RISK ASSESSMENT

FOR

4,4'-METHYLENEDIANILINE

CAS NO. 101-77-9

OFFICE OF TOXIC SUBSTANCES
U.S. ENVIRONMENTAL PROTECTION AGENCY

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TABLE OF CONTENTS

LIST OF FIGURES AND TABLES

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EXECUTIVE SUMMARY

This document characterizes the cancer risks posed by 4,4'-methylenedianiline (4,4'-MDA).

4,4'-MDA is considered to be a probable human carcinogen (B2) using the criteria of the Revised Interim Guidelines for the Health Assessment of Suspect Carcinogens. Evidence for this classification includes observation of elevated tumor incidence at multiple sites in rats and mice in NTP bioassays, observation of an elevated incidence of bladder tumors in a group of exposed workers, observation of the chemical's ability to react with genetic material in short-term studies, indications that the chemical is rapidly absorbed and distributed in mammals, and a structual relationship with a number of 2-ring aromatic diamines that are known carcinogens in animals and/or humans.

4,4'-MDA is produced at an annual volume of 400-500 million pounds in the United States. About 97% of production is converted to methylene diphenyldiisocyanate, a ployurethane intermediate, and about 600 workers are exposed through these processes. The remaining 3% of production is used as a component of epoxy resins or other polymer systems, and about 13,000 workers may be exposed through these uses.

There appears to be little or no consumer use of products containing free, un-reacted 4,4'-MDA, although some adhesives and sealants used in such trades as foundation wall crack patching are known to contain the chemical.

Based on the available information, risks of tumor development in workers exposed to 4,4'-MDA appear to be

RISK ASSESSMENT OF

4,4'-METHYLENEDIANILINE (4,4'-MDA)

I. INTRODUCTION

In 1979, the Interagency Testing Committee (ITC), established under section 4 of the Toxic Substances Control Act (TSCA), recommended that 4,4'-MDA (CAS No. 101-77-9) be considered for testing for carcinogenicity, teratogenicity, mutagenicity, other chronic effects, environmental effects and epidemiology (44 FR 31885, June 1, 1979) under authority of section 4 of the Toxic Substances Control Act (TSCA). In making this recommendation, the ITC cited sketchy toxicity information that included some cancer studies, along with concern about high production volume and reports of adverse health effects among exposed humans.

The Office of Toxic Substances (OTS) within the Environmental Protection Agency (EPA) then undertook a review of available information on 4,4'-MDA. Contractors were employed to gather this information, and by 1982 most of it had been summarized in five reports by Springborn Laboratories (Springborn, 1982), JRB Associates (JRB, 1980, 1981), MathTech (MathTech, 1982), and Environmental Science and Engineering, Inc. (ESE, 1981).

In mid-1982, the Chemical Manufacturers Association (CMA) established a 4,4'-MDA Project Panel consisting of representatives of BASF Wyandatte Corp., The Upjohn Co., Mobay Chemical Corp. Olin Corp., Rubicon Chemicals (ICI Americas

Inc.), and Uniroyal, Inc.* The Panel began to gather production, use and exposure information for submission to EPA and to develop a voluntary testing program.

In June 1982, EPA made 4,4'-MDA subject to the reporting requirements of section 8(a) of TSCA. As a result, manufacturers and importers were obligated to report on the amount of the chemical produced or imported and on certain other information related to uses and releases to the environment (47 FR 26992, June 22, 1982). In addition, a rule issued under section 8(d) of TSCA in September 1982 (47 FR 38780, Sept. 2, 1982) required reporting of unpublished health and safety studies.

As all of this information was being studied by OTS, the preliminary results of National Toxicology Program (NTP) carcinogenesis bioassays on the dihydrochloride salt of 4,4'-MDA became available. This information, coupled with exposure reports, led the Administrator of EPA in early 1983 to find that there is a reasonable basis to conclude that 4,4'-MDA may present a significant risk of serious harm to humans from cancer. This finding resulted in the invocation of section 4(f), the priority review provision of TSCA, and a 180-day priority review of the reasonableness of the cancer risks associated with 4,4'-MDA began in March (48 FR 19078, April 27, 1983).

Since most of the identified exposure to 4,4'-MDA occurs in the workplace, EPA contacted the Occupational Safety and Health Administration (OSHA), and the two agencies agreed that any

* Shell Chemical Co., CIBA-GEIGY Corp., and Pacific Anchor Corp. subsequently became members of the Panel.

action needed to control the chemical would be undertaken jointly.

The National Institute of Occupational Safety and Health (NIOSH) was contacted in May 1983, and plans to increase the amount of information on workplace exposures were made. Subsequently, NIOSH independently decided to determine whether an epidemiology study of 4,4'-MDA was feasible.

At the end of the 180-day priority review period, EPA and OSHA published Advance Notices of Proposed Rulemaking (ANPR) (OSHA: 48 FR 42836; EPA: 48 FR 42898; Sept. 20, 1983), announcing a joint effort by the agencies to initiate regulatory action to determine and implement the most effective means of controlling exposures to the chemical under TSCA and/or the Occupational Safety and Health Act.

During the 180-day priority review, EPA published its decision not to pursue further testing of 4,4'-MDA at that time because of the apparent need to control exposures to the chemical to lower risks from cancer (48 FR 31806, July 11, 1983).

The present assessment uses the information obtained by EPA during the period described above, monitoring information obtained by NIOSH from two plant visits, information submitted in response to the April 1983, section 4(f) designation and the ANPRs of September 20, 1983, and product use information obtained by a CMA sponsored survey of firms that use and/or process 4,4'-MDA commercially. Since the information obtained so far is still incomplete, especially regarding workplace exposure levels,

potential surface water contamination and skin penetration potential, the risk assessment will be augmented by further analysis as those data become available.

II. CHEMICAL IDENTITY (ESE, 1981)

The name approved by the International Union for Pure and Applied Chemistry for 4,4'-MDA is 4,4'-diaminodiphenylmethane. Other synonyms and common names are:

4,4'-methylenedianiline

4,4'-methylenebisaniline

4,4'-methylenebisbenzeneamine

p,p'-methylenedianiline

methylenedianiline

dianilinomethane

Trade names for the compound and for mixtures containing it are (CMA, 1983d):

97% Minimum Assay 4,4'-MDA

p,p'-Methylene Dianiline

Phenyl Base G

Laromin B-250

Hardner HT 972

Eposand 112 B

Crude 4,4'-MDA (Mixture with Isomers and Oligomers)

Curithane 103

Curithane 116

Tonox

Tonox R

Tonox 22

Tonox M

Modified Raw Materials Containing Free 4,4'-MDA

Tonox 60/40

Tonox JB

Tonox LC

Araldite Hardener 830

Araldite Hardener 850

HY 932 (XU 205)

HY 2969

Ancamine LO

Ancamine LOS

Ancamine LT

Ancamine TL

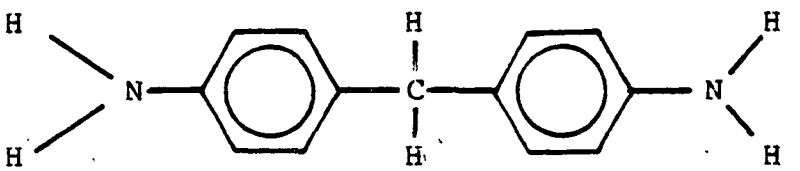
Ancamine TLS

Ancamine 1482

Curing Agent Y

Curing Agent Z

The structure of the compound is:



$C_{13}\ H_{14}\ N_2$

The compound in commercially pure form is a light brown to white crystalline solid with a faint amine-like odor. It is prepared commercially by the acid-catalyzed condensation of formaldehyde and aniline.

$$2\ C_6H_5NH_2 + H_2CO \xrightarrow{H^+} H_2NC_6H_4CH_2C_6H_4NH_2 + H_2O$$

In addition to the 4,4'-product, some 2,2'- and 2,4'- by-products are formed, as are isomeric polycondensates.

$$2X\ C_6H_5NH_2 + 2X - 1\ H_2CO \longrightarrow H_2NC_6H_4(CH_2C_6H_4NH_2)_{2x-1} + 2X - 1\ H_2O$$

The physical properties of 4,4'-MDA follow:

Molecular weight	198.3
Boiling range (768 mm Hg), °C	398-399
Melting point, °C	91-92
Density at 100°/4°C	1.056
Viscosity at 100°C (cP)	8.04
Flash point, °C	221.1
Fire point, °C	248.9
Heat of vaporization, kJ/mole (kcal/mole)	95.4 (22.8)
Specific heat at 29°C (solid), J/(g°C) [cal/(g °C)]	1.46 (0.35)
Specific heat at 109°C (liquid), J/(g °C) [cal/(g °C)]	2.01 (0.48)
Heat of fusion, kJ/mol (kcal/mole)	19.6 (4.7)
Log P	1.76-2.52
Approximate solubility, g/100 g of solvent at 25° C	
Acetone	273.0
Benzene	9.0
Carbon tetrachloride	0.7
Ethyl ether	9.5
Methanol	143.0
Water	0.1

Source: Moore (1978), Windholz (1976), as reported in ESE (1981).

III. HEALTH EFFECTS

Information relating to the ability of 4,4'-MDA to be absorbed by mammals and then to interact with genetic material will be presented in this chapter along with summaries of studies on animals aimed at determining the chemical's carcinogenic potential. Additionally, information from an epidemiology study and a structure-activity analysis will be given. Then all the evidence relating to the carcinogenic potential of 4,4'-MDA will be pulled together in a weight-of-evidence summary.

Since the purpose of this assessment is to investigate the cancer risks associated with 4,4'-MDA, the principal thrust of the health effects review given here will be on that topic. However, it should be noted that 4,4'-MDA has been recognized as a causative agent in acute liver toxicity in humans and animals (NIOSH, 1976a, 1976b). Liver toxicity in humans has been observed following oral exposure in the so-called "Epping Jaundice" incident in which people in Epping, England consumed bread made with flour contaminated with 4,4'-MDA (Kopelman et al., 1966a). Kopelman (1966b) reported a 2-year follow-up study on 43 of the 84 persons known to have suffered injury in the case. While no evidence of progressive liver disease was seen, some patients reported fat, fruit or alcohol intolerance, weight loss or other troublesome symtoms.

Dermal exposure to 4,4'-MDA also has been associated with acute liver toxicity. McGill and Motto (1973) and Williams et al. (1974) reported on dermal exposures in the workplace which resulted in liver toxicity. Additional information on these incidents is given in Section IV.

Retinopathy has also been cited as a toxic effect (Schilling v. Constatt et al., 1966; NIOSH, 1981; Leong et al., 1984), as has acute myocardiopathy (Brooks et al., 1979) and allergic dermititis (Emmett, 1976). Retinopathy has been observed in the cat and the guinea pig and may have occurred in humans, while myocardiopathy has been seen in humans.

A. Absorption and Distribution (Thies, 1983)

1. General

Tortoreto et al. (1961) administered pure (100%) or technical grade (56%) 4,4'-MDA to male $B6C3F_1$ mice intraperitonealy in corn oil at the maximum tolerated dose of 250 mg/kg. Animals were examined at intervals between 5 minutes and 12 hours after administration of 4,4'-MDA for distribution of the chemical to the blood, liver, kidneys, lungs and spleen.

These workers found that 4,4'-MDA is rapidly absorbed and reaches peak concentrations in the blood between 10 and 20 minutes after administration. They found the half-life in blood to be about 6 hours and the rate constant for the beta (elimination) phase to be about 2×10^{-3} minutes.

They found that 4,4'-MDA is distributed preferentially to the liver and kidneys and is eliminated from all examined organs at similar rates. No notable difference in distribution was seen between the pure and technical grades.

This study shows that 4,4'-MDA is rapidly absorbed and well distributed and that impurities up to 44% have negligible effect on blood partitioning of the chemical. The liver appears to be the organ receiving the greatest systemic dose.

2. Inhalational and Dermal Absorption

For the purposes of this analysis, the structural analogue, methylenebis (ortho-chloroaniline) (MBOCA), is used to predict the behavior of 4,4'-MDA while more data on the latter are being obtained. MBOCA is a good structural analogue for 4,4'-MDA, and it has similar physicochemical properties so that it can be used to make inferences regarding the behavior of 4,4'-MDA.

Some physicochemical properties of 4,4'-MDA and MBOCA follow:

	4,4'-MDA	MBOCA
	CAS No.: 101-77-9	**CAS No.: 101-14-4**
Molecular Weight:	198.26	269.06
Log P:	1.84*	1.38**
pKa_1 (estimated):	4.89	3.13

It is generally recognized that compounds which exhibit some degree of lipid and water solubility, which are predominately in an un-ionized state at physiological pH values, and which have sufficiently low molecular weight (less than 500) will tend to be more easily absorbed.

a. MBOCA Data

i. Percutaneous Penetration

Several studies show that MBOCA binds to and penetrates through human and animal skin.

Chin et al. (1983) demonstrated in vitro percutaneous absorption by, accumulation in, and penetration through neonatal human foreskin by radiolabelled MBOCA.

* See Section IV.
** Glowinski et al., 1978.

Workers exposed during the manufacture of MBOCA were shown by Linch et al. (1971) to demonstrate measurable levels of the chemical in urine.

Radiotracer studies by several groups (Braselton et al., 1982; Groth as reported by Morton, 1981; Tobes et al., 1983) using ^{14}C labelled MBOCA demonstrated that MBOCA penetrates human and animal skin.

Based on these studies, which show a range of skin penetration rates from about 0.13 to about 8% of the applied dose per hour, a logarithmic mean of 1% absorption per hour can be used as the dermal penetration rate of MBOCA for humans (Beal, 1982).

ii **Gastro-Intestinal Tract Penetration**

MBOCA, its metabolites, or both, penetrate through gastro-intestinal tract tissue.

Stula et al. (1975 and 1977) and Kommineni et al. (1979) conducted long-term feeding studies in mice, rats, and dogs that resulted in production of malignancies in the lungs and urinary bladder, demonstrating penetration of MBOCA through gastro-intestinal tract tissue.

Oral LD_{50} studies in male rats by Miller and Sherman (1965) and Reinke (1963) demonstrated that MBOCA, its metabolites, or both, penetrate gastro-intestinal tract tissue.

Recent single- and multiple-dose pharmacokinetic studies in rats by Morton et al. (1981) and Groth (1981, as cited by Morton et al., 1981) showed that MBOCA penetrates gastro-intestinal tract tissue.

Barnes (1964) reported profound effects on the blood of dogs orally exposed to MBOCA, and demonstrated recovery of MBOCA and its metabolites in urine, thus showing gastro-intestinal tract absorption.

After oral administration of MBOCA, the major route of elimination is *via* the feces, which may indicate that the gastro-intestinal tract does not completely absorb MBOCA or its metabolites, or that absorption is followed by some degree of biliary cycling as shown by Morton *et al.* (1981).

iii. Respiratory Tract Penetration

No test data are available regarding the penetration of MBOCA or its metabolites through respiratory tract tissue. But based on the knowledge that MBOCA penetrates other biological membranes and its physicochemical properties, it can be assumed that if MBOCA reaches the alveolar regions of the lung, it will be absorbed, but to an unknown extent.

A critical factor in estimating the potential for penetration of substances through lung tissue is particle size. Particles of MBOCA (or 4,4'-MDA) greater than 5 microns in size will not be expected to reach the alveolar regions where extensive absorption could occur; however, such material could still reach systemic circulation due to the generally capillary-laden nature of the nasopharyngeal region. Particle sizes greater than 2, but less than 5 microns will deposit in the upper respiratory tract, where very little may be absorbed *via* alveolar or capillary diffusion; most will be cleared by mucocilliary movement with subsequent swallowing, and absorption *via* gastro-intestinal tract tissue.

Particle size less than 2 microns stand the best chance of reaching the alveolar regions and, depending on lipid solubility, crossing the alveolar membrane. MBOCA or 4,4'-MDA in the vapor phase can be expected to penetrate lung tissue fairly well. This conclusion is based on knowledge that MBOCA can cross other biological membranes and on its solubility characteristics. It is assumed that this penetration may reach at least 50% of the inhaled material. This assumption is based on gastro-intestinal absorption of radiolabelled MBOCA in rats of approximately 30% (Morton et al., 1981).

b. Inferences About 4,4'-MDA

As previously stated, MBOCA is an acceptable analogue to 4,4'-MDA and provides adequate information to conclude that 4,4'-MDA has a high potential to penetrate biological membranes.

NTP bioassays (NTP, 1983a), on 4,4'-MDA dihydrochloride indicate the probability that 4,4'-MDA itself will cross gastro-intestinal tissue. In these studies, rats and mice received the dihydrochloride salt of 4,4'-MDA in drinking water. The dihydrochloride moieties would be expected to dissociate rapidly in the gastro-intestinal tract, leaving 4,4'-MDA as the essential toxicant. From the NTP studies it is clear that orally administered dihydrochloride of 4,4'-MDA is a carcinogen in rats and mice. This provides indirect evidence that 4,4'-MDA, its metabolites, or both, penetrated gastro-intestinal tract tissue.

While 4,4'-MDA would be almost entirely un-ionized in the gastro-intestinal tract, it is difficult to support the concept of 100% absorption, especially when dose levels are not defined

by pharmacokinetic studies. Furthermore, Morton et al. (1981) demonstrated that the major route of MBOA excretion was *via* the feces, which may indicate incomplete absorption from the gastro-intestinal tract. It can probably be assumed that gastro-intestinal tract absorption of 4,4'-MDA may be approximately 50%.

The assumption that absorption through lung tissue is roughly equivalent to gastro-intestinal absorption is plausible, especially if 4,4'-MDA is in the vapor phase or has a particle size of less than 2 microns.

In addition to the inferences about 4,4'-MDA's ability to be absorbed by humans that are based on structural analogy with MBOCA, further direct evidence for 4,4'-MDA's absorption potential is given by Vaudaine *et al.* (1982), Williams *et al.* (1974), McGill and Motto (1974), Dunn and Guirguis (1979) and Brooks (1979). These workers reported that 4,4'-MDA was found in the urine of industrial workers who were exposed to the chemical (Vaudaine *et al.*) or that various toxic manifestations of exposure occurred in industrial settings. Further information is given in Section IV. Additional evidence of absorption of 4,4'-MDA by humans is given by Kopelman *et al.* (1966a, 1966b), who reported on cases of liver toxicity in people who had eaten bread contaminated with the chemical.

c. Limits of this Analysis

As with most structure activity relationship analyses, conclusions must be made with the understanding that nothing is a good substitute for actual testing. While MBOCA appears to be a good analogue, it is not known what specific effects the two

chlorine molecules may have on penetration characteristics. The strongest conclusion that can be inferred based on the available information is that 4,4'-MDA crosses biological membranes. Quantitative estimates of the rate of this absorption require testing, and such testing is being done in an EPA-sponsored dermal penetration study using radio-labeled 4,4'-MDA.

For the purpose of this assessment, a dermal absorption rate of 1% per hour of deposited material is assumed, based on MBOCA data.

B. Mutagenicity

4,4'-MDA induces mutation in the Salmonella typhimurium/ mammalian microsomal assay (Ames assay), induces sister chromatid exchanges (SCE) in femoral bone marrow of male mice and binds covalently to DNA in vivo in the livers of treated mice. It does not induce chromosomal aberrations in vitro in human peripheral lymphocytes and is reported to be negative in a Drosophila melanogaster sex-linked recessive lethal assay, the details of which were not available for review and whose validity, therefore, cannot be assessed.

Since the human peripheral leukocyte assay does not measure the same endpoint as the Ames and SCE assays, a mixture of positive and negative results is not unusual, and the positive results seen in the latter are, thus not negated by the negative results seen in the former. Although not a test for genotoxicity per se, covalent binding to DNA demonstrates that 4,4'-MDA is capable of interaction with macromolecules in vivo. Such binding may be indicative of the ability of this agent to induce

mutations and cancer. Taken together the weight of evidence from all these studies supports the conclusion, reached on the basis other evidence too, that 4,4'-MDA is an oncogen.

4,4'-MDA has repeatedly been found to be mutagenic in tests with S. typhimurium strains TA-98 and TA-100 with metabolic activation (Godek et al., 1982; Rao et al., 1982; Parodi et al., 1981; Darby et al., 1978; and Brusick, 1976. While Brusick (1976) reported positive results with metabolic activation in a test on strain TA-1538, other workers have found that 4,4'-MDA is not active in that strain or in strains TA-1535 and TA-1537, either with or without metabolic activation.

The Ames assay is known to correlate with in vivo oncogenicity with approximately 81% reliability. In a review performed for the Gene-Tox Program (EPA, 1983), 122/151 (81%) of the oncogens which were tested in the Ames assay were correctly identified.

Parodi et al. (1983) reported that 4,4'-MDA induced SCE in the femoral bone marrow of male mice. Although SCE formation cannot be used as a quantitative measure of carcinogenic potency, it can be used as a qualitative indicator of potential in vivo oncogenicity. In the Gene-Tox Review referred to above, 17/17 (100%) oncogens were correctly identified in this assay. While admitedly a limited data base, it does appear that the in vivo SCE assay is a sensitive indicator of potential in vivo oncogenicity.

Pantarotto (1983) and Parodi et al. (1981) have both reported that 4,4'-MDA is capable of covalent binding in vivo to

mouse liver DNA. While not a test for genotoxicity per se, these results do show that 4,4'-MDA is capable of reaching target tissue *in vivo* and once there of interacting with cellular macromolecules in a manner which may lead to mutations or cancer.

Although Ho *et al.* (1979) reported that MDA did not induce sex-linked recessive lethal mutations in *Drosophila*, the cited study is an abstract with no experimental data. In the absence of such data, no conclusions can be drawn about the validity of the study.

Nunziata (1983) reported that 4,4'-MDA did not induce chromosomal aberrations *in vitro* in cultured human lymphoctes. The negative results in this study do not lessen the weight of evidence presented by the studies cited above.

4,4'-MDA induces gene mutation, SCE, and DNA damage. Gene mutation and chromosomal aberration are separate endpoints. It is not unusual for a chemical to induce one but not both of these endpoints. Based upon the results of the studies summarized above, 4,4'-MDA should be considered a probable oncogen.

C. Carcinogenicity

1. Human Data (Scott-Siegel, 1984)

The National Institute of Occupational Safety and Health (NIOSH) conducted a health hazard evaluation of workers employed by the Boeing Vertol Company, a manufacturer of helicopters and helicopter parts (NIOSH, 1983). NIOSH evaluated exposures in two buildings, the blade and pattern shop, where exposure to 4,4'-MDA, epoxy resins, and solvents (toluene, methyl isobutyl ketone, and cyclohexanone) were known to occur. A medical evaluation of

workers who had been employed in these areas was also done in two parts: a medical study of dermatologic conditions and an epidemiologic evaluation -- a proportionate mortality (PMR) and proportionate cancer mortality (PCMR) study. Among a group of 179 "exposed" worker deaths, NIOSH observed in the PMR study statistically significant elevations in mortality from cancer of the bladder, large intestine, and lymphosarcoma/ reticulosarcoma. The elevation in bladder cancer mortality remained significant in the PCMR study. This epidemiologic evaluation of the pattern and blade shops suggests the existence of an increased risk of mortality from bladder cancer. NIOSH, additionally, conducted environment monitoring in the pattern and blade shops to determine current exposure. They found detectable levels of 4,4'-MDA, epoxy resins, and solvents (See Section IV).

Analysis of deaths in the "exposed" group show significant elevations in site-specific mortality from cancer of the bladder (PMR=374, 3 observed, $p<0.05$), large intestine (PMR=226, 7 observed, $p<0.05$), lymphosarcoma/reticulosarcoma (PMR=343, 3 observed, $p\leq0.05$), and skin (PMR=343, 3 observed, $p\leq0.05$). No significant excesses in mortality were observed for non-neoplastic sites. In the PCMR analysis, the excess in bladder cancer mortality remained significantly elevated (PCMR=341, $p<0.05$).

Apart from the mortality studies, interviews with living current and living former employees who worked in either "exposed" areas or "non-exposed" areas were conducted. Two additional bladder cancer cases were found in a living current

and a living former employee. Both employees had worked in either the pattern or blade shop, where measurable levels of 4,4'-MDA were detected. A history of cancer was reported by no workers in a comparison group who worked in packing and storeroom areas with virtually no exposure to 4,4'-MDA.

PMR and PCMR analyses measure the relative frequencies of different causes of deaths occuring in a study population. Limitations of the PMR and PCMR study designs are that they provide no information on the total force of mortality, the ratios across diseases are not independent, and the distribution of deaths not included in the analysis may differ from the distribution of those included. Proportionate analyses are most effective when the disease of interest is relatively rare. Thus, the above biases may be reduced when a PCMR analysis is employed.

Likewise, the ability or power of a particular study to detect an increase in risk depends upon several factors. These factors are sample size, magnitude of the increased risk, background incidence of the disease, desired statistical significance, and type of analysis. Thus, a study might not observe significant increases in mortality, when in fact an increased risk exist, if any one of the above factors is unfavorable to the study.

Given the discussed design constraints, the epidemiologic evaluation of the blade and pattern shops suggests the existence of an increased risk of mortality from bladder cancer. This finding confirmed the *a priori* concern for bladder cancer based on 4,4'-MDA's stuctural analogy to benzidine, a known human

bladder carcinogen. However, since two of the three bladder cancer deatns nad latencies of 10 years or less, one cannot completely discount the possibility of these deaths being a random cluster, unrelated to 4,4'-MDA exposure.

Exposure monitoring revealed detectable levels of 4,4'-MDA, methyl isobutyl ketone, toluene, cyclohexanone, and butyl glycidyl ether. All were found below OSHA and ACGIH standards, but NIOSH reported that it appeared as though former work practices may have resulted in exposure levels higher than those measured in this study (NIOSH, 1983).

Epoxy resins and 4,4'-MDA have been shown to cause cancer in laboratory animals. Separating the influences of these two exposures to identify an etiologic agent of the excess bladder cancer would be difficult. However, as NIOSH pointed out in their conclusion, the following factors lend weight in implicating 4,4'-MDA as the etiologic agent: 1) detectable airborne levels of 4,4'-MDA and suggestion of greater exposures in the past (dermal contact was also a route of exposure); 2) known toxicological evidence; 3) similarity of 4,4'-MDA to known human bladder carcinogens such as benzidine; 4) the bladder site was of concern a priori; and 5) the fact that there were cases of bladder cancer among living employees with longer exposures and compatible latency.

In summary, while the confounding exposure to epoxy compounds and the study design render this epidemiology work inadequate for establishing a causal relationship between exposure to 4,4'-MDA and increased incidence of bladder cancer,

the data are suggestive of such a relationship. This is especially so because of 1) evidence of higher exposure levels existing at the Boeing plant in prior years; 2) the close structural relationship between 4,4'-MDA and benzidine -- a chemical known to produce bladder cancer in humans; and 3) 4,4'-MDA caused urinary bladder tumors in rats in the NTP bioassay. The evidence presented in this section, along with that in the following section which is adequate to establish 4,4'-MDA's carcinogenicity in animals, leads to classify the chemical as a probable human carcinogen, (B2).

2. Animal Data

a. NTP Studies

The National Toxicology Program tested 4,4'-MDA dihydrochloride (4,4'-MDA·2HCl) for carcinogenicity by administering the chemical in drinking water to both sexes of Fischer 344 rats and B6C3F1 mice (NTP 1983a). Fifty rats and mice of each sex received drinking water containing 150 ppm or 300 ppm 4,4'-MDA·2HCl for 104 weeks, ad libitum. Fifty controls for each species and sex received no 4,4'-MDA·2HCl.

These studies were selected as the basis for a quantitative estimate of possible human risks of contracting cancer from exposure to 4,4'-MDA because 1) the design is far superior to the others cited in this section, and 2) the results lend themselves well to statistical analysis. Statistically significant, treatment-related increases in malignant and non-malignant tumors, including several rare tumor types, were seen at multiple sites in both sexes of both species (Milman, 1984). A discussion

of the statistical analysis of the results of these bioassays is given in Section V of this assessment. A summary of the results is given here.

Results observed included compound-related, non-neoplastic lesions of the thyroid in both sexes of rats and mice including follicular cysts and hyperplasia. An increase in the incidence of thyroid neoplasms was observed in the high-dose groups compared to control groups for both sexes of both species. Liver degeneration was observed in 80% of the low-dose and 60% of the high-dose male mice, but not in controls.

