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Subject: Reports of Health and Safety Studies
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Diethylamine (CAS Reg. No. 109-89-7)
Toluene Diisocyanate (TDI) (CAS Reg. No. 26471-62-5)
Benzene, 1,1'-methylenebis[4-isocyanate- (MDI)
(CAS Reg. No. 101-68-8)
Isocyanic Acid, Polymethylene Polyphenylene Ester
(Poly-MDI) (CAS Reg. No. 9016-87-9)

Enclosed is a material safety data sheet for diethylamine and a Kaiser Chemicals toxicology report on urethane chemicals for MDI, Poly-MDI and TDI.

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Please note that we are claiming portions of the cover letter confidential, however, we are not maintaining confidentiality for the attached studies.

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KAISER CHEMICALS

KAISER ALUMINUM & CHEMICAL SALES, INC.

URETHANE BULLETIN

TOXICOLOGY REPORT ON URETHANE CHEMICALS

MDI, POLY-MDI, TDI, AND POLY-MDA

The information contained herein is believed to be reliable and is intended for use by persons having technical skill, at their own discretion and risk. Since conditions of use are outside of Kaiser Aluminum & Chemical Corporation's control, we assume no liability for results obtained or damages incurred through the application of the data presented.

AN EVALUATION OF THE ACUTE TOXICITY AND IRRITANTCY POTENTIAL OF FOUR POLYURETHANE INTERMEDIATES, 4,4'-DIPHENYLMETHANE DIISOCYANATE (MDI) POLYMETHYLENEPOLYPHENYLENE POLYISOCYANATE (Poly-MDI) POLYMETHYLENEPOLYPHENYLENE POLYAMINE (Poly-MDA) 2,4-TOLYLENE DIISOCYANATE (TDI)

A Confidential Report Prepared for the
Kaiser Aluminum and Chemical Company
Oakland, California

July 1967

The Hine Laboratories, Inc.
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FDA License No. 29-13576

State Laboratory License No. 481

This study was carried out under standard conditions for animal care as recommended by the Department of Public Health, State of California.

Report Approved: _____
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Director
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TABLE OF CONTENTS

		Page
	SUMMARY	1
I.	INTRODUCTION	2
II.	MATERIALS AND METHODS	
	A. Materials	2
	B. Methods	3
III.	RESULTS	
	A. Oral Range and Acute LD_{50}	7
	B. Percutaneous Range Find	9
	C. Primary Eye Irritation	9
	D. Primary Skin Irritation	11
	E. Repeated Skin Exposure	12
	F. Respiratory Range Find	13
IV.	DISCUSSION	15
	REFERENCES	19

	Table No.
Results of Intragastric Injection in the Rat with TDI, MDI, Poly-MDI and Poly-MDA	1 - 4
Results of Primary Eye Irritation Study with TDI, MDI, Poly-MDI and Poly-MDA	5 - 8
Evaluation of Skin Reactions	9
Results of Primary Skin Irritation Study with TDI, MDI, Poly-MDI and Poly-MDA	10 -13
Results of Repeated Application for 20 Days of MDI and Poly-MDI on Rabbit Skin	14
Summary of the Toxicity Classification of the Four Compounds Studied	15
Verbal Description of Irritation Scores Used at The Hine Laboratories, Inc.	16

SUMMARY

A toxicity evaluation has been carried out on MDI, Poly-MDI, Poly-MDA and TDI. TDI was the most toxic of the compounds studied. MDI and MDA are somewhat less toxic, though in the same order of toxicity. All but Poly-MDA may be sensitizers of the respiratory tract. The only other toxic manifestation is a severely irritating action on the eyes. Handling procedures are described which enable users to handle the compounds safely.

I. INTRODUCTION

Polyurethane chemistry has resulted in the production of a number of consumer products manufactured on a large scale. The majority of these products are made from rigid or flexible foams. These new products which find wide acceptance can be used as substitutes for foam rubber, cork and other traditional materials.

One of the most widely used intermediates in the past has been tolylene diisocyanate (TDI). Newer advances have led to the utilization of diphenylmethane diisocyanate (MDI). Since TDI has been shown to produce an asthma-like syndrome and skin sensitization, a comparison of the toxicity of TDI with MDI and related intermediates used in the manufacture of urethane products was deemed necessary in order to establish safe-handling practices and to evaluate the comparative toxicity of these compounds. Consequently the following studies were carried out: Acute Oral Toxicity, Acute Percutaneous Toxicity, Evaluation of the Irritantcy to the Eyes and Skin on Single Contact, Evaluation of Repeated Exposures of the Skin, and the Effects of Inhalation of Vapors and Aerosols.

