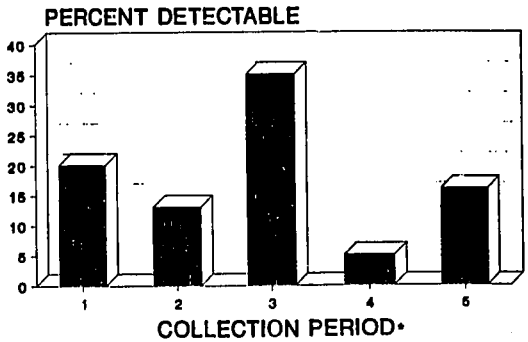

FIGURE 4. Percent incidence of detectable 4,4'-MDA by sample collection period. (*1 = overnight until 7 a.m.; 2 = until 11:3 a.m.; 3 = until 3:30 p.m.; 4 = until dinner; 5 = until bedtime.)

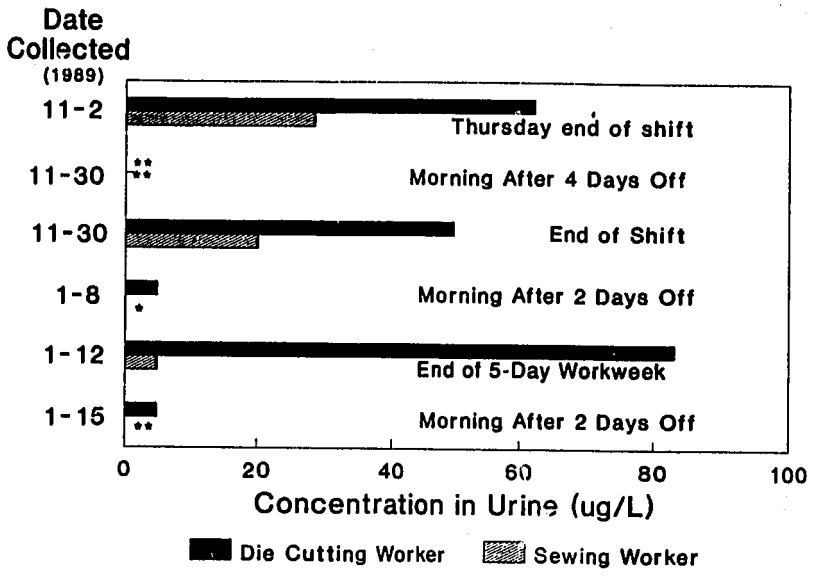

FIGURE 5. Elimination of 4,4'-MDA in urine initially at Facility B.

tions had been measured and were between 8 and 16 $\mu g/m^3$ (1 and 2 ppb) in the sewing and press areas.

During the second sampling period that occurred in March 1990 only one worker (DC) was monitored over a period of 7 consecutive days. The company's health and safety staff was attempting to improve this employee's work practices and personal hygiene (e.g., regular washing, changes of personal clothing), which they regarded as being often inconsistent with good practice, and it was further desired to better define this worker's individual extent of exposure. During this period, worker DC was engaged in both die cutting and sewing operations. Personal air samples and urine samples were collected. Wipe and glove samples were collected but could not be analyzed because of incorrect storage. The results of the air and urine samples are presented in Table VI. The air concentrations, calculated range of the estimated inhalation dose, the measured urine concentrations, duration of urine collection, and the calculated mass of 4,4'-MDA excreted in each urine sample are given. During the task of die cutting, air concentrations were about 7.5 $\mu g/m^3$ (0.9 ppb) for a period of 3.5 hours, giving an 8-hour TWA of 3.1 $\mu g/m^3$. During sewing, personal exposures were about 4.6 $\mu g/m^3$ (0.5–0.7 ppb) during this job which lasted about 5 hours, giving an 8-hour TWA of about 2.5–5.5 $\mu g/m^3$. Inhalation dose was calculated assuming light work and moderate work for the period worked.[14] The mass of 4,4'-MDA excreted in the urine was calculated from the concentration of a sample and the total sample volume.

When sewing prepreg, this employee's personal protection consisted of a vinyl apron and vinyl gloves worn over thin cotton gloves. He was instructed to wash his hands prior to putting on the apron and gloves. Aprons and gloves were located in a cabinet outside the sewing room. The employee was also instructed to change gloves every 2 hours and to wash his face and hands prior to eating or smoking and again after each break and lunch period. Upon returning to the work area, a fresh pair of gloves were to be donned and the vinyl apron put on. When die cutting prepreg, this worker was to wear a white lab coat and latex gloves over thin cotton gloves.

Of interest in Table VI is the rise in elimination seen on Saturday (a day off work) and the persistence of a small amount of 4,4'-MDA in this worker's urine on Monday after presumably no exposure for 3 days. Elimination resumed at more typical levels on Tuesday with the sewing of 4,4'-MDA prepregs. Inhaled dose, assuming 100 percent retention and absorption and light or moderate work activity, was calculated and upon first inspection, appears to exceed the mass excreted in the urine. This would suggest that either a smaller percentage of the inhaled concentration is biologically available or only a small fraction of the absorbed dose is excreted in humans. However, this

TABLE VI. Results of Second Sampling Survey Sample, March 1990 — Facility B, Worker DC

Day of Week	Description of Job	Measured Air Concentration ($\mu g/m^3$, 8-hr TWA)	Estimated Daily Inhalation Dose[A]		Excretion of 4,4'-MDA in Urine			
			Light Work (μg/shift)	Moderate Work (μg/shift)	Collection End Time	Duration (min)	Concentration ($\mu g/L$)[B]	Mass (μg)
Friday	Die cut for 5 hours	3.1	45	68	1040	245	19	7.7
					1930	530	6	3.1
					2330	240	14	4.2
Saturday	No activity	No exposure	NA[C]	NA	1310	290	35	11
					1710	240	33	17
Sunday	No activity	No exposure	No samples	NA	No samples	NA	NA	NA
Monday	No 4,4'-MDA prepreg work	No sample	NA	NA	1410	443	2.4	1.4
Tuesday	Sewed prepreg 5 hours	2.6	31	47	1415	NA	14	4.1
Wednesday	Sewed prepreg 5 hours	3.3	63	95	1415	508	13	4
Thursday	Sewed prepreg 5 hours	No sample	NA	NA	1030	400	27	11
					1415	400	18	7

[A]Inhalation rate was assumed to be 25 L/min during light work and 38 L/min during moderate activity with 100 absorption.