Thyroid follicular-cell carcinomas were seen in male rats at rates of: 0/49 control, 0/47 low-dose, and 7/48 high-dose. Combined thyroid follicular-cell carcinomas and adenomas in male rats occurred with incidences of: 1/49 control, 4/47 low-dose, and 10/48 high-dose. Liver neoplastic nodules occurred in male rats with incidences of: 1/50 control, 12/50 low-dose, and 25/50 high-dose. In female rats, combined thyroid follicular-cell carcinomas and adenomas showed incidences of: 0/47 control, 4/47 low-dose, and 19/48 high-dose. These animals also showed incidences of thyroid C-cell carcinomas and adenomas of: 1/47 control, 5/47 low-dose, and 7/48 high-dose. Male mice displayed incidence of liver hepatocellular carcinomas of: 10/49 control, 33/50 low-dose, and 29/50 high-dose. Combined incidences of liver hepatocellular carcinomas and adenomas in male mice were: 17/49 control, 43/50 low-dose, and 37/50 high-dose. In male mice adrenal pheochromocytomas were seen at rates of: 2/48 control, 12/49 low-dose, and 14/49 high-dose. Female mice had lung-

alveolar/bronchiolar adenomas and carcinomas at rates of: 2/50 control, 3/50 low-dose, and 8/49 high-dose. Malignant lymphomas occurred in these animals with incidences of: 13/50 control, 28/50 low-dose, and 29/50 high-dose. Liver hepatocellular carcinomas were seen in female mice at rates of: 1/50 control, 6/50 low-dose, and 11/50 high-dose. Combined liver hepatocellular carcinomas and adenomas occurred in these mice at rates of: 4/50 control, 15/50 low-dose, and 23/50 high-dose. And, finally, thyroid follicular-cell adenomas and carcinomas occured in female mice at rates of: 0/50 control, 1/47 low-dose, and 13/50 high-dose.

Several extremely rare tumor types, the probability of whose spontaneous occurrance is discussed in Section V, were also observed. These include one bile duct adenoma in a male rat (none previously diagnosed in 3,633 NTP controls), transitional cell papillomas of the urinary bladder in three female rats (3 previously diagnosed in 3,644 NTP controls), and granulosa-cell tumors, including one carcinoma in five female rats (11 such tumors and 1 such carcinoma previously diagnosed in 3,462 NTP controls).

b. Hiasa et al. Study

Hiasa et al. (1984) treated male inbred Wistar rats i.p. with a subeffective dose of N,N-bis(2-hydroxypropyl) nitrosamine (DHPN) namely, 280 mg/100 g body weight followed by a diet containing 1,000 ppm 4,4'-MDA for 19 weeks. The incidence of follicular-cell carcinomas of the thyroid was 2/21 (9.5%) and that of total thyroid tumors was 19/21 (90%). DHPN alone

produced only 6/21 (28%) thyroid tumors, and these were all benign neoplasms, while rats receiving 4,4'-MDA alone or saline controls had no thyroid tumors at the end of the study. The authors concluded that 4,4'-MDA promoted the action of DHPN, an initiator of thyroid tumors in this test. Similar results were seen by these authors with phenobarbital and barbital, known promoters of hepatocarcinogenesis, and with 3-amino-1,2,4-triazole a goiter-causing agent (Hiasa et al. 1982a, 1982b).

It should be noted that 4,4'-MDA is also a goiter-inducer (NTP, 1983a). Thus the findings of Hiasa et al. in this limited bioassay of 4,4'-MDA are consisent with the findings of studies on other known tumor promoters and goiter-causing agents.

c. **Deichmann Study**

Deichmann et al. (1978) studied the carcinogenic potential of purified 4,4'-MDA and crude 4,4'-MDA by oral administration to dogs. Nine female beagle dogs, five to six months of age, received doses of 70 mg by gelatin capsule three days a week until death or termination of the study at 86 months. No control groups were reported. Study parameters included body weight gain, cystoscopic examination of the urinary tract (started after two years of dosing and made at 15-month intervals until termination), and serum biochemical tests, which included fasting blood sugar, blood urea nitrogen, creatinine, uric acid, albumin, total protein, and alkaline phosphatase activity.

Moderate to severe histopathological changes occurred in the livers of all dogs. These changes included "swollen hepatic cells, moderate disruption of the lobular patern, passive

congestion, fatty infiltration distorting the lobular pattern, hepatic cell degeneration, portal fibrosis, central zonal fatty degeneration with hepatic cell necrosis, hemosiderosis, and lymphoreticular cell infiltration of the portal areas, and bile ducts distention." Less severe changes were observed in the kidneys, spleen, and lungs. The authors concluded that purified and crude 4,4'-MDA produced no tumors in the urinary bladder or liver of any dog.

The small number of animals, the lack of controls, and the less-than-lifetime duration of the study render this study of limited value in assessing carcinogenic risk.

d. Schoental Studies

Schoental (1968a and 1968b) prepared a purified 4,4'-MDA sample from an epoxy resin hardener containing 54% 4,4'-MDA dissolved in gamma-butyrolactone. The epoxy resin hardener was known to have contaminated flour used in bread that had been eaten by the "Epping jaundice" patients (see above) (Kopelman et al., 1966a and 1966b). Two to five 50 mg doses of 4,4'-MDA in arachis oil were administered by stomach tube to eight male and eight female weanling rats (strain not specific), weighing 45 to 60 g.

All rats were maintained until they became ill or died, at which time they were autopsied. A liver hepatoma with many cells in mitosis and a kidney tumor having a hemangioma-like appearance were observed in one male that received five doses. An adenocarcinoma of the uterus was found in one female 24 months after the first dose. Pituitary tumors were observed in five

females and one male. Non-neoplastic lesions of the kidneys, liver, and lungs were found in most rats.

Twelve white CFW mice, about one month old (sex not specified), were given a single subcutaneous injection of 5 to 10 mg 4,4'-MDA in arachis oil (50 mg/ml) (Schoental 1968b). Seven months later one mouse was killed. No tumors were found. The remaining 11 mice were given a second dose of 5 mg 4,4'-MDA in arachise oil by stomach tube. Nodular hyperplasia of the liver and a possible hepatoma were observed in one mouse that was killed when it was 18.5 months old. No other lesions were considered to be compound-related.

These studies are of extremely limited value for assessing cancer risks. The number of animals used was small and the dosing was for a very short period.

e. Griswold Study

Griswold et al. (1968) evaluated the carcinogenic potential of 35 aromatic amines including 4,4'-MDA. The induction of mammary gland tumors in female Sprague-Dawley rats was the test system. Twenty female Sprague-Dawley rats, 40 days of age, received 10 mg doses of 4,4'-MDA in 1 ml sesame oil by stomach tube at three-day intervals for 30 days, then were observed for an additional eight months without treatment. A negative control group of 140 rats received sesame oil, and a positive control group of 40 rats received a single dose of 18 mg of 7,12-dimethylbenz[a]anthracene (DMBA). 4,4'-MDA did not induce tumors in this test.

The limited number of animals, the short duration of the study, the low number of doses administered and the lack of a complete pathology study of the animals make this study of low value for assessing carcinogenic risks.

f. **Fukushima Studies**

Five groups of male Wistar rats were fed 1,000 ppm 4,4'-MDA in the diet for 8, 16, 26, 32, or 40 weeks (Fukushima et al., 1979). Within each group, three to six rats were killed at eight-week intervals after cessation of 4,4'-MDA feeding until termination of the study at 40 weeks. A control group (eight rats) received diet alone for 40 weeks. One rat from the control group and one from each treated group were killed on the first day of the study. No tumors were reported in any organ.

The less-than-lifetime duration of this study, along with the limited pathology information reported, hinders its use in assessing carcinogenic risk.

Fukushima et al. (1977) studied the effect of prior administration of 4,4'-MDA on colon cancers produced by 1,2-dimethylhydrazine (DMH) in rats. Two groups of eight-week-old male Wistar rats were fed 4,4'-MDA (concentration unspecified) in their diets for eight weeks. After eight weeks, one group (24 rats) received 4,4'-MDA-containing diet only. The second group (30 rats) received 12 weekly subcutaneous injections of 10 mg/kg DMH, starting two weeks after 4,4'-MDA was removed from the diet. A third group (24 rats) received untreated diet and 12 weekly subcutaneous injections of 10 mg/kg DMH, starting at 18 weeks of age. A control group (18 rats) received only untreated

diet. All rats were killed 52 weeks after the first injection of DMH (70 weeks of age).

The 4,4'-MDA-treated groups showed evidence of liver toxicity but tumorigenic activity was not demonstrated.

The design of this study, especially its limited duration and endpoint, limits its utility in assessing cancer risks associated with exposure to 4,4'-MDA alone.

g. Steinhoff and Grundmann Study

Steinhoff and Grundmann (1970) reported that 4,4'-MDA was a weak carcinogen when injected subcutaneously into rats. A group of 25 male and 25 female Wistar rats (age unspecified) received subcutaneous injections of 30 to 50 mg/kg 4,4'-MDA at intervals of one to three weeks, up to a total of 1.41 g/kg. A control group (specifics not given) received subcutaneous injections of saline. The rats were maintained for their lifetime. The mean life span of male 4,4'-MDA-treated rats was 970 days, for females 1,060 days, and for controls (sex not specified) 1,007 days. The 4,4'-MDA-treated rats had 33 malignant and 29 benign tumors and four hepatomas, while the control had 16, 15, and 0, respectively. Statistical analysis was not provided. The authors concluded that 4,4'-MDA had weak carcinogenic activity.

While carcinogenic activity was observed in this study, the small number of animals used, the short treatment time, and the lack of complete pathology information limit its utility in a quantitative estimation of risk.

h. Zylberszac Study

Zylberszac (1951) reported cirrhosis of the liver after implantation of crystals of 4,4'-MDA under the skin of 25 male rats of mixed strain, weighing between 150 and 220 g. Each implanation was 25 mg, and seven implantations were made in five months. The time of sacrifice was not specified. The surface of tne livers appeared granular and nodular, but no hepatomas were found.

The route of exposure and limited information on study execution make this study of little value.

i. Munn Study

Munn (1967) administered 4,4'-MDA dissolved in arachis oil by gavage in male rats five days per week for 121 days, delivering a total of 330 mg/100 g. Of 24 treated rats, three were lost through cannibalism. Of the remaining 21 animals, 12 survived more than two years. All animals had cirrhosis of the liver, but none developed tumors during the first two years of the study. Two rats, however, killed at 792 days and 947 days, respectively, had hepatomas, while a variety of miscellaneous tumors (not specified) were observed in older animals.

A second experiment was performed (neither dosing regimen nor number of animals specified) during which treatment continued for 18 months. The total dose of 4,4'-MDA per animal averaged 600 mg/100 g.

Two liver tumors were observed. One tumor (unspecified) occurred at the end of the first year, while the second appeared more than two years after treatment began. In addition, one

intestinal tumor, one pituitary tumor, and two subcutaneous fibromas were observed more than two years after teatment began.

The small number of animals used and incomplete pathology information limit the utility of this study in quantitative risk assessment.

j. Gohlke Study

Gohlke (1978) conducted a chronic study on the oncogenic effects of 4,4'-MDA. Male albino rats were divided into four groups of 120 each and treated as negative controls, positive controls, or with 4,4'-MDA (8 or 20 mg/kg) by stomach tube five days/week for 16 weeks. Ten animals from each group were killed after ten days and six weeks of treatment, or at termination (16 weeks). In each group, 66-68 additional animals were examined at their natural death.

In another experiment, 60 animals were divided into two groups of 30 each and used as positive controls, or given 3.2 mg/kg 4,4'-MDA, five days/week for 16 weeks. After six weeks of treatment, at termination of treatment (16 weeks), and at 20 weeks, between four and nine animals were killed from both the control and 4,4'-MDA-treated groups for histological examination.

No differences were observed between livers of animals given 4,4'-MDA at 3.2 mg/kg and controls at up to ten weeks of exposure. At 8 mg/kg, increased hepatocyte mitoses were seen after ten days of exposure. After six weeks of exposure to 8 mg/kg, 50% of the animals showed hepatocyte swelling with disseminated isolated fatty degeneration, increased mitoses, and enlarged nuclei. Increased mitoses also occurred in the bile ducts. At 16 weeks, no changes were reported.

At 20 mg/kg, a decrease in glycogen in all animals, proliferation in bile ducts, and large vesicular bile duct nuclei were observed after ten days of exposure. After six weeks, 50% of the animals showed the following effects: increased hepatocyte and bile duct mitoses; hepatocytes with triple nuclei; bile duct proliferation with large vesicular nuclei; expanded fibrous connnective tissue in the portal fields; and septal interlobular and intralobular connective tissue bridges. After 16 weeks of treatment, bile duct proliferation and the connective tissue changes were still apparent in 50% of the animals.

Hyperplasias developed after four months and were present mainly in 4,4'-MDA-treated animals. These were benign, localized reticular hyperplasias, benign hepatomas, excessive bile duct proliferations, and benign vascular tumors of the liver.

Of a total of 437 animals examined, 17 developed 16 tumors and six systemic diseases, while seven developed partly tumor-like hyperplasias.

The life-span of the animals (groups unspecified) used in these experiments was low due to pulmonary and otogenic inflammation that extended into the meninges. The average age at death was 11.9 months (11.3 months in 4,4'-MDA-treated, 12.5 months in controls). All four animal groups had similar growth curves.

This study clearly demonstrtes the hepatotoxicity of 4,4'-MDA, but the short duration of exposure (16 weeks) puts a severe limitation on the use of this study for quantitative risk estimation.

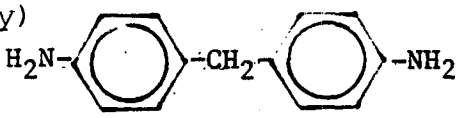
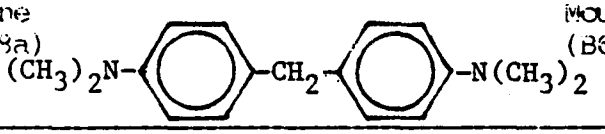
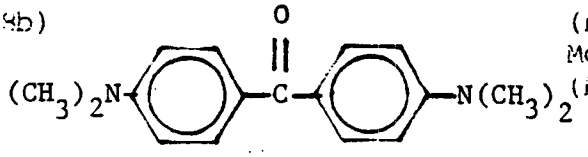
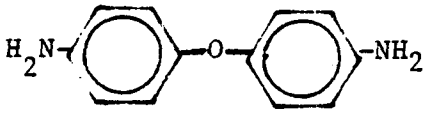
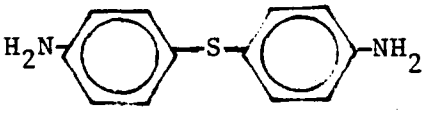
3. Structure-Activity Relationships

Evidence from NTP/NCI studies suggests that compounds belonging to the class of bis-benzenamines separated by $-CH_2$, -O or -S are carcinogenic for the thyroid gland of rodents. As can be seen in Table 1, the National Cancer Institute tested three additional analogues of 4,4'-MDA [4,4'-methylenebis-(N,N-dimethylaniline), 4,4'-oxydianiline and 4,4'-thiodianiline] for carcinogenicity by the oral route in long-term bioassays in rats and mice. All three analogues caused thyroid tumors in rats of each sex and two (4,4'-oxydianiline and 4,4'-thiodianiline) were also carcinogenic for the thyroid of female mice. 4,4'-Thiodianiline was also carcinogenic for the thyroid of male mice. Additionally, all three analogues were carcinogenic for the liver of female mice which also was a target for carcinogenicity by 4,4'-MDA. 4,4'-Thiodianiline was also carcinogenic for the liver of male mice. However, when the methyl substituent between the benzene rings was oxidized to -CO, the compound (Michaler's ketone) lost its carcinogenic activity for the thyroid, but retained its hepatocarcinogenic activity (NCI 1978b).

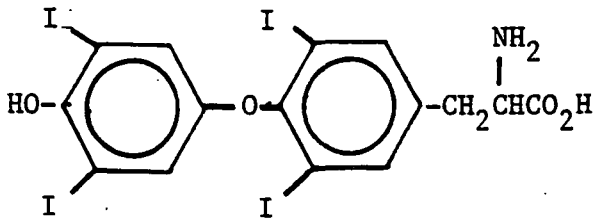
The carcinogenicity of this class of compounds for the thyroid gland is of particular interest since these chemicals bear a structural resemblance to the thyroid hormones triiodothyronine and thyroxine shown below. Thus 4,4'-MDA may be upsetting the hormone balance in the thyroid or be interfering with the gland's normal functioning in some other way.

TABLE 1

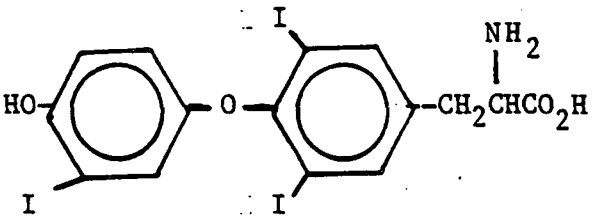
COMPARISON OF RESULTS OF CHRONIC NCI/NTP STUDIES ON 4,4'-MDA AND RELATED COMPOUNDS

Test Substance	Structure	Species	Sex	Dose (ppm)	Site of Neoplastic Lesion Observed: Liver	Thyroid
4,4'-MDA (Current Study)		Rat (F344)	M	300[a]	N[b]	N
			F	300		N
		Mouse (B6C3F1)	M	300	N	N
			F	300	N	N
4,4'-Methylenebis (N,N-dimethyl) benzenamine (NCI, 1978a)		Rat (F344)	M	750[c]		N
			F	750		N
		Mouse (B6C3F1)	M	2500		
			F	2500	N	
Michler's Ketone (NCI, 1978b)		Rat (F344)	M	500[c]	N	
			F	1000	N	
		Mouse (B6C3F1)	M	2500		
			F	2500	N	
4,4'-Oxydianiline (NCI, 1980)		Rat (F344)	M	500[c]	N	N
			F	500	N	N
		Mouse (B6C3F1)	M	800		
			F	800	N	N
4,4'-Thiodianiline (NCI, 1978c)		Rat (F344)	M	3000[c]	N	N
			F	3000		N
		Mouse (B6C3F1)	M	5000	N	N
			F	5000	N	N

(a) In drinking water.
(b) N = Neoplastic lesion occurred at statistically significant incidence (P<0.025 by the Fisher exact test.
(c) In feed.



Thyroxine



Triiodothyronine

The thyroid gland is also the target organ for non-neoplastic effects of bis-benzenamines. For example, 4,4'-MDA, 4,4'-oxydianiline, 4,4'-thiodianiline and 4,4'-methylenebis-(N,N-dimethylaniline) all produced follicular-cell or papillary hyperplasia of the thyroid gland in both sexes of mice (NTP, 1983a, NCI 1980, 1978c, 1978a). 4,4'-MDA also caused follicular-cell hyperplasia in rats. Additionally, two such chemicals also caused adenomatous goiters in mice [4,4'-methylenbis-(N,N-dimethylaniline] or rats (4,4'-MDA).

The analogue MBOCA was also found to be carcinogenic in studies in rats (Kommineni et al. 1979; Stula et al. 1975), mice (Russfield et al. 1975) and dogs (Stula et al. 1977).

In summary, the structure-activity relationship between 4,4'-MDA and other proven animal and human carcinogens is strong.

- 4,4'-MDA is a member of the class of bis-benzenamines of which several analogues are carcinogenic.

- o With the exception of Michler's ketone, all the tested analogues of the class of bis-benzenamines, including 4,4'-MDA, are carcinogenic for the thyroid gland of mice.
- o All the tested analogues of the class of bis-benzenamines, including 4,4'-MDA, are carcinogenic for the liver of rats and mice.
- o 4,4'-MDA is also structurally related to benzidine and 4,4'-methylene bis(2-methylaniline). All three compounds are associated with cancer of the urinary bladder in rats (i.e., 4,4'-MDA) or humans [i.e., benzidine, 4,4'-methylene bis-(2-methylaniline) and, possibly, 4,4'-MDA].
- o All the tested analogues of the class of bis-benzenamines, including 4,4'-MDA, also produce non-neoplastic effects in the thyroid gland (i.e., follicular-cell or papillary hyperplasia). Additionally, at least two analogues, including 4,4'-MDA, are goiterogenic in mice and rats.

4. Summary of Animal Data

There is sufficient evidence from the NTP bioassays, other whole animal studies, mutagenicity studies, and structural analogy with other compounds that have been shown to be carcinogenic in animals to classify 4,4'-MDA as a carcinogen in animals.

5. Weight of Evidence

Taken together, the strongly positive results in the NTP cancer bioassays on the dihydrochloride salt of 4,4'-MDA, evidence of the carcinogenicity in animals and humans of 4,4'-MDA structural analogues, the demonstrated ability of 4,4'-MDA to induce bladder tumors in animals and suggestive evidence of MDA-induced bladder tumors in humans, and data indicating the ability of 4,4'-MDA to interact with genetic material, lead to the conclusion that this chemical is carcinogenic in animals and is probably carcinogenic in humans.

In conducting risk assessments of suspect carcinogens, EPA generally evaluates the overall weight of evidence including both primary and secondary evidence of carcinogenicity. As specified in the draft EPA Guidelines for the Health Assessment of Suspect Carcinogens (EPA, 1984), primary evidence derives from long-term animal studies and available epidemiological data. Secondary, or supplemental, evidence includes structure-activity relationships, the results of short-term tests, pharmacokinetic studies, comparative metabolism studies, and other toxicological responses which may be relevant.

Based upon the weight of available evidence, EPA classifies 4,4'-MDA as a probable human carcinogen and places it in category (B2). The Guidelines cited above give this classification when:

> evidence of carcinogenicity from epidemiological studies ranges from almost 'sufficient' to 'indequate.' To

> reflect this range, the category is divided into higher (Group B1) and lower (Group B2) degrees of evidence. Usually, category B1 is reserved for agents for which there is at least limited evidence of carcinogenicity to humans from epidemiological studies. In the absence of adequate data in humans it is reasonable, for practical purposes, to regard agents for which there is sufficient evidence of carcinogenicity in animals as if they presented [sic] a carcinogenic risk to humans. Therefore, agents for which there is inadequate evidence from human studies and sufficient evidence from animal studies, [as with 4,4'-MDA] would usually result in a classification of B2.

a. Animal Studies

There is sufficient evidence of carcinogenicity in animals to support the cited classification of 4,4'-MDA. In NTP bioassays, the dihydrochloride of the chemical was found to be carcinogenic upon oral administration in both sexes of two species (rats and mice) and caused tumors at multiple sites in each species. Significantly increased incidences of tumors were observed in the thyroid and the liver in both species. The sites

of response in the mouse also included the adrenal glands (males), and the lung and lymphatic system (females). Several extremely rare tumor types with very low spontaneous incidence were also observed. These included one bile duct adenoma in a male rat (spontaneous incidence in historical control rats of 0/3633), transitional cell papillomas of the urinary bladder in three female rats (spontaneous incidence in historical controls of 3/3644), and granulosa-cell tumors, including one carcinoma, in five female rats (11 such tumors and one such carcinoma in 3462 historical control rats). Observation of these rare tumors in these studies in test groups consisting of only 50 animals is a sign of chemical specificity and is highly significant evidence of the carcinogenic potential of 4,4'-MDA. Thyroid tumors in rats were also observed in a limited bioassay performed by Hiasa et al. (1984). In another study of rats treated with 4,4'-MDA by subcutaneous injection, Steinhoff and Grundmann (1970) concluded that the results suggested carcinogenic activity. This study was limited in value by the small number of test animals (50) and incomplete pathology reporting. Other studies on the carcinogenic potential of 4,4'-MDA have been conducted, but were not adequate in design or performance for conclusions to be reached.

b. Epidemiological Studies

Only one epidemiology study is available. This proportional mortality study was reported in 1983 by NIOSH (1983). It was conducted at a site of manufacture of helicopters where exposure to 4,4'-MDA and other chemicals was measured. NIOSH studied

information on 179 white male deaths that occurred among these workers from all causes and found a significant excess over the expected proportion of bladder cancer-related deaths. This excess remained significant in analysis of only the cancer deaths. In addition, two cases of bladder cancer were found in 4,4'-MDA - exposed living persons. 4,4'-MDA could not be definitively concluded to be the causative agent because of confounding exposure, but the evidence is suggestive given the corresponding observation of urinary bladder tumors in the NTP bioassay in rats cited above, and 4,4'-MDA's structural similarity to benzidine -- an agent known to produce this type of tumor in humans.

c. Structure-Activity Relationships

Structure-activity considerations are strongly supportive evidence of the human carcinogenic potential of 4,4'-MDA. The chemical is a member of the structural class of bis 4-aminobenzenes in which two benzene rings are separated by $-CH_2-$, -O-, or -S- groups. Members of this structural class include 4,4'-oxydianiline, 4,4'-thiodianiline, and 4,4'-methylenebis (N,N-dimethylaniline), all of which have been found to cause neoplasms in the liver and thyroid of rodents, as does 4,4'-MDA. Other members of this class, 4,4'-methylene bis (2-methylaniline), and benzidine, the structual analogue of 4,4'-MDA in which the methylene bridge between the aromatic rings is absent, have been associated with an increased risk of bladder tumors in humans.

d. Absorption

Further support for EPA's conclusion that the chemical poses a risk of cancer to humans is the fact that the chemical is absorbed by the human body. 4,4'-MDA is known to be absorbed by humans through the skin in workplace settings. Information from the United States, Canada and France attests to the dermal absorption of the chemical, and the scientific literature documents cases of the liver toxicity of 4,4'-MDA following dermal exposure along with detection of the chemical in the urine of workers exposed by this route.

Since the chemical has been shown to penetrate human skin and to be absorbed through the human gastrointestinal tract (in the so-called Epping Jaundice Incident), EPA believes it reasonable to anticipate that the chemical will penetrate lung tissue as well.

e. Mutagenicity

In short-term tests, 4,4'-MDA has been shown to be a gene mutagen in prokaryotic systems. The chemical induces sister chromatid exchanges in femoral bone marrow of male mice; it does not induce chromosomal aberrations *in vitro* in human peripheral lymphocytes. (A mixture of positive and negative results is not unusual in tests for genotoxicity since the tests for gene mutations and chromosomal aberrations measure different endpoints.) In addition, the compound binds covalently to DNA *in vivo* in the livers of treated mice, indicating its ability to interact with macromolecules *in vivo*.

D. Other Human Health Effects

This section presents a summary of reports of adverse effects that 4,4'-MDA exposure has caused in humans.

Kopelman et al. (1966a, 1966b) reported that 84 people who had eaten bread contaminated with 4,4'-MDA developed jaundice, with hepatocellular damage evidenced by biochemical tests and needle biopsy examinations.

Williams et al. (1974) reported six cases of hepatitis among workers using 4,4'-MDA in a surface coating operation at a construction site, and McGill and Motto (1974) reported 13 cases of hepatitis among workers exposed inhalationally (at 0.1 ppm in air) and dermally while producing an epoxy resin compound. Of special significance in the McGill and Motto report is the fact that workers who were exposed only via the inhalation route (at 0.1 ppm in air), in the same work stations as those who also were exposed dermally and experienced hepatitis, did not display overt signs of hepatotoxicity. This is a strong indication of the ability of 4,4'-MDA to penetrate human skin in biologically significant amounts.

Brooks (1979) documented adverse effects in a worker exposed to 4,4'-MDA dust when a ventilation system malfunctioned. The worker experienced severe abdominal and chest pain and displayed an abnormal electrocardiogram upon hospitalization six days after exposure.

Acute jaundice occured in 11 workers exposed chiefly via the dermal route in a Canadian facility that processed 4,4'-MDA (Dunn and Guirguis, 1979).

These reports indicate that 4,4'-MDA can be absorbed by humans in biologically significant amounts, and that apparent exposure at 0.1 ppm in air does not result in overt signs of acute hepatotoxicity, thus there may be no warning of exposures that could present significant cancer risks. (See Section V).

IV. EXPOSURE ASSESSMENT

In this section information on the potential for exposure to 4,4'-MDA by workers, consumers and the general public will be given. This information will include the production and use patterns for the chemical and exposure levels, durations and routes for workers classified as to the various uses of 4,4'-MDA. Also included will be estimates of releases of 4,4'-MDA into the air, water and land, the fate of such releases, and the levels of the chemical that might occur in certain drinking water supplies.

Humans may be exposed to 4,4'-MDA in the workplace, through contact with articles or other products containing the chemical, or through consumption of contaminated water or food. In order to assess these possible exposures, EPA, in conjunction with NIOSH, has gathered data on work practices and exposure levels in facilities that manufacture, process or use 4,4-MDA. In addition, the Agency has gathered information on the types of articles and products that may contain the chemical, and on the amount and rate of releases of 4,4'-MDA to the environment throughout its commercial life cycle.

The assessment indicates 1) that exposures experienced in some workplace situations are significant and 2) that exposures through drinking contaminated surface water are probably not significant.

It is important to note that several different analytical methods for determining levels of 4,4'-MDA in air, water, and biological samples have been used, and that a systematic attempt

at concordance among these methods is underway. Appendix A summarizes the methods that have been used to measure airborne concentrations of 4,4'-MDA. In particular, the Marcali colorimetric method for 4,4'-MDA, used by some 4,4'-MDA manufacturers who reported levels of the chemical to EPA, suffers from interference from aromatic amines and isocyanates, both of which can be present in the air of 4,4'-MDA/methylene diphenyl diisocyanate (MDI) manufacturing facilities. Such interferences are less likely to occur at 4,4'-MDA user and processor facilities. This assessment is based on the assumption that the exposure levels reported in the literature or to EPA are accurate.