II. MATERIALS AND METHODS

A. Materials

1. Test Animals: All rats used in these studies were of the Long-Evans strain and weighed between 250 and 350 grams.

All rabbits used were of the New Zealand White strain weighing between 2 and 3 kilograms.

2. Test Compounds: All test compounds were provided by the Kaiser Chemical Company through the courtesy of Dr. F. W. Blodgett. The TDI was a product of the Mobay Chemical Company, of Pittsburgh, Pennsylvania. The other materials were manufactured by Kaiser Aluminum and Chemical Corporation and reported to be typical of production products.

a. Tolylene diisocyanate (TDI) was a 80/20 mixture by weight of 2,4-tolylene diisocyanate and 2,6-tolylene diisocyanate. It was identified as Mobay Mondur TD-80 Lot 2889. It is a clear, non-viscous liquid and has a distinctive odor.

b. 4,4'-Diphenylmethane diisocyanate (MDI) was a mixture of crystals and liquid. It was identified as Lot 1485.

c. Polymethylenepolyphenylene polyisocyanate (Poly-MDI) was a dark brown viscous liquid identified as Lot 1374.

d. Polymethylenepolyphenylene polyamine (Poly-MDA) was a light beige sticky solid identified as Lot 1238.

Compounds were protected from decomposition by storage under dry nitrogen.

B. <u>Methods</u>

1. Oral range and acute oral LD_{50} graded doses of the compound being studied were given by intragastric injection to groups of 2 rats per level for range find studies, and 6 rats per level for LD_{50} studies. Animals were denied food for 24 hours prior to administration of the compound. TDI and Poly-MDI were given as the pure liquid, whereas MDI and Poly-MDA were dissolved in a minimum of pure dimethyl sulfoxide (DMSO). Observations of behavior and physical condition of treated

animals were made hourly for the first 4-6 hours and 3 times daily afterward for 14 days or until death. Autopsies were performed on all animals which died; survivors were sacrificed at 14 days and autopsies performed (1-4). The LD_{50} was calculated according to the method of Litchfield and Wilcoxon (5).

2. Percutaneous range find: Three rabbits per compound were clipped and wrapped in a rubber dam. Two thousand milligrams per kilogram of the compound being studied was placed under the dam in close contact with the skin. Twenty-four hours later, the dam was removed and excess material wiped off. Animals were observed daily for 14 days or until death.

All four compounds were used undiluted or as the solid.

3. Primary eye irritation: Six rabbits per compound were used in these studies. One-tenth milliliter of the liquid compounds or 100 milligram of the solids were instilled in the right eye of each rabbit. The eye was then held closed for one second and the animal released. Readings of conjunctival redness and chemosis, discharge, iritis, and corneal opacity were made at 24, 48, and 72 hours after application, and scored according to the methods of Draize as amended in the Federal Register, September 17, 1964 F.R. 13009.

4. Primary skin irritation: Six rabbits were clipped and one side abraded by making a series of cross-hatched incisions through the epidermis. One-half milliliter of liquid or one-half gram of solid was placed over the skin on both the intact and abraded areas. A gauze bandage was placed over the compound and the animal restrained. Twenty-four hours later,

the bandage was removed and excess material wiped off. Readings of erythema and edema were made at 24 and 72 hours after application and scored according to the method of Draize (6).

5. Repeated skin exposure: Six rabbits were clipped, and one side was abraded. One-half gram of MDI and 0.5 milliliter of polyisocyanate were placed on separate areas of intact and abraded skin. A gauze patch was placed over the compound and the animal restrained. After one hour, the patch was removed, and any remaining material was wiped off. This procedure was repeated daily, except weekends, for 20 exposure days. Readings of edema and erythema were made daily and scores were assigned according to the Draize method.

6. Respiratory range find:

a. Vapor

Groups of six rats were exposed for 4 hours to air saturated with the vapors of each compound at 25° C.

The compound was placed in two vaporizers in series, which were immersed in a 90° C water bath. Dry air was bubbled through the compounds at a rate of 3.4 liters/minute and into a 20-liter exposure chamber, with an open exhaust.

After exposure, animals were kept 14 days or until death ensued. Autopsies were performed on all animals dying, and at 14 days survivors were sacrificed and autopsies performed. Concentration was measured with a Wilkens Model 600B Gas-Liquid Chromatograph using a 5-foot column of SE-30 on 60-80 Chromasorb W. Oven temperature and injection temperature were 250° C. A hydrogen flame detector was used.

Temperatures in the exposure chamber were measured with a mercury thermometer taped to the internal wall.

b. Aerosols

Two experiments were conducted.