[B]The limit of detection = 2 $\mu g/L$, analyzed by Pacific Toxicology Laboratories.

[C]NA indicates samples not assessed because there was no sample or information was lacking for a calculation.

TABLE VII. Wipe Sample Results for 4,4'-MDA, Third Sampling Period, April 1990 — Facility B

Sample Number	Surface Area (cm^2)	Wipe Location	Result 4,4'-MDA (µg/sample)[A]
01	100	Wipe of control panel at die-cutting machine	31
02	–	Wipe of control starter button	58
03	100	Wipe of prepreg material	24
04	100	Wipe of table top in break room upstairs	[0.4]
06	–	Blank	< 0.3

[A]Limit of detection (LOD) = 0.3 µg/sample; limit of quantitation (LOQ) = 0.7 µg/sample. Result in brackets in between LOD and LOQ.

is not actually the case, as discussed in an exploration of these data in a subsequent subsection of this report.

Further attempts were made to improve this individual's work practices and personal hygiene. In April 1990, this worker (DC) was again monitored during which 16 air, 27 urines, 32 glove rinse samples, and 4 wipe samples were collected. The few wipe samples collected indicate contamination of the work environment, including the table top in the break room (Table VII). The glove rinse samples in Table VIII-A show the outside and inside concentrations retrieved from the latex gloves worn by DC during die cutting and during sewing of prepregs. The concentrations found on the outside of these gloves were less than found on the outside of gloves from Facility A, possibly because dry prepregs were handled here without the use of methanol and because less physical handling might be involved. Also, when sewing prepregs, there was less 4,4'-MDA inside and outside the gloves than when die cutting, which paralleled the finding of less 4,4'-MDA excreted when sewing than when die cutting. Some additional data are presented in Table VIII-B which suggest that 4,4'-MDA is distributed equally on average over the gloved hand when die cutting. It appears that the palm obtains an appreciable portion of the total hand contact.

The results from the above survey of personal air sampling and urine monitoring are presented in Table IX. The urine data support the earlier observation that die cutting presents a higher level of exposure than when sewing prepregs. Weekend urine monitoring again shows excretion persisting through these days. The timed collections taken over the first weekend allowed calculation of the rate (µg/hr) of 4,4'-MDA excretion. This means of expression indicates a smooth transition of elevation and decline in excretion and allows a determination in this particular case of the peak excretion time, which was 34 hours after the last probably work-related exposure. Upon resumption of exposure, excretion rapidly became elevated.

Table X shows the results of additional urine monitoring that was performed in May 1990. Urinary excretion in worker DC was still elevated and was again highest when die cutting was performed. Additional samples from a worker using the oven press

TABLE VIII-A. Glove Rinse Results for 4,4'-MDA, Third Survey, April 1990 — Facility B

Sample Number	Hand	Part of Glove	Outside Concentration (µg/sample)[A]	Inside Concentration (µg/sample)[A]
1	Right	All	64	[1]
2	Left	All	36	[5]
3	Right	All	70	[2]
4	Left	All	47	[6]
5	Right	All	22	[1]
6	Left	All	[8]	[2]

[A]Limit of Detection (LOD) = 8 µg/sample; limit of quantitation (LOQ) = 20 µg/sample. Results in brackets are between LOD and LOQ.

TABLE VIII-B. Distribution of 4,4'-MDA Over Gloved Hand During Die Cutting, Third Survey — Facility B

Sample Number	Hand	Part of Glove	Concentration (µg/ml)[A]
1	Right	Fingers	[2]
1	Right	Palm	[5]
2	Left	Fingers	[2]
2	Left	Palm	[4]
3	Right	Fingers	[8]
3	Right	Palm	29
4	Left	Fingers	34
4	Left	Palm	[4]

[A]Limit of detection (LOD) = 1 µg/ml; limit of quantitation (LOQ) = 20 µg/ml. Values in brackets are between LOD and LOQ.

and from a third worker who was sewing prepreg were below the limit of detection. Samples collected from a fourth worker when he was also engaged with die cutting prepreg also contained 4,4'-MDA at levels comparable to DC when he performed this operation.

Table XI shows the results of air samples and urine monitoring during the final sampling survey at this location during the end of September 1990. Work practices were further improved, primarily in alerting the employees to the possibility of contaminated surfaces and in wearing personal protection, including gloves, whenever in the 4,4'-MDA prepreg work area, which was defined as a regulated area. Fresh prepreg was first vacuumed with a high-efficiency particulate air (HEPA) filter when received by the kit cutter, although this did not appear to appreciably reduce air concentrations. In addition, the type of personal protection was changed to include wearing a yellow, polyethylene-coated, encase lab coat with four front snaps and elastic sleeves. Thin, white, cotton inner gloves were worn underneath a copolymer laminate (4H®) glove and a latex outer glove. The outer latex glove was worn to afford better dexterity when handling prepregs. The laminate glove was used for 4 hours before changing and the latex glove was changed every 2 hours or as needed if damaged. A written description of the revised work practices was prepared and made available to all workers in the regulated area where 4,4'-MDA was used. End-of-shift (about 1400 hours) urine samples were collected from worker DC during the workweek for 2 weeks. Inhalation exposure was still variable but was not noticeably different from earlier exposures measured on this employee. However, the urine concentrations were significantly lower ($p = 0.01$) than the previous results. Even during die cutting days, considered from past experience to be the worst case, the urine concentrations never exceeded 20 µg/L. During the second week, excretion concentrations were just above the LOD. The mean urine concentration during this last sampling survey was 7 ± 6 µg/L, while the mean concentration during the survey in April, excluding weekend and nonwork days, was 42 ± 36 µg/L. This represents an 84 percent reduction from April and an 89 percent reduction from the average 65 ± 16 µg/L seen initially (Figure 6).

Additional wipe sampling was again performed during the last survey, and these results are presented in Table XII. Because these surfaces are in regular contact with 4,4'-MDA prepregs and were not decontaminated prior to sampling, it is not surprising that they all contained analyte. These data make it imperative that the worker know and appreciate this fact and that he is adequately protected when touching surfaces and tools used in an area that is probably contaminated.