Information regarding exposure of workers to 4,4'-MDA is derived from anecdotal reports cited in Versar (1983a), data voluntarily submitted by the Chemical Manufacturers Association (CMA, 1983a), individual companies (Docket No. OPTS 64,000a), a report prepared by PEDCo Environmental, Inc. (PEDCo, 1983) and the National Institute for Occupational Safety and Health (NIOSH, 1983 and 1984a,b).

Information regarding exposure of the general public is derived from a draft report prepared by Versar Inc. (Versar 1983b).

A. Workplace Exposure--4,4'-MDA/MDI Manufacturing

1. Production Processes

a. 4,4'-MDA (PEDCo, 1983)

4,4'-MDA is produced commercially by the acid-catalyzed condensation of aniline and formaldehyde. The initial product is acidified, crude 4,4'-MDA, almost all of which is purified as

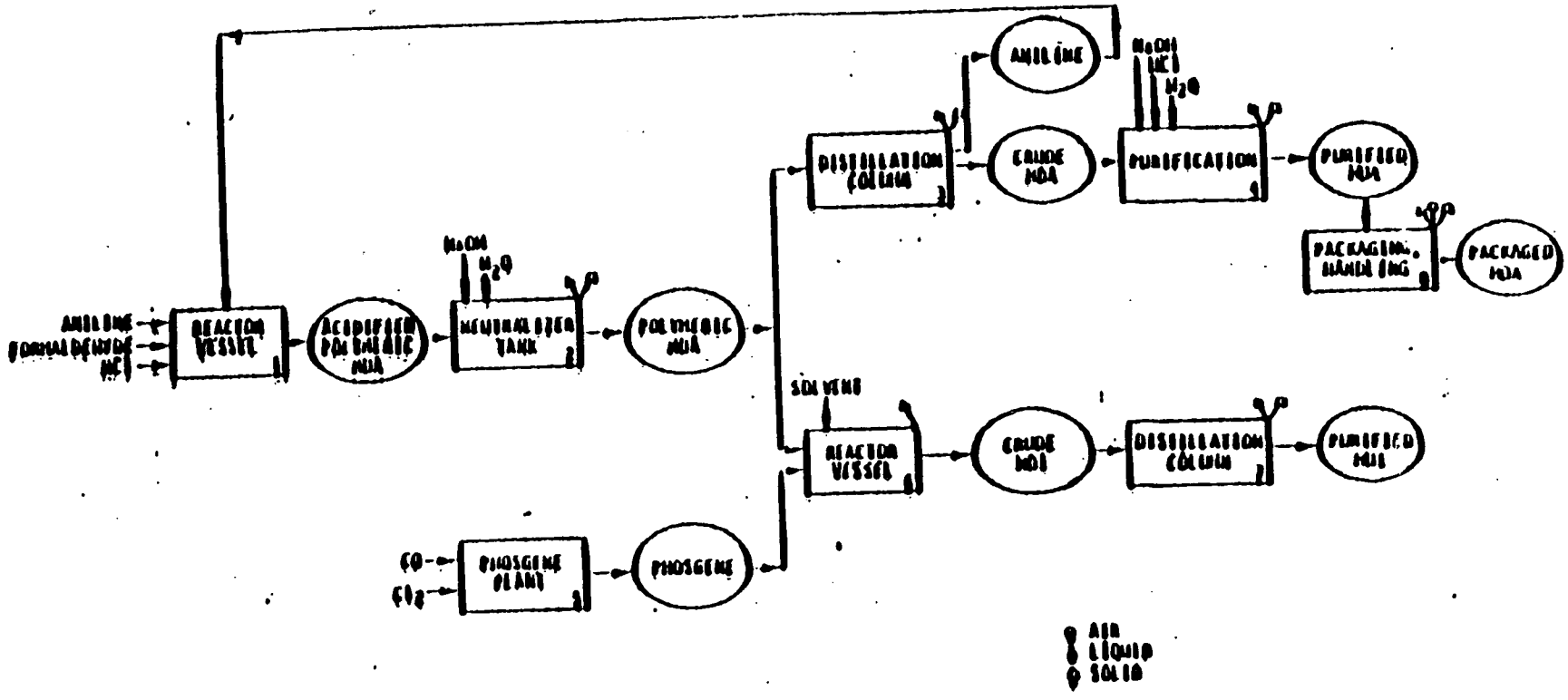


Figure 1. 4,4'-MDA/MDI Flow Diagram. (PEDCo, 1983)

outlined below for use as an intermediate for methylenediphenyl diisocyanate (MDI) at the same production facilities.* Figure 1 As a flow diagram for this process, and for conversion of 4,4'-MDA to MDI.

The production process can be either continuous or batch. Acid is added to the aniline, followed by addition of formaldehyde under agitation. The reaction occurs in a closed vessel at atmospheric pressure and a temperature of 60° to 100°C. The only product is acidified crude 4,4'-MDA; there are no significant byproducts, except that up to 40-50% of the crude 4,4'-MDA consists of isomers and higher homologues.

There are no 4,4'-MDA exposure points other than those that might occur as a result of fugitive emissions or malfunction of the vessel or its plumbing. There are no purge or off-gas streams.

In the neutralization step, the reaction mass from the reactor tank is neutralized with caustic soda to produce crude 4,4'-MDA. Two layers are formed, a lower layer containing water and salt, and an upper layer containing the product and unreacted aniline. The organic layer is washed with water in a closed, stainless steel tank at ambient pressure and temperature.

The input materials are the acidified reaction mass, aqueous sodium hydroxide, and water. The principal output is crude 4,4'-MDA, which may either be further purified or used for the production of MDI. A large quantity of sodium chloride is also

* One domestic plant further processes the polymeric 4,4'-MDA to yield a purified product that finds a number of specialized end uses.

formed and removed in an aqueous purge stream likely contaminated with 4,4'-MDA and other organics.

The potential for worker exposure in this process is expected to be limited. The purge stream likely contains some 4,4'-MDA, so exposure could occur in an "open" system around holding ponds. Neutralizer purge stream levels of 4,4'-MDA are not well documented in the literature, but monitoring work now in progress is expected to provide some information on 4,4'-MDA levels in total process effluent streams.

The crude 4,4'-MDA from the neutralizer is subjected to distillation to separate unreacted aniline. The distillation process is conducted at atmospheric pressure at temperatures above 185^{o}C in a closed, stainless steel distillation column. The residual product which solidifies to a hard waxy material at temperatures below 89^{o}C, may be drummed for distribution and sale or further purified.

The only input to this step is crude 4,4'-MDA. The product is a technical grade 4,4'-MDA, which is about 50% 4,4'-MDA plus oligomers. The process by-products are water and aniline. The latter is recycled to the reactor vessel.

Liquid and solid wastes containing 4,4'-MDA are produced in this process. Liquids may be retained in holding ponds and the solids sent to landfills. No data are currently available regarding 4,4'-MDA levels in either stream.

Because the distillation system is closed, worker exposure is not expected except in the case of system disruption. Filling, sealing, storage, and distribution activities could

result in inhalational or dermal exposure to 4,4'-MDA at various points.

High-purity (97-99% assay) 4,4'-MDA can be isolated from technical grade 4,4'-MDA. A re-crystallization process (PEDCo, 1983) involves the reformation of the hydrochloride salt of 4,4'-MDA, followed by filtration and neutralization with sodium hydroxide. The product 4,4'-MDA is packaged for distribution and sale. The equipment that would be used is not described in the literature, but would probably be a closed, stainless steel tank. The process would take place at ambient pressure and temperature. The input materials would be technical grade 4,4'-MDA, hydrochloric acid, sodium hydroxide, and water. The product would be purified 4,4'-MDA in the form of tan flakes. There would be an aqueous contaminated salt stream that may contain some 4,4'-MDA.

The system would be closed until output, so worker exposure during purification would be unlikely, although dermal exposures during manufacture and packaging of the purified form of the chemical have been reported (NIOSH, 1984a). Subsequent purge stream holding and disposal operations could also result in inhalational or dermal exposure.

Technical grade and purified 4,4'-MDA is used in a number of non-MDI processes. It is packaged and sold as a viscous liquid or lumps in the technical grade form, or as flakes or granules in the purified form. Liquid 4,4'-MDA is sold in bulk (tank cars or tank wagons) or in 55-gallon drums. The lump form of 4,4'-MDA is sold in bags. Purified 4,4'-MDA is available in bags or kegs.

Workers who fill the containers with liquid or solid 4,4'-MDA are subject to potential exposure, though 4,4'-MDA's vapor pressure is low even in the liquid state (0.2 mm Hg for Tonox®, Uniroyal's trade name for 4,4'-MDA, in the melt range). Inhalation of dust or skin contact from a bagging or drum-filling operation represent potential risk to the worker. NIOSH (1984a) reports that such exposure occurs.

Workers may also be exposed to 4,4'-MDA, via inhalational and dermal routes when handling the filled containers. Drums and bags must be relocated, stored, and placed on trucks for shipment. Damage to the container in any of these operations could expose workers to 4,4'-MDA

b. **MDI**

Technical grade 4,4'-MDA is reacted with phosgene to produce the desired product, a crude MDI known commercially as PAPI®. 4,4'-MDA and phosgene are dissolved in a solvent, and the two solutions are mixed and allowed to react for several hours. The reaction occurs in a series of closed, agitated, stainless steel reactor vessels at ambient pressure and a temperature of 200°C.

Input materials are polymeric 4,4'-MDA, phosgene, and a solvent such as xylene, monochlorobenzene, dichlorobenzene, or 1,2,4-trichlorobenzene. Outputs are the product isocyanate mixture and a liquid waste stream containing hydrogen chloride, solvent, and miscellaneous organics. The reaction is reportedly capable of a 90% yield of isocyanate mixture. Theoretically, the waste streams generated could contain some unreacted 4,4'-MDA, although this is unlikely.

Workers may be exposed to 4,4'-MDA through dermal contact with the liquid product or waste streams, or through inhaling MDI vapors that could be hydrolyzed in the body to 4,4'-MDA.

Crude MDI may be fractionated through several intermediate grades to a high-purity MDI. Dimers and trimers can also be made through use of a catalyst, triethyl phosphate. The process takes place in a closed, stainless steel distillation column, the operating conditions for which are not reported in the literature. Temperatures would be elevated.

Input material is crude MDI. The outputs are higher grades of MDI, as well as recyclable hydrogen chloride and solvent, which are diverted to a purge stream. This stream also contains additional organic distillation residue. The product MDI is a very dark amber, viscous liquid with very low volatility.

The amount of unreacted 4,4'-MDA remaining through this step depends upon the purity of the MDI produced. There is virtually no unreacted 4,4'-MDA with high-purity MDI. Waste disposal consists of extraction of hydrochlogen chloride for process reuse, disposal to holding ponds, and finally municipal wastewater treatment.

2. Production History and Forecast

U.S. production of 4,4'-MDA has been increasing steadily since the early 70's. Production is driven primarily by the demand for MDI, manufacture of which consumes about 98% of 4,4'-MDA production (JRB, 1981). Since no production data for 4,4'-MDA have been published in recent years, the estimates presented in Table 2 below are based on published MDI production data. CMA

has estimated that 230 million pounds of 4,4'-MDA were produced in 1981 by all manufacturers except DuPont (Cox, 1982). Since it has been reported that DuPont produces approximately 10 million pounds/year, this would amount to an estimated 240 million pounds/year 4,4'-MDA production. The difference between CMA's estimate and that of PEDCo is probably due to the former's reporting only the production of the 4,4'-isomer, while the latter includes all isomers and oligomers in technical grade 4,4'-MDA which is converted to commercial grade MDI. Consolidated data received under the TSCA section 8(a) Level A reporting rule (47 FR 38780, September 2, 1982) indicate that between 209 and 286 million pounds were produced in 1981 (Knutson, 1983). Estimates thus range from 209 to 414 million pounds/year.

Polymeric MDI is used in polyurethane production; demand is increasing for two major reasons (JRB, 1981):

o Increased substitution of MDI for toluene diisocyanate (TDI) in the production of polyurethanes due to concern about the toxicity of MBOCA in MBOCA/TDI systems.

o Increased demand for polyurethane in automotive body interior applications as a result of Federal regulations for impact resistance, improved vehicle safety, and improved gas mileage.

TABLE 2

ESTIMATED 4,4'-MDA PRODUCTION 1976-1980 (PEDCo, 1983)

Year	Production (millions of pounds) MDI (USITC)	4,4'-MDA (MATHTEC, 1982)
1976	312.2	249
1977	352.3	289
1978	439.5	352
1979	487.7	390
1980	511.1	409
1981(a)	517.9	414

(a) PEDCo update to referenced data.

MDI production is projected to increase steadily through 1985 at an annual rate of 9% (Mannsville, 1980). Consumption for the non-MDI uses of 4,4'-MDA are estimated in Table 5.

Imports of 4,4'-MDA have been small, accounting for less than 0.4% of total supply (1977-1979) (MATHTEC, 1982). Export data are not published separately for 4,4'-MDA and are assumed to be small. Exports of MDI, however, accounted for 15 to 18% of MDI production in 1980 (Mannsville, 1980). Several foreign MDI plants are expected to begin operation, and this will probably reduce the demand for MDI exports (MATHTEC, 1982).

4,4'-MDA is currently manufactured by six companies at seven locations in four states, as shown in Table 3. One additional company (BASF), which produced 4,4'-MDA in the past, is presently importing the chemical and plans to open a manufacturing facility in the future. Three of these companies--Mobay, Rubicon, and Upjohn--appear to account for over 90% of 4,4'-MDA production (Springborn, 1982, 1983).

TABLE 3

PRODUCERS OF 4,4'-MDA AND MDI
PLANT LOCATIONS AND ESTIMATED CAPACITY (MATHTEC, 1982)

Company	Location	1979-1980 MDA Capacity (million pounds)	1979-1980 MDI Capacity (million pounds)	1985 MDI Capacity (estimated) (million pounds)
Olin Chemical	Moundsville, WV	NA	NP	---
BASF Wyandotte	Geismar, LA	NP	NP	150
E.I. duPont	Belle, WV	10-50	NP	---
Mobay Chemical	New Martinsville, WV	79	100	100
	Baytown, TX	79	100	200
Rubicon Chemical (ICI Americas)	Geismar, LA	79	100	250
Uniroyal	Naugtuck, CT	NA	NP	NA
Upjohn	LaPorte, TX	213	270	270
	TOTALS	460-500+	570	970+

NA = Not available NP = Not a producer

3. Characterization of Non-MDI Uses of 4,4'-MDA

Information from several sources (CMA 1983a; ICF, 1983; Springborn, 1982, 1983) was used to characterize the commercial fate of the 4,4'-MDA that is not converted to MDI. Table 4 (ICF, 1983) summarizes the information from these data sources. Additional information from a CMA-sponsored survey of users and processors of 4,4-MDA is in general agreement with the material presented in Table 4 (CMA, 1984).

For each of the ICF (1983) categories in Table 4, exposure level information is presented below. The amounts used in each ICF (1983) category are shown in Table 5.

4. Exposure Levels and Duration

Two populations of potentially exposed workers are of concern: workers who manufacture 4,4'-MDA and convert it to MDI, and workers who use or process MDA for other than MDI applications.

Two major sources of exposure information are used in this assessment: 1) data submitted voluntarily by manufacturers and processors, and data compiled by PEDCo (1983), summarized in Tables 6 and 9; and 3) measurements made by NIOSH representatives during visits to a 4,4'-MDA manufacturing plant that makes 99% assay product (NIOSH, 1984a) and to a facility that uses 4,4'-MDA as a curing agent for epoxy-coated, filament-wound pipe (NIOSH, 1984b), which are summarized in the text of Section V below.

TABLE 4
NON-MDI USES OF 4,4'-MDA

Springborn (1983) Categories	ICF (1983) Categories	CMA (1983a) Categories
Epoxy curing	Epoxy uses	Epoxy curing
		Producing of TGMDA
Urethane curing MBOCA production Ketimine production	Co-reactant in polyurethane	Co-reactant in polyurethane
Wire coating production	Wire coating	Polyester-imide wire coatings
Production of coatings for circuit boards and aircraft parts	PMR-15 as a polyimide	PMR 15 polyimide MDA as an intermediate for polybis maleimides
Dye intermediate	Dye intermediates	MDA as an intermediate for dyes and pigments
Qiana© intermediate (not used)[a]		Qiana© intermediate (not used)[a]
Rubber processing chemical (not used)[a]		Rubber Processing Chemical (not used)[a]
Anti-oxidant in lubricating oil (not researched)[b]		
Corrosion inhibitor (not researched)[b]		

(a) Reporting entites indicate that 4,4'-MDA has been, or could be, used for this purpose, but is not presently so used.
(b) Springborn (1982) shows zero pounds used.

TABLE 5
ANNUAL PRODUCTION OF 4,4'-MDA FOR NON-MDI USES (ICF, 1983)

Use	Thousands of Pounds
Epoxy Curing	5,000-7,000[a]
Wire-Coating	200[b]
Coreactant in Production of Polyurethane	250
Dyes	1,500-2,000
Nuclear Weapons Production[c]	10
PMR-15	N/A
TOTAL	6,950-9,450

(a) High estimate consists of 4 million lbs. of crude (65% 4,4'-MDA) and 3 million lbs. pure 4,4'-MDA (97-100% 4,4'-MDA).
(b) Springborn (1983).
(c) DOE (1983b).

The estimates of dermal exposure to 4,4'-MDA used in this assessment in both MDI- and non-MDI manufacturing facilities are based on data from the NIOSH visits just described. The conclusion should not be drawn that the exposures -- and the estimated doses and risks derived from those exposures -- are identical to those in all workplaces. There are not enough data points to permit such a conclusion. Nevertheless, the data used in this preliminary assessment to estimate dermal exposures were obtained using reasonable industrial hygiene and analytical procedures, and this analysis assumes that they are reasonable estimates of the kind of exposures that may occur in many workplaces. The information submitted to EPA by users and processors of 4,4'-MDA (Docket No. 64000a) and that obtained from the open literature (Dunn and Guirguis, 1979; Vaudaine et al., 1982; Brooks et al., 1979; McGill and Motto, 1974; Dunn, as cited

in NIOSH, 1976a; Emmett, 1976; NIOSH, 1976b) supports this conclusion.

a. 4,4'-MDA and MDI Production Workers

As described above, 4,4'-MDA is produced in the United States by six companies at seven locations (PEDCo, 1983). At these facilities, 284 workers are exposed to 4,4'-MDA for less than 8 hours per week, 159 are exposed for 9 to 20 hours per week, and 139 are exposed for more than 20 hours per week. This information, aggregated here, was submitted to EPA by the CMA project panel on 4,4'-MDA under claims of confidentiality for data from individual companies (CMA, 1983c) and is in substantial agreement with information submitted under section 8(a) of TSCA (Knutson, 1984).

These workers are exposed to 4,4'-MDA chiefly through inhalation of vapors or particles, or through dermal contact with the chemical*. Levels of exposure for both routes have been measured, although there are uncertainties in these measurements.

Chief among the uncertainties in inhalation exposure measurements is the accuracy of analytical methods used (see Appendix A). For the dermal route, the rate of absorption is the least accurately known factor. A dermal absorption study is planned for completion in 1984, and work is proceeding in several laboratories toward resolving analytical difficulties.

A reasonable estimate of the exposures that these workers experience can be made using information supplied by the

* Ingestion, via contaminated smoking material or food, could occur, but is not considered here due to lack of data on this route of exposure.

manufacturers of 4,4'-MDA (CMA, 1983c) and information obtained during a visit by NIOSH industrial hygienists (NIOSH, 1984a) to a 4,4'-MDA manufacturing plant. The former data include ranges and average 8-hour Time Weighted Average (TWA) measurements of air levels of 4,4'-MDA in the workplace, while the latter include the results of dermal studies.

Table 6 presents estimates of airborne exposure that workers in the less than 8 hours-, 9 to 20 hours- and more than 20 hours per week categories may experience.

Table 7 gives the dermal dose estimates for 4,4'-MDA production workers. These estimates are based on the assumption that the exposure experienced by the chemical operator studied in NIOSH (1984a) is a reasonable estimate of exposures that may occur under similar working conditions. This worker was supplied with new gloves at the beginning of his shift, and under the glove were mounted pads on the palm and back of the hand, using a golf-glove-like device, which collected 4,4'-MDA during the shift. It should be noted that NIOSH representatives observed conditions, such as apparently routine re-use of gloves, that might result in higher doses than those calculated here.

TABLE 6
4,4'-MDA MFG. WORKPLACE AIRBORNE EXPOSURE LEVELS (PPM) (CMA, 1983c)

Company[a]	Sample Type[b]	DURATION					
		<8 hrs/wk		9-20 hrs/wk		>20 hrs/wk	
		Range	Ave.	Range	Ave.	Range	Ave.
A	bz	<.0002	—	—	—	<.001-.009	.004
B	a	ND-0.6	0.07	.001-0.7	.02(2)	ND-0.6	.07
C	bz	<.005	<.005	<.005	<.005	—	—
D	a	.001-.89	.06	.001-.89	.06	.001-.89	.06
E	bz	—	—	—	—	.01-.10	.05

(a) The sixth domestic 4,4'-MDA manufacturer is not a member of the CMA Panel and did not submit monitoring information to EPA.

(b) a = area, bz = breathing zone.

TABLE 7

ESTIMATED DERMAL DOSES IN 4,4'-MDA MFG PLANTS[a]

8 HRS/WK	20 HRS/WK	40 HRS/WK
0.40 mg/day	2.3 mg/day	4.9 mg/day

(a) Calculations shown in Appendix B. Workers classified in the <8 hr/wk group are assigned 8 hr/wk exposure; those in the 9-20 hr/wk group are assigned 20 hr/wk; etc.

Table 8 shows lifetime average daily doses (LADDs)* based on the combined inhalational and dermal exposures presented in Tables 6 and 7. The inhalational component of these LADDs is based on the highest reported average 8-hour TWA, not the highest range, reported in CMA (1983c). An average is considered more representative of actual exposures than a high range number would be, and the use of the highest reported average from all reporting manufacturers is a conservative measure in this risk assessment. The analytical method used to determine the TWA used here is subject to interference from aniline also known to be

*LADDs are a tool that makes possible the quantitative estimate of risk to humans using the results of studies on animals. In most cancer studies using animals, the animals are exposed to a known level of the test chemical at a known frequency for their entire lifetime, and this results in some incidence of cancer. Some comparable expression of the dose received by exposed humans is required to translate the dose-response seen in animals to the human case, and this comparable expression, the LADD, is but an imperfect estimate of exposure, since humans are almost never exposed in exactly the same way as the test animals. For instance, in the 4,4'-MDA case, animals were exposed to the chemical each time they drank water, over their whole lifetime, while workers are exposed, at most, for 8 hours per day, 250 workdays per year for as long as they work -- perhaps as long as 40 years. Some workers may be exposed for fewer years than others, some may experience higher or lower levels of exposure, and some may be exposed for fewer days or a different number of hours each workday. These various factors are combined as illustrated in Appendix B to produce a LADD.

The artificiality of the LADD can be exemplified by looking at the Epping Jaundice Incident which people ate 4,4'-MDA-contaminated bread. Surely these people are at higher risk of cancer from 4,4'-MDA than they would have been had they not been exposed. In order to quantitatively estimate what their elevated risk is, one would have to translate the dose they received into terms that could make use of the dose-response seen in the animal bioassay. That would be an LADD. We are virtually certain that they are not being exposed anymore, so to say that they are receiving X mg/kg/day, as a LADD does, even now, is pure artifice. One notes, nevertheless, that those people did suffer from liver disease, and this illustrates that a short term, high level exposure to 4,4'-MDA does have a different outcome from chronic, low-level exposure (See subsection b, below).

present in the workplace. Because of this possible interference, the TWA value used here may be high (by as much as a factor of 10 [CMA, 1983c]). This would reduce the LADDs given in Table 8 by from about 50% (for 8 hours/week duration) to about 25% (for 40 hours/week duration).

TABLE 8

ESTIMATED 4,4'-MDA MFG. WORKPLACE LADDs

LADD[a] by Route	DURATION		
	8 hrs/wk	20 hrs/wk	40 hrs wk
Inhalation (mg/kg/day)	0.0031	0.0064	0.015
Dermal (mg/kg/day)	0.0020	0.014	0.027
Total (mg/kg/day)	0.0051	0.020	0.042

(a) Lifetime Average Daily Dose. Calculations shown in Appendix B.

b. Non-MDI Uses of 4,4'-MDA

i. Epoxy Curing

a. Exposures Related to the Curative Package

Epoxy curing uses of 4,4'-MDA can result in exposures during the formulation, packaging, and subsequent handling of the curative "package", which would consist typically of pulverized 4,4'-MDA, fillers and pigments, and during handling and uses of the blended epoxy resin/curative mixture. These two types of exposures are discussed below. The total number of workers exposed is not known, but could range from about 1,500 to about

13,000 (NOHS, 1983). Exposure durations are not known, but have been estimated based on assumptions outlined in Section V below. Exposure levels for the non-MDI uses that were reported by manufacturers or processors are summarized in Table 9.

The number of firms engaged in formulating epoxy curative packages is not known. One such firm responded to EPA's 4(f) notice on 4,4'-MDA and submitted information on its products and on worker exposure levels (Ameron, 1983). Among other products, this firm manufactures curatives for epoxy coatings used to protect concrete structures in nuclear power plants, steel members in certain marine structures, and chemical tanks. From 10 to 20 employees are reportedly exposed to airborne concentrations of 4,4'-MDA ranging from 0.073 to 0.68 mg/m^3.

TABLE 9
ESTIMATES OF MDA AVAILABLE FOR ABSORPTION
BY NON-MDI USE
(PEDCO, 1983)

Process	Operation	Exposure route	Measured level ppm	Measured level mg/m^3	Estimated exposure time hrs/day	Estimated exposure time day/yr	Amount available for absorption: Inhalation mg/kg/yr	Amount available for absorption: Dermal mg-hr/kg/yr
Reprocessing of MDA	Dumping	Inhalation	-	0.12-3.11	1	250	7	N/A
	Mixing	Inhalation	-	0.48	1	250	2	N/A
	Packaging	Inhalation	-	0.53-0.68	6	250	16	N/A
	Unspecified	Dermal	(a)	(a)	8	250	N/A	3,600[(a)]
Epoxy uses	Mixing of MDA to make filament-wound pipe	Inhalation	0.0125	0.10	2	250	1	N/A
	Manufacture of TGMDA	Inhalation	0.0075	0.06	8	250	2	N/A
	Pulverization of MDA	Inhalation	0.1	0.82	1	250	4	N/A
	Unspecified	Dermal	Unknown	-	-	250	N/A	-
Polyurethane curing	Potting room near oven	Inhalation	0.01	0.08	8	250	3	N/A
		dermal	(a)	(a)	8	250	N/A	3,600[(a)]

CONTINUED

TABLE 9 - CONTINUED

Process	Operation	Exposure route	Measured level ppm	Measured level mg/m^3	Estimated exposure time hrs/day	Estimated exposure time day/yr	Amount available for absorption: Inhalation mg/kg/yr	Amount available for absorption: Dermal mg-hr/kg/yr
Intermediate for polyimides for wire coating	Dumping of MDA	Inhalation	Unknown	-	1	100	-	N/A
Intermediate for polymaleimides for aircraft parts	Unspecified	Inhalation/ dermal	Unknown	-	-	-	-	-
Intermediate for dyes	Dumping of MDA into	Inhalation/ dermal	Unknown	-	1	40	-	-
Intermediate for rubber additive	Dumping of MDA into reactor	Inhalation dermal	Unknown	-	-	250	-	-

N/A - Not applicable

(a) Based on wipe samples taken of a similar chemical, MBOCA, used to cure polyurethane, averaging 72 ug/cm^2 (17 samples). Other estimates of the amount of 4,4'-MDA available for absorption in some of these settings are given in Section V.

Eleven cases of acute jaundice related to 4,4'-MDA exposure in a curative formulation plant between 1967 and 1976 were reported by Dunn and Guirguis (1979). At this plant, located in Ontario, Canada, previously ground and screened 4,4'-MDA was received, blended with silica sand, and packaged. Blending was carried out in two blenders located in a separate room with roof exhaust. The materials were mixed for 20 minutes, then packaged. Five to seven workers were employed in the manufacturing area at any one time. Workers wore respirators when adding 4,4'-MDA and sand to the mixer. After 1976, the company began providing workers with coveralls, gauntlets, shoe covers, head and neck covers, and positive-pressure airline breathing apparatus. Despite these changes, some workers were still affected, indicating that special care in the use of protective clothing and equipment must be taken to ensure against inadvertent contamination that can lead to exposures via dermal, inhalational, or ingestion routes (see the report of Vaudaine et al., 1982, below).