1. Solutions of MDI, Poly-MDI and Poly-MDA and pure TDI were placed in a nebulizer and sprayed into a 200-liter exposure chamber containing 6 rats. Dry nitrogen was used to disperse the compounds. After spraying the material, the chamber was sealed and the animals exposed for one hour. Survivors were held and observed 14 days and then sacrificed and autopsies performed. The solutions used, spraying times, and total weight dispersed for each compound are given below:

Compound	Concentration (Wt/Wt)	Spray Time	Weight of Compound
TDI	Pure	8 sec.	5 grams
MDI	1/1 Acetone	13 sec.	2.9 grams
Poly-MDI	15/1 Acetone	188 sec.	9 grams
Poly-MDA	1/1 Acetone	22 sec.	5.8 grams

In all four exposures, 90% of the particles were between 0.5 and 2.5 μ as determined by visual count using coated slides and a microscope.

2. A standard type chromatography spray bottle was fitted with a tube one foot long and one inch in diameter which extended from the spraying orifice.

TDI was used undiluted. The remaining substances were diluted in acetone to give the following percent W/V solutions: MDI 65; Poly-MDI 50; and Poly-MDA 40.

Positive pressure was applied from a Gast oilless pump at a pressure of 20 psig. The four compounds were sprayed from this apparatus directly at a group of six rats housed in a 7500-liter exposure chamber. The exposure residence time in the chamber in all cases was four hours. The rates of spray in ml/hour were as follows: TDI 120; MDI 187; Poly-MDI 120; and Poly-MDA 120.

In addition, one group of six rats was sprayed with acetone at a rate of 187 ml/hour. Animals were held for 14 days, sacrificed with sodium pentobarbital and examined for gross pathology.

Particle size of the aerosol was determined by placing slides coated with magnesium oxide on the outside of each animal's cage. The slides were then observed under a light microscope at 400X and an estimate of the average particle size determined.

Approximately 50% of the particles observed were less than 20 microns in diameter. Of these, a great many were smaller than 7 microns in diameter.

III. RESULTS

A. Oral Range and Acute LD_{50}

1. TDI: The calculated LD_{50} was 5200 mg/kg, with 95% confidence limits of 4193 to 6448 mg/kg. Signs of intoxication appeared between 1 and 24 hours after administration of the compound. Signs included progressive inactivity to the point of paralysis, hyporeflexia, arching, piloerection, and flexure of all four limbs when the rat was held by the scruff of the neck. Death occurred between 1 and 5 days after injection.

Gross autopsies revealed in all cases the formation of a rigid plastic cast in the stomach, duodenum and proximal portion of the ilium. The nature of the cast and its position were such as to completely block the lumen of the portion of the gut which it occupied. There were no other gross abnormalities observed.

Doses administered and mortality figures are given in Table 1.

2. MDI: The calculated LD_{50} was 9200 mg/kg with 95% confidence limits of 4700 to 19,000 mg/kg. Signs of intoxication appeared between 2 and 24 hours after administration, and included inactivity, hyporeflexia, loss of coordination, hypothermy and arching. Death occurred between 3 and 4 days after injection. No consistent gross changes were found at autopsy. No casts were seen in the stomach.

Doses administered and mortality figures are given in Table 2.

3. Poly-MDI: Doses as high as 30.0 grams/kg did not cause mortality. At a level of 49 grams/kg, 3/6 rats died. This was the highest dose level it was practical to administer. The approximate LD_{50} was 49.0 grams/kg. Death occurred overnight in all 3 cases. The only unusual finding at autopsy was the formation of a rigid plastic mass in the gut. Survivors autopsied at 14 days showed traces of plastic in the gastrointestinal tract. Signs of intoxication included decreasing activity, hyporeflexia, diarrhea and hypothermy.

Table 3 gives dose levels and mortality figures.

4. Poly-MDA: The lethal range of this compound was from 500 to 2000 mg/kg. The approximate LD_{50} based on the method of

Deichmann (7) was 1000 mg/kg. Signs of intoxication included arching, loss of motor ability, and piloerection which became worse with time. Animals appeared incoordinated and movements were sluggish. Autopsy showed no gross abnormalities.

Doses and mortality are given in Table 4.

B. Percutaneous Range Find

1. TDI: There were no deaths or signs of intoxication as late as 14 days after administration of the compound.

2. MDI: There were no deaths or signs of intoxication as late as 14 days after administration of the compound.

3. Poly-MDI: There were no deaths or signs of intoxication as late as 14 days after the administration of the compound.

4. Poly-MDA: There were no deaths or signs of intoxication as late as 14 days after administration of the compound.

C. Primary Eye Irritation

1. TDI: At 24 hours, there was marked inflammation of the conjunctiva and iris. A definite dulling of the cornea was apparent in 4/6 rabbits. By 48 hours, the swelling had decreased somewhat, as had the inflammation of the iris. Two rabbits still showed a slight corneal opacity.