Facility C

The results from initial urine sampling at Facility C in July 1990 are presented in Table XIII. Samples were collected during a Wednesday and Thurs day at the end of shift from 11 workers primarily as a screening exercise. Among the 11 workers sampled, 2 were considered nonexposed and were used as local control blanks. In addition, the nine potentially exposed workers had each provided a sample on Monday morning after a 9-day plant maintenance closing. Although air samples had been taken previously and the results were almost always below a limit of detection of 2 µg/m^3 (< 0.25 ppb), urine samples had not been previously collected for 4,4'-MDA. Each worker, because of the intermittent nature of their work with 4,4'-MDA-containing materials, was asked to keep a personal log of their job activities.

The results from the nonexposed workers and from all other workers after the post-nonwork period were all nondetectable (< 1 µg/L). The urine results from the workers later sampled while working with 4,4'-MDA-containing materials did not always contain analyte. For instance, dry winders did not eliminate 4,4'-MDA, while a wet resin winder excreted 4,4'-MDA during both days. This latter worker was found to eliminate increasingly more 4,4'-MDA with continued exposure. The two wet lay-up workers also excreted analyte. Also found eliminating 4,4'-MDA was a mixer who only occasionally handled pure 4,4'-MDA flakes and a pre-impregnating worker who frequently touched wet roving. Both workers wore latex gloves when handling these materials.

Personal air samples were collected on the above individuals on the Thursday of this survey. The air sample taken on mixing worker 1 contained 0.8 µg/m^3 (0.1 ppb) of 4,4'-MDA (7-hour sample), while all other samples were below the limit of detection. The LOD in air was about 0.12 µg/m^3 or 0.01 ppb. Wipe samples collected on various surfaces indicated low to no presence of 4,4'-MDA on most surfaces sampled. However, this was only a preliminary survey and not all surfaces that workers might touch were sampled.

The results of an initial glove assessment are presented in Table XIV. Sampling consisted of rinsing the outside and inside of used gloves and cutting off parts of the cotton inner gloves (if worn) for analysis, as described above. Exposure to the hand is suggested by many of these sample results that detected 4,4'-MDA inside the outer glove or in the cotton liner. The results also help to explain some of the urine excretion data (e.g., Worker CC). The need for

TABLE IX. Results of Airborne and Urine Monitoring for 4,4'-MDA, Third Survey, April 1990 — Facility B, Worker DC

Day of Week	8-Hour TWA Air Conc. ($\mu g/m^3$) and Activity	Estimated Inhalation Dose: Light Work (µg/shift)	Estimated Inhalation Dose: Moderate Work (µg/shift)	Urine Sampling Results: End Time	Duration (min)	Concentration (µg/L)	Mass (µg)	Rate (µg/hr)
Tuesday	0.09 Sewing prepreg	1.1	1.6	1215		12	1.8	
Wednesday	0.06 Sewing prepreg	0.7	1.1	1345		14	4.2	
Thursday	0.06 Sewing prepreg	0.7	1.1	1140		7	1.4	
Friday	3.0 Die-cutting prepreg	36	55	1430		15	2.2	
Saturday	No exposure			1145	180	14	4.2	1.4
				1900	290	62	12.5	2.6
				2400	165	45	22.6	8.2
Sunday	No exposure			1030	240	20	5.0	1.3
				1250	130	18	7.1	3.0
				2100	240	3	3.0	0.8
Monday	No exposure			430		4	1.9	
Tuesday	Sewing prepreg			No	Samples	Collected		
Wednesday	Die-cutting prepreg			1430		132	26.4	
Thursday	13.0 Die-cutting prepreg	156	237	1430		101	23.2	
Friday	1.1 Sewing prepreg	13	20	830	240	45	6.8	1.7
Monday	No exposure			415		< 2.5		
Tuesday	< 0.07 Die-cutting prepreg			1430		49	12.3	
Wednesday	1.8 Sewing prepreg	22	33	1430		46	9.2	
Thursday	1.8 Sewing prepreg	22	33	1430		25	7.6	
Friday	No samples Sewing prepreg			1430		25	3.3	
Monday	No samples			433		2.5	1.0	

[A]The limit of detection = 2.5 µg/L; all urine samples analyzed by Pacific Toxicology Laboratories, Inc.

TABLE X. Urine Monitoring Results for 4,4'-MDA, Fourth Sampling Survey, May 1990 — Facility B

Day of Week	Employee	End Time	Concentration[A] (µg/L)	Mass (µg)	Description
Tuesday, 5/15	DC	1415	44	8.8	Die cut 4,4'-MDA prepreg
Wednesday, 5/16	DC	1415	22	3.5	Sewing prepreg
Thursday, 5/17	DC	140	29	5.8	Sewing prepreg
Monday, 5/21	DC	445	< 5	0.0	First Monday void
Wednesday, 5/30	DC	1415	50	7.5	Die cut 4,4'-MDA prepreg
Thursday, 5/31	DC	1315	23	2.8	Sewing prepreg
Friday, 6/1	DC	445	21	2.1	First Monday void
Wednesday, 5/16	A	1420	< 5	0.0	Operated oven press
Friday, 5/18	A	1415	< 5	0.0	Operated oven press
Tuesday, 5/15	B	140	< 5	0.0	Sewing prepreg
Tuesday, 5/15	C	1415	31	6.8	Die cut 4,4'-MDA prepreg

TABLE XI. Results of Airborne and Urine Monitoring for 4,4'-MDA , Fifth Sampling Survey, September 1990 — Facility B, Worker DC

		Estimated Inhalation Dose		Urine Sampling Results		
Day of Week	8-Hour TWA Air Conc. (µg/m^3)[A] and Activity	Light Work[B] (µg/shift)	Moderate Work (µg/shift)	End Time	Concentration[C] (µg/L)	Mass Excreted (µg)
Tuesday	5 Die cut 15 kits	60	91	1335	7	1.8
Wednesday	8 Die cut 6 kits	96	146	1400	18	4.6
Thursday	[0.4] Sewed 10 kits	[5]	7	1425	13	3.5
Friday	[< 0.04] Sewed 10 kits	[<5]	[<7]	1405	3	0.3
Monday	No sample Die cut 22 kits			No Sample		
Tuesday	[0.7] Die cut 4.5 hours; Lay-up 3.5 hours	8.4	9	1400	7	0.7
Wednesday	[1.2] Manual cutting and lay-up	14	22	1345	7	0.4
Thursday	1.5 Die cut and sewed 6 kits	18	27	1420	2	0.5
Friday	[1.1] Sewed 8 kits	13	20	1400	2.5	0.8

[A]Limit of detection (LOD) was at least 0.25 µg/m^3 in air. Results in brackets are between the LOD and the limit of quantitation (LOQ).