Air sampling data (15-minute samples) taken during charging of 4,4'-MDA to the blender ranged from 0.2 to 3.11 mg/m^3; during mixing the measurement was 0.48 mg/m^3; and during packaging the measurement ranged from 0.53 to 0.68 mg/m^3. Improper gasketing of equipment accounted for a large proportion of dust during the blending. A flexible exhaust hose (20 cm in diameter) placed near the operation during charging and bagging was found to have a large hole and was replaced. During production, the workers wore coveralls which were changed twice a day, a hat with a wide

brim, impervious gloves, and an airline respirator. Coveralls were found not to be impervious to 4,4'-MDA. (While Dunn and Guirguis reported no quantitative information of the penetration of coveralls by 4,4'-MDA, this permeability is used as one of the assumptions in applying NIOSH (1984a, 1984b) dermal exposure data to calculation of dermal LADDs in Appendix B.)

Additionally, the armpits of affected workers were stained with 4,4'-MDA because these individuals had defeated the protection of the coveralls by making cuts in the material to relieve the heat stress of summer days. The main route of entry of 4,4'-MDA to the affected persons was believed to be dermal.

The type and extent of controls used by other curative formulators is not known, though investigation of both controls and exposure levels are currently being investigated.

b. Exposures Related to Handling/Use of Complete Epoxy Resin Formulations

Epoxy resins are used in a variety of applications including: coatings, laminates and composites, casting and molding, flooring, and adhesives. 4,4'-MDA has been used in epoxy molding powders, stick solders, fiberglass cloth-epoxy laminates, and casting compounds (Springborn, 1982).

Since the applications for epoxies are so varied, there is no simple process or operation that can be described for curing of epoxy resins with 4,4'-MDA. In general, either purified or polymeric 4,4'-MDA is added to the epoxy resin and mixed just prior to use of the polymer. This can be done at a construction site, as with use of the epoxy as a concrete coating, or in a

closed and automated process, as in the manufacturing of filament windings. In all cases, the process involves adding the 4,4'-MDA, mixing with the epoxy resin, and applying the mixture to a surface or forming the product. All three steps are potential points of worker exposure, but most information, including NIOSH, (1984b) indicates that the addition of 4,4'-MDA to the resin is the operation of greatest concern, because of the propensity for 4,4'-MDA, especially the high assay material, to "dust" and contaminate nearby surfaces during such handling. The epoxy cross-linking reaction forming the epoxy is exothermic, and the mixing and curing processes are usually at elevated temperatures.

4,4'-MDA is used as a curing agent for epoxy resins in a wide variety of structural laminates including filament winding, wet lay-up laminates, and potting, casting, and encapsulation (CMA, 1983a). Filament-wound epoxy pipe cured with 4,4'-MDA has numerous uses including casings of rockets (Trident, Pershing, MX, and space shuttle), oil drilling pipe, pipes for chemicals, and fuel tanks for military aircraft (CMA, 1983a). CMA (1983a) reports exposure in a European filament winding plant ranged from 0.002 mg/m^3 to 0.1 mg/m^3, with the high value during the preparation of the mixture of epoxy resin and 4,4'-MDA.

Wet lay-up laminates cured with 4,4'-MDA are used as structural parts for aircraft. The epoxy is used to impregnate a reinforcing fiber cloth. The impregnated cloth, called "pre-preg", is then refrigerated to arrest curing until final molding occurs under heat and pressure. CMA (1983a) reports 4,4'-MDA concentrations below the detection limit of 0.001 mg/m^3

in the pressroom. No measurements are given for the mixing operation. NIOSH, however, reports that breathing zone measurements done on a molder of helicopter blades showed concentrations of 0.23, less than 0.022, and 0.46 mg/m^3 of 4,4'-MDA for three different 20-minute periods in one shift (NIOSH, 1983).

Liquid epoxy resins cured with 4,4'-MDA are used in the potting, casting, and encapsulation of electrical components. 4,4'-MDA is preferred because of excellent insulation characteristics and low shrinkage of the polymer it produces. Casting and curing occur in closed vacuum chambers (CMA, 1983a). 4,4'-MDA has been specified in numerous nuclear power plant applications (CMA, 1983a; Brechna, 1965). One manufacturer of 4,4'-MDA-cured epoxy concrete coatings ships the amine in a screw-top container into which the liquid epoxy resin is poured. Mixing thus occurs in the same vessel in which the 4,4'-MDA is shipped, reducing dusting and worker exposure. However, in one report (Williams et al., 1974), 6 of approximately 300 men who applied epoxy resins containing 4,4'-MDA to concrete walls at a nuclear power plant developed clinical hepatitis 2 days to 2 weeks after starting work. 4,4'-MDA had been mixed with liquid epoxide at the work site and applied to walls with trowels or a spray gun. Exposure levels were not reported.

Special epoxy resins described as tetraglycidyl-methylenedianiline (TGMDA)-derived resins, are reinforced with glass, graphite, boron, or aramide fibers and used in aerospace and leisure products, structural adhesives, laminates, tooling

and casting applications, and structures such as aircraft wings and fuselages (Kirk-Othmer, 1980). The only point of exposure is the introduction of the 4,4'-MDA into the process vessels. The synthesis reaction is carried out in closed vessels, and the 4,4-MDA is consumed. Controls used in the operation are not known. The maximum concentration reported in TGMDA manufacture was 0.06 mg/m^3, but no further data were provided (CMA, 1983a).

A second reported incident of human exposure involved production of a component of an insulating material (McGill and Motto, 1974). Between 1966 and 1972, twelve male workers whose job it was to manually mix 4,4'-MDA into an epoxy resin contracted hepatitis. A thirteenth individual also contracted hepatitis; his 4,4'-MDA exposure reportedly occurred during the pulverization of 4,4'-MDA flakes for the process. Atmospheric 4,4'-MDA levels were measured at 0.1 ppm (analytical method not reported) during the first survey. Workers who experienced only inhalational exposure did not contract hepatitis. Each worker who did contact the disease had at least one hand exposed to the mixture for several hours per shift. Thus, the probable critical exposure to 4,4'-MDA by the affected workers was through skin contact. This is a consistent theme throughout the investigation of workplace exposure to 4,4'-MDA.

About 100 employees were potentially exposed to 4,4'-MDA at the facility. Various means were undertaken to reduce 4,4'-MDA levels, including construction of exhaust ports and respiratory protection described as breathing helmets. The process has subsequently been automated to prevent worker skin exposure to 4,4'-MDA (McGill and Motto, 1974).

c. Exposure in an Un-Characterized Setting

Vaudaine et al. (1982) described a toxic agent monitoring program at a Rhone-Poulenc Industrie facility,* focussing on 4,4'-MDA. Rather than monitor air levels of the chemical, these researchers chose to monitor workers' urine for 4,4'-MDA on a "present" or "not-present" basis.

During the period of 1970 to 1978, the chemical was handled by workers in full protective suits ("divers' suits"), yet workers' urine showed levels of 4,4'-MDA of at least 200 ug/l in 144 of 965 samples (14.9%) in 1970. Dust from inside the suits showed "fairly significant" levels of the chemical.

As the decade wore on, the need to avoid dust contamination was gradually recognized, resulting in lower percentages of 4,4'-MDA-positive urine samples and reduced levels of the chemical in those samples that were positive. By 1978, the threshold of detection of the amine in urine was lowered to 20 ug/l, and 2.7% of samples contained 20 to 80 ug/l, 2.0% contained 80 to 200 ug/l, and 4.0% contained over 200 ug/l -- for a combined 8.7% "positivity index."

From 1978 through 1980, "there was an improvement in working conditions brought about by cooperation among the company physician, the manufacturing engineer and the shop personnel." In 1980, the sampling program found 0.9% of urine samples contained 20-80 ug/l, with no samples showing higher

* The report did not state the type of use or processing of 4,4'-MDA carried out at the facility, but did mention empty drums and 4,4'-MDA powder as being exposure concerns. Contact with the authors is being sought.

concentrations. This case clearly demonstrates that an informed workforce and committed management can reduce exposure significantly.

ii. Co-reactant in Polyurethanes

A small quantity of 4,4'-MDA, estimated at 50 thousand pounds/year, is used as a polyurethane curing agent (Springborn, 1982). The primary use of 4,4'-MDA as a polyurethane curing agent is with aliphatic isocyanates, in which system pot life is long enough to permit use in spray applications.

The options for adding 4,4'-MDA to polyurethane batches are the same as for epoxy curing. However, due to the smaller quantities used, it is more likely that the operation may be done by hand. This increases the opportunity for dermal and inhalation exposure. Unit operations are the same as for epoxy curing: addition of the 4,4'-MDA, mixing, and application or formation of the product. There is no estimate of the number of workers involved nor of the frequency and duration of exposure.

All three operations involve potential worker exposure to 4,4'-MDA, with the potential for skin contact and inhalation depending on the work practices at the individual facility. Controls used in these operations are not known. However, it is likely that cloth gloves, at least, are used for protection from heat from the 4,4'-MDA melting pot, hot molds, and other equipment in the work place. As note above, cloth gloves are permeable to 4,4'-MDA.

Three cases of worker exposure to 4,4'-MDA during polyurethane molding have been reported. In one case reported in 1976, during a 6 month period at least 8 employees in a polyurethane molding plant developed dermatitis on skin areas exposed to 4,4'-MDA, usually during the second or third week of work (Emmett, 1976). Four other employees who worked as molders during this time did not develop symptoms. No measurements of exposure levels were reported.

In another case, also reported in 1976, workers requested that NIOSH inspect the facility due to the presence of a wide variety of toxic chemicals, including 4,4'-MDA (NIOSH, 1976b). The 4,4'-MDA was used in the formulation of a polyurethane resin used to make plastic belts. The operation involved preparation of special molds, mixing of the polyurethane, and curing of the polyurethane in molds to form belts. Liquid polyurethane resin containing free methylene bis(4-cyclohexyl isocyanate) was mixed with heated liquid 4,4'-MDA. The storage, heating, and mixing of the chemicals were performed in closed, highly automated systems. On the initial visit NIOSH industrial hygienists noticed that conditions and work practices were not consistent with good industrial hygiene practices. Uncovered containers of 4,4'-MDA were left open in the work area, and open containers of waste chemicals were discarded in wastepaper baskets, exposing janitorial workers to skin contact with these materials. During a second visit, three months later in May of 1975, the work area and work practices had been improved. Local exhaust ventilation was being installed at the pouring and curing stations. Twelve

air samples were collected on this visit and analyzed for 4,4'-MDA. All samples showed 4,4'-MDA below the detectable limit of 0.05 mg/sample. Samples ranged from 2.9 to 13.42 liters. Thus, airborne concentrations were below 3.8 mg/m^3. Dermal exposure measurements were not made.

In a third case, NIOSH was asked by the Independent Union of Rotameter Workers to investigate the health effects of asbestos fibers and organic vapors upon workers at the Fischer and Porter Company in Warminster, Pennsylvania (NIOSH, 1980). 4,4'-MDA was being used to cure polyurethane that covered an epoxy system employed to hold and encapsulate water flow measuring instruments in water pipe. The 4,4'-MDA was weighed, heated in an oven, mixed with the isocyanate, and poured on the previously set epoxy. The molding was then ground and sprayed with enamel. Of three ambient measurements taken by NIOSH, the highest 4,4'-MDA level was 0.08 mg/m^3 in the potting room near the oven.

iii. Wire Coating, Polyimides and PMR-15

Methylenedianiline is used as an ingredient in the production of polyester-polyimide electrical conductor coatings and polymeric amide-imide-ester wire enameling compositions. 4,4'-MDA is also used to produce a high-temperature-resistant polyimide, PMR-15. PMR-15 is beginning to be used commercially as a replacement for titanium in jet engine components. It is planned for use in the engines of the F-18 fighter, the B-1 bomber, and new versions of the Boeing 747 and 767 airplanes (CMA, 1983a).

There are no quantitative data on exposure levels for these uses of 4,4'-MDA. The processes involved indicate that partially cured, or B-stage, resin systems are handled by wire coaters or aircraft workers. The B-stage systems are then heated to effect complete polymerization to cross-linked material. There would be potential inhalational and dermal exposure to 4,4'-MDA if some of that monomer were present in the B-stage resin.

Additionally, workers who charge 4,4'-MDA to the reactors in which the B-stage polyimide is produced may be exposed to the chemical at levels comparable to those experienced by epoxy curative workers (see above).

iv. Other Uses

4,4'-MDA is used as a curing agent for polymer systems used in fabricating nuclear weapons (DOE, 1983a, b, c, d). About 10,000 pounds/year of the amine is used at six sites, with the greatest (>90%) usage at the Bendix Corp. facility at Kansas City, Missouri (DOE, 1983b).

Personal air monitoring at the Bendix plant failed to show detectable levels of 4,4'-MDA, while the highest recorded level (DOE, 1983c) at any DOE facility was 0.232 mg/m^3. However, DOE states that respirators are worn for the operation that involved this exposure level in ambient air, and that dermal exposure is prevented by the use of protective equipment.

Information on the quantity of 4,4'-MDA used in synthesis of antioxidants for lubricating oils and greases and general descriptions of the processes involved can be found in PEDCo (1983), though CMA (1984) indicates that no 4,4'-MDA is currently being used for these purposes.

In some of the non-MDI uses the purified form of 4,4'-MDA is required, and the physical form may result in some "dusting" during use. There are virtually no data on the extent of such "dusting" in these workplaces. In order to estimate the extent of possible dermal exposure to workers in these situations, several different hypothetical cases are considered in conjunction with dermal monitoring data (NIOSH, 1984a and b). In one scenario, worker protection is assumed to be equivalent to that of workers packaging pure 4,4'-MDA at the manufacturing site, and 4,4'-MDA would be handled throughout the shift. For this scenario, dermal exposure calculations are made in the same way as in the 4,4'-MDA manufacturing section. However, actual exposures, especially dermal exposures, may be higher if management and workers are less aware of the hazards of 4,4'-MDA than their counterparts in the manufacturing setting, and separate exposure calculations have been made for these conditions. Another situation covers workers in Department of Energy contractor facilities where nuclear weapons are fabricated.

As in the manufacturing setting, workers in these processing/using cases may be exposed to 4,4'-MDA intermittently or continuously as they handle the chemical while charging reactors, mixing batches of ingredients for repackaging, etc. Recognizing these variables, Table 10 presents lifetime average daily dose estimates (LADDs) for workers in these cases of varied exposure durations and settings. Details of each setting considered here are given in Section V and in Appendix B.

The inhalational component of the exposures and LADDs in Table 10 is based on the mean of airborne exposure level measurements reported by Ameron (1983) and cited in subsection a. above. These measurements were made in the vicinity of a work station where dry ingredients for a protective coating resin system were packaged. For the DOE workplace no dermal component is included. Information received from DOE (DOE, 1983 a,b,c,d) indicates that special care is taken in these workplaces, where handling of highly toxic or otherwise hazardous substances is routine, to preclude dermal contact with 4,4'-MDA. Monitoring data from DOE (1983c) were used to estimate inhalational exposures and LADDs. The highest recorded exposure level, 0.232 mg/m^3, was not used in the calculations since DOE indicates (DOE, 1983c) that respirators are worn during this operation. Exposure to 0.02 mg/m^3 for 0.2 hours/day was used in the calculations.

B. Potential Exposure Related to Consumer Contact With 4,4'-MDA-Containing Articles or Products

There is no evidence that 4,4'-MDA is used in consumer products. The Chemical Manufacturers Association recently sponsored a survey (CMA, 1984) of 312 companies, that buy 4,4'-MDA from U.S. producers. Sixty-one companies, representing 47% of the merchant market of 2.64 million pounds in 1982, responded. The results indicated no consumer products containing the unreacted chemical. With 53% of the merchant market unaccounted

TABLE 10

4,4'-MDA USING/PROCESSING WORKPLACE LADDs

	Exposure Duration Per Week			
	2.5 hrs.	8 hrs.	20 hrs.	40 hrs.
Minimal Dermal Exposure[a] Duration (Appendix B, Section 2)				
LADD by Route in mg/kg/day				
Dermal	0.00040	0.0032	0.0067	0.010
Inhalational	0.00066	0.0021	0.0052	0.010
Total	0.0011	0.0053	0.012	0.020
Continuous Exposure (Appendix B, Section 3)				
LADD by Route in mg/kg/day				
Dermal				0.16
Inhalational				0.010
Total				0.17
Variable Exposure Durations (Appendix B, Section 4)				
LADD by Route in mg/kg/day				
Dermal	0.000016	0.0010	0.0042	0.0095
Inhalational	0.00066	0.0021	0.0052	0.010
Total	0.00068	0.0031	0.0094	0.020
Short-Term Exposures (Appendix B, Section 5)				
LADD by Route in mg/kg/day				
Dermal		0.0011		
Inhalational		0.00066		
Total		0.0018		
DOE contractors (Appendix B, Section 6)				
LADD by Route in mg/kg/day				
Dermal		nil		
Inhalational		0.000013		
Total		0.000013[b]		
Short-Term Intermittent Exposure-Best Industrial Hygiene (Appendix B, Section 7A)				
LADD by Route in mg/kg/day				
Dermal			0.000028	0.000028
Inhalational			0.0052	0.010
Total			0.0052	0.010

TABLE 10 — CONTINUED

	Exposure Duration Per Week			
	2.5 hrs.	8 hrs.	20 hrs.	40 hrs.
Appendix B, Section 7B)				
LADD by Route in mg/kg/day				
Dermal			0.00028	0.00028
Inhalational			0.0013	0.0026
Total			0.0013	0.0026
Hypothetical Workplace Standard in Effect (Appendix B, Section 8)				
LADD by Route in mg/kg/day				
Dermal				0.00011
Inhalational				0.00022
Total				0.00033

The Exposure Duration Headings for this case correspond to various delay periods between time of dermal exposure and removal of the 4,4'-MDA by washing. Thus, 2.5-, 8-, 20- and 40- hours per per week headings correspond, for the dermal component of the LADD, to wash-up 0.25, 2, 4 or 6 hours after exposure.

(b) Exposure is for 1 hour per week.

for, however, it is not possible to state absolutely that no 4,4'-MDA is present as such in consumer products, although use of 4,4'-MDA in production of TGMDA appears to account for most of the "missing" material. Aggregated data from the TSCA section 8(a) reporting rule, reported by 4,4'-MDA manufacturers, indicate that in 1982, 660 to 2,600 pounds of the chemical may have been used by their downstream customers to manufacture consumer articles from which "limited release" of 4,4'-MDA might occur (Knutson, 1984). It does not appear that this quantity of 4,4'-MDA, even were it in fact finding its way into "limited release" consumer articles, would lead to chronic levels of exposure that could cause significant cancer risks.

Two patents have been issued for products containing 4,4'-MDA for the purpose of treating hair. Available information does not indicate whether 4,4'-MDA is actually being used in this application, although, as stated above, 4,4'-MDA suppliers claim that there are no consumer uses for 4,4'-MDA (Springborn, 1983).

The Color Index lists two dyes made using 4,4'-MDA, CI 24750 (Acid Red 9, Milling Red R) and CI 42500 (Basic Red 9, pararosaniline), but indicates that only CI 42500 is currently being manufactured. The manufacturer listed is American Cyanamid Organic Chemicals Division at the Bound Brook Works in New Jersey. However, contact with the facility indicated the dye is no longer produced. Contacts at the Dyes Environmental and Toxicology Organization stated that they knew of no dyes being produced using 4,4'-MDA (PEDCo, 1983). However, information submitted by CMA (1983a) indicates that 4,4'-MDA is a non-isolated intermediate in production.

C. Potential Exposure Related to Drinking Water and Ambient Air Contamination

There is, at this time, no evidence that any drinking water supply is contaminated with 4,4'-MDA. Surface waters that are used for drinking water supply, however, do receive effluents, directly or indirectly, from 4,4'-MDA, MDI and polyurethane manufacturing operations, which could contain 4,4'-MDA. [MDI can hydrolyze to 4,4'-MDA when a large excess of water and favorable mixing conditions are present. It is converted to a stable area derivative under other conditions (CMA, 1983b)].

Likewise, groundwater used for drinking water supply might be contaminated through migration of 4,4'-MDA from various wastes. At present, EPA has no information indicating that such contamination has occurred, so no risk estimate for this potential route of exposure can be made beyond that given in the text discussing Table 11.

EPA is studying the potential for exposure through surface-supplied drinking water by measuring the amount of 4,4'-MDA discharged from the treatment works of a 4,4'-MDA/MDI manufacturing plant. If significant levels are found, steps will be taken to determine the fate of the discharged 4,4'-MDA. The Agency is taking this approach, rather than attempting to measure 4,4'-MDA levels at drinking water intakes, because of the current limitations on analytical sensitivity. A level of about 0.3 ug/l in drinking water produces an estimated added lifetime risk of developing cancer by humans of about one in one million (see Table 11), whereas current analytical methods have a practical detection limit of about 1-10 ug/l.

If a significant level of 4,4'-MDA is being discharged, data on stream dilution and environmental fate will be obtained and used together with discharge data to calculate possible doses of 4,4'-MDA received by people drinking contaminated water.

In the interim, while this investigation proceeds, estimates of 4,4'-MDA releases and the associated, consequent doses and risks have been made. These release estimates are summarized in Table 11 and explained in further detail below. Because some of the information used in these estimations has been claimed confidential, the identities of the companies involved are not disclosed. Only four of the seven 4,4'-MDA manufacturing plants discharge waste water into streams that provide drinking water supplies. These four sites are designated Plants A through D.

TABLE 11
ESTIMATED 4,4'-MDA LEVELS IN SURFACE WATERS

Plant	Estimation	Concentration mg/l
A	Worst Case	5.0×10^{-4}
	Best Estimate	1.8×10^{-4}
B+C[a]	Worst Case	1.2×10^{-3}
	Best Estimate	3.0×10^{-4}
D	Worst Case	4.8×10^{-3}
	Best Estimate	1.2×10^{-3}
	10^{-6} Excess Risk	2.8×10^{-4}

(a) Both plants discharge into the same stream.

The concentrations presented as "Worst Case" and "Best Estimate" are derived from assumptions about production volume, process losses, and operating schedules, detailed in Versar, (1983b), coupled with information on each plant site, such as total plant effluent flow rate (from waste water discharge permits) and hydrologic characteristics of the receiving streams. Instantaneous and complete mixing is assumed to take place as the effluent enters the river, and no partitioning to suspended solids or degradative processes are assumed to operate to remove the 4,4'-MDA from the water column. Since it is expected that some degradation in the receiving stream, especially photo - and chemical-oxidation, does occur (EPA, 1982), and since these plants treat their effluent prior to discharge (CMA, 1983b), these estimated concentrations are believed to be considerably higher than those that are actually occurring.

The concentration estimation titled "10^{-6} Excess Risk" is a calculated value, derived by assuming a 70-year lifetime consumption of 2 liters/day of contaminated water by a person weighing 70 kg and using tumor incidence of hepatocellular carcinomas and adenomas in female mice with the multistage model (Crump, 1980) upper 95% confidence limit. This tumor type was selected because it afforded one of the highest estimated risks of all observed tumor types in the bioassay (NTP, 1983a), and represents a conservative assumption.

1. Releases from 4,4'-MDA Manufacturing (Versar, 1983b)

During manufacturing, it is expected that nearly all of the 4,4'-MDA releases will occur from neutralization, aniline separation, and product purification. These production procedures, described in Section IV A above, are briefly summarized below.

Neutralization: The crude reaction product is acidic and must be neutralized. It is piped to a tank where concentrated aqueous sodium hydroxide is added (Moore, 1978). The water and salt created in this step are not released at this point, but piped, with the product, to the next step.

Aniline separation: During aniline separation, the organic layer is separated and washed with water and then sent to a distillation facility which removes unreacted aniline (Moore, 1978). This step probably releases the largest quantity of 4,4'-MDA in the form of contaminated wastewater.

Purification: Not all 4,4'-MDA is purified. Little information is available on this step. Either distillation or re-crystallization processes could be employed. Some releases, in the form of contaminated water and organic wastes, are possible.

Gaseous wastes contaminated with 4,4'-MDA have been reported to be insignificant (JRB, 1980; ESE, 1981). Furthermore, it is expected that 4,4'-MDA will not volatilize from the aquatic environment because of its extremely low Henry's law constant (ratio of vapor pressure to aqueous solubility). It is therefore assumed that airborne 4,4'-MDA emissions will be negligible.

No information could be found quantifying 4,4'-MDA water releases from manufacturing. These releases will depend on several factors, including: production level, water requirements, processing conditions, and the level of pollution control. Since most of these data are unavailable, it was necessary to use a number of simplifying assumptions in estimating releases, and these are presented below. Again, the effluent monitoring work, now underway, is expected to provide data in this area.

a. The ratio of grams of process and wash water to grams of product is 4.3 to 1 (Perkins, 1968; Ramney, 1972; Powers, 1970; MATHTECH, 1982). The assumptions used to derive this value are presented in Appendix A of Versar (1983b).

b. It is assumed that both the process- and the wash water will be saturated with MDA (1 gm of MDA/liter of water).

Therefore, total MDA water releases from manufacturing become:

$$187{,}988 \frac{\text{kkg of MDA}}{\text{yr}} \times 4.3 \frac{\text{gm } H_2O}{\text{gm MDA}} \times 1000 \frac{\text{liters}}{\text{kkg of water}} \times 1 \times 10^{-6} \frac{\text{kkg}}{\text{gm}} = 808 \frac{\text{kkg of MDA released}}{\text{yr}}$$

This is a worst-case estimate. In another estimate, it was assumed that the 4,4'-MDA concentration in the wastewater (process and wash water) will reach only 10% of the maximum solubility (0.1 gm MDA/liter of water) due to the salt effect and the dilution of process water with relatively uncontaminated wash water. For this latter case, the total MDA releases are 80.8 kkg/yr*. It should be noted, however, that it is possible for sodium chloride to complex 4,4'-MDA (CMA, 1983a) under certain conditions, and, thus, sodium chloride might enhance, rather than diminish, the aqueous solubility of 4,4'-MDA.

2. Releases from 4,4'-MDA Use as a Feedstock (Versar, 1983b)

Most of the 4,4'-MDA produced in the United States (about 90%) is captively converted to MDI at the manufacturing site; approximately 9% of the total production is converted to MDI at other locations, and the remaining production is used in other applications (Springborn, 1982; ESE, 1981).

Background data and some release estimates for the use of 4,4'-MDA as a feedstock are discussed below. Most of the

* Aggregated data reported by manufacturers under TSCA Section 8(a) indicate that up to 180 kkg of 4,4'-MDA is lost during manufacture, and that 5 to 15 kkg of this amount is lost to the

discussion deals with the production of MDI; however, some information is also presented on the other uses. It was estimated that in 1981, the 4,4'-MDA releases to air and water from MDI manufacturing range from 26.9 to 269 kkg.

a. Releases from MDI Manufacturing

In 1982, approximately 361,000 kkg of MDI were produced; this material was used to manufacture rigid and semiflexible polyurethane foams and urethane elastomers.

MDI releases from manufacturing could significantly affect 4,4'-MDA releases, since MDI can hydrolyze to 4,4'-MDA under certain conditions. However, no quantitative data could be found concerning MDI manufacturing releases. Therefore, release estimates were based on a number of simplifying assumptions. Assumptions for air and water releases are presented below.

Because the vapor pressure of MDI is low (5×10^{-6} mm Hg at $25^{\circ}C$) (Woolrich, 1982), it was assumed that air releases of MDI leaving the manufacturing facility will be very small.

Water releases were estimated based on the data found in three patents concerning MDI manufacturing (Beck, 1958; Hidetosh et al., 1968; Pistor et al., 1977). These patents indicated that process water is not used in the manufacture of MDI. One patent (Hidetosh, 1968) called for the use of non-contact cooling water, which is expected to remain uncontaminated.

Since MDI is known to react with water, no water is used to wash MDI. However, it is expected that some water will be used for maintenance, equipment cleaning, and work area washdowns. It has been assumed that such water requirements for MDI production

will be the same as those of 4,4'-MDA production. This is a worst-case assumption since the organic 4,4'-MDA layer is known to be washed with water. Wash water constitutes one-third of the water used in 4,4'-MDA manufacturing, i.e. 8.1×10^8 l/yr. Therefore, the water requirements for MDI manufacturing are assumed to be 2.7×10^8 l/yr.

As a worst case estimate, it is assumed that any MDI contacted by wash water would be immediately hydrolyzed to 4,4'-MDA, and that sufficient 4,4'-MDA would be produced for the water to become completely saturated. As a more realistic case, it is assumed that the water would only reach one-tenth of the saturation point.

According to the worst-case assumptions, 4,4'-MDA releases from MDI manufacturing become:

$$2.7 \times 10^8 \text{ l/yr} \times 1 \frac{\text{gm 4,4'-MDA}}{\text{liter}} \times 1 \times 10^{-6} \frac{\text{kkg}}{\text{gm}} =$$

270 kkg/yr of 4,4'-MDA released

For the more realistic case, the total releases of 4,4'-MDA are estimated to be 27 kkg/yr*.

b. Releases from Other Product Manufacturing

Releases from the manufacturing of the ICF category products listed earlier in Table 4 could not be estimated because of the lack of information on the various manufacturing processes.

* At this time there are no TSCA Section 8(a) data on losses during manufacture of MDI; however, EPA's monitoring of effluents from a 4,4'-MDA/MDI manufacturing site is expected to help determine the accuracy of release estimates made in this section.