At 72 hours, the swelling and redness was similar to that noted at 48 hours, but the cornea of one rabbit showed a moderate opacity over about 1/4 of the surface. TDI may be classified as an extreme irritant to the eye by the classification used in this laboratory (8).

Supporting data appear in Table 5.

2. MDI: At 24 hours, there was moderate swelling and extreme irritation of the conjunctiva. In addition, there was a slight opacity of the cornea present in 2/6 rabbits. Moderate iritis occurred in 5/6 rabbits. At 48 hours, there was little change. At 72 hours, the swelling had decreased slightly, and the iritis was less noticeable. MDI may be classified as an extreme eye irritant.

Supporting data appear in Table 6.

3. Poly-MDI: At 24 hours, there was moderate swelling and irritation of the conjunctiva. Three rabbits showed a slight iritis.

At 48 hours, irritation had increased somewhat, and one rabbit showed a slight opacity of the cornea.

At 72 hours, the level of irritation had not changed, but the slight opacity seen in one rabbit at 48 hours had increased to a definite translucent area involving about 3/4 of the surface of the cornea. The compound would be classified as an extreme eye irritant.

At seven days, however, all irritation had disappeared. Supporting data are given in Table 7.

4. Poly-MDA: At 24 hours, 4/6 rabbits showed a slight reddening of the conjunctiva. There was no swelling, discharge or corneal or iridial involvement.

At 48 hours, only 2/6 rabbits showed slight redness.

At 72 hours, conditions remained the same.

Poly-MDA may be classified as a minimal eye irritant.

Supporting data appear in Table 8.

D. Primary Skin Irritation

1. TDI: At 24 hours, there was a slight edema formation on abraded skin in 5/6 rabbits; slight edema was noted in 3/6 rabbits on intact skin. No erythema was noted at this time.

At 72 hours, 4/6 showed slight edema on abraded skin and 2/6 showed slight to moderate edema on intact skin. Slight erythema was noted in 2/6 on both intact and abraded skin.

The combined average score for skin irritation was 0.8.

See Table 9 for explanation of the grading scale.

Supporting data are in Table 10.

2. MDI: At 24 hours, 1/6 rabbits showed a slight edema on abraded skin. No erythema was noted on either abraded or intact skin, and no edema was noted on intact skin.

At 72 hours, 3/6 rabbits showed slight edema and erythema on abraded skin, and 2/6 showed slight edema and erythema on intact and abraded skin. The combined average primary irritation score was 0.47.

Supporting data are given in Table 11.

3. Poly-MDI: At 24 hours, one rabbit showed a slight edema on abraded skin, and 3 showed slight erythema on abraded skin. There was no reaction on intact skin.

At 72 hours, 2/6 showed slight edema, and 3/6 showed slight erythema on abraded skin. One rabbit showed both edema and erythema on intact skin. The combined average primary irritation score was 0.46.

Supporting data are given in Table 12.

4. Poly-MDA: At 24 hours, 1/6 rabbits showed slight edema on abraded skin, and 4/6 showed slight erythema, and 1/6 showed moderate edema on abraded skin. Two out of 6 rabbits showed slight erythema on intact skin.

At 72 hours, 1/6 showed slight edema, and 2/6 showed slight erythema on abraded skin. Two out of 6 showed slight erythema on intact skin.

The combined average primary irritation score was 0.6.

Supporting data are given in Table 13.

E. Repeated Skin Exposure

1. MDI: There was no reaction of any kind during the first two exposure days. On the third day, a slight edema appeared on 4/6 rabbits on intact skin. Two out of six showed slight erythema on intact skin, and one of 6 showed slight edema on abraded skin. Throughout the remainder of the experiment, edema and erythema varied from none to moderate. There was no incidence of severe irritation, eschar formation or skin necrosis. The irritation reached a maximum at 12-14 days and then began to subside. Fourteen days after the last application, healing was complete and no signs of irritation remained. Average daily scores are given in Table 14.

2. Poly-MDI: There was no reaction on the first 3 exposure days. On day 4, two rabbits showed a slight erythema on abraded skin. By the next day, 3 rabbits showed moderate edema and erythema. By day 9, all 6 rabbits showed reactions ranging from slight to moderate. This continued through day 17, when the rabbits showed only slight reaction.

Supporting data are given in Table 14.