[B]Inhalation dose is calculated based on respiration at 25 and 38 L/min and 100% absorption of the measured air concentration.

[C]The LOD = 1 µg/L, analyzed by the Health Safety Executive, London.

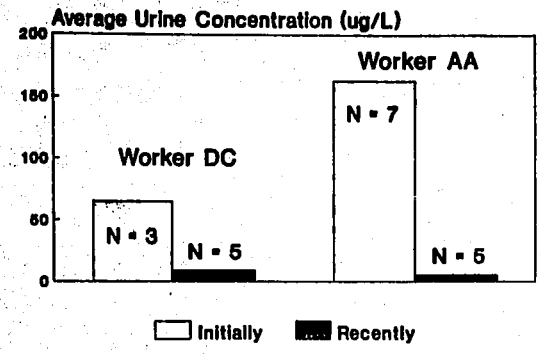

FIGURE 6. Comparison of the initial urine concentrations with most recent concentrations after minimizing the extent of exposure for two workers at Facilities B and C.

modifications in glove selection and use were evident. Initial impressions were that workers may sometimes wear the same gloves for extended periods of time. Employees working with wet resin frequently washed their gloves in an acetone bath to remove the resin. It was suspected that this practice could accelerate break-through and if holes in the glove existed, acetone-containing 4,4'-MDA could enter under the glove.

In late September 1990, an expanded urine collection survey was begun. This survey included some workers handling wet resins and others who were suspected of having the potential for exposure. The wet resin workers were asked to collect at least a first morning void and an end-of-shift void to be used to assess their exposure to 4,4'-MDA. They collected their urines on this schedule for 3 workweeks. During this period, the use of various glove types were explored, including finally the use of a copolymer laminate glove underneath a latex glove. During the weekends, they collected as many voids as possible, with the goal being complete collection. Although a total of 159 samples were collected, only the most complete examples from four of the nine workers monitored are presented in Table XV. Samples from workers performing dry winding were still below the LOD. Mixer CC was still excreting some (< 10 µg/L) 4,4'-MDA, although few samples were collected. The excretion data for workers AA, GG, FF, and an additional worker, referred to as JJ who was substituting for HH on lay-up work, are presented in the table. Almost all of the results of samples obtained from these workers contained 4,4'-MDA at levels above the detection limit. The highest concentration measured was 416 µg/L. Generally, elimination follows exposure during the workweek and declines during the weekend (weekend values in bold print). The number of hours reported as worked with 4,4'-MDA are estimated by the participants and may not necessarily reflect their potential for skin contact.

In spite of efforts to improve personal protective equipment during this 3-week sampling period, no direct benefit was observed as indicated by the urine results. Assessments of the amount of 4,4'-MDA under the glove indicated that the combination laminate glove plus latex outer glove reduced hand contact when wearing the gloves (not shown). This led to the conclusion that work practices (inconsistently wearing the glove combination provided) might be responsible for this continued exposure.

Three ways of expressing the elimination of 4,4'-MDA in urine are shown using the results from worker GG which were transformed from simple concentration units (µg 4,4'-MDA/L), as a rate (µg 4,4'-MDA/hr), and after adjustment for creatinine ex-

TABLE XII. Results from Wipe Samples for 4,4'-MDA, Fifth Sampling Survey, September 1990 — Facility B

Sample Number	Surface Sampling Area (cm^2)	Surface Description	Concentration[A] (µg/sample)
01	100	Stitching table of sewing machine 1	93
03	100	Stitching table of sewing machine 2	30
02	Undefined	Handle on sliding board used during die-cutting of prepregs	2
04	Undefined	Handle of heat gun 1 used on prepregs	5
07	Undefined	Handle of heat gun 2 used on prepregs	6
05	100	Surface of plastic-covered prepreg	23
09	100	Surface of plastic-covered prepreg	24
06	100	Surface of cutting table near press 1	4

[A]Limit of detection (LOD) = 0.5 µg/L; limit of quantitation (LOQ) = 2 µg/sample. Results in brackets are between the LOD and LOQ.

TABLE XIII. Initial Urine Screen Results for 4,4'-MDA, July 1990 — Facility C

Job Title	Worker Identification	Urine Collected Day of Week	Collection Time	Urine Concentration[A] (µg/L)	Record of Working with 4,4'-MDA			
					Monday	Tuesday	Wednesday	Thursday
Preimpregnator	AA	Wednesday	1500	ND[B]	Yes	No	Yes	No
		Thursday	1425	14				
Preimpregnator	BB	Wednesday	1500	ND	No	No	No	No
Mixer 1	CC	Wednesday	1510	20	Yes	Yes	Yes	No
		Thursday	1430	62				
Winder (dry)	DD	Wednesday	1510	ND	Yes	Yes	Yes	No
		Thursday	1420	ND				
Winder (dry)	EE	Wednesday	1500	ND	No	No	No	No
Winder (wet bath)	FF	Wednesday	1230	7	Yes	Yes	Yes	Yes
		Wednesday	1420	13				
		Wednesday	1530	24				
		Thursday	1150	30				
Lay up (wet)	GG	Wednesday	1530	35	Brief	Yes	Yes	Yes
		Thursday	1530	97				
Lay up (wet)	HH	Wednesday	1530	10	No	Yes	Yes	No
		Thursday	1530	18				
Mixer 2	II	Wednesday	1530	ND	Yes	Yes	Yes	No

[A]The limit of detection (LOD) was 1 µg/L, analyzed by the Health and Safety Executive, London.

[B]ND = below the LOD.