3. Releases from Use of MDI in Polyurethane Manufacture (Versar, 1983b)

No information could be located that quantified the MDI (4,4'-MDA) releases from polyurethane manufacturing. However, one report (Smith and LaSalle, 1974) provided total air emissions data from polyurethane resin manufacturing for a chemical analogous to MDI, toluene diisocyanate (TDI). Smith and LaSalle (1974) reported emissions of 1.8×10^{-8} lbs TDI released/lb of polyurethane foam produced. Assuming that MDI and TDI emissions are about the same, airborne MDI releases from a given manufacturing site would be under 1 kg/yr, since MDI is used to produce only a portion of polyurethane foams manufactured at various sites. Thus, the MDI/4,4'-MDA air emissions from a particular foam manufacturing site would be relatively insignificant, especially since MDI has a lower vapor pressure than TDI.

Numerous factors influence water releases of MDI/4,4'-MDA including the following: production volume, manufacturing process, amount of excess diisocyanate, water requirements, processing conditions, ratio of other constituents to MDI, and level of pollution control. Information on these factors, as they relate to quantitative releases, could not be found. Therefore, the following assumptions were necessary to roughly estimate MDI/4,4'-MDA water releases from polyurethane manufacturing:

- From the patent literature (Metzler, 1971), it was estimated that the water requirement for polyurethane

manufacturing is between 0 and 10% of all other ingredients. The exact percentage depends on the type of polyurethane foam being manufactured and the production process. The worst case scenario was assumed to require 10% water.

o The amount of process water consumed during the production of polyurethane foam is not known. As a worst-case scenario, it was assumed that a negligible amount of water will actually be consumed in this process. Therefore, process water releases were still assumed to be 10% of all other raw materials.

o Also from the patent literature (Metzler, 1971), it was found that more than the stoichiometric amount of diisocyanate (MDI) was required to complete the reactions and ensure proper foaming. As a worst case, it was assumed that MDI will rapidly hydrolyze to 4,4'-MDA and that there will be sufficient excess MDI present for the resulting 4,4'-MDA to reach maximum concentration (1 gm of MDA/liter) in the process water.

o According to Youer (1969), in conventional polyurethane processing, the finished polyurethane foam is steam cured and washed. Furthermore, the manufacturing site will use water for maintenance, equipment cleaning, and work area washdowns. It is assumed that the miscellaneous water requirements will be equal to 50% of the process water requirement. This is the same worst case assumption used for 4,4'-MDA manufacturing. It was assumed that the 4,4'-MDA concentration in this wash water (from hydrolysis of unreacted MDI) is 10% of the maximum solubility, i.e. 0.1 gm MDA/liter of water. This is a worst case assumption since actual emissions from polymer formation operations are expected to be insignificant (Hedley et al., 1975).

o It was assumed that MDI is used to produce approximately 40% of all polyurethane products manufactured in the United States. This is based on information that indicates TDI is used in slightly more than 50% of all polyurethane products and that other non-MDI isocyanates are used in approximately 10% of all polyurethane products (Suh, 1980). Based on this information, MDI is used to manufacture approximately 501,600 kkg of polyurethane foam.

o MDI and 4,4'-MDA are not removed from the effluent during waste treatment.

The calculations for 4,4'-MDA releases from polyurethane manufacturing are given below:

Releases from process water

Amount of wastewater:

501,600 kkg x 0.10 = 50,160 kkg x 1000 liters/1 kkg

= 50,160,000 liters

Releases:

50,160,000 liters x 1 gm 4,4'-MDA/liter = 50,160,000 gm
= 50.2 kkg of 4,4'-MDA released in process wastewater

Releases from wash water

Amount of wash water: 25,080,000 liters

Releases:

25,080,000 x 0.1 gm 4,4'-MDA/liter = 2,508,000 gm
= 2.5 kkg of 4,4'-MDA released in wash water

Total release (from all polyurethane manufacture)
= 50.2 kkg + 2.5 kkg = 52.7 kkg of 4,4'-MDA

As a more realistic case, it was assumed that all the process water is consumed during the foaming reaction or recycled during the production of polyurethane foam. Therefore, the only water releases would be from wash water. The wash water releases for this case are assumed to be the same as those in the worst-case scenario. Consequently, for the more realistic case, 2.5 kkg of 4,4'-MDA are assumed to be released to surface waters.

4. Releases from Polyurethane Products (Versar, 1983b)

One report (David, 1969) stated that there may be trace quantities of isocyanate encapsulated in polyurethane foam. However, most of this isocyanate, especially MDI which has a low vapor pressure, is expected to remain in the foam polymer matrix. Thus, it was assumed that 4,4'-MDA releases from such polyurethane products will be insignificant.

NIOSH (1981) reported finding 4,4'-MDA in the off-gas from a spandex fiber sample heated to 200°C to simulate a heat-forming operation in the apparel industry. This report is being investigated to determine whether 4,4'-MDA was used, as such, in the preparation of the fiber, or if urethane linkages (known to be labile at high temperatures) might have been broken (after having been formed from the possible use of MDI in the fiber) to release 4,4'-MDA. The results of this investigation could have implications regarding potential exposures to 4,4'-MDA in a workplace setting not previously identified.

5. Releases from Disposal of Wastes (Versar, 1983b)

No information could be found concerning the disposal practices for 4,4'-MDA-containing wastes from the manufacture of the amine or MDI.

CMA (1984) reports that of the 312 users and processors it surveyed, 38 reported some information on environmental releases, though mostly in a qualitative fashion.

Twenty respondents reported on air emissions. Four reported using scrubbers or baghouses to limit releases. Six firms reported air emission values (other than "trace"). One reported 1315 pounds/year released based on mass balance, but there was some question whether this included material removed by their scrubber. Another reported 193 pounds/year released. Two reported about 10 pounds/year. Another firm reported emission levels at 1.3 parts per billion.

Eight companies (CMA, 1984) reported that their aqueous effluent contain 4,4'-MDA; seven of these send their effluent to a publicly owned treatment works. Of these seven, five said the effluents contained "trace" amounts of the amine and the others release 50 pounds/year by this route.

Of the 38 respondents (CMA, 1984), 33 reported sending solid wastes, including spillage, clean-up materials, containers, reactor rinse solvents and other 4,4'-MDA-containing solutions, to landfills. Sixteen of these reported that all 4,4'-MDA was "fully reacted" before being sent to the landfill. Eleven companies reported disposing of 5 to 100 pounds/year to landfills. Another firm reported landfilling 270,000 pounds/year. Three firms reported incineration of waste 4,4'-MDA and empty bags.

Other disposal methods reported included "RCRA" or "EPA" disposal and use of waste chemical reclaimer companies.

6. Potential Releases from Degradation of Polyurethane

Since about 98 to 99% of 4,4'-MDA production is converted to MDI and PMDI and thence to various polyurethane products, and since degradation of such polyurethanes could generate 4,4'-MDA, there is concern over the fate of polyurethanes disposed of in landfills.

An example of the behavior of monomers used as starting materials in the manufacture of such plastics was submitted to EPA by the International Isocyanate Institute (III, 1979). III submitted the results of a research effort to determine whether polyether diol-based polyurethane flexible foams made from toluene diisocyanate, an analogue of MDI, would biodegrade under the conditions of sanitary landfills, and whether corresponding amine analogs, 2,4- and 2,6-toluene diamines (TDA), would be released. Polyurethane foam made with ^{14}C-labelled toluene diisocyanates was subjected to three experimental media--sanitary land fill medium, refuse compost medium, and parabrown earth medium--of different bacterial activity for three months. The sanitary fill medium and the refuse compost medium were subjected to temperatures of 22°C and 50°C. After three months, at 50°C, 0.04% of the ^{14}C-tagged starting activity in foam extracts was identified as 2,4- and 2,6-TDA. At 22°C no TDA could be detected, and no release of $^{14}CO_2$ was identified from any experiments done with sanitary fill medium. In refuse compost medium and parabrown earth medium, no detectable TDA was formed. However, at 22°C and at 50°C, 0.01% and 0.1% of the starting activity of the labelled foam was detectable as $^{14}CO_2$.

The III paper concludes that polyurethane is very resistant to microbial degradation. EPA believes that 4,4'-MDA in polyurethane could be expected to behave in a manner similar to TDA. Therefore, very little 4,4'-MDA release would be expected in landfill situations; and the 4,4'-MDA released is expected to be degraded chemically or microbially fairly rapidly. Since 50°C is an extreme (though sometimes attainable) environmental temperature, release of 4,4'-MDA during normal environmental conditions would not be expected. However, even at the higher temperatures, any 4,4'-MDA release would probably be very slow and at very low levels. There are no monitoring data available for 4,4'-MDA in the terrestrial environment.

7. Environmental Fate and Transport of 4,4'-MDA Releases

a. Environmental Transport of 4,4'-MDA

Most 4,4'-MDA is converted at the site of its manufacture to MDI, which is then used to produce polyurethanes. 4,4'-MDA can be expected to be released as a waste during the conversion to MDI. It was estimated above that most of the releases will be to aquatic systems. Typical treatment processes used by 4,4'-MDA production plants involve the discharging of aqueous waste to a holding lagoon from which the wastewater is ultimately diverted to a municipal sewage treatment plant (Young and Parker, 1978) or surface waters.

In general, no significant quantities of gaseous or solid wastes contaminated with 4,4'-MDA have been reported (JRB, 1980; ESE, 1981), although one processor reportes landfilling 270,000

lbs. of waste that contains some 4,4'-MDA (CMA, 1984). It is not expected that 4,4'-MDA will be transported from aquatic systems to the atmosphere since its aqueous solubility (1,000 mg/l) and low vapor pressure (10^{-7} torr at 25°C) make volatilization from water unlikely (Callahan et al., 1979). Deposition in sediment or sorption to soils also is unlikely for 4,4'-MDA dissolved in water, because of its solubility and its partitioning preference. Values calculated for the log octanol/water partition coefficient are 1.76 (Kenaga and Goring, 1980), 1.84 (Banerjee et al., 1980), 1.88 (Leo and Hansch, 1979), and 2.52 (Chiou et al., 1977). Values calculated for the log organic carbon distribution coefficient are 1.79 (Karickhoff et al., 1979), 1.90 (Briggs, 1973), 1.99 to 2.47 (Kenaga and Goring, 1980), and 2.62 (Karickhoff et al., 1979).

b. **Photodegradation**

Although no data have been found regarding photolysis of 4,4'-MDA in the aquatic environment, indirect evidence indicates that photo-oxidation may be the major fate of the compound released in aqueous waste. 4,4'-MDA crystals darken when they are exposed to air (Moore, 1978). Similar behavior of phenols and other aromatic amines has been attributed to the formation and photolysis of charge-transfer complexes with oxygen (Joschek and Miller, 1966). Free radical intermediates and hydroxylated products are reported.

Landrum and Crosby (1981) report that dilute aqueous solutions of p-toluidine are oxidized rapidly enough to make its aquatic fate difficult to study. The structure of 4,4'-MDA is

sufficiently similar to p-toluidine (both bear benzylic hydrogens) to expect similar photochemical reactivity. Moreover, free radical intermediates of 4,4'-MDA, analogous to those which can be postulated for p-toluidine, should be more readily formed (Laity et al., 1973) from structures such as 4,4'-MDA. Zabik and Kawaguchi (1982) have shown that structurally analogous 4,4'-methylenebis-2-chloraniline photodecomposes in water with a half-life of 3.69 hours.

c. Oxidation

Aromatic amines are susceptible to oxidation by a variety of chemical oxidizing agents (Cason, 1948). The resultant products are usually quinones. Aromatic amines, such as aniline and p-chloroaniline, become more easily oxidized after being adsorbed to the aquatic clay, montmorillonite (Cloos et al., 1979). Similar enhanced reactivity toward oxygen also should be expected with 4,4'-MDA.

d. Hydrolysis

There are no data to suggest that aromatic amines undergo hydrolysis under environmentally relevant conditions. The covalent bond of a substituent attached to an aromatic ring is resistant to hydrolyis because of the high negative charge-density of aromatic structures (Morrison and Boyd, 1973).

e. Volatilization

4,4'-MDA's solubility in water (1,000 mg/l) coupled with its low vapor pressure (10^{-7} torr at 25°C) diminish the importance of volatilization as an environmental transport process (Callahan et al., 1979).

f. Sorption

The adsorption by soil of two similar aromatic amines, aniline and p-chloroaniline, has been found to depend both on organic matter and clay content of the soil (Moreale and Van Blade, 1976; Cloos et al., 1979). The extent of partitioning, however, between soil and water depends on the solute's relative affinity for the soil and water phases. The values which have been calculated for 4,4'-MDA's log organic carbon distribution coefficient (1.79 to 2.62) and log octanol/water partition coefficient (1.76 to 2.52) indicate that the compound will not be strongly sorbed to soils, and that if it were sorbed, it would probably be subject to leaching (ESE, 1981).

g. Bioaccumulation

Although no direct evidence has been found in the literature regarding bioconcentration of 4,4'-MDA, bioconcentration factors have been estimated which range from 1.83 to 46 (ESE, 1981). Metcalf and Sanborn (1975) point out that compounds with solubilities of 50 mg/l or more generally have little potential for aquatic bioaccumulation. Lu et al. (1977) reported that although benzidine was taken up by the organisms of their aquatic ecosystem, it was not bioaccumulated, and it remained in equilibrium with the benzidine dissolved in the water. The structure of benzidine differs from the structure of 4,4'-MDA only by the absence of the central methylene group.

h. Biodegradation

No information regarding the microbial degradation of 4,4'-MDA was found. Subba-Rao and Alexander (1977), however, have

reported that Pseudomonas putida, isolated from soil, was capable of degrading structurally similar bis(p-nitrophenyl)-methane slowly. Bis(p-hydroxyphenyl)methane was not degraded. Inasmuch as activated sludge can be acclimated to degrade benzidine (Baird et al., 1977), 4,4'-MDA could probably be treated in a similar manner.

i. Summary

Photoxidation may be the major fate of 4,4'-MDA released in aquatic waste. Volatilization, sorption, and bioaccumulation are probably not important, leaving dilution as the principal pathway for dissipating MDA which remains undegraded. Biodegradation probably would become a viable process only in acclimated sludge.

8. Estimated Surface Water Concentrations of 4,4'-MDA

Concentrations of 4,4'-MDA in surface waters that could be used as drinking water supplies were estimated using the release estimates given above, information in EPA's Exposure Analysis Modeling System (EXAMS), and confidential production data for 4,4'-MDA (and MDI) manufacturing plants derived from the TSCA section 8(a) Information System. This material is discussed at the beginning of Section IV C above and summarized in Table 11.

9. Populations Potentially Exposed to Contaminated Surface Waters

This section identifies and estimates the sizes of populations potentially exposed to 4,4'-MDA through ingestion of drinking water and through dermal contact with contaminated surface waters. Populations exposed through other pathways, such as ingestion of potentially contaminated groundwater, could not

be identified and were not considered within the scope of this report.

a. Potential Drinking Water Exposures

Drinking water may be contaminated by 4,4'-MDA released from 4,4'-MDA, MDI and/or polyurethane manufacturing plants. The Water Supply Data Base (WSBD) was checked to determine whether any drinking water intakes were located downstream of 4,4'-MDA/MDI manufacturing plants. The WSDB is a computerized data base, maintained by the Monitoring and Data Support Division (MDSD) of EPA, that contains information on the location of surface water utilities; the locations of the utilities' treatment plants, intakes, and sources of raw water; the populations served; and the average and maximum daily production. Table 12 enumerates the populations served by drinking water facilities at various points downstream from each plant. 4,4'-MDA manufacturing plants not listed in the table do not discharge upstream of any drinking water intakes (i.e., no drinking water intakes are located between the plant discharge point and the confluence of the receiving water with a salt water body). As stated above, there is at present no indication that any drinking water supply is contaminated with 4,4'-MDA. Ongoing work will resolve the question of whether such contamination occurs.

b. Potential Ambient Environmental Exposures

Populations may be exposed to 4,4'-MDA in the ambient environment through inhalation or through dermal contact with surface waters. Only the later will be considered here, since

TABLE 12
POPULATIONS POTENTIALLY EXPOSED TO 4,4'-MDA IN DRINKING WATER DOWNSTREAM OF 4,4'-MDA MANUFACTURING PLANTS

Plant	Location	Receiving Stream	Location of Drinking Water Intake (Miles Downstream from Plant)[b,c,d]	Exposed Population
Olin Chemicals	Moundsville, WV	Ohio River	0.5	900
			35.3	2,500
			62.7	25
Mobay[a]	New Martinsville, WV	Ohio River	15.4	2,500
BASF[a] and ICI Americas Inc.[a,e]	Geismar, LA	Mississippi River	27.9	4,000
			38.2	2,000
			44.9	12,500
			46.2	5,850
			71.6	54,800
			78.9	232,000
			80.3	550,000
			83.8	12,000
			85.4	60,000
			87.5	25,000
			88.7	62,700
Dupont	Belle, WV	Kanawha River	11.3	1,950

(a) Also produces MDI.
(b) All drinking water intakes between the Olin and Mobay plants and the confluence of the Hocking River with the Ohio River (a distance of about 100 miles from the Olin plant and about 60 miles from the Mobay plant) are listed.
(c) All drinking water intakes located within 90 miles downstream of the BASF and ICI Americas plants are listed.
(d) All drinking water intakes between the Dupont plant and the confluence of the Kanawha River with the Ohio River (a distance of about 70 miles) are listed.
(e) ICI Americas owns Rubicon, which is the name used by CMA's 4,4-MDA Project Panel member that operates this plant.

Source: EPA's Water Supply Data Base.

TABLE 13
POPULATIONS SWIMMING IN SURFACE WATER
NEAR 4,4'-MDA MANUFACTURING PLANTS

Plant	Location	Receiving stream	Exposed population
Olin Chemical	Moundsville, WV	Ohio R. (Marshall Co.)	insignificant[a]
Mobay	New Martinsville, WV	Ohio R. (Wetzel Co.)	insignificant[a]
Mobay	Baytown, TX	Cedar Bayou	0[c]
BASF	Geismar, LA	Mississippi R.	0[c]
ICI Americas, Inc. (Rubicon)	Geismar, LA	Mississippi R.	0[b]
DuPont	Belle, WV	Kanawha R. (Kanawha Co.)	0[b]
DuPont[d]	Deepwater, NJ	Delaware R. (Salem Co.)	insignificant[a]
Uniroyal	Naugatuck, CT	Naugatuck R.	0[b]
UpJohn	LaPorte, TX	San Jacinto Bay	0[c]

(a) Swimming unauthorized but may occur.
(b) Swimming does not occur.
(c) Swimming does not occur (Versar judgment).
(d) Not in production.

Source: Receiving streams identified via the Industrial Facilities Discharge File (USEPA): Data in footnote (b) and (c) derived from personal communications between representatives of county parks and recreation departments and T. Faha, Versar, July 14, 1983.

V. QUANTITATIVE RISK ESTIMATION (COOK AND GRINDSTAFF, 1983; Grindstaff, 1984)

In this section the method and results of the quantitative estimation of cancer risks posed by 4,4'-MDA are presented.

The model used to extrapolate from the dose-response region of the NTP bioassays down into the estimated human exposure range was the one-stage version of the Crump (1980) multistage model. Estimated human response to these exposures (a.k.a. the risk level) were calculated based on tumor incidences at individual sites for each sex and species as well as on pooling tumor incidences in various sexes and species.

The human exposures, or LADDs, that were used in the risk estimation are explained. They are based on monitoring data and hypothetical constructions of a variety of workplace and drinking water exposure situations.

A. Introduction

In National Toxicology Program bioassays (NTP, 1983a) for the carcinogenicity of 4,4'-MDA, F344/N rats and B6C3F1/N mice of both sexes were administered the dihydrochloride salt ad libitum in drinking water at concentrations of 150 parts per-million (ppm) and 300 ppm for 104 weeks. Controls of each species were given no 4,4'-MDA. Results from these bioassays were used in high-to-low dose extrapolations to derive human carcinogenic risk following inhalation, dermal, and oral exposure to 4,4'-MDA.

While the bioassays were conducted using the dihydrochloride of 4,4'-MDA, for the reasons set forth in Section III, this assessment assumes that the results can be used to estimate cancer risks associated with the parent amine. Likewise, while

the bioassays involved drinking water exposures, because of the demonstrated capability of 4,4'-MDA to penetrate human skin, to be absorbed through the human gastro-intestinal tract, and to be rapidly distributed in mammals, this assessment uses the bioassays to estimate cancer risks for humans exposed dermally, via inhalation or ingestion.

Certain tumor types displaying a consistent dose-related increase in incidence in the bioassays were judged appropriate for use in calculating human carcinogenic risk at that site (Milman, 1984). These sites are listed in Table 14, along with incidence rates of tumors in the test animals for different dose levels. Also listed in Table 14 are data on four tumor types whose incidence, while statistically signficant, do not permit their use in quantitative risk estimations; this information is discussed further in subsection B.3, below.

Also given in Table 14 are the incidences of those statistically significant tumors useful in assessing risk aggregated by species/sex, and a similar aggregation of such tumor incidences in which the malignant tumors alone were statistically significant. These aggregations have been proposed for use in estimating total cancer risk that a substance might pose (EPA, 1984).

The true mathematical relationship between dose and response to 4,4'-MDA for animals or humans is not known. To provide an indicator of risk, data from the NTP bioassays were fitted to the Global 83 high-to-low dose extrapolation model (Crump, 1980), modified to reflect the fact that only 2 positive dose-levels

were suitable for use in the extrapolation. This method provided carcinogenic risk estimates for human exposure to low levels of 4,4'-MDA by extrapolating from the higher levels of 4,4'-MDA given to the test animals.

For the purpose of this assessment, several different sets of exposure situations representing occupational and environmental exposures to 4,4'-MDA, described above in Section IV, were used to estimate carcinogenic risk. These exposures include environmental exposure through drinking water and workplace exposure situations. Lifetime average daily doses (LADDs) for humans were calculated for each situation, and these LADDs are given in Tables 19 and 20, along with estimated extra lifetime cancer risks. These situations are described in detail below, and the calculations are given in Appendix B.

Data were handled using two significant figures in this section, except where it was obvious that more were appropriate. Risk estimations are given with one significant figure.

B. Methods and Results

1. High-Dose to Low-Dose Extrapolation Model

The NTP bioassay data were fitted to the Crump multistage model (Crump, 1980). The multistage model has been in wide use in the EPA since the summer of 1980, and is used by EPA's Carcinogen Assessment Group to set air and water quality criteria and standards. This model was expected to provide a good fit to the dose-response data. Other models, such as the logit, probit, Weibull and the gamma multi-hit were not appropriate for this analysis, because the number of dose levels in the NTP bioassay

was equal to the number of parameters being estimated using these models. The maximum likelihood estimate of carcinogenic risk and the upper 95% confidence limit of this risk were calculated for the human exposure situations (LADDs) at eight sex- and species-specific tumor sites in the test animals. Risk estimates were also calculated based on incidences of all the statistically significant tumors in male and female rats and in female mice, and another set of risk estimates was derived from incidences of all the statistically significant tumors in male rats and female mice for which the incidences of malignant tumors alone were statistically significant. The "pooling" of tumor incidences was done only on the sexes/species indicated because it was those sex/species which responded in the bioassay in a manner amenable to mathematical analysis. No pooling of male mouse data was done because only one tumor type showed monotonic dose-response, and in the female rat there were no statistically significant malignancies. Liver neoplastic nodules were not taken into account in any of these calculations, even though the incidence of this lesion was statistically significant, because the proper use of such lesions in quantitative risk estimation has not yet been satisfactorily resolved.

Upon examination of the risk levels presented in Tables 19 and 20, one notes that there is little or no differences between the levels calculated for the two different kinds of tumor data pooling. This means that most of the calculated risk is due to malignancies. If the risk level from pooling tumor data in which the malignancies alone are statistically significant had been

much lower than that derived from pooling all tumors, then one would conclude that the contribution of malignancies to risk was relatively low. This was not the case.

Goodness-of-fit tests were performed to evaluate how well the experimental data fit the model. P-values are presented for each site, and these are given in Table 15.

2. Animal to Human Extrapolation

In order to extrapolate the expected response in humans to various lifetime average daily doses of 4,4'-MDA, one must first determine what the dose-response relationship is in the test animals from the bioassay data. Then one must take the expected human LADDs and convert them to animal LADDs using a species conversion factor, and, using the model described above, calculate the response that the animals would have shown at those lower doses. This response is then represented as the "risk to humans" -- in reality, of course, it is the response one would have expected in the test animals at doses equivalent to those that humans receive.

a. Dose-Response in the Bioassay

The animal exposures, in ppm in drinking water, were converted to mg/kg/day LADD by the following relation:

$$\text{LADD (mg/kg/day)} = \frac{d\ (\text{ppm})\ F\ (\text{kg/day})}{W\ (\text{kg})}$$

where LADD is lifetime average daily dose, d is the concentration of the test chemical in the animals' drinking water, F is the amount of water a test animal consumes per day, and W is the weight of the test animal. For this analysis it is assumed that rats weigh 350 grams, mice weigh 20 grams, rats consume 20 grams

of water per day, and mice consume 5.5 grams of water per day. Hence, mice receiving 4,4'-MDA ·2HCL at 150 ppm in water is equivalent to 30 mg 4,4'-MDA/kg/day LADD, and a dose-level of 300 ppm is the equivalent of 61 mg 4,4'-MDA/kg/day LADD. For rats, 150 ppm in water equals 6.3 mg 4,4'-MDA/kg/day and 300 ppm equals 13 mg 4,4'-MDA/kg/day. The absorption rate through the gastro-intestinal tract in both mice and rats is assumed to be 50% (Thies, 1983), so these doses are divided by 2, reducing the LADDs for mice to 15 and 30 mg 4,4'-MDA/kg/day, and for rats to 3.2 and 6.5 mg 4,4'-MDA/kg/day.

b. Extrapolation of Human LADDs to Animal LADDs

The relationship between experimental animal doses and human doses assumes that the locus of a characteristic agent is on body surface area. Assuming all mammalian organisms have equal densities, body surface area is proportional to the 2/3 power of the weight of the organism. Hence, equivalent human dose in mg is given by Mantel and Schneiderman (1975) as:

$$\frac{\text{human dose (mg)}}{\text{human surface area}} = \frac{\text{animal dose (mg)}}{\text{animal surface area}}$$

then,

$$\frac{\text{human dose (mg)}}{\text{human weight } 2/3} = \frac{\text{animal dose (mg)}}{\text{animal weight } 2/3}$$

and,

$$\text{human dose (mg)} = \text{animal dose (mg)} \times \left(\frac{\text{human weight}}{\text{animal weight}}\right)^{2/3}$$

Conventing to a mg/kg basis, one uses the 1/3 power of the weight ratios, thus

$$\text{human dose (mg/kg)} = \text{animal dose (mg/kg)} \times \left(\frac{\text{animal weight}}{\text{human weight}}\right)^{1/3}$$

Since human weight is assumed to be 70 kg and the rat and mouse weight, 0.35 and 0.020 kg, respectively, the ratio of animal dose to human dose is 0.17 for rats and 0.066 for mice. Hence, for rats,

Human LADD = 0.17 x Animal LADD

and for mice,

Human LADD = 0.066 x Animal LADD

3. Tumors Observed in the Bioassay

Table 14 presents the incidence of tumors from the NTP bioassays. Thirteen different species-, sex- and/or site-specific tumors/lesions were observed in the bioassays at statistically significant incidences, and 12 were judged biologically appropriate for use in estimating risks to humans (Milman, 1984). As stated above, there is at present no consensus on the proper use of liver neoplastic nodules in this sort of assessment, so that particular statistically significant lesion in male rats was not used here. Further, since the goodness-of-fit to the one-stage model displayed (Table 15) by the data on male mice liver hepatocellular carcinoma, male mice liver hepatocellular carcinoma and adenoma, female mice malignant lymphoma, and female mice thyroid follicular cell carcinoma and adenoma was either inadequate or marginal, no risk calculations were made using these individual tumor data.

In order to obtain insight into the total risk for each sex and species, the incidences of all statistically significant tumors that each species and sex experienced in the bioassay were tabulated. That is, for instance, in the case of female mice,

all controls and test animals that had at least 1 tumor of the statistically significant classes: all malignant lymphomas, liver hepatocellular carcinoma or adenoma, thyroid follicular-cell carcinoma or adenoma, or lung alveolar/bronchiolar carcinoma or adenoma; were counted. Each animal bearing such a tumor was counted only once, even if it had more than one of these tumor types. Further, in order to obtain insight into the contributions of benign tumors to the overall risk, a "pooling" similar to that described above was done, but only for those tumor types in which the observed malignancies, alone, were statistically significant. In this assessment, rather than present risk calculations in the text for all these sets of data, estimates based on the individual and pooled tumor types showing highest risk are given in the text, in Tables 19 and 20. Risk estimates made using the remaining bioassay data are given in Appendix C in Tables 19A and 20A.