F. Respiratory Range Find

1. Vapors

a. TDI: Concentration in the chamber was determined by GLC to be approximately 480 ppm. At this level, 2/6 rats died, one at 24 hours after exposure, and one at 72 hours post exposure. Both showed pulmonary edema and congestion. Survivors were sacrificed at 14 days, and the lungs were found to be pale and emphysematous. No other pathologic conditions were noted.

b. MDI: Concentration of this compound was less than could be determined by our GLC procedure, however, deposits on the exposure chamber walls indicated that some MDI was present in the chamber. None of the animals died. At the conclusion of the exposure, 5/6 rats showed respiratory distress in the form of rales. This disappeared by 12 hours, and all the rats were alive and healthy at 14 days. At autopsy there were no significant gross or microscopic changes.

c. Poly-MDI: All rats survived the exposure, and all had respiratory distress evidenced by rales. At 14 days, all 6 were alive and healthy. These rats were sacrificed and found to have no abnormal tissue changes.

d. Poly-MDA: GLC monitoring of the chamber showed practically no Poly-MDA to be present in the chamber. The 6 rats did not show any respiratory distress, and all 6 were alive and healthy. At 14 days, they were sacrificed and no gross changes were noted.

2. Aerosols

(1) First Method

a. TDI: There were no deaths as late as 14 days after exposure, although animals gave evidence of respiratory distress (wheezing sounds) for the first one or two days. At sacrifice, all 6 showed evidence of irritation in the form of dark mottled lungs.

b. MDI: No signs of toxicity were noted. There were no deaths as late as 14 days after exposure. Lungs appeared normal at autopsy.

c. Poly-MDI: No signs of toxicity were noted. There were no deaths as late as 14 days after exposure. At autopsy, lungs appeared mottled red on a dull pink background.

d. Poly-MDA: No signs of toxicity were noted. There were no deaths as late as 14 days after exposure. At autopsy, lungs appeared inflamed and did not deflate completely.

(2) Second Method

No deaths occurred in any of the groups, including the acetone control group. Animals exposed to TDI gave early signs of respiratory distress which disappeared by the second or third day. Animals sprayed with MDI exhibited similar but less intense signs. Neither Poly-MDI, Poly-MDA or acetone produced any signs.

At autopsy the lungs of all animals were examined. Animals exposed to TDI, MDI, Poly-MDI and Poly-MDA did not deflate entirely, and showed various degrees of inflammation. The lungs of animals exposed to MDI and TDI showed somewhat greater mottling.

The lungs of animals exposed to acetone aerosol alone deflated completely and were somewhat darker in color than normal, but not inflamed.

IV. DISCUSSION

The findings of this study indicate that the toxicity of the sample of TDI used in this investigation was similar to that which has been reported by other investigators. Banks (9) reported that the LD_{50} value in rats by the oral route for TDI was 5800 mg/kg, that the skin toxicity exceeded 16,000 mg/kg, and that the toxicity on inhalation lay between 60 and 600 ppm. Eye irritation was reported as extreme. A study on PAPI, a diisocyanate reported by the Upjohn Company (10) to be principally polymethylenepolyphenylene polyisocyanate, furnishes some additional data to which our results on the MDI and Poly-MDI could be compared. In that report there were no deaths on exposure to saturated vapors of PAPI, though following 6 hours exposure at concentrations which approach a total air load of 2.2 ppm mortality occurred. No toxicity was obtained when single doses of 10,000 mg/kg or less when given orally to rats. Mild irritation resulted from instillation into the eyes of animals; acute dermal LD_{50} in rabbits was determined to be greater than 9.4 gm/kg.

The data obtained by our toxicity studies are summarized in Table 15. While the data generated by experiments in this laboratory indicate that Poly-MDI would be rated as an extreme irritant to the eyes using standard scoring, the compound was not irritating when read at 7 days and is comparable to the PAPI. With reference to this table it should be noted that TDI

has a slightly greater toxicity than MDI, based on the lower oral LD_{50} value for TDI, the lethality produced in rats on vapor exposure, and the slightly higher irritantcy score. The Poly-MDI was the least toxic of the compounds, though its irritantcy potential was similar to MDI and TDI. The toxicity class as determined for these compounds was not more than "moderately toxic" in the most severe case and was "practically non-toxic" by most routes. The skin irritating properties are also low, though an appraisal could not be made of sensitizing properties by the tests carried out. TDI is of course known to produce both pulmonary tract and skin irritation. As assessed by the repeated skin application tests of MDI and Poly-MDI, both were only slight skin irritants. Based on their toxicity determination, it may be concluded that these compounds do not present any unusual toxicity problems. There is a known hazard associated with TDI based on its use experience which indicates a problem may occur on chronic exposures. The hazard here arises from the asthmatic-like syndrome which has occurred in a small number of exposed persons. Walworth and Virchow (12) indicated that most illnesses among workers in an activity manufacturing polyurethan foam appeared after three or four weeks of exposure to TDI and generally did not occur thereafter. There was apparently a relationship between the air concentration and the number of persons affected with the allergic response. Concentration limits below 0.1 ppm have been recommended. Industrial experience has shown that concentrations of TDI greater than 0.5 ppm is irritating to the nose and throat. While MDI is somewhat less toxic than TDI, the