TABLE XIV. Results from Initial Glove Assessment for 4,4'-MDA Among Study Cohort, July 1990 — Facility C

Worker Identification	Cotton Glove Results: Finger Part	Cotton Glove Results: Concentration[A] (µg/sample)	Solvent Wash Results (µg/sample)[B]: Outside Glove	Solvent Wash Results (µg/sample)[B]: Inside Glove[C]
AA	Index	11	3580	[20]
	Middle	9.7		
BB	No samples		No samples	
CC	Index	190	1920	[220]
DD	Index	9.3	2480	[60]
	Middle	31		
EE	No samples		No samples	
FF	No samples		2980	[180]
GG	All digits	ND	2340	[60]
			2540	[100]
			600	[20]
HH	No samples		No samples	

[A]The limit of detection (LOD) for 4,4'-MDA was 0.3 µg/10 ml sample, while the limit of quantitation (LOQ) was 0.7 µg/10 ml sample.

[B]The practical LOD for 4,4'-MDA was 20 µg/sample, while the calculated LOQ was 400 µg/sample.

[C]Values in brackets are between the LOD and the LOQ.

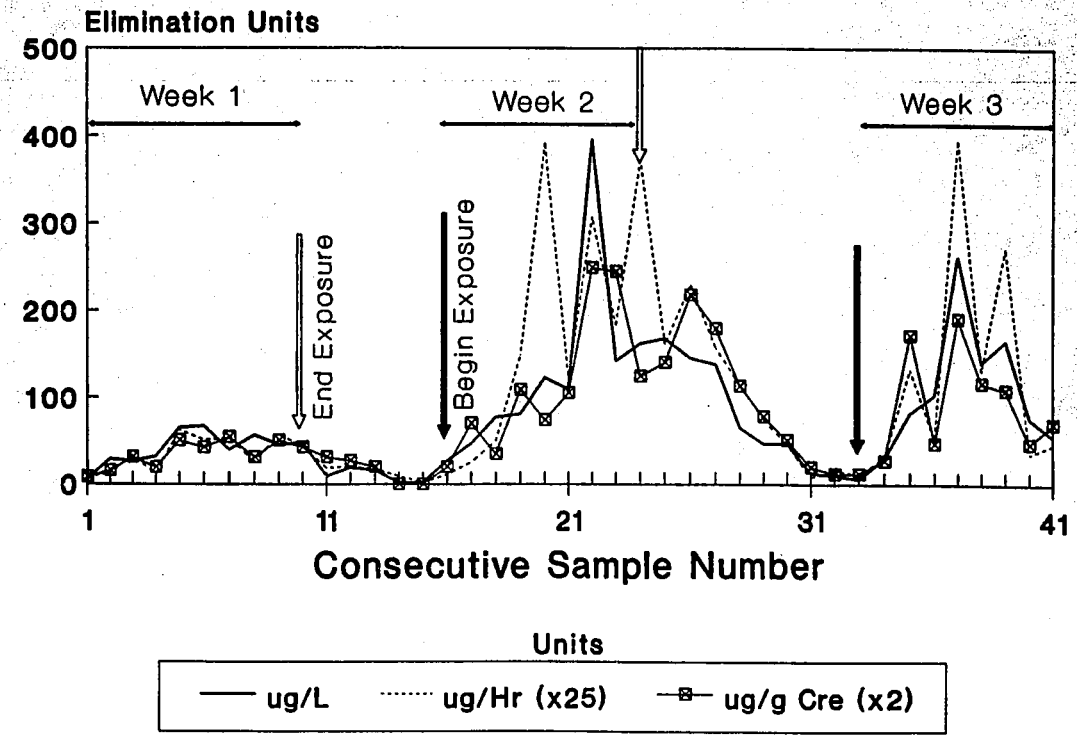

FIGURE 7. 4,4'-MDA in urine expressed three different ways. Sample results from worker GG, Facility C, reported in Table XV.

cretion (μg 4,4'-MDA/g creatinine). The corresponding 41-sample results expressed by these three methods are graphed in Figure 7. There is no appreciable difference between methods of expression for most of the data, although the creatinine adjustment tends to produce results that are two- to threefold lower than the simple concentration results. The most desirable method of expression is one that produces the least variability in consecutive samples. The rate method should be the most reflective means of expressing excretion, provided that the rate of excretion is constant and independent of endogenous and exogenous factors other than exposure, and the collection times are recorded accurately. However, it is suggested in this data set that the rate expression does not provide the best expression of these results because it tends to fluctuate the most in this example, which presumably occurred during various states of hydration. The simple concentration expression shows a general tendency for gradual change. This suggests that 4,4'-MDA may be eliminated passively, passing more amine through the kidney during high urine flow and less when urine flow is low, making concentration independent of urine flow. Figure 7 also visually portrays the week-to-week changing levels of excretion (note that x-axis is not chronologically linear but that the samples are consecutively plotted).

Further efforts are in progress, primarily in improved work practices while working in contaminated areas, which are intended to reduce exposure at Facility C. Workers are being instructed to either wear a combination plastic glove (4H® or other) covered with a latex glove or wear two pairs of latex gloves when entering and performing any job in a 4,4'-MDA designated work area. When wearing dual latex gloves, the outer glove only is removed when it is soiled, always leaving the clean inside glove to provide protection until a fresh outer glove is replaced. When working with 4,4'-MDA-containing materials, additional personal protection, including aprons and arm sleeves which are relatively impervious to 4,4'-MDA (made of laminates such as Chemrel®, Chemron, Inc., or others), are to be worn. Initial success has been documented for worker AA, whose initial average urine concentrations of 163 μg/L was reduced to 5 μg/L primarily by changing his work practices and by using improved personal protection (Figure 6). The work practice of washing gloves in acetone has not yet been abandoned in this facility but is being considered. Additional urine monitoring will continue to be conducted and will be used to indicate the extent of any reduction in exposure gained from the recent changes made at this site.

