90-101

90-101

NIOSH

Current Intelligence Bulletin 53

December 1989

TOLUENE DIISOCYANATE (TDI) AND TOLUENEDIAMINE (TDA)

Evidence of Carcinogenicity

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

CURRENT INTELLIGENCE BULLETIN 53

TOLUENE DIISOCYANATE (TDI) and TOLUENEDIAMINE (TDA)

Evidence of Carcinogenicity

U.S. Department of Health and Human Services
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health
Division of Standards Development and Technology Transfer

December 1989

DISCLAIMER

Mention of the name of any company or product does not constitute endorsement by the National Institute for Occupational Safety and Health.

This document is in the public domain and may be freely copied or reprinted. Copies of this and other NIOSH documents are available from

Publications Dissemination, DSDTT
National Institute for Occupational Safety and Health
4676 Columbia Parkway
Cincinnati, Ohio 45226
(513) 533-8287

For information about other occupational safety and health problems, call 1-800-35-NIOSH

DHHS (NIOSH) Publication No. 90-101

FOREWORD

Current Intelligence Bulletins (CIBs) are issued by the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control, Atlanta, Georgia, to disseminate new scientific information about occupational hazards. A CIB may draw attention to a formerly unrecognized hazard, report new data on a known hazard, or disseminate information on hazard control.

CIBs are distributed to representatives of academia, industry, organized labor, public health agencies, and public interest groups, as well as to Federal agencies responsible for ensuring the safety and health of workers.

Copies are available to individuals upon request from the Division of Standards Development and Technology Transfer, NIOSH (Robert A. Taft Laboratories, 4676 Columbia Parkway, Cincinnati, Ohio 45226). We welcome suggestions concerning the content, style, and distribution of these documents.

The purpose of this bulletin is to disseminate new information on the potential carcinogenicity of toluene diisocyanate (TDI) and toluenediamine (TDA). Recent data from studies of chronic toxicity in animals have produced evidence that cancer is associated with exposure to commercial-grade TDI (an 80:20 mixture of 2,4- and 2,6-TDI) and to 2,4-TDA, a reagent used in the manufacture of TDI and a hydrolysis product of TDI. The tumorigenic responses observed in both rats and mice treated with TDI and TDA meet the criteria of the Occupational Safety and Health Administration (OSHA) Cancer Policy for classifying a substance as a potential occupational carcinogen [Title 29 of the *Code of Federal Regulations*, Section 1990.112]. Because insufficient data exist to evaluate the carcinogenic potential of the other TDI and TDA isomers, NIOSH concludes that occupational exposure to all TDI and TDA isomers should be reduced. NIOSH therefore recommends that all the isomers of TDI and TDA be regarded as potential occupational carcinogens and that occupational exposures be limited to the lowest feasible concentrations. Although the potential for TDI- or TDA-induced cancer in humans has not been determined, reducing exposure to TDI and TDA in the workplace should reduce the risk.

NIOSH urges (1) that producers and users of TDI and TDA disseminate this information to their workers and customers, (2) that professional and trade associations and unions inform their members of the potential hazards of working with TDI and TDA, and (3) that

appropriate engineering controls and work practices be used to minimize the exposure of workers. Readers seeking more detailed information on the studies cited in this CIB are encouraged to consult the original publications.

J. Donald Millar, M.