In addition to the tumors in Table 14, other rarer tumors were observed in the bioassay. These are listed below along with their incidence in a large group of control animals and the probability (p-value by Fisher's Exact Test) of observing this tumor by chance alone, given the incidence in the historical NTP program control population. A bile duct adenoma was found in one (p-value = 0.0136) 150 ppm dose male rat. This tumor had not been previously diagnosed in 3,633 control male rats in the NTP bioassay program. Transitional cell papillomas of the urinary bladder were found in 2/50 (p-value = 0.0017) low-dose and 1/50 (p-value = 0.0531) high-dose female rats compared with 3/3644

TABLE 14

TUMOR INCIDENCE BY SPECIES, SEX AND SITE OF TUMOR.
(NTP, 1983a)

	Control	150 ppm	300 ppm
Male Rats			
Liver-Neoplastic Nodule (d)	1/50 $P_S<0.001$[a] $P_L=0.791$[b]	12/50 $P_f=0.001$[c]	25/50 $P_f<0.001$
Thyroid-Follicular Cell Carcinoma	0/49 $P_S<0.001$ $P_L=0.428$	0/47	7/48 $P_f=0.006$
Thyroid-Follicular Cell Adenoma or Carcinoma	1/49 $P_S=0.001$ $P_L=0.590$	4/47 $P_f=0.175$	10/48 $P_f=0.005$
Female Rats			
Thyroid-Follicular Cell Adenoma or Carcinoma	0/47 $P_S<0.001$ $P_L=0.086$	4/47 $P_f=0.058$	19/48 $P_f=0.001$
Thyroid-C-cell Adenoma or Carcinoma	1/47 $P_S=0.055$ $P_L=0.153$	5/47 $P_f=0.102$	7/48 $P_f=0.032$
Male Mice			
Liver-Hepatocellular Carcinoma	10/49 $P_S=0.047$ $P_L<0.001$	33/50 $P_f=0.001$	29/50 $P_f=0.001$
Liver-Hepatocellular Adenoma or Carcinoma	17/49 $P_S<0.001$ $P_L<0.001$	43/50 $P_f<0.001$	37/50 $P_f<0.001$
Adrenal-Pheochromocytoma	2/48 $P_S=0.116$ $P_L<0.002$	12/49 $P_f=0.004$	14/49 $P_f=0.001$
Female Mice			
Lung-Aveolar/Bronchiolar-Adenoma or Carcinoma	2/50 $P_S=0.010$ $P_L=0.992$	3/50 $P_f=0.150$	8/49 $P_f=0.043$

TABLE 14 - CONTINUED

	Control	150 ppm	300 ppm
All Malignant Lymphomas	13/50 P_S<0.001 P_L=0.105	28/50 P_f=0.002	29/50 P_f=0.001
Liver-Hepatocellular Carcinoma	1/50 P_S<0.001 P_L=1.000	6/50 P_f=0.056	11/50 P_f=0.002
Liver-Hepatocellular Adenoma or Carcinoma	4/50 P_S<0.001 P_L=0.700	15/50 P_f=0.005	23/50 P_f<0.001
Thyroid-Follicular cell adenoma or carcinoma	0/50 P_S<0.001	1/47 P_f=0.485	13/50 P<.001

POOLED DATA: ALL STATISTICALLY SIGNIFICANT TUMORS (e)

	Control	150 ppm	300 ppm
Male rats with thyroid follicular cell carcinoma or adenoma	1/49 P_S=0.001 P_L=0.590	4/47 P_f=0.175	10/48 P_f=0.005
Female rats with thyroid follicular cell carcinoma or adenoma or thyroid C-cell carcinoma or adenoma	1/47 P_S<0.001 P_L=0.301	9/47 P_f=0.005	25/48 P_f<0.001
Female mice with liver hepatocellular carcinoma or adenoma, thyroid follicular cell carcinoma or adenoma, lung alveolar/bronchiolar carcinoma or adenoma or any malignant lymphoma	16/50 P_S<0.001 P_L=0.052	38/50 P_f=0.002	44/50 P_f<0.001

TABLE 14 - CONTINUED

POOLED DATA: ALL STATISTICALLY SIGNIFICANT TUMORS FOR WHICH MALIGNANCIES ALONE ARE SIGNIFICANT [e][f]

	Control	150 ppm	300 ppm
Male rats with thyroid follicular cell carcinoma or adenoma	1/49 P_s=0.001 P_L=0.590	4/47 P_f=0.175	10/48 P_f=0.005
Female mice with liver hepatocellular carcinoma or adenoma or any malignant lymphoma	16/50[g] P_s<0.001 P_L0.119	36/50 P_f=0.004	43/50 P_f<0.001

(a) P_s=two-sided p-value for positive slope. Small values indicate that the slope is significantly different from zero, meaning that there is a tendency for increasing dose to be associated with increasing response.

(b) P_L=two-sided p-value for departure from linear trend. Small values indicate that the association between dose and response is not linear.

(c) P_f=Fisher Exact Test p-value. Small values indicate response in the control animals is statistically significantly different from the response in the control animals.

(d) At this time there is no consensus on the proper use of this tumor type in quantitative risk estimations, so it is not used in this assessment.

(e) Male mouse data were not used because response did not increase monotonically with dose.

(f) Female rats did not display a response in which malignancies alone were statistically significant.

(g) NTP report did not identify the animal (could it have been Minnie?) bearing a liver hepatocellular carcinoma, so this numerator could change by one.

control female rats in the bioassay program. Finally, granulosa cell tumors were found in the ovaries of 2/50 (p-value = 0.0140) high dose female rats and 3/50 (p-value = 0.0009) low-dose female rats and 1 (p-value = 0.0283) of the latter tumors was a granulosa-cell carcinoma. Granulosa-cell tumors were identified in 11/3462 controls, and granulosa-cell carcinomas have been observed in only 1/3462 control animals.

Tables 16 and 17 give the historical tumor incidence for a large group of control animals from the NTP bioassay program (1983b) for mice and rats, respectively. Included are all tumors with a spontaneous frequency of at least 0.5%. They are presented to put the tumor incidence in the controls of this NTP bioassay into perspective with the incidence of tumors in a large historical control population. The incidence of specific tumors in the control group of this bioassay appears to be consistent with historical groups. For example, the incidence of tumors in control animals appears to be high in three sites in this bioassay, yet it is consistent with the historical group. In control male mice 20% (10/49) developed hepatocellular carcinomas and 35% (17/49) developed hepatocellular carcinomas or adenomas. In the historical control population 21.3% (498/2334) of the male mice developed hepatocellular carcinomas and 31.1% (725/2334) developed either hepatocellular nodules, adenomas or carcinomas. In this bioassay, 26% (13/50) of the control female mice had a malignant lymphoma of the hematopoietic system compared to 27.2% in the large control population.

TABLE 15

X^2 GOODNESS -OF-FIT TEST p-VALUES FOR EACH TUMOR TYPE IN TABLE 14

Species And Sex	Tumor Type	p-Value*
Male Rats	Liver Neoplastic Nodules	----
Male Rats	Thyroid Follicular Cell Carcinomas	$p > 0.995$
Male Rats	Thyoid Follicular Cell Adenomas or Carcinomas	----
Female Rats	Thyroid Follicular Cell Adenomas or Carcinomas	$0.750 < p < 0.900$
Female Rats	Thyroid C-Cell Adenomas or Carcinomas	$0.900 < p < 0.950$
Male Mice	Liver Hepatocellular Carcinomas	$0.025 < p < 0.050$
Male Mice	Liver Hepatocellular Adenomas or Carcinomas	$p < 0.005$
Male Mice	Adrenal Pheochromocytomas	$0.500 < p < 0.750$
Female Mice	Lung Alveolar/Bronchiolar Adenomas or Carcinomas	$0.950 < p < 0.975$
Female Mice	All Malignant Lymphomas	$0.250 < p < 0.500$
Female Mice	Liver Hepatocellular Carcinomas	----
Female Mice	Liver Hepatocellular Adenomas or Carcinomas	$p > 0.995$
Female Mice	Thyrid Follicular Cell Adenomas or Carcinomas	$0.250 < p < 0.500$

* This p-value is from the X^2 goodness-of-fit test. The higher the p-value the better the fit of the model to the data. Inadequate fits commonly show $p \leq 0.05$, marginal fits show $0.05 < p < 0.10$, and adequate fits show $p \geq 0.10$. A dash indicates that the test was not appropriate, as the number of experimental dose levels was equal to the number of free parameters in the model.

TABLE 16

HISTORICAL INCIDENCES OF PRIMARY TUMORS[a] IN UNTREATED CONTROL B6C3F1/N MICE. (NTP, 1983b)

Tumor Site	Male	Female
Lung	2343[b]	2468
Alveolar/Bronchiolar Adenoma	282(12.1)[c]	131(5.5)
Alveolar/Bronchiolar Carcinoma	119(5.1)	47(2.0)
Liver	2334	2469
Neoplastic Nodule or Adenoma	240(10.3)	98(4.0)
Carcinoma	498(21.3)	101(4.1)
Nodule or Adenoma or Carcinoma	725(31.1)	196(7.9)
Adrenal	1903	2051
Pheochromocytoma	28(1.2)	16(0.7)
Pheochromocytoma, Malignant	2(0.1)	0(0.0)
Thyroid	2178	2203
C-cell Adenoma	0(0.0)	2(0.0)
C-cell Carcinoma	0(0.0)	0(0.0)
Follicular Cell Adenoma	22(1.1)	40(1.8)
Carcinoma	5(0.2)	6(0.3)
Reproductive System	2343	2486
Mammary Gland Fibroadenoma	0(0.0)	8(0.3)
Adenocarcinoma	0(0.0)	40(1.6)
Hematopoietic System	2343	2468
Leukemia	17(0.7)	52(2.1)
Lymphoma	280(12.0)	625(25.1)
Leukemia/Lymphoma[d]	297(12.7)	677(27.2)

(a) Includes all tumors occurring with a frequency of 0.5% or greater.
(b) Number of animals examined histopathologically (or, for certain lesions, the number of animals necropsied).
(c) Numbers in parentheses are percentages.
(d) This combination is included because certain early studies in the data base tended to use these terms interchangeable.

TABLE 17

HISTORICAL INCIDENCE OF PRIMARY TUMORS[a] IN UNTREATED CONTROL F344 RATS (NTP, 1983b)

Tumor Site	Male	Female
Lung	2305[b]	2345
Alveolar/Bronchiolar Adenoma	35(1.5[c])	18(0.8)
Alveolar/Bronchiolar Carcinoma	20(0.9)	9(0.4)
Liver	2306	2356
Neoplastic Nodule or Adenoma	78(3.4)	71(3.0)
Carcinoma	18(0.8)	4(0.2)
Nodule or Adenoma or Carcinoma	96(4.2)	74(3.1)
Adrenal	2280	2262
Pheochromocytoma	388(17.0)	81(3.5)
Pheochromocytoma, Malignant	23(1.0)	11(0.5)
Thyroid	2230	2265
C-cell Adenoma	114(5.1)	111(4.9)
C-cell Carcinoma	84(3.8)	81(3.6)
Follicular Cell Adenoma	22(1.0)	10(0.4)
Carcinoma	17(0.8)	10(0.4)
Reproductive System	2320	2370
Mammary Gland Fibroadenoma	51(2.2)	527(24.1)
Adenocarcinoma	6(0.3)	48(2.0)
Hematopoietic System	2320	2370
Leukemia	648(27.9)	414(17.5)
Lymphoma	51(2.2)	36(1.5)
Leukemia/Lymphoma[d]	699(30.1)	448(18.9)

(a) Includes all tumors occurring with a frequency of 0.5% or greater.
(b) Number of animals examined histopathologically (or, for certain lesions, the number of animals necropsied).
(c) Numbers in parentheses are percentages.
(d) This combination is included because certain early studies in the data base tended to use these terms interchangeably.

TABLE 18

INCIDENCE OF ANY MALIGNANCY IN F344/N RATS AND B6C3F1/N MICE BY SEX FOR DIFFERENT DOSE LEVELS FROM NTP BIOASSAYS ON 4,4'-MDA.

F344/N Rats	Control	150 ppm	300 ppm
Male	19/50	15/50	17/50
Total animals with[a] tumors uncertain	1/50	13/50	25/50
Female	16/50	20/50	14/50
B6C3F1/N Mice[b]			
Male	25/49	38/50	40/50
Total animals with[a] tumor uncertain	1/49	-	-

(a) Tumor diagnosis is uncertain, may be benign or malignant. May include the same animals as above in each case.

(b) Data for female B6C3F1/N mice not available.

Table 18 shows the incidence of any malignancy observed in the test animals in the 4,4'-MDA bioassays by dose level.

4. Exposure Situations

Several situations of human exposure were used to estimate LADDs and human carcinogenic risk. The LADDs were calculated for each situation's combination of exposure concentration, exposure duration, frequency and extent. The LADDs were then applied to calculate carcinogenic risk using the one-stage model and tumor incidence data given in Table 14. This section will describe the various exposure situations which include both workplace and drinking water situations.

a. Workplace Situations

Mathematical details of the calculation of LADDs from the situations described here can be found in Appendix B, as can the assumptions used in the calculations.

There are several important caveats regarding the assumptions used to calculate workplace LADDs. First, while a skin absorption rate of 1% per hour of deposited material was used based on data for MBOCA, the actual penetration rate of 4,4'-MDA remains to measured. Second, while a uniform permeability of skin to 4,4'-MDA was assumed (to give a uniform absorption rate of 1% over all surfaces), it is well known that different skin surfaces display different permeabilities, and this element of uncertainty does not appear to be amenable to resolution in this type of assessment. Third, in certain of the hypothetical exposure cases studied the assumption is made that all 4,4'-MDA is removed by washing, and preliminary data from the

skin penetration study now underway indicate that soap and water may not remove all the compound in a simple wash. Fourth, the data used from NIOSH (1984a) were collected over six hour periods. At the end of that time the hand pads were removed and analyzed for 4,4'-MDA. The total amount collected over six hours was divided by six to derive an hourly deposition rate. It is not known whether, in fact, deposition occurred linearly with time.

i. Case 1: 4,4'-MDA/MDI Manufacturing

Information supplied by CMA (1983c) indicates that workers are potentially exposed to 4,4'-MDA for varying periods during the work week. LADDs were calculated for workers in the three exposure-duration classes that were reported by CMA, viz., 8 hours or less-, 9 to 20 hours-, and more than 20 hours-per-week. For the first class, exposure for 8 hours per week was assumed; for the second, 20 hours per week; and for the third, 40 hours per week.

Inhalational exposure levels were assumed to be to the highest average 8-hour Time Weighted Average (TWA) values for the three exposure duration classes reported by the five 4,4'-MDA manufacturers who are members of CMA's 4,4'-MDA Project Panel. It is believed that use of the highest average TWA was a realistically conservative assumption. The highest of the TWA ranges reported, viz. 7.2 mg/m^3, was judged unrealistically high because it was based on area monitoring in the vicinity of fugitive emissions to which workers are not exposed throughout their work time in the unit. Furthermore, the 7.2 mg/m^3 value

was obtained using the Marcali method, and analytical interference from aniline is likely to have been significant. Aniline would be more likely to be a chief constituent of fugitive emissions from this sort of equipment than would 4,4'-MDA, because of physico-chemical properties and process conditions.

Dermal exposures were also considered in this situation, and the dermal information from NIOSH (1984a) was used to calculate the dermal component of the LADDs. The data were obtained as described in Section IV above.

ii. Case 2: 4,4'MDA Using/Processing

In this situation, the impact of washing off 4,4'-MDA from exposed skin, either immediately after exposure or with delays of 2, 4 or 6 hours, is assessed. Workers are considered who may handle the chemical for varying periods during the work day, viz. 0.5 hours-, 1.6 hours-, 4 hours-, or 8 hours per day as they mix 4,4'-MDA with other materials, charge reactors, or conduct similar operations, and who then wash-up after some delay.

The inhalational component of the LADDs calculated for these workers is based on measured air levels (personnel monitoring) of 4,4'-MDA reported by Ameron (1983), a firm that manufactures epoxy surface coatings for concrete and steel structures and corrosion resistant piping, among other products. The analytical method employed by Ameron was to collect 4,4'-MDA on silica gel tubes and then to measure the amount collected colorimetrically, a modification of the Marcali method. The employees that were monitored were engaged in pulverizing, mixing, blending and

packaging of dry 4,4'-MDA containing coatings products. Ameron presented no dermal exposure data.

The dermal component of LADDs derived from this situation is based on dermal monitoring reported in NIOSH (1984b). This monitoring was conducted in the epoxy resin mixing room of a facility than produces filament-wound piping and pipe fittings.

The worker was fitted with a "golf-glove-like" device which covered glycerine-wetted cotton gauze pads on the palm and back of the hand. The worker wore no protective gloves. The gauze pads were collected and analyzed after the worker's exposure, as described in NIOSH (1984b). The worker was engaged for less than 10 minutes in weighing about 150 lbs. of granular*, 99% assay 4,4'-MDA into a resin mixing vat.

In the situations analyzed in this case, the hypothetical worker is assumed to handle 4,4'-MDA for only about as long as the worker studied in NIOSH (1984b) and to receive the same dermal exposure as that worker, but the worker remains in a work station where air levels are as indicated for the indicated durations.

The hypothetical worker wears no gloves, and is exposed via the palms at the level recorded on the palm of the worker who was monitored. He or she is exposed through the rest of the hand, forearms, face and neck at the level recorded on the back of the hand of the worker who was monitored.

* Use of granular material had recently been instituted in hope of diminishing the amount of dust formation and distribution that apparently had been experienced with the previously used flake form of 99% assay 4,4'-MDA.

LADDs are calculated for situations in which the hypothetical worker washes thoroughly all exposed skin 0.25, 2, 4 or 6 hours after being exposed, completely removing all deposted 4,4'-MDA. These situations were analyzed in order to assess the impact of washing after a limited-duration dermal exposure.

iii. Case 3: 4,4'-MDA Using/Processing

In this case the impact of shift-long exposure without the protection of gloves is assessed.

Inhalational exposures are assumed to be at the level reported by Ameron (1983), and to be for 8 hours per day. Assumptions regarding worker weight, breathing rate, etc., used in calculating doses are the same as in Case 1 and are given in Appendix B.

Dermal exposure is assumed to occur at the rate experienced by the worker who was monitored in NIOSH (1984b), namely 43 ug/cm^2/10 minutes (250 ug/cm^2/hr) for the palms and 4.6 ug/cm^2/10 minutes (27 ug/cm^2/hr) for the rest of the hands, forearm, face and neck. Exposure is assumed to occur for four hours on these body areas twice during the shift, with a mid-shift wash-up for lunch, but presumably the face and neck are not cleansed until an after-work shower, when all deposited 4,4'-MDA is removed. Deposition is assumed not to continue during the mid-shift break, though absorption of already deposited material does continue during this time.

iv. Case 4: 4,4'-MDA Using/Processing

In this case, the impact of wearing protective gloves is assessed.

Inhalation exposures and workplace routines considered here are identical to those described in Case 3, above.

The dermal exposure, however, is continuous for 0.25, 2, 4 or 6 hours per day, and 4,4'-MDA is deposited on the skin at a linear rate derived from data in NIOSH (1984a) for the 4,4'-MDA flakker-bagger. This worker wore mid-forearm length latex gloves, inside of which was mounted a hand-pad device as described above.

v. Case 5: 4,4'-MDA Using/Processing

In this case the inhalational exposures and work routines considered are the same as in Cases 3 and 4 above.

The impact of wearing protective gloves during a single 0.5 hour per day dermal exposure, followed by immediate, thorough washing to remove deposited 4,4'-MDA from hands and forearms is assessed. 4,4'-MDA deposited on the rest of the upper body is assumed to remain there until a shower at shift's end (6 hours exposure).

vi. Case 6: 4,4'-MDA Using/Processing

This case assesses the impact of the level of worker protection used by DOE contractors (DOE, 1983c) who use 4,4'-MDA to fabricate nuclear weapons.

vii. Case 7: 4,4'-MDA Using/Processing

The impact of very protective industrial hygiene practices is assessed in this case.

Inhalational exposures and work routines are similar to those described in Cases 3, 4 and 5, except that exposure is for either 4 or 8 hours per day, which relatively long exposures

prompt the use of very protective industrial hygiene practices. Also, another inhalational exposure level is used in addition to the one reported by Ameron (1983). The additional level is the one reported for a resin mixing operation at a filament winding factory (CMA, 1983a). Thus, this case is divided into two sections, reflecting the two different inhalational exposure levels.

The industrial hygiene practices assumed in this case include wearing gloves, as described above, during two 0.5 hour exposure periods per shift*, during which dermal exposure could occur, followed by immediate and thorough washing to remove deposited material from hands and forearms. Use of a full face shield and impervious outer garments during periods when dermal depositon could occur is also assumed, thus restricting dermal deposition of 4,4'-MDA to that which the worker in NIOSH (1984a) experienced under the gloves.

viii. Case 8: MDA Using/Processing --- Hypothetical Workplace Standard

This case presents a hypothetical situation in which a workplace standard is in effect that mandates a 0.001 ppm (0.0081 mg/m^3) 8-hr TWA airborne exposure level and use of protective clothing described in Case 7 above. The worker is assumed to handle 4,4'-MDA for one hour, to wash the exposed areas of the hands following exposure to completely remove deposited amine, to handle 4,4'-MDA for and additional hour in the second half of the shift, and then to wash up, removing any deposited amine.

* The 0.5 hour exposures occur at the beginning of each half-shift.

b. Drinking Water Case

In this case it is assumed that an individual consumes 2 liters of water daily over a 70-year lifespan, and that the person weighs 70 kg during the lifespan and that 50% of the ingested dose is absorbed.

5. Estimation of Risks for Exposed Populations

a. Workers

Table 19 summarizes the lifetime extra cancer risks for workers in 4,4'-MDA/MDI manufacturing plants and in 4,4'-MDA using and processing plants under conditions outlined above and detailed in Appendix B. These estimates are based on data from the bioassay (NTP, 1983a) results with female rats that developed thyroid follicular cell carcinomas and adenomas, female mice, pooling all statistically significant tumors, and female mice, pooling all tumors in which malignancies alone were statistically significant, using the one-stage extrapolation model. Tumors were observed in both sexes of mice and rats at multiple sites. Risk estimations based on data for other tumor types and other tumor poolings are given in Appendix C, Table 19A.

b. People Drinking Contaminated Water

Confidence in the risk estimations for the drinking water case is low because of the lack of data at this time on actual releases of 4,4'-MDA into waters that could serve as drinking water supplies and the parallel lack of information on the fate of any such releases.

The LADDs shown in Table 20 were derived using the assumptions stated above and the Best Estimate water

concentrations for the locales A through D in Table 11. Absorption of 50% of the ingested dose is assumed (Thies, 1983).

Risk estimates in Table 20 were based on the same species/sex tumor data cited in the previous subsection for worker risks, and additional estimates based on other tumor types and other tumor poolings are given in Appendix C, Table 20A.

C. Risk Characterization

Since we do not have sufficient quantitative data detailing the carcinogenic effects of 4,4'-MDA in humans, this risk assessment relies on the available data showing animal carcinogenicity as the source of estimates of human risk from exposure to the substance. Moreover, when, as here, animal effects data are available only for exposures at a higher level than the level of estimated human exposure, we rely on statistical models to extrapolate the risk to animals from high to low exposure, then derive human risk estimates from the low exposure animal risk estimates. The confidence we have in the estimates of human risk derived in this way is dependant on, among other things, our degree of confidence that the animal data demonstrate a carcinogenic response, and that the character of the human response will be comparable to the animal response. Confidence also depends on how accurately we can quantitatively estimate and compare the doses of the chemical received by the animals with those received by humans, and on how well the statistical model portrays the relationship between dose and response. These matters are discussed in depth separately in this risk assessment. The purpose of this section is to give a

more brief, overall perspective on the results, highlighting some of the more important observations.

There is evidence demonstrating 4,4-MDA's carcinogenicity in animals. This evidence is chiefly found in the NTP bioassays on rats and mice. These studies were well designed and well conducted, and they showed strong dose-response in both sexes of both species. In addition to tumors of the liver and thyroid, which were seen in both species, lymphomas, adrenal, and lung tumors were observed at statistically significantly elevated incidences in the mice. Tumors of the urinary bladder occurred in rats.

Close structural analogues of 4,4-MDA have also been found to be carcinogenic in the liver and/or thyroid of these two rodent species.

A number of studies in addition to the NTP bioassays showed carcinogenic activity in animals, and several others failed to show such activity. All of these studies, however, were flawed in terms of duration, number of animals exposed, pathology reporting or overall design.

Several additional lines of evidence are consistent with a conclusion that 4,4'-MDA will also be carcinogenic in humans.

The chemical is genotoxic, and it binds to DNA in vivo. Thus, carcinogenic activity may occur, at least in part, by a direct genotoxic mechanism involving attack on DNA. If this is the mechanism, it should operate in humans as well as animals.

Additionally, the chemical is a close structural analogue of chemicals that are carcinogenic in both animals and humans.

Moveover, while the one available epidemiology study is limited by the presence of confounding exposure to epoxy compounds, the fact that an elevated incidence of bladder tumors was observed--a tumor type produced in humans by benzidine, a close structural analogue of 4,4'-MDA--may be significant, especially in light of the occurrence of urinary bladder tumors in rats in the NTP bioassay. Furthermore, 4,4'-MDA is absorbed by humans.

All of these factors, combined with sufficient evidence of carcinogenicity in animals give a high degree of confidence that the character of the response in humans will be comparable to that in animals. An EPA classification of this chemical as a probable carcinogen in humans [B2] has therefore been assigned.

The chief sources of uncertainty in this assessment relate to the different exposure routes that humans and the test animals of the bioassays experience, and to the inherent uncertainties in extrapolating human risks resulting from low level exposure based on experiments with animals who experienced relatively high exposures.

In the workplace, humans are exposed to 4,4'-MDA intermittently, chiefly via dermal and inhalational routes, while the test animals were exposed to the dihydrochloride continuously via drinking water. As discussed earlier, in performing the risk assessment, the assumption has been made that the dihydrochloride dissociated to the free amine in the intestine. The differences between the animals and human routes of exposure, and our lack of certainty in estimating the absorption rate, and thus exact dose received, affect the quantitative estimation of human risk.

These uncertainties are explained throughout this assessment and are highlighted below.

Confidence is high that humans absorb the chemical. Evidence from several industrial hygiene reports shows that dermal exposure to humans results in absorption of significant amounts of 4,4'-MDA. The structure of the chemical indicates that inhalational exposure will also result in absorption, and gastro-intestinal absorption also occurs, as evidence by the "Epping Jaundice" case described earlier.

The state-of-the-art of quantitatively assessing dermal exposures under industrial chemical processing conditions is relatively primitive, but is rapidly developing. Thus, while it is clear that 4,4'-MDA is absorbed through human skin, and that this phenomenon occurs in the chemical processing workplace, the rate of deposition of 4,4'-MDA on the skin and the rate of absorption of deposited material are not precisely known. The estimates of each of these rates used in this assessment are reasonable, based on existing experimental data. These estimates will be refined using data from studies now ongoing to measure the in vivo absorption rate of 4,4'-MDA through the skin of animals, including rhesus monkeys.

There is some question regarding the coupled use of the estimated deposition and absorption rates in an integral form to assess dermal exposure in this assessment. It is the author's view that such coupling is defensible, in that it uses all the available experimental data, and the uncertainties are duly noted. It should be noted that an alternate approach that has

been used by EPA in the past, namely assuming 100% absorption, would yield much higher risk estimates.

There are also uncertainties related to high-to-low-dose extrapolation modeling and animal-to-human extrapolations. In this case the quantitative risk estimates were made using only tumor incidence that showed monotonic dose-response behavior using the one-stage version of the linearized multi-stage model. The fact that the maximum likelihood estimates of risk differ from the upper 95% confidence limits generally by less than a factor of 2 indicates a good fit of these experimental dose-response data to the model used, and the linear shape of the dose-response curve at the low doses expected from human exposures is consistent with the apparent genotoxic mechanism of 4,4'-MDA carcinogenic action.

The reader is cautioned against an assumption that the quantitative risk estimates made in this assessment represent the true, known risk to humans. The risk estimates given here are an upper bound estimate, not a declaration of actual risk levels.