Inhalation versus Skin Contact

While it appears that inhalation dose may play an important role in Facilities A and B, as suggested by the calculated inhalation dose, the total mass excreted in the urine is appreciably greater than the mass inhaled. For instance, using the example of the first weekend excretion data in Table IX, it was estimated that the worker inhaled no more than 36 to 55 μg 4,4'-MDA, and it was assumed that all was biologically available for absorption. If the samples collected are indicative of the amounts of 4,4'-MDA being excreted during Friday evening through Sunday midnight, approximately 140 μg 4,4'-MDA was excreted. Dermal dosing of rhesus monkeys showed that only 19 percent of the dose was excreted in the urine over a period of 7 days, while 53 percent of the dose was estimated to be absorbed or retained in the skin and other organs. In comparison, 84 percent of an intravenous dose was recovered in the urine. This would suggest that, although an inhalation exposure might be excreted more rapidly and to a greater extent than a dermal dose, excretion due solely to skin exposure represents a proportionally greater dose. That inhalation exposure is not singularly responsible for exposure is supported entirely by the results from Facility C, where inhalation exposures would have been below 1.3–1.9 μg per day. To explain the levels of excretion at Facility C, daily skin absorption would have probably been in the range of at least 1 mg.

Conclusions

The experience of environmental and urine sampling at three aerospace manufacturing companies using 4,4'-MDA was presented. At each facility, urine monitoring played a vital role in determining the initial extent of exposure to 4,4'-MDA and, in the latter two cases, the extent of success of attempts to control exposure.

In each case, skin exposure appeared to play an important role, a route of exposure that, without having collected urine samples, could not have otherwise been as easily assessed. At Facility A, workers *appeared* at first glance to be protected, suggested by the use of gloves and wearing coats of impervious material when working with preprgs.

However, the selection and use of the chosen gloves was inappropriate, and ventilation slots were commonly cut into the impervious coats, negating their protective ability. At Facility B, it was demonstrated that substituting better personal protective equipment and improving work practices could appreciably reduce skin exposures, as measured by

TABLE XV. Excretion of 4,4'-MDA, Second Sampling Survey, September 1990 — Facility C

Date of Collection	End Time Hr	End Time Min	Elapsed Time (min)	Sample Volume (ml)	Conc. (µg/L)	MDA Expos. (hr)
Worker AA — Preimpregnation of Roving						
09/24	13	45	105	379	6	6
09/25	3	45	275	417	99	
09/25	13	45	65	425	8	7
09/26	5	20	410	399	142	
09/27			no samples			0
09/28	13	30	95	396	3	0
09/29–30			no samples			
10/01	14	0	130	342	25	7
10/02	2	0	280	206	308	
10/02	14	40	170	382	151	12
10/03	5	20	430	427	416	
10/04–08			no samples			
10/09	14	40	190	526	4	8
10/10	5	15	465	321	77	
10/10	15	20	210	359	23	5
10/11	5	15	435	367	127	0
10/12	13	30	120	446	37	0

Date of Collection	End Time Hr	End Time Min	Elapsed Time (min)	Sample Volume (ml)	Conc. (µg/L)	MDA Expos. (hr)
Worker GG — Wet Lay Up						
09/24	5	30	390	355	6	
09/24	21	30	345	103	29	4
09/25	5	30	480	400	27	
09/25	22	15	390	93	32	4
09/26	7	0	450	288	65	
09/26	20	0	240	123	67	4
09/27	6	30	420	372	40	
09/27	21	30	180	56	57	3
09/28	4	45	315	262	46	
09/28	19	30	240	145	48	3
09/29	7	0	360	493	9	
09/30	0	30	150	105	19	
09/30	8	0	450	332	16	
09/30	22	0	120	375	2	
10/01	7	0	540	312	2	
10/01	19	35	175	48	27	2
10/02	6	30	525	190	47	
10/02	23	30	300	130	77	5
10/03	7	0	240	293	81	
10/03	19	45	75	159	123	2
10/04	6	0	480	356	109	
10/04	21	30	180	93	396	3
10/05	5	45	420	362	142	
10/05	19	30	120	184	162	2
10/05	23	0	210	134	168	
10/06	7	0	480	506	145	
10/06	11	0	240	182	138	
10/06	15	0	240	262	65	
10/06	20	0	300	320	47	
10/07	7	0	660	430	47	
10/07	16	0	540	229	13	
10/07	20	45	285	317	10	
10/08	6	30	420	478	6	
10/08	19	30	90	62	30	4
10/09	6	15	360	385	82	
10/09	21	30	150	50	103	3
10/10	8	0	300	301	252	
10/11	5	30	600	373	140	
10/11	19	30	270	296	165	2
10/11	21	30	630	196	76	
10/12	7	0	470	263	55	

TABLE XV . Excretion of 4,4'-MDA, Second Sampling Survey, September 1990 — Facility C, continued...

Date of Collection	End Time Hr	End Time Min	Elapsed Time (min)	Sample Volume (ml)	Conc. (µg/L)	MDA Expos. (hr)
Worker FF — Wet Bath Winding						
09/24			no samples			8
09/25	11	0	180	134	6	
09/25	15	30	270	160	18	0
09/26	9	10	175	117	33	
09/26	14	0	150	85	28	0
09/27	9	0	180	86	24	
09/27	15	30	210	65	16	0
09/28	3	30	360	281	8	
09/28	12	0	150	68	6	0
09/29	8	0	360	432	3	
09/29	13	15	315	251	< 1	
09/29	15	0	105	253	< 1	
09/29	18	45	225	89	1	
09/30	7	20	530	296	1	
09/30	23	0	150	402	1	
10/01	6	15	435	93	2	
10/01	15	30	135	150	11	8
10/02	6	15	465	226	75	
10/02	14	20	170	69	55	0
10/03	6	10	550	419	20	
10/03	15	30	110	129	23	0
10/04	6	15	495	408	21	
10/04	15	0	60	132	12	0
10/05	6	50	210	130	9	
10/05	15	0	240	126	24	8
10/05	23	45	165	183	43	
10/06	7	20	455	247	61	
10/06	21	15	435	156	10	
10/07	7	0	585	302	18	
10/07	11	55	295	154	13	
10/07	14	30	155	234	2	
10/07	18	0	210	230	3	
10/07	20	F0	120	190	< 1	
10/07	21	30	90	130	< 1	
10/08	6	5	515	386	1	
10/08	15	30	270	380	3	8
10/09	7	0	45	45	36	
10/09	14	40	190	87	15	0
10/10	6	30	540	347	21	
10/10	15	20	260	329	9	8
10/11	6	15	475	328	28	
10/11	16	35	75	71	22	0
10/12	6	0	465	369	14	
10/12	15	15	75	93	13	8