same general problems associated with TDI probably will occur with MDI. The frequency of this may be somewhat lower, based on the lower vapor pressures of MDI and Poly-MDI. One report indicated that there had been a case of induced respiratory sensitivity in a person who had been working for four years with MDI (13). No cases have come to our attention of any problems with Poly-MDI, and it is probable that based on its structure no respiratory tract difficulties would be associated with absorption of this compound.

Konzen (14) has demonstrated the production of antibodies in persons exposed to MDI when concentrations reached 1.3 ppm/minute. He recommended this as a diagnostic proof of recent exposure to isocyanates. No evidence of a sensitivity response was found by this test. Again individual susceptibility was indicated as important in the response to this type of agent, since pharmacologic response occurred in only one of seven individuals who had an average exposure of 0.13 ppm for 30 minutes.

In summary, then, based on the hygienic experiences obtained with TDI, it is possible to formulate safe-handling procedures to decrease the likelihood of untoward physiologic responses from working with MDI. These recommended procedures would include the following: Effort should be expended in avoiding any unnecessary contact with the material, especially insofar as breathing vapors is concerned. While TDI vapors may be released from foams or coatings that are not completely cured, this would be unlikely with MDI due to its lower vapor pressure. The material should be kept out of the eyes, off the skin and off clothing. Hands

should be washed before eating or smoking. The following protective equipment is useful: Impervious gloves, head covers, coveralls, chemical-type goggles and face shields. When spray application is used or other situations exist where satisfactory control of vapors cannot be maintained, a filter mask capable of removing aerosol particles should be used. Preplacement physical examinations should be conducted, with documentation of the status of the respiratory tract and elimination of any persons who have strong family histories of allergies, who have had significant allergic responses to other agents in the past or who have suffered from chronic bronchitis, bronchial asthma or emphysema. Adequate ventilation should be provided and the exhaust vapors should be released outside the area at a point where possible re-entry of the vapors to other occupied areas would not take place.

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Table 1: Results of Intragastric Injection in the Rat with TDI

Dose in mg/kg	Mortality	Signs of Toxicity	Survival Time (Days)
6,000	4/6	Arching, hyporeflexia, lethargy. Dead animals show plastic formations in gut	2 - 5
5,000	3/6		2 - 5
4,500	2/6		2 - 5
4,000	0/6	---	---

LD_{50} = 5,200 mg/kg with 95% confidence limits of 4,193-6,448 mg/kg

Table 2: Results of Intragastric Injection in the Rat with MDI

Dose in mg/kg	Mortality	Signs of Toxicity	Survival Time (Days)
16,000	4/6	Arching, hyporeflexia, lethargy, hypothermy	2 - 4
8,000	3/6		2 - 4
4,000	1/6		2
2,000	0/6	---	---

LD_{50} = 9,200 mg/kg with 95% confidence limits of 4,700-19,000 mg/kg

Table 3: Results of Intragast.. :n the Rat with Poly-MDI

Dose in mg/kg	Mortality	Signs of Toxicity	Survival Time (Days)
24,000	0/6	--	--
30,000	0/6	--	--
49,000	3/6	Hyporeflexia, hypothermy, paresis, diarrhea	12

Approximate LD_{50} estimated as 49.0 g/kg.

Table 4: Results of Intragastric Injection in the Rat with Poly-MDA

Dose in mg/kg	Mortality	Signs of Toxicity	Survival Time (Days)
500	1/2	Arching, loss of motor ability, piloerection	3
1000	1/2		1
2000	2/2		1
5000	2/2		1

Approximate LD_{50} value 1000 mg/kg by the method of Deichmann(7)