TABLE 19
ESTIMATED EXTRA LIFETIME RISK OF CANCER FOR WORKERS
(EPA, 1984)

Exposure Setting	Total LADD (mg/kg/day)	ADDED RISK BASED ON FRFC/A[a] MLE[d]	FRFC/A[a] U95CL[e]	FMPA[b] MLE	FMPA[b] U95CL	FMPM[c] MLE	FMPM[c] U95CL
4,4'-MDA/MDI Mfg.							
Appendix B, Sec. 1							
8 hr/wk	0.0051	2×10^{-3}	3×10^{-3}	5×10^{-3}	7×10^{-3}	4×10^{-3}	6×10^{-3}
20 hr/wk	0.020	7×10^{-3}	1×10^{-2}	2×10^{-2}	2×10^{-2}	2×10^{-2}	2×10^{-2}
40 hr/wk	0.040	1×10^{-2}	2×10^{-2}	4×10^{-2}	5×10^{-2}	3×10^{-2}	4×10^{-2}
4,4'-MDA Use/Proc.							
Appendix B, Sec. 2							
2.5 hr/wk	0.0011	4×10^{-4}	5×10^{-4}	1×10^{-3}	1×10^{-3}	9×10^{-4}	1×10^{-3}
8 hr/wk	0.0053	2×10^{-3}	3×10^{-3}	5×10^{-3}	7×10^{-3}	4×10^{-3}	6×10^{-3}
20 hr/wk	0.012	4×10^{-3}	6×10^{-3}	1×10^{-2}	1×10^{-2}	1×10^{-2}	1×10^{-2}
40 hr/wk	0.020	7×10^{-3}	1×10^{-2}	2×10^{-2}	2×10^{-2}	2×10^{-2}	2×10^{-2}
4,4'-MDA Use/Proc.							
Appendix B, Sec. 3	0.17	6×10^{-2}	8×10^{-2}	1×10^{-1}	2×10^{-1}	1×10^{-1}	2×10^{-1}
Appendix B, Sec. 4							
2.5 hr/wk	0.00068	2×10^{-4}	3×10^{-4}	6×10^{-4}	8×10^{-4}	6×10^{-4}	7×10^{-4}
8 hr/wk	0.0031	1×10^{-3}	1×10^{-3}	3×10^{-3}	4×10^{-3}	3×10^{-3}	3×10^{-3}
20 hr/wk	0.0094	3×10^{-3}	4×10^{-3}	7×10^{-3}	9×10^{-3}	6×10^{-3}	8×10^{-3}
40 hr/wk	0.020	7×10^{-3}	1×10^{-2}	2×10^{-2}	2×10^{-2}	2×10^{-2}	2×10^{-2}
Appendix B, Sec. 5	0.0018	6×10^{-4}	9×10^{-4}	2×10^{-3}	2×10^{-3}	2×10^{-3}	2×10^{-3}
Appendix B, Sec. 6							
8 hr/wk	0.000013	5×10^{-6}	6×10^{-6}	1×10^{-5}	2×10^{-5}	1×10^{-5}	1×10^{-5}

TABLE 19
CONTINUED

Exposure Setting	Total LADD (mg/kg/day)	ADDED RISK BASED ON FRFC/A[a] MLE[d]	FRFC/A[a] U95CL[e]	FMPA[b] MLE	FMPA[b] U95CL	FMPM[c] MLE	FMPM[c] U95CL
Appendix B, Sec. 7A							
20 hr/wk	0.0052	2×10^{-3}	3×10^{-3}	5×10^{-3}	6×10^{-3}	4×10^{-3}	6×10^{-3}
40 hr/wk	0.010	4×10^{-3}	5×10^{-3}	9×10^{-3}	1×10^{-2}	8×10^{-3}	1×10^{-2}
Appendix B, Sec. 7B							
20 hr/wk	0.0013	5×10^{-4}	6×10^{-4}	1×10^{-3}	2×10^{-3}	1×10^{-3}	1×10^{-3}
40 hr/wk	0.0026	9×10^{-4}	1×10^{-3}	2×10^{-3}	3×10^{-3}	2×10^{-3}	3×10^{-3}
Appendix B, Sec. 8							
40 hr/wk	0.00033	1×10^{-4}	2×10^{-4}	3×10^{-4}	4×10^{-4}	3×10^{-4}	4×10^{-4}

(a) Female rat, thyroid follicular cell carcinoma and adenoma. See Appendix C for additional risk data.
(b) Female mouse, pooled, all significant tumors.
(c) Female mouse, pooled, all tumors in which malignancies alone are significant.
(d) MLE = maximum likelihood estimate of risk, multi-stage model.
(e) U95CL = upper 95% confidence limit on estimate of risk, multi-stage model.

TABLE 20

ESTIMATED EXTRA LIFETIME RISK OF CANCER FROM DRINKING WATER EXPOSURES

Locale	4,4'-MDA conc. (mg/l)	LADD (mg/kg/day)	ADDED RISK BASED ON FRFC/A[a] MLE[d]	FRFC/A[a] U95CL[e]	FMPA[b] MLE	FMPA[b] U95CL	FMPM[c] MLE	FMPM[c] U95CL
A	0.00018	0.0000026	9×10^{-7}	1×10^{-6}	2×10^{-6}	3×10^{-6}	2×10^{-6}	3×10^{-6}
B	0.00015	0.0000021	7×10^{-7}	1×10^{-6}	2×10^{-6}	3×10^{-6}	2×10^{-6}	2×10^{-6}
C	0.00015	0.0000021	7×10^{-7}	1×10^{-6}	2×10^{-6}	3×10^{-6}	2×10^{-6}	2×10^{-6}
B + C	0.00030	0.0000042	1×10^{-6}	2×10^{-6}	4×10^{-6}	5×10^{-6}	3×10^{-6}	5×10^{-6}
D	0.0012	0.000017	6×10^{-6}	8×10^{-6}	2×10^{-5}	2×10^{-5}	1×10^{-5}	2×10^{-5}

(a) Female rat, thyroid follicular cell carcinomas and adenomas. See Appendix C for additional risk data.
(b) Female mouse, pooled, all significant tumors.
(c) Female mouse, pooled, all tumors in which malignancies alone are significant.
(d) Maximum likelihood estimate of risk, multi-stage model.
(e) Upper 95% confidence limit of risk, multi-stage model.

VI. DISCUSSION

While this assessment focusses on quantitatively estimating cancer risks, it should be noted that other health effects have been linked with 4,4'-methylenedianiline (4,4'-MDA). The last Federal health authority action on 4,4'-MDA, the 1976 Current Intelligence Bulletin issued by NIOSH, (1976a), addressed the chemical's acute toxicity to the liver. Retinopathy has also been cited as a toxic effect (Schilling Von Canstatt et al., 1966; NIOSH, 1981; Leong et al., 1984), as has acute myocardiopathy (Brooks et al., 1979) and allergic dermatitis (Emmett, 1976). Retinopathy has been observed in two animal species, the cat and the guinea pig, and may have occurred in humans, while liver toxicity and myocardiopathy have been observed in humans.

These adverse health effects, coupled with the results of the NTP bioassays on the chemical, evidence from mutagenicity studies, evidence of the carcinogenicity of close structural analogues in animals and humans, epidemiologic evidence and evidence of present inhalational and dermal exposures to the chemical in workplaces that lead to estimated extra lifetime risks as high as from about one in one hundred to about one in ten (B2) in certain situations, combine to make 4,4'-MDA a prime candidate for exposure controls and hazard warnings to those exposed.

Of special concern is the dermal route of exposure. This route is insidious. Many workers and managers appear to be unaware of its significance. For instance, in Vaudaine et al.

(1982) it is reported that knowledge of the hazards of 4,4'-MDA prompted the use of "divers' suits," an extreme measure, to protect against exposure. Yet 15% of urine samples taken during that time contained measurable levels of 4,4'-MDA which subsequent events have shown to have resulted from unsuspected dermal exposure.

Likewise in Dunn and Guirguis (1979), even after workers had been supplied with positive-pressure, supplied air breathing apparatus to protect against inhalational exposure, cases of jaundice were still observed among workers who were being exposed dermally.

The liver toxicity reported in McGill and Motto (1974) occurred only in workers who were dermally exposed, while co-workers in the same work station who breathed the same air as affected workers, but who did not touch the 4,4'-MDA-containing resin system, were not affected.

While no cases of acute toxicity were reported, the exposure of the resin mixer reported in NIOSH (1984b) is a concern in the same regard. Apparently, attempting to lower the potential for exposure, the company involved had recently switched from the flake form of the chemical to the granular form. Even with the material of "lower dusting potential," (NIOSH, 1984b) the worker involved received a substantial exposure. This might have resulted, at least in part, because the worker assumed that "dusting" had been eliminated, or at least reduced to a sufficient degree to dispense with the use of protective clothing. How many other examples of such inadvertant exposure may there be in such workplaces?

Clearly, as shown in Vaudaine et al. (1982), once workers and managers are made aware of the dermal exposure route and the hazards it can pose, exposures can be reduced. Such an educational program for those who manufacture, use or process 4,4'-MDA in the United States is clearly indicated by the evidence of exposure and the carcinogenicity of the chemical.

While the dermal exposure route is particularly worrisome, inhalational exposures are also of concern. The LADD calculations in Appendix B, Cases 4 and 7 and the corresponding risk estimations in Table 19 illustrate this. When dermal exposures are sharply limited, inhalational exposures at levels that have been reported by industry sources still result in significant risks. It is obvious that attention to both routes of exposure is called for in order to bring risks down. It is also obvious from reports of airborne levels of 4,4'-MDA submitted by CMA (1983a) that control of airborne levels is feasible. Thus, control of airborne levels by use of engineering methods and control of dermal exposures by use of protective clothing and good industrial hygiene practices is feasible, and these controls result in risk estimations in the range of about one in ten thousand extra lifetime risk of cancer (Cases 7 and 8).

Aside from the overriding issue of acting expeditiously to protect workers' health, there are scientific questions the answers to which could help to reduce the uncertainties in our understanding of the risks associated with 4,4'-MDA.

A metabolism study in Fischer 344 rats coupled with worker urine monitoring would help to relate the external dose that rats received in the NTP bioassay to the internal dose that resulted in the observed tumor incidence in the animals and to the internal dose that exposed workers are receiving.

Follow-up of workers who were exposed and who were studied by Vaudaine et al. (1982), Dunn and Guirguis (1979) and McGill and Motto (1974) could prove useful. Some of these exposures occurred as long ago as 17 years and may have lasted for as long as 9 years.

The skin penetration rate of 4,4'-MDA will be a valuable tool in reducing uncertainty in this case, as will data on effluent levels of 4,4'-MDA and on the fate of the chemical in natural surface waters.

Development and use of an analytical method for measuring airborne levels of 4,4'-MDA that does not suffer from interference from aniline will be of value in reducing uncertainty about exposures in the 4,4'-MDA manufacturing workplace. Likewise, a kinetic study on the rate of deposition of 4,4'-MDA on various parts of the body would be useful in this regard. Such studies should not, however, impede exposure control and hazard warning programs for this probable human carcinogen.

APPENDIX A

ANALYTICAL METHODS

A key issue in assessing workplace exposures to and associated risks from 4,4'-MDA is the analytical methodology used for measuring airborne concentrations of the chemical. A related issue is the determination of 4,4'-MDA levels in workers' urine as a possible assessment tool for relating workplace exposures with actual received doses. The latter issue is under study by NIOSH, which is developing a protocol for measuring 4,4'-MDA in urine. Dr. Mark Boeniger, of the Cincinnati office of NIOSH, is the leader on this project.

Regarding analytical techniques for measuring airborne levels of 4,4'-MDA, a summary of methods used in the past and those undergoing development will be given here.

1. Marcali Method

This method, of which there are several permutations, involves drawing air through a liquid collecting medium of acetic and hydrochloric acids. The resulting amine salt is then converted to the diazonium compound and thence to an azo dye by coupling with 1-N-naphthylethylenediamine. The concentration of the azo compound is then colorimetrically determined.

The major limitation of this method is its inability to discriminate among 4,4'-MDA, MDI (which is hydrolyzed to the amine in the collection medium), aniline (which is often present at 4,4'-MDA manufacturing plants) or other aromatic amines. This

limitation results in reports of 4,4'-MDA levels which may be erroneously high when interfering compounds are present (CMA, 1983a).

2. Liquid Chromatographic Methods

The most promising methods for measuring 4,4'-MDA levels in air in the presence of MDI, aniline, and other aromatic amines involve high-pressure liquid chromatographic (HPLC) separation of analyte desorbed from a variety of collection media and converted to elutable derivatives.

a. Acid-Treated Glass Fiber Filter Method

This technique, used by DOE contractors (DOE, 1983c), involves uniformly coating a 37 mm glass fiber filter with dilute sulfuric acid, followed by driving off the water in an oven. Air containing 4,4'-MDA is drawn through the filter, which captures the amine and stabilizes it toward re-volatilization and against oxidative loss by converting the amine to the hydrogen sulfate salt. The analyte is then desorbed using 0.26N NaOH that is 5% (v/v)acetonitrile and converted to the diacetyl derivative with acetic anhydride. The resulting solution is then analyzed on a high pressure liquid chromatograph using a solvent gradient (water/ acetonitrile) and a UV detector.

DOE reports (DOE, 1983c) that the method is still under study, but filter collection efficiency and recovery of 4,4'-MDA from spiked samples are greater than 90%.

EPA and NIOSH are working to further validate this general method.

b. Glass-Fiber Filter/Silica Gel Method

NIOSH (1984a, b) conducted the referenced surveys using an untreated glass-fiber filter in series with a silica gel tube for the area monitoring portion of the work. The filter was designed to trap particulate matter and the silica to collect vapor-phase material. However, it has been discovered that severe loss of 4,4'-MDA particles from non-acid-treated filters occurs, rendering the results of those studies suspect insofar as the reported results of area monitoring are probably lower than actual levels. Duplicate area and personnel samples were analyzed by NIOSH and the company using this method (and the Marcali method for area samples). Agreement among the samples was not good, and air monitoring data from these NIOSH visits were not used in this assessment.

c. Silica Gel Collection Method

This method (several permutations) involves collection of 4,4'-MDA from the vapor phase on treated or untreated silica gel. Silica treated with diethylamine has been used to sample atmospheres containing 4,4'-MDA, MDI, and dimethyl formamide. The diethylamine converts MDI to a stable urea, rendering chromatographically separable the MDI and 4,4'-MDA components (Lipski, 1982).

Desorption has been accomplished with methanol or diethyl ether, and the 4,4'-MDA has been analyzed using HPLC, with UV detection, either *per se* or as a benzoyl derivative (CMA, 1983a).

There is concern that use of a standard, untreated silica gel collection system might not efficiently remove particles of 4,4'-MDA.

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The assumption has been made in this assessment that results obtained with the Marcali method can give an upper bound on actual exposure levels (and is probably quite reliable in the absence of interferences), while results obtained with the untreated glass fiber filter/HPLC method would give a lower bound on actual exposure levels.

APPENDIX B

LIFETIME AVERAGE DAILY DOSE (LADD) CALCULATIONS

1. 4,4'-MDA/MDI Manufacturing Workplace

Inhalational Component

Assumptions:

- o 1.2 m^3/hr breathing rate
- o 250 day/year exposure
- o 50% absorption of airborne 4,4'-MDA through the lung
- o 40 year working career
- o 70 year lifetime
- o 70 kg worker weight
- o exposure levels for different exposure durations are highest values from average TWA columns in Table 5.

8 hrs/week = 1.6 hrs/day

AVE. TWA = 0.07 ppm = 0.57 mg/m^3

$$0.57\ mg/m^3 \times 1.2\ m^3/hr \times 1.6\ hr/day \times \frac{250}{365} \times \frac{40}{70} \times 0.5 \div 70\ kg =$$

LADD = 0.0031 mg/kg/day

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20 hrs/week = 4 hrs/day

AVE. TWA = 0.059 ppm = 0.48 mg/m^3

$$0.48\ mg/m^3 \times 1.2\ m^3/hr \times 4\ hr/day \times \frac{250}{365} \times \frac{40}{70} \times 0.5 \div 70\ kg =$$

LADD = 0.0064

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40 hrs/week = 8 hrs/day

AVE. TWA = 0.07 ppm = 0.57 mg/m^3

$$0.57\ mg/m^3 \times 1.2\ m^3/hr \times 8\ hr/day \times \frac{250}{365} \times \frac{40}{70} \times 0.5 \div 70\ kg =$$

LADD = 0.015 mg/kg/day

Dermal Component

Assumptions:

- Deposition rate of 4,4'-MDA is uniform over time.
- Absorption through all skin areas is at a uniform rate of 1%/hr of deposited material.
- Body surface areas (male and female averages, Snyder et al., 1975).

  Face = 650 cm^2

  Back of neck = 110 cm^2

  Front of neck and V of chest = 150 cm^2

  Chest and stomach = 3550 cm^2

  Back = 3500 cm^2

  Upper arms = 1320 cm^2

  Forearms = 1210 cm^2

  Hands = 820 cm^2

- Exposure of the back of the hand under a cotton glove mimics exposure to the entire upper body (face, neck, arms, back of hands, chest, stomach and back), which area totals 10,900 cm^2. Area of two palms is 410 cm^2.
- Worker showers at the end of the shift, completely removing all 4,4'-MDA remaining on skin.
- Deposition occurs on both palms at a rate of 9 ug cm^{-2} hr^{-1} and on the rest of the upper body at 2.5 ug cm^{-2} hr^{-1} (NIOSH, 1984a, Table IV). There is zero deposition on other body surfaces.
- For 40 hr/wk workers, two 3.5 hour half shifts under the above conditions is assumed, along with a 1 hour lunch period during which no deposition occurs. It is assumed that the hands and forearms are washed free of 4,4'-MDA at lunch, and that absorption of material already deposited on the rest of the upper body continues during lunch.

Dose through the Palms (40 hr/wk)

Daily Dose =

$$2 \times 0.01\ hr^{-1} \times 9\ ug\ cm^{-2}\ hr^{-1} \times 410\ cm^2 \int_0^{3.5} t\,dt$$

$$= 74 \times \tfrac{1}{2} \times t^2 \Big]_0^{3.5} = 450\ ug$$

Dose through back of hand and forearms (40 hr/wk)

Daily Dose =

$$2 \times .01\ hr^{-1} \times 2.5\ ug\ cm^{-2}\ hr^{-1} \times 2830\ cm^2 \int_0^{3.5} tdt$$
$$= 140 \times \tfrac{1}{2} \times t^2 \Big]_0^{3.5} = 860\ ug$$

Dose through rest of upper body (40 hr/wk)

Daily Dose =

$$2 \times .01\ hr^{-1} \times 2.5\ ug\ cm^{-2}\ hr^{-1} \times 9280\ cm^2 \int_0^{3.5} tdt$$
$$+ 0.01\ hr^{-1} \times 2.5\ ug\ cm^{-2}\ hr^{-1} \times 3.5\ hr \times 1\ hr \times 9280\ cm^2 =$$
$$460 \times \tfrac{1}{2} \times t^2 \Big]_0^{3.5} + 810 = 3600\ ug$$

Dose through the palms (8 hr/wk and 20 hr/wk)

Daily Dose =

$$0.01\ hr^{-1} \times 9\ ug\ cm^{-2}\ hr^{-1} \times 410\ cm^2 \int_0^{x} tdt \quad \text{where } X = \begin{matrix} 4.0 \\ 1.6 \end{matrix}$$

$$10 \times \tfrac{1}{2} \times t^2 \Big]_0^{4} = 80\ ug$$

$$10 \times \tfrac{1}{2} \times t^2 \Big]_0^{1.6} = 13\ ug$$

Dose through rest of upper body (8 hr/wk and 20 hr/wk

Daily Dose =

$$0.01\ hr^{-1} \times 2.5\ ug\ cm^{-2}\ hr^{-1} \times 10{,}900\ cm^2 \int_0^{x} tdt \text{ where } x = \begin{matrix} 4.0 \\ 1.6 \end{matrix}$$

$$270 \times \tfrac{1}{2} \times t^2 \Big]_0^{4} = 2200\ ug$$

$$270 \times \tfrac{1}{2} \times t^2 \Big]_0^{1.6} = 350\ ug$$

Total daily dermal doses at:

40 hrs/wk = 4900 ug = 4.9 mg
20 hrs/wk = 2300 ug = 2.3 mg
8 hrs/wk = 360 ug = 0.36 mg

$$\text{LADD} = \text{daily dose} \times \frac{250}{365} \times \frac{40}{70} \div 70\ kg$$

Dermal LADDs for:

40 hrs/wk = 0.027 mg/kg/day
20 hrs/wk = 0.014 mg/kg/day
8 hrs/wk = 0.0020 mg/kg/day

Total LADDs for Durations of

	8 hr/wk	20 hr/wk	40 hr/wk
		in mg/kg/day	
Dermal	0.0020	0.014	0.027
Inhalational	0.0031	0.0064	0.015
TOTAL	0.0051	0.020	0.042

2. **4,4'-MDA Using/Processing Workplace with Minimal Dermal Exposure Duration and Delayed Wash-up Following Exposure**

Inhalational Component

Assumptions:

- Same as above inhalational assumptions, and
- Respirable 4,4'-MDA concentration in air is 0.38 mg/m^3 (Ameron, 1983; mean of range limits, Page 4, Section 5.3).
- Worker spends 0.5, 1.6, 4 or 8 hrs/day in a work station with the above 4,4'-MDA air concentration.

2.5 hrs/wk = 0.5 hr/day

$$0.38\ mg/m^3 \times 1.2\ m^3/hr. \times 0.5\ hr/day \times 0.5 \times \frac{250}{365} \times \frac{40}{70} \div 70\ kg =$$

LADD = 0.00066 mg/kg/day

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8 hrs/wk = 1.6 hrs/day

$$0.38\ mg/m^3 \times 1.2\ m^3/hr \times 1.6\ hr/day \times 0.5 \times \frac{250}{365} \times \frac{40}{70} \div 70\ kg =$$

LADD = 0.0021 mg/kg/day

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20 hrs/wk = 4 hrs/day

LADD = 0.0052 mg/kg/day

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40 hrs/wk = 8 hrs/day

LADD = 0.0104 mg/kg/day

Dermal Component

Assumptions:

- Same as above dermal assumptions, and

- Physical form of 4,4'-MDA used is capable of producing the same "dusting" experienced by the worker in NIOSH (1984b).
- Worker wears no gloves or other protective gear,
- Worker actually handles 4,4'-MDA only long enough (about 10 minutes) to receive the dermal exposure cited in NIOSH (1984b), Table IV, and no longer, though he/she may remain in the same general work area longer.
- Worker thoroughly washes forearms, face, and neck 0.25, 2, 4, or 6 hours after handling 4,4'-MDA.
- Worker is exposed through the palms (410 cm^2) at 43 ug cm^{-2} and through the rest of the hands, forearm, face and neck-V (2400 cm^2) at 4.6 ug cm^{-2} (NIOSH, 1984b, Table IV).

Dose through palms

Daily dose =

For 0.25 hr exposure:

$.01\ hr^{-1} \times 43\ ug\ cm^{-2} \times 0.25\ hr \times 410\ cm^2 = 44\ ug$

For 2 hr exposure:

$.01\ hr^{-1} \times 43\ ug\ cm^{-2} \times 2\ hr \times 410\ cm^2 = 360\ ug$

For 4 hr exposure:

$.01\ hr^{-1} \times 43\ ug\ cm^{-2} \times 4\ hr \times 410\ cm^2 = 720\ ug$

For 6 hr exposure:

$.01\ hr^{-1} \times 43\ ug\ cm^{-2} \times 6\ hr \times 410\ cm^2 = 1100\ ug$

Dose through rest of hands, forearms, face, and neck-V

Daily dose =

$.01\ hr^{-1} \times 4.6\ ug\ cm^{-2} \times 0.25\ hr \times 2400\ cm^2 = 28\ ug$

For 2 hr exposure:

$.01\ hr^{-1} \times 4.6\ ug\ cm^{-2} \times 2\ hr \times 2400\ cm^2 = 220\ ug$

For 4 hr exposure:

$.01\ hr^{-1} \times 4.6\ ug\ cm^{-2} \times 4\ hr \times 2400\ cm^2 = 440\ ug$

For 6 hr exposure:

$$.01\ hr^{-1} \times 4.6\ ug\ cm^{-2} \times 6\ hr \times 2400\ cm^2 = 660\ ug$$

Total daily dose @: 0.25 hrs/day = 72 ug = 0.072 mg
2 hrs/day = 580 ug = 0.58 mg
4 hrs/day = 1200 ug = 1.2 mg
6 hrs/day = 1800 ug = 1.8 mg

$$LADD = \text{daily dose} \times \frac{250}{365} \times \frac{40}{70} \div 70\ kg$$

LADDs @: 0.25 hrs/day = 0.00040 mg/kg/day
2 hrs/day = 0.0032 mg/kg/day
4 hrs/day = 0.0067 mg/kg/day
6 hrs/day = 0.010 mg/kg/day

Total LADDs for Duration of

	2.5 hr/wk	8 hr/wk	20 hr/wk	40 hr/wk
	in mg/kg/day			
Dermal	0.00040	0.0032	0.0067	0.010
Inhal.	0.00066	0.0021	0.0052	0.010
Total	0.0011	0.0053	0.012	0.020

3. **4,4'-MDA Using/Processing Workplace Without Use of Gloves. Exposure Duration for Entire 8-Hour Shift**

Inhalational Component

The same inhalational component of exposure for the 40-hours per week situation as given in Case 2, above, is assumed, namely: LADD = 0.010 mg/kg/day.

Dermal Component

- Same general assumptions as in Case 2, except that the worker is exposed to 4,4'-MDA deposition for the entire shift (two 4-hour periods, broken by the mid-shift 0.5 hr break) at the rate given in NIOSH, 1984b, Table IV.C, namely 43 ug cm^{-2}/10 minutes (250 ug cm^{-2} hr^{-1}), palms (410 cm^2); and 4.6 ug cm^{-2}/10 minutes (27 ug cm^{-2} hr^{-1}), rest of hands, forearms, face and entire neck (2500 cm^2).

- Worker washes off all deposited 4,4'-MDA from hands and forearms at mid-shift break, leaving face and neck (910 cm^2) un-washed, and removes all 4,4'-MDA with a shift-end shower.

- Deposition does not continue during 0.5 hr mid-shift break, though absorption of already deposited material continues through this period.

Dose through palms

$2 \times .01\ hr^{-1} \times 250\ ug\ cm^{-2}\ hr^{-1} \times 410\ cm^2 \int_0^4 tdt$

$2100 \times \frac{1}{2} \times t^2 \Big]_0^4 = 17{,}000\ ug$

Dose through rest of exposed skin

$2 \times .01\ hr^{-1} \times 27\ ug\ cm^{-2}\ hr^{-1} \times 2500\ cm^2 \int_0^4 tdt$

$+ .01\ hr^{-1} \times 0.5\ hr \times 4\ hr \times 27\ ug\ cm^{-2}\ hr^{-1} \times 910\ cm^2$

$= 1400 \times \frac{1}{2} \times t^2 \Big]_0^4 + 490\ ug$

$= 11{,}000 + 490\ ug = 11{,}000\ ug$

Total daily dermal dose = 28,000 ug = 28 mg

$LADD = \text{daily dose} \times \frac{250}{365} \times \frac{40}{70} \div 70\ kg$

Dermal LADD = 0.16 mg/kg/day

Inhalational LADD = 0.010 mg/kg day

Total LADD = 0.17 mg/kg/day

4. 4,4'-MDA Using/Processing Workplace with Better than Minimal Industrial Hygiene and Variable Durations of Exposure

Inhalational Component

The same inhalational component of exposure, for the same time periods, is assumed for this workplace setting as in Case 2, above.

Dermal Component

Assumptions:

- Same general assumptions as in Case 2, above.
- Worker wears fresh mid-forearm-length neoprene/latex gloves while handling 4,4'-MDA.
- No further dermal exposure occurs after handling 4,4'-MDA and removing gloves.

- Worker handles 4,4'-MDA for 0.25, 2, 4 or 6 hr/day, using both hands freely so that there is no difference between right- and left-hand exposure.
- Deposition of 4,4'-MDA occurs linearly with time, as in NIOSH, 1984a (Table IV, Samples DM2A, DMB), at 4.2 ug cm^{-2} hr^{-1} on the palms (410 cm^2) and 0.7 ug cm^{-2} hr^{-1} on the rest of the upper body (10,900 cm^2). No other dermal exposure.
- 4,4'-MDA penetrates upper body clothing and deposits on the skin at the same rate as it penetrates the neoprene/latex gloves, viz. 0.7 ug cm^{-2} hr^{-1}.
- Mid-shift handwashing is not accounted for in these calculations.
- Workers shower at shift's end, completely removing remaining 4,4'-MDA.