Date of Collection	End Time Hr	End Time Min	Elapsed Time (min)	Sample Volume (ml)	Conc. (µg/L)	MDA Expos. (hr)
Worker JJ — Wet Lay Up						
09/24	6	0	540	417	15	
09/24	18	0	720	498	11	0
09/25	6	0	720	471	5	
09/25	12	30	390	304	11	8
09/26	5	50	500	535	12	
09/26	6	10	490	567	25	
09/26	13	0	410	414	25	4
09/27	13	25	455	295	17	0
09/28	4	15	435	501	3	
09/28	15	30	675	160	20	4
09/28	23	30	480	352	51	
09/29	7	10	460	510	26	
09/29	19	40	750	298	19	
09/29	23	50	250	417	9	
09/30	7	15	445	514	5	
09/30	9	50	155	381	5	
09/30	13	0	190	342	5	
09/30	16	45	225	404	< 1	
09/30	22	0	315	269	2	
10/01	5	55	475	525	3	
10/01	15	12	557	315	12	2
10/02	5	0	525	482	56	
10/02	12	25	445	185	136	2
10/03	3	49	364	476	30	
10/03	14	0	611	189	105	8
10/04	7	15	255	140	190	
10/04	15	25	490	155	204	8
10/05	7	30	330	223	113	
10/05	13	45	375	197	63	0
10/05	20	30	405	506	90	
10/06	6	15	585	352	30	
10/06	10	15	240	328	45	
10/06	14	0	225	339	25	
10/06	21	50	470	409	8	
10/07	6	55	545	529	8	
10/07	18	0	180	464	< 1	
10/07	23	20	320	320	4	
10/08	6	0	400	394	5	
10/08	15	20	560	266	6	0
10/09	7	15	255	127	3	
10/09	13	25	370	105	20	2
10/10	7	15	285	279	64	
10/10	15	20	485	194	53	0
10/11	7	30	225	196	148	
10/11	13	25	235	125	93	2
10/12	7	15	285	189	140	

Bold type indicate no work periods (weekends). Urine samples analyzed by Health and Safety Executive, London.

urine sample results which were subsequently reduced more than 80 percent. Facility C worked exclusively with wet 4,4'-MDA-containing materials, and air sampling indicated essentially no airborne analyte; however, the highest concentrations of 4,4'-MDA were detected among urine samples from this site.

Our data indicate that the best time to collect a urine sample for screening purposes appears to be the end-of-shift or the first next-morning void. It is shown by experimental animal studies that 4,4'-MDA is excreted much more rapidly when given intravenously that when applied topically, which is due to the rate of introduction into the body. Since workplace exposures may comprise both inhalation and the skin as routes of exposure, one might expect to see a biphasic pattern of elimination, as was seen in the results from Facility A. The initial elimination, seen during the end of the work shift, may be due primarily to inhalation exposure, while the next day elimination might be primarily from skin contact. In some of the examples given, peak excretory rates were not observed until a day after the last workplace exposure.

Because of the variable nature of both exposure and excretion which may be influenced by the route of exposure, it is suggested that urine samples be collected frequently until a satisfactory level of protection is achieved. If urine samples are to be used as a means of monitoring the effectiveness of protective measures over time, a good, initial baseline value of exposure is necessary, which can be obtained by multiple urine collections.

With the data at hand, it appears that excretion of 4,4'-MDA may be expressed simply as concentration (μg/L or ppb) with satisfactory results. Adjustment for creatinine does not appear to add any degree of precision to the results. Others have found that the excretion of creatinine is highly variable over time and is dependent on urine flow, diet, and other factors.[27-30] An analysis of the creatinine flow rate from the example given (Figure 7) showed that the average creatinine excretion rate was 0.11 g/hr, but the coefficient of variation was 81 percent (41 samples). Thus, creatinine is not necessarily a good surrogate for untimed samples or for correcting for diuresis.

Concerning criteria for an acceptable level of exposure and urine concentration, NIOSH recommends that workplace exposures be reduced to the lowest feasible limit due to the carcinogenic nature of 4,4'-MDA.[9,10] Although OSHA specifies an acceptable inhalation dose based upon risk analysis, the pharmacokinetic relationship between a given dose and the resulting level of urinary elimination is unknown for humans. Thus, establishing a defensible biologically equivalent urine concentration corresponding to the OSHA PEL would be difficult. Assumptions could be made about the elimination of 4,4'-MDA based upon the animal data, but large interspecies differences have been demonstrated even among rodents. The NIOSH recommendation to reduce exposure to the lowest feasible level is reasonable in light of the relatively simple efforts that were demonstrated to reduce exposure dramatically in Facilities B and C.

Protecting employees from skin contact with 4,4'-MDA cannot be effectively performed only by providing the appropriate personal protective clothing. The experience gained here indicated that appropriate training of employees must be performed to assure the proper use of personal protective clothing and to reinforce the necessity for its use whenever employees are in a potentially contaminated area. Special incentives and/or enforcement efforts might be required to assure ongoing compliance with established procedures. As a final measure, surface decontamination procedures should be adopted, whenever possible, to reduce the likelihood of skin exposure if surface contact occurred.