Table 5: Results of Primary - Study with TDI

Time of Reading	Animal Number	Cornea		Iris	Conjujctivae		
		Opacity	Area		Redness	Discharge	Chemosis
24 hour	D 71	1	4	1	2	1	4
	D 74	1	4	2	3	1	4
	D 77	1	4	2	3	1	4
	D 78	1	4	2	2	1	4
	D 80	0	0	0	3	2	4
	D 81	0	0	0	3	2	4
24 Hour Average 35.2							
48 hour	D 71	0	0	0	3	0	3
	D 74	1	4	2	3	3	4
	D 77	0	0	1	3	1	2
	D 78	0	0	1	3	3	4
	D 80	1	4	1	3	3	4
	D 81	0	0	1	3	2	3
48 Hour Average 28.[illegible]							
72 hour	D 71	0	0	0	2	0	2
	D 74	2	1	1	3	3	4
	D 77	0	0	0	3	1	2
	D 78	1	4	1	3	3	4
	D 80	1	4	1	3	2	4
	D 81	0	0	0	2	3	4
72 Hour Average 27.2							

Table 6: Results of Primary Eye Irritation Study with MDI

Time of Reading	Animal Number	Cornea		Iris	Conjunctivae		
		Opacity	Area		Redness	Discharge	Chemosis
24 hour	D 95	1	4	2	3	3	3
	D 96	0	0	1	3	2	2
	D 97	0	0	1	3	3	2
	D 98	0	0	0	2	2	1
	D 99	1	4	2	2	3	4
	D 11	1	4	2	3	3	4
24 Hour Average 32.7							
48 hour	D 95	1	4	2	3	2	3
	D 96	0	0	1	2	2	3
	D 97	0	0	2	3	2	3
	D 98	0	0	0	1	0	1
	D 99	0	0	1	2	1	2
	E 11	?	?	?	3	3	4
48 Hour Average 21.6							
72 hour	D 95	1	4	1	3	1	2
	D 96	0	0	1	3	1	2
	D 97	0	0	1	3	2	2
	D 98	0	0	0	1	0	0
	D 99	1	1	0	2	1	2
	E 11	?	?	?	3	3	4
72 Hour Average 18.3							

Table 7: Results of Primary Eye Irritation Study with Poly-MDI

Time of Reading	Animal Number	Cornea		Iris	Conjunctivae		
		Opacity	Area		Redness	Discharge	Chemosis
24 hour	D 72	0	0	1	3	2	4
	D 73	0	0	0	1	1	1
	D 75	0	0	0	0	0	2
	D 76	0	0	1	2	1	3
	D 79	0	0	0	2	1	2
	D 82	0	0	1	2	1	4
24 Hour Average 13.2							
48 hour	D 72	1	4	1	3	2	4
	D 73	0	0	1	2	1	0
	D 75	0	0	1	2	2	3
	D 76	0	0	1	3	2	1
	D 79	0	0	1	2	1	1
	D 82	0	0	0	2	2	4
48 Hour Average 19.8							
72 hour	D 72	2	4	1	3	3	4
	D 73	0	0	0	2	1	0
	D 75	0	0	0	3	1	3
	D 76	0	0	0	2	1	1
	D 79	0	0	0	2	0	1
	D 82	0	0	0	2	3	4
72 Hour Average 19.5							

Table 8: Results of Primary Eye Irritation Study with Poly-MDA

Time of Reading	Animal Number	Cornea		Iris	Conjunctivae		
		Opacity	Area		Redness	Discharge	Chemosis
24 hour	E 8	0	0	0	1	0	0
	E 9	0	0	0	0	0	0
	E 10	0	0	0	1	0	0
	E 13	0	0	0	1	0	0
	E 14	0	0	0	0	0	0
	E 15	0	0	0	1	0	0
24 Hour Average 1.3							
48 hour	E 8	0	0	0	0	0	0
	E 9	0	0	0	0	0	0
	E 10	0	0	0	1	0	0
	E 13	0	0	0	0	0	0
	E 14	0	0	0	0	0	0
	E 15	0	0	0	1	0	0
48 Hour Average 0.7							
72 hour	E 8	0	0	0	0	0	0
	E 9	0	0	0	1	0	0
	E 10	0	0	0	0	0	0
	E 13	0	0	0	0	0	0
	E 14	0	0	0	0	0	0
	E 15	0	0	0	1	0	0
72 Hour Average 0.7							

Table 9: Evaluation of Skin Reactions

	Value[1]
Erythema and eschar formation:	
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4
Edema formation:	
No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised approximately 1 millimeter)	3
Severe edema (raised more than 1 millimeter and extending beyond the area of exposure)	4

[1]The "value" recorded for each reading is the average value of the six or more animals subject to the test.