Dose through the palms

Daily Dose =

$$.01\ hr^{-1} \times 4.2\ ug\ cm^{-2}\ hr^{-1} \times 410\ cm^2 \int_0^x t\,dt \qquad x = \begin{matrix} 0.25 \text{ hrs} \\ 2 \text{ hrs} \\ 4 \text{ hrs} \\ 6 \text{ hrs} \end{matrix}$$

$$17 \times 1/2 \times t^2 \Big]_0^{0.25} = 0.53 \text{ ug}$$

$$17 \times 1/2 \times t^2 \Big]_0^{2} = 34 \text{ ug}$$

$$17 \times 1/1 \times t^2 \Big]_0^{4} = 140 \text{ ug}$$

$$17 \times 1/2 \times t^2 \Big]_0^{6} = 310 \text{ ug}$$

Dose through rest of upper body

Daily Dose =

$$.01\ hr^{-1} \times 0.7\ ug\ cm^{-2}\ hr^{-1} \times 10{,}900\ cm^2 \int_0^x t\,dt \qquad x = \begin{matrix} 0.25 \text{ hrs} \\ 2 \text{ hrs} \\ 4 \text{ hrs} \\ 6 \text{ hrs} \end{matrix}$$

$$76 \times 1/2 \times t^2 \Big]_0^{0.25} = 2.4 \text{ ug}$$

$$76 \times 1/2 \times t^2 \Big]_0^{2} = 150 \text{ ug}$$

$$76 \times 1/2 \times t^2 \Big]_0^{4} = 610 \text{ ug}$$

$$76 \times 1/2 \times t^2 \Big]_0^{6} = 1400 \text{ ug}$$

Total daily dose @: 0.25 hr/day = 2.9 ug = 0.0029 mg
2 hr/day = 180 ug = 0.18 mg
4 hr/day = 750 ug = 0.75 mg
6 hr/day = 1700 ug = 1.7 mg

$$\text{LADD} = \text{daily dose} \times \frac{250}{365} \times \frac{40}{70} \div 70 \text{ kg}$$

LADDs @ 0.25 hr/day = 0.000016 mg/kg/day
2 hr/day = 0.0010 mg/kg/day
4 hr/day = 0.0042 mg/kg/day
6 hr/day = 0.0095 mg/kg/day

Total LADDs for Duration of

	2.5 hr/wk	8 hr/wk	20 hr/wk	40 hr/wk
		in mg/kg/day		
Dermal	0.000016	0.0010	0.0042	0.0095
Inhal.	0.00066	0.0021	0.0052	0.010
Total	0.00068	0.0031	0.0094	0.020

5. 4,4'-MDA Using/Processing Workplace with Better than Minimal Industrial Hygiene and Short-Term Exposures

Inhalational Component

Assumptions:

- Same general inhalational assumptions as in Case 1, above, and
- Respirable 4,4'-MDA air concentration is 0.38 mg/m^3 (Ameron, 1983)
- Worker is exposed only in this work station and only for 0.5 hr/day.

$$0.38 \text{ mg/m}^3 \times 1.2 \text{ m}^3/\text{hr} \times 0.5 \text{ hr} \times 0.5 \times \frac{250}{365} \times \frac{40}{70} \div 70 \text{ kg} =$$

LADD = 0.00066 mg/kg/day

Dermal Component

Assumptions:

- Same general dermal assumptions as in Case 4, above, and
- Worker has but one 0.5 hr exposure/day and thoroughly washes hands and forearms immediately following the exposure.

- Area of forearms is 1210 cm^2.
- Remainder of the upper body (9280 cm^2) is exposed for 6 hours before shower.

Dose through the palms

Daily dose =

$$.01\ hr^{-1} \times 4.2\ ug\ cm^{-2}\ hr^{-1} \times 410\ cm^2 \int_0^{.5} tdt$$

$$17 \times 1/2 \times t^2 \Big]_0^{0.5} = 2.1\ ug$$

Dose through the forearms

Daily dose =

$$.01\ hr^{-1} \times 0.7\ ug\ cm^{-2}\ hr^{-1} \times 1210\ cm^2 \int_0^{.5} tdt$$

$$8.5 \times 1/2 \times t^2 \Big]_0^{0.5} = 1.1\ ug$$

Dose through rest of upper body

Daily dose =

$$.01\ hr^{-1} \times 0.7\ ug\ cm^{-2}\ hr^{-1} \times 0.5\ hr \times 9280\ cm^2 \times 6\ hr = 195\ ug$$

Total daily dermal dose = 200 ug = 0.200 mg

$$LADD = 0.20\ mg/day \times \frac{250}{365} \times \frac{40}{70} \div 70\ kg$$

$$= 0.0011\ mg/kg/day$$

Total LADD (Inhal. and Dermal) = 0.0018 mg/kg/day

6. **DOE Contractor Workplace (DOE, 1983c)**

Assumptions:

- As described in the text, only inhalational exposures occur
- Other inhalational assumptions in Case 1, above, apply

$$0.02\ mg/m^3 \times 1.2\ m^3/hr \times 0.2\ hr/day \times 0.5 \times \frac{250}{365} \times \frac{40}{70} \div 70\ kg$$

$$LADD = 0.000013\ mg/kg/day$$

7. A. **4,4'-MDA Using/Processing Workplace: Intermittent Daily Exposure: Best Industrial Hygiene Practices**

Inhalational Component

Same as Case 2 above, but with 4 or 8 hours total exposure per day, delivering 0.0052 and 0.010 mg/kg/day LADD, respectively.

Dermal Component

Assumptions:

- Worker handles 4,4'-MDA for 0.5 hrs in first half and 0.5 hrs in second half of shift.
- Worker wears neoprene/latex, mid-forearm gloves, a suitable over garment and full face shield while handling the chemical, which limit exposure to

  --palms (410 cm^2) at a deposition rate of 4.2 ug cm^{-2} hr^{-1} (NIOSH 1984a, Table IV, Sample DM2A).

  --back of hands (410 cm^2) at a deposition rate of 0.7 ug cm^{-2} hr^{-1} (NIOSH 1984a, Table IV, Sample DM2B).
- Worker receives no other dermal exposure
- Worker washes hands immediately after exposure, completely removing any 4,4'-MDA.

Dose to palms

Daily dose =

$$2 \times .01\ hr^{-1} \times 4.2\ ug\ cm^{-2}\ hr^{-1} \times 410\ cm^2 \int_0^{.5} tdt$$

$$34 \times 1/2 \times t^2 \Big]_0^{.5} = 4.3\ ug$$

Dose to back of hand

Daily dose =

$$2 \times .01\ hr^{-1} \times 0.7\ ug\ cm^{-2}\ hr^{-1} \times 410\ cm^2 \int_0^{.5} tdt$$

$$5.7 \times 1/2 \times t^2 \Big]_0^{.5} = 0.71\ ug$$

Total daily dermal dose = 5.0 ug = 0.0050 mg

$$LADD = \text{daily dose} \times \frac{250}{365} \times \frac{40}{70} \div 70\ kg$$

$$= 0.000028\ mg/kg/day$$

Total LADD = Dermal and Inhalational LADDs

For 4 hr/day inhalational exposure:

(0.000028 + 0.0052) mg/kg/day

0.0052 mg/kg/day

For 8 hr/day inhalational exposure:

(0.000028 + 0.010) mg/kg/day
0.010 mg/kg/day

B. 4,4'-MDA Using/Processing Workplace: Intermittent Daily Exposure: Best Industrial Hygiene Practices

Inhalational Component

Same general assumptions as in Case 2 above, except that the airborne concentration of 4,4'-MDA is the same as that reported by CMA (1983a) for the resin mixing operation in a filament winding plant, namely 0.1 mg/m^3 (See p. 64), and exposure to this level is for 4 or 8 hours per day.

4 hr/day

$$0.1 \text{ mg/m}^3 \times 1.2 \text{ m}^3/\text{hr} \times 4 \text{ hr/day} \times 0.5 \times \frac{250}{365} \times \frac{40}{70} \div 70 \text{ kg}$$

LADD = 0.0013 mg/kg/day

8 hr/day

LADD = 0.0026 mg/kg/day

Dermal Component

Same as in Case 7. A above.

Total LADD = Dermal + Inhalational LADDs

4 hr/day inhalational exposure:

(0.000028 + 0.0013) mg/kg/day

0.0013 mg/kg/day

8 hr/day inhalational exposure:

(0.000028 + 0.0026) mg/kg/day

0.0026 mg/kg/day

8. 4,4'-MDA Using/Processing Workplace: Workplace Standard in Effect

Inhalational Component

Same general assumptions, except that exposure is at 0.001 ppm (0.0081 mg/m^3) for 8-hours.

$$0.0081\ mg/m^3 \times 1.2\ m^3/hr \times 8\ hr/day$$

$$\times \frac{250}{365} \times \frac{40}{70} \times 0.5 \div 70kg = 0.00022\ mg/kg/day\ LADD$$

Dermal Component

Assumptions:

- Worker handles 4,4'-MDA for two 1-hour periods at the beginning of each half-shift, following which deposited material is immediately washed off.
- Deposition occurs on the palms (410 cm^2) at 4.2 ug cm^{-2} hr^{-1} (NIOSH, 1984a, Table IV, Sample DM2A); on the back of the hands (410 cm^2) at 0.7 ug cm^{-2} hr^{-1} (NIOSH, 1984a, Table IV, Sample DM2B).
- All other dermal exposure is prevented.

Dose to palms

Daily dose =

$$2 \times .01\ hr^{-1} \times 4.2\ ug\ cm^{-2}\ hr^{-1} \times 410\ cm^2 \int_0^1 tdt$$

$$34 \times 1/2 \times t^2]_0^1 = 17\ ug$$

Dose to back of hand

Daily dose =

$$2 \times .01\ hr^{-1} \times 0.7\ ug\ cm^{-2}\ hr^{-1} \times 410\ cm^2 \int_0^1 tdt$$

$$5.7 \times 1/2 \times t^2]_0^1 = 2.8\ ug$$

Total daily dermal dose = 20 ug = 0.020 mg

$$\text{LADD} = \text{daily dose} \times \frac{250}{365} \times \frac{40}{70} \div 70 \text{ kg}$$

$$= 0.00011 \text{ mg/kg/day}$$

$$\text{Total LADD} = (0.00022 + 0.00011) \text{ mg/kg/day}$$

$$= 0.00033 \text{ mg/kg/day.}$$

APPENDIX C

TABLE 19A

ESTIMATED EXTRA LIFETIME RISK OF CANCER FOR WORKERS

Exposure Setting	Total LADD mg/kg/day	Extra Risk Based on Tumor Types: MRFC[a] MLE[c]	MRFC[a] U95CL[d]	MRFC/A[b] MLE	MRFC/A[b] U95CL
4,4'-MDA/MDI mfg.					
Appendix B, Sec. 1					
8 hr/wk	0.0051	5×10^{-4}	9×10^{-4}	1×10^{-3}	1×10^{-3}
20 hr/wk	0.020	2×10^{-3}	3×10^{-3}	4×10^{-3}	6×10^{-3}
40 hr/wk	0.042	4×10^{-3}	7×10^{-3}	7×10^{-3}	1×10^{-2}
4,4'-MDA Use/Proc[e]					
Appendix B, Sec. 2					
2.5 hr/wk	0.0011	1×10^{-4}	2×10^{-4}	2×10^{-4}	3×10^{-4}
8 hr/wk	0.0053	5×10^{-4}	9×10^{-4}	1×10^{-3}	1×10^{-3}
20 hr/wk	0.012	1×10^{-3}	2×10^{-3}	2×10^{-3}	3×10^{-3}
40 hr/wk	0.020	2×10^{-3}	3×10^{-3}	4×10^{-3}	6×10^{-3}
Appendix B, Sec. 3	0.17	2×10^{-2}	3×10^{-2}	3×10^{-2}	5×10^{-2}
Appendix B, Sec. 4					
2.5 hr/wk	0.00068	7×10^{-5}	1×10^{-4}	1×10^{-4}	2×10^{-4}
8 hr/wk	0.0031	3×10^{-4}	5×10^{-4}	5×10^{-4}	9×10^{-4}
20 hr/wk	0.0094	7×10^{-4}	1×10^{-3}	1×10^{-3}	2×10^{-3}
40 hr/wk	0.020	2×10^{-3}	3×10^{-3}	4×10^{-3}	6×10^{-3}
Appendix B, Sec. 5	0.0018	2×10^{-4}	3×10^{-4}	3×10^{-4}	5×10^{-4}
Appendix B, Sec. 6	0.000013	1×10^{-6}	2×10^{-6}	2×10^{-6}	4×10^{-6}
Appendix B, Sec. 7A					
20 hr/wk	0.0052	5×10^{-4}	9×10^{-4}	9×10^{-4}	1×10^{-3}
40 hr/wk	0.010	1×10^{-3}	2×10^{-3}	2×10^{-3}	3×10^{-3}
Appendix B, Sec. 7B					
20 hr/wk	0.0013	1×10^{-4}	2×10^{-4}	2×10^{-4}	4×10^{-4}
40 hr/wk	0.0026	2×10^{-4}	4×10^{-4}	5×10^{-4}	7×10^{-4}
Appendix B, Sec. 8	0.00033	3×10^{-5}	6×10^{-5}	6×10^{-5}	9×10^{-5}

(a) Male rat, thyroid follicular-cell carcinoma
(b) Male rat, thyroid follicular-cell carcinoma and adenoma
(c) Maximum likelihood estimate
(d) Upper 95% confidence limit
(e) Remaining exposures are all in use/processing category

TABLE 19A -CONTINUED

Exposure Setting	Total LADD mg/kg/day	Extra Risk Based on Tumor Types: FRCC/A(f) MLE	FRCC/A(f) U95CL	MMAP(g) MLE	MMAP(g) U95CL
4,4'-MDA/MDI mfg.					
Appendix B, Sec. 1					
8 hr/wk	0.0051	7×10^{-4}	1×10^{-3}	9×10^{-4}	1×10^{-3}
20 hr/wk	0.020	3×10^{-3}	5×10^{-3}	3×10^{-3}	5×10^{-3}
40 hr/wk	0.042	5×10^{-3}	9×10^{-3}	7×10^{-3}	1×10^{-2}
4,4'-MDA Use/Proc					
Appendix B, Sec. 2					
2.5 hr/wk	0.0011	1×10^{-4}	3×10^{-4}	2×10^{-4}	3×10^{-4}
8 hr/wk	0.0053	7×10^{-4}	1×10^{-3}	9×10^{-4}	1×10^{-3}
20 hr/wk	0.012	2×10^{-3}	3×10^{-3}	2×10^{-3}	3×10^{-3}
40 hr/wk	0.020	3×10^{-3}	5×10^{-3}	3×10^{-3}	5×10^{-3}
Appendix B, Sec. 3	0.17	2×10^{-2}	4×10^{-2}	3×10^{-2}	4×10^{-2}
Appendix B, Sec. 4					
2.5 hr/wk	0.00068	9×10^{-5}	2×10^{-4}	1×10^{-4}	2×10^{-4}
8 hr/wk	0.0031	4×10^{-4}	7×10^{-4}	5×10^{-4}	8×10^{-4}
20 hr/wk	0.0094	1×10^{-3}	2×10^{-3}	1×10^{-3}	2×10^{-3}
40 hr/wk	0.020	3×10^{-3}	5×10^{-3}	3×10^{-3}	5×10^{-3}
Appendix B, Sec. 5	0.0018	2×10^{-4}	4×10^{-4}	3×10^{-3}	5×10^{-3}
Appendix B, Sec. 6	0.000013	2×10^{-6}	3×10^{-6}	2×10^{-6}	3×10^{-6}
Appendix B, Sec. 7A					
20 hr/wk	0.0052	7×10^{-4}	1×10^{-3}	9×10^{-4}	1×10^{-3}
40 hr/wk	0.010	1×10^{-3}	2×10^{-3}	2×10^{-3}	3×10^{-3}
Appendix B, Sec. 7B					
20 hr/wk	0.0013	2×10^{-4}	3×10^{-4}	2×10^{-3}	3×10^{-3}
40 hr/wk	0.0026	4×10^{-4}	6×10^{-4}	5×10^{-3}	7×10^{-3}
Appendix B, Sec. 8	0.00033	5×10^{-5}	8×10^{-5}	6×10^{-5}	8×10^{-5}

(f) Female rat, thyroid C-cell carcinoma and adenoma
(g) Male mouse, adrenal pheochromocytoma

TABLE 19A -CONTINUED

Exposure Setting	Total LADD mg/kg/day	Extra Risk Based on Tumor Types: FMABC/A[h] MLE	FMABC/A[h] U95CL	FMLHC[i] MLE	FMLHC[i] U95CL
4,4'-MDA/MDA Mfg.					
Appendix B, Sec. 1					
8 hr/wk	0.0051	3×10^{-4}	6×10^{-4}	6×10^{-4}	9×10^{-4}
20 hr/wk	0.020	2×10^{-3}	2×10^{-3}	2×10^{-3}	3×10^{-3}
40 hr/wk	0.042	2×10^{-3}	4×10^{-3}	5×10^{-3}	7×10^{-3}
4,4'-MDA Use/Proc.					
Appendix B, Sec. 2					
2.5 hr/wk	0.0011	6×10^{-5}	1×10^{-4}	1×10^{-4}	2×10^{-4}
8 hr/wk	0.0053	3×10^{-4}	6×10^{-4}	6×10^{-4}	9×10^{-4}
20 hr/wk	0.012	7×10^{-4}	1×10^{-3}	1×10^{-3}	2×10^{-3}
40 hr/wk	0.020	1×10^{-3}	2×10^{-3}	2×10^{-3}	3×10^{-3}
Appendix B, Sec. 3	0.17	1×10^{-2}	2×10^{-2}	2×10^{-2}	3×10^{-2}
Appendix B, Sec. 4					
2.5 hr/wk	0.00068	4×10^{-5}	7×10^{-5}	8×10^{-5}	1×10^{-4}
8 hr/wk	0.0031	2×10^{-4}	3×10^{-4}	4×10^{-4}	5×10^{-4}
20 hr/wk	0.0094	4×10^{-4}	8×10^{-4}	8×10^{-4}	1×10^{-3}
40 hr/wk	0.020	1×10^{-3}	2×10^{-3}	2×10^{-3}	3×10^{-3}
Appendix B, Sec. 5	0.0018	1×10^{-4}	2×10^{-4}	2×10^{-4}	3×10^{-4}
Appendix B, Sec. 6	0.000013	8×10^{-7}	1×10^{-6}	1×10^{-6}	2×10^{-6}
Appendix B, Sec. 7A					
20 hr/wk	0.0052	3×10^{-4}	6×10^{-4}	6×10^{-4}	9×10^{-4}
40 hr/wk	0.010	6×10^{-4}	1×10^{-3}	1×10^{-3}	2×10^{-3}
Appendix B, Sec. 7B					
20 hr/wk	0.0013	8×10^{-5}	1×10^{-4}	1×10^{-4}	2×10^{-4}
40 hr/wk	0.0026	1×10^{-4}	3×10^{-4}	3×10^{-4}	5×10^{-4}
Appendix B, Sec. 8	0.00033	2×10^{-5}	4×10^{-5}	4×10^{-5}	6×10^{-5}

(h) Female mouse, alveolar-bronchiolar carcinoma and adenoma
(i) Female mouse, liver hepatocellular carcinoma

TABLE 19A -CONTINUED

Exposure Setting	Total LADD mg/kg/day	Extra Risk Based on Tumor Types: FMLHC/A[j] MLE	FMLHC/A[j] U95CL	MRPA[k] MLE	MRPA[k] U95CL
4,4'-MDA/MDA Mfg.					
Appendix B, Sec. 1					
8 hr/wk	0.0051	1×10^{-3}	2×10^{-3}	9×10^{-4}	1×10^{-3}
20 hr/wk	0.020	5×10^{-3}	8×10^{-3}	4×10^{-3}	6×10^{-3}
40 hr/wk	0.042	1×10^{-2}	1×10^{-2}	7×10^{-3}	1×10^{-2}
4,4'-MDA Use/Proc.					
Appendix B, Sec. 2					
2.5 hr/wk	0.0011	3×10^{-4}	4×10^{-4}	2×10^{-4}	3×10^{-4}
8 hr/wk	0.0053	1×10^{-3}	2×10^{-3}	9×10^{-4}	1×10^{-3}
20 hr/wk	0.012	3×10^{-3}	5×10^{-3}	2×10^{-3}	3×10^{-3}
40 hr/wk	0.020	5×10^{-3}	8×10^{-3}	4×10^{-3}	6×10^{-3}
Appendix B, Sec. 3	0.17	5×10^{-2}	6×10^{-2}	3×10^{-2}	5×10^{-2}
Appendix B, Sec. 4					
2.5 hr/wk	0.00068	2×10^{-4}	3×10^{-4}	1×10^{-4}	2×10^{-4}
8 hr/wk	0.0031	8×10^{-4}	1×10^{-3}	6×10^{-4}	9×10^{-4}
20 hr/wk	0.0094	2×10^{-3}	3×10^{-3}	1×10^{-3}	2×10^{-3}
40 hr/wk	0.020	5×10^{-3}	8×10^{-3}	4×10^{-3}	6×10^{-3}
Appendix B, Sec. 5	0.0018	5×10^{-4}	7×10^{-4}	3×10^{-4}	5×10^{-4}
Appendix B, Sec. 6	0.000013	4×10^{-6}	5×10^{-6}	2×10^{-6}	4×10^{-4}
Appendix B, Sec. 7A					
20 hr/wk	0.0052	1×10^{-3}	2×10^{-3}	9×10^{-4}	1×10^{-3}
40 hr/wk	0.010	3×10^{-3}	4×10^{-3}	2×10^{-3}	3×10^{-3}
Appendix B, Sec. 7B					
20 hr/wk	0.0013	4×10^{-4}	5×10^{-4}	2×10^{-4}	4×10^{-4}
40 hr/wk	0.0026	7×10^{-4}	1×10^{-3}	5×10^{-4}	7×10^{-4}
Appendix B, Sec. 8	0.00033	9×10^{-5}	1×10^{-4}	6×10^{-5}	9×10^{-5}

(j) Female mouse, liver hepatocellular carcinoma and adenoma
(k) Male rat, pooled all statistically significant tumors

TABLE 19A -CONTINUED

Exposure Setting	Total LADD mg/kg/day	Extra Risk Based on Tumor Types: FRPA(1) MLE	FRPA(1) U95CL	MRPM(m) MLE	MRPM(m) U95CL
4,4'-MDA/MDA Mfg.					
Appendix B, Sec. 1					
8 hr/wk	0.0051	3×10^{-3}	4×10^{-3}	9×10^{-4}	1×10^{-3}
20 hr/wk	0.020	1×10^{-2}	1×10^{-2}	4×10^{-3}	6×10^{-3}
40 hr/wk	0.042	2×10^{-2}	3×10^{-2}	7×10^{-3}	1×10^{-2}
4,4'-MDA Use/Proc.					
Appendix B, Sec. 2					
2.5 hr/wk	0.0011	6×10^{-4}	8×10^{-4}	2×10^{-4}	3×10^{-4}
8 hr/wk	0.0053	3×10^{-3}	4×10^{-3}	9×10^{-4}	1×10^{-3}
20 hr/wk	0.012	7×10^{-3}	9×10^{-3}	2×10^{-3}	3×10^{-3}
40 hr/wk	0.020	1×10^{-2}	1×10^{-2}	4×10^{-3}	6×10^{-3}
Appendix B, Sec. 3	0.17	9×10^{-2}	1×10^{-1}	3×10^{-2}	5×10^{-2}
Appendix B, Sec. 4					
2.5 hr/wk	0.00068	4×10^{-4}	5×10^{-4}	1×10^{-4}	2×10^{-4}
8 hr/wk	0.0031	2×10^{-3}	2×10^{-3}	5×10^{-4}	9×10^{-4}
20 hr/wk	0.0094	4×10^{-3}	5×10^{-3}	1×10^{-3}	2×10^{-3}
40 hr/wk	0.020	1×10^{-2}	1×10^{-2}	4×10^{-3}	6×10^{-3}
Appendix B, Sec. 5	0.0018	1×10^{-3}	2×10^{-3}	3×10^{-4}	5×10^{-4}
Appendix B, Sec. 6	0.000013	7×10^{-6}	9×10^{-6}	2×10^{-6}	4×10^{-6}
Appendix B, Sec. 7A					
20 hr/wk	0.0052	3×10^{-3}	4×10^{-3}	9×10^{-4}	1×10^{-3}
40 hr/wk	0.010	5×10^{-3}	7×10^{-3}	2×10^{-3}	3×10^{-3}
Appendix B, Sec. 7B					
20 hr/wk	0.0013	7×10^{-4}	9×10^{-4}	2×10^{-4}	4×10^{-4}
40 hr/wk	0.0026	1×10^{-3}	2×10^{-3}	5×10^{-4}	7×10^{-4}
Appendix B, Sec. 8	0.00033	2×10^{-4}	2×10^{-4}	6×10^{-5}	9×10^{-5}

(1) Female rat, pooled all statistically significant tumors
(m) Male rat, pooled all tumors for which malignancies, alone, are statistically significant

TABLE 20A

Estimated Extra Lifetime Risk of Cancer From Drinking Water

Locale	4,4'-MDA Conc. mg/l	LADD mg/kg/day	Extra Risk Based on Tumors: MRFC[a] MLE[c]	MRFC[a] U95CL[d]	MRFC/A[b] MLE	MRFC/A[b] U95CL
A	0.00018	0.0000026	2×10^{-7}	4×10^{-7}	5×10^{-7}	7×10^{-7}
B	0.00015	0.0000021	2×10^{-7}	4×10^{-7}	4×10^{-7}	6×10^{-7}
C	0.00015	0.0000021	2×10^{-7}	4×10^{-7}	4×10^{-7}	6×10^{-7}
B + C	0.00030	0.0000042	4×10^{-7}	7×10^{-7}	7×10^{-7}	1×10^{-6}
D	0.0012	0.000017	2×10^{-6}	3×10^{-6}	3×10^{-6}	5×10^{-6}

(a) Male rat, thyroid follicular-cell carcinoma
(b) Male rat, thyroid follicular-cell carcinoma and adenoma
(c) Maximum likelihood estimate
(d) Upper 95% confidence limit

TABLE 20A - CONTINUED

Locale	4,4'-MDA Conc. mg/l	LADD mg/kg/day	Extra Risk Based on Tumors FRCC/A(e) MLE	FRCC/A(e) U95CL	MMAP(f) MLE	MMAP(f) U95CL
A	0.00018	0.0000026	4×10^{-7}	6×10^{-7}	5×10^{-7}	7×10^{-7}
B	0.00015	0.0000021	3×10^{-7}	5×10^{-7}	4×10^{-7}	5×10^{-7}
C	0.00015	0.0000021	3×10^{-7}	5×10^{-7}	4×10^{-7}	5×10^{-7}
B + C	0.00030	0.0000042	6×10^{-7}	1×10^{-6}	7×10^{-7}	1×10^{-6}
D	0.0012	0.000017	2×10^{-6}	4×10^{-6}	3×10^{-6}	4×10^{-6}

(e) Female rat, thyroid C-cell carcinoma and adenoma
(f) Male mouse, adrenal pheochromocytoma

TABLE 20A - CONTINUED

Locale	4,4'-MDA Conc. mg/l	LADD mg/kg/day	Extra Risk Based on Tumors FMABC/A[g] MLE	FMABC/A[g] U95CL	FMLHC[h] MLE	FMLHC[h] U95CL
A	0.00018	0.0000026	1×10^{-7}	3×10^{-7}	3×10^{-7}	5×10^{-7}
B	0.00015	0.0000021	1×10^{-7}	2×10^{-7}	2×10^{-7}	4×10^{-7}
C	0.00015	0.0000021	1×10^{-7}	2×10^{-7}	2×10^{-7}	4×10^{-7}
B + C	0.00030	0.0000042	2×10^{-7}	4×10^{-7}	5×10^{-7}	7×10^{-7}
D	0.0012	0.000017	1×10^{-6}	2×10^{-6}	2×10^{-6}	3×10^{-6}

(g) Female mouse, alveolar-bronchiolar carcinoma and adenoma
(h) Female mouse, liver hepatocellular carcinoma

TABLE 20A - CONTINUED

Locale	4,4'-MDA Conc. mg/l	LADD mg/kg/day	Extra Risk Based on Tumors FMLHC/A(i) MLE	FMLHC/A(i) U95CL	MRPA(j) MLE	MRPA(j) U95CL
A	0.00018	0.0000026	7×10^{-7}	1×10^{-6}	5×10^{-7}	7×10^{-7}
B	0.00015	0.0000021	6×10^{-7}	8×10^{-7}	4×10^{-7}	6×10^{-7}
C	0.00015	0.0000021	6×10^{-7}	8×10^{-7}	4×10^{-7}	6×10^{-7}
B + C	0.00030	0.0000042	1×10^{-6}	2×10^{-6}	7×10^{-7}	1×10^{-6}
D	0.0012	0.000017	5×10^{-6}	6×10^{-6}	3×10^{-6}	5×10^{-6}

(i) Female mouse, liver hepatocellular carcinoma and adenoma
(j) Male rat, pooled all statistically significant tumors

TABLE 20A - CONTINUED

Locale	4,4'-MDA Conc. mg/l	LADD mg/kg/day	Extra Risk Based on Tumors FRPA(k) MLE	FRPA(k) U95CL	MRPM(l) MLE	MRPM(l) U95CL
A	0.00018	0.0000026	1×10^{-6}	2×10^{-6}	5×10^{-7}	7×10^{-7}
B	0.00015	0.0000021	1×10^{-6}	1×10^{-6}	4×10^{-7}	6×10^{-7}
C	0.00015	0.0000021	1×10^{-6}	1×10^{-6}	4×10^{-7}	6×10^{-7}
B + C	0.00030	0.0000042	2×10^{-6}	3×10^{-6}	7×10^{-7}	1×10^{-6}
D	0.0012	0.000017	9×10^{-6}	1×10^{-5}	3×10^{-6}	5×10^{-6}

(k) Female rat, pooled all statistically significant tumors
(l) Male rat, pooled all tumors for which malignancies, alone, are statistically significant

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