References

1. U.S. Department of Labor, Occupational Safety and Health Administration: 29 CFR Part 1910, Health and Safety Standards; Methylenedianiline (MDA) Mediated Rulemaking Advisory Committee Recommendations. Fed. Reg. 52:26776–26903 (July 16, 1987).
2. Dunn, G.W.; Guriguis, S.S.: Methylene Dianiline (MDA) as an Occupational Health Problem: A Suggested Time-Weighted Average Exposure Level and Medical Program. Arh. Hyg. Rada Toksikol. 30:639–645 (1979).
3. McGill, D.; Motto, J.: An Industrial Outbreak of Toxic Hepatitis due to Methylene Dianiline. N. Engl. J. Med. 296:278–282 (1974).
4. American Conference of Governmental Industrial Hygienists: Documentation of the Threshold Limit Values and Biological Exposure Indices. ACGIH, Cincinnati, OH (1986).
5. National Toxicology Program: Carcinogenesis Bioassay of 4,4'-Methylene Dianiline Dihydrochloride in F384/N Rates and B6C3F/N Mice. DHHS (NTP) Pub. No. 82-2504. NTP, Research Triangle Park, NC (1982).
6. International Agency for Research on Cancer: IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, Vol. 39, Some Chemicals Used in Plastics and Elastomers, pp. 347. IARC, Lyon, France (1986).
7. Cragle, D.: Health Study of ORGDP Centrifuge Workers, Oak Ridge Associated Universities, Medical Sciences Division, Center for Epidemiological Research, Oak Ridge, TN (1990).
8. National Institute for Occupational Safety and Health: Health Hazard Evaluation Report 82-146-1388 Boeing Vertol Company, Philadelphia, PA. NTIS Pub. No. PB-

85-179-323. National Technical Information Service, Springfield, VA (1983).
9. National Institute for Occupational Safety and Health: Current Intelligence Bulletin #47, 4,4'-Methylenedianiline (MDA) (Revised). DHHS (NIOSH) Pub. No. 86-115; NTIS Pub. No. PB-87-104-527. National Technical Information Service, Springfield, VA (1986).
10. National Institute for Occupational Safety and Health: Testimony of NIOSH on the Occupational Safety and Health Administration's Proposed Rule on Occupational Exposure to 4,4'-Methylenedianiline (MDA), 29 CFR Parts 1910 and 1926, Docket No. H-040. Presented at the OSHA Informal Public Hearing, Washington, DC (March 20, 1990).
11. Notices: 4,4'-Methylenedianiline; Decision to Report to the Occupational Safety and Health Administration. CFR 500 (129). Fed. Reg. 49:27674–27681 (July 4, 1985).
12. El-hawari, M.; Stolz, M.; Czarnecki, D.; Alm, P.: Dermal Absorption of ^{14}C-Labeled 4,4'-Methylenedianiline in Rats, Guinea Pigs, and Monkeys. EPA-560/5-86-011. U.S. Environmental Protection Agency, Office of Toxic Substances, Washington, DC (1986).
13. Guy, R.: Personal communication concerning *in vitro* mouse skin study with 4,4'-Methylenedianiline. University of California–San Francisco, School of Pharmacy, San Francisco, CA (1989).
14. Mason, R.W.; Johnson, B.L.: Ergonomic Factors in Chemical Hazard Control. In: Handbook of Human Factors. G. Salvendy, Ed. Wiley–Interscience, New York (1987).
15. Dalhamn, T.; Edfors, M.-L.; Rylander, R.: Retention of Cigarette Smoke Components in Human Lungs. Arch. Environ. Health 17:746–748 (1968).
16. Albert, R.M.; Lippman, H.T.; Peterson, J.; et al.: Bronchial Deposition and Clearance of Aerosols. Arch. Intern. Med. 131:115–127 (1973).
17. Leung, H.-W.; Paustenback, D.J.: Application of Pharmacokinetics to Derive Biological Exposure Indexes from Threshold Limit Values. Am. Ind. Hyg. Assoc. J. 49(9):445–450 (1988).
18. Cocker, J.: *In-vivo* and *In-Vitro* Acetylation of Two Industrial Aromatic Amines. Unpublished report. Health and Safety Executive, Research and Laboratory Services Division, Occupational Medicine and Hygiene Laboratories, London, U.K. (1987).
19. Cocker, J.; Gristwood, W.; Wilson, H.K.: Assessment of Occupational Exposure to 4,4'-Diaminodiphenylmethane (Methylene Dianiline) by Gas Chromatography–Mass Spectrometry Analysis of Urine. Br. J. Ind. Med. 43:620–625 (1986).
20. Cocker, J.: Personal communication. Organic Toxicology Section, Occupational Medicine and Hygiene Laboratories, Health and Safety Executive, London, U.K. (1987).
21. National Institute for Occupational Safety and Health: Method 5029. In: NIOSH Manual of Analytical Methods, 3rd ed., 1990 Supplement. DHHS (NIOSH) Pub. No. 84-100; NTIS Pub. No. PB-85-179-018. National Technical Information Service, Springfield, VA (1984, 1990).
22. Schoch, D.H.; Tersegno, L.K.; Winter, J.E.; et al.: Testing of "Impervious" Gloves for Permeation by Organic Solvents. Presented at the American Industrial Hygiene Conference, Cincinnati, OH (June 6-11, 1982).
23. Brown, K.: Memo, Report of IWSB Study #143, Worker Exposure to 4,4'-Methylenedianiline. Analytical Toxicology Section, Applied Biology Branch, Division of Biomedical and Behavioral Science, National Institute for Occupational Safety and Health, Cincinnati, OH (January 9, 1990).
24. Gristwood, W.; Robertson, S.W.; Wilson, H.K.: The Determination of 4,4'-Methylene-bis(2-chloroaniline) in Urine by Electron Capture Gas Chromatography. J. Anal. Toxicol. 8:109–114 (1984).
25. Peterson, J.: Determination of 4,4'-MDA in Urine by High Performance Liquid Chromatography. J. Chromatography 564:205–212 (1991).
26. Boeniger, M.: Industrial Hygiene Survey Report of General Electric Company, Albuquerque, New Mexico. IWSB Report No. 143.21. National Institute for Occupational Safety and Health, Cincinnati, OH (1991).
27. Greenberg, G.; Levine, R.J.: Urinary Creatinine Excretion is not Stable: A New Method for Assessing Urinary Toxic Substance Concentrations. J. Occup. Med. 31:832–838 (1989).
28. Curtis, G.; Fogel, M.: Creatinine Excretion: Diurnal Variation and Variability of Whole and Part-Day Measures. Psychosom. Med. 32:337 (1970).
29. Alessio, L.; Berlin, A.; Dell'Orto, A.; et al.: Reliability of Urinary Creatinine as a Parameter Used to Adjust Values of Urinary Biological Indicators. Int. Arch. Occup. Environ. Health 55:99–106 (1985).
30. Turner, W.J.; Cohn, S.: Total Body Potassium and 24-Hour Creatinine Excretion in Health Males. Clin. Pharm. Therap. 18:405 (1975).

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