Table 10: Results of Primary Skin Irritation Study with TDI

Time of Reading	Animal Number	Abraded Skin		Intact Skin	
		Edema	Erythema	Edema	Erythema
24 hours	D 77	0	0	0	0
	D 78	1	0	1	0
	D 79	1	0	1	0
	D 80	1	0	0	0
	D 81	1	0	0	0
	D 82	1	0	1	0
72 hours	D 77	0	0	0	0
	D 78	1	0	1	0
	D 79	1	0	2	0
	D 80	1	1	0	1
	D 81	1	1	0	1
	D 82	0	0	0	0
Combined Average: 0.8					

Table 11: Results of Primary Skin Irritation Study with MDI

Time of Reading	Animal Number	Abraded Skin		Intact Skin	
		Edema	Erythema	Edema	Erythema
24 hours	D 71	0	0	0	0
	D 72	0	0	0	0
	D 73	0	0	0	0
	D 74	0	0	0	0
	D 75	1	0	0	0
	D 76	0	0	0	0
72 hours	D 71	0	1	0	0
	D 72	0	0	0	0
	D 73	0	0	0	0
	D 74	1	1	1	1
	D 75	1	1	0	1
	D 76	1	0	1	0
Combined Average: 0.5					

Table 12: Results of Primary Skin Irritation Study with Poly-MDI

Time of Reading	Animal Number	Abraded Skin		Intact Skin	
		Edema	Erythema	Edema	Erythema
24 hours	D 77	0	1	0	0
	D 78	0	1	0	0
	D 79	0	1	0	0
	D 80	0	0	0	0
	D 81	0	0	0	0
	D 82	1	0	0	0
72 hours	D 77	1	0	0	0
	D 78	0	1	0	0
	D 79	0	1	0	0
	D 80	1	1	1	1
	D 81	0	0	0	0
	D 82	0	0	0	0
Combined Average: 0.5					

Table 13: Results of Primary Skin Irritation Study with Poly-MDA

Time of Reading	Animal Number	Abraded Skin		Intact Skin	
		Edema	Erythema	Edema	Erythema
24 hours	D 71	0	1	0	1
	D 72	0	1	0	0
	D 73	0	1	0	0
	D 74	0	1	0	1
	D 75	1	0	0	0
	D 76	0	2	0	0
72 hours	D 71	1	1	0	1
	D 72	0	0	0	0
	D 73	0	0	0	0
	D 74	0	1	0	1
	D 75	0	0	0	0
	D 76	0	0	0	0
Combined Average: 0.6					

Table 14: Results of Repeated Application for 20 Days of MDI and Poly-MDI on Rabbit Skin

Day	Compound MDI		Compound Poly-MDI	
	Abraded	Intact	Abraded	Intact
1	0	0	0	0
2	0.2	1.0	0	0
3	1.2	1.2	0.2	0
4	1.2	1.2	0	0
5	1.0	0.8	0.3	0.3
6	0.8	0.3	0.3	0.2
7	0.8	0.7	1.5	0.7
8	0.8	0.7	1.5	0.7
9	1.2	0.5	2.0	0.5
10	1.1	0.5	2.0	0.5
11	1.2	1.3	1.8	1.5
12	1.3	1.5	1.8	2.2
13	2.0	2.3	2.8	2.2
14	0.9	0.3	1.3	0.5
15	1.5	1.0	1.2	0.3
16	1.3	1.0	1.7	1.3
17	0.9	0.9	2.0	0.9
18	1.5	0.9	1.5	0.9
19	1.2	0.9	1.8	1.5
20	1.0	0.5	1.7	1.7

Table 15: Summary of the Toxicity Classification of the Four Compounds Studied

Toxicity Evaluation	Compound			
	TDI	MDI	Poly-MDI	Poly-MDA
Oral	Slightly Toxic	Practically Non-Toxic	Relatively Harmless	Slightly Toxic
Percutaneous	Practi-cally Non-Toxic	Practically Non-Toxic	Practically Non-Toxic	Practically Non-Toxic
Vapor	Moderately Toxic	SVNTARP[a]	SVNTARP	SVNTARP
Eye Irritantcy	Extreme	Extreme	Extreme	Minimal
Skin Irritantcy	Minimal	Minimal	Minimal	Minimal
Chronic Skin Irritantcy	Slight[b]	Slight	Slight	Slight[b]

(a) SVNTARP = saturated vapors non-toxic at room temperature

(b) = extrapolated data

Table 16: Verbal Description of Irritation Scores Used at The Hine Laboratories, Inc.

EYE IRRITATION

Category	Score
Minimal	0 - 2
Slight	2+- 4
Moderate	4+-10
Marked	10+-15
Extreme	>15 and/or corneal damage

SKIN IRRITATION

Category	Score
Absent	<0.2
Minimal	0.2 - 1
Slight	1 - 2
Moderate	2.1 - 4
Severe	4.1 - 7
Escharotic	>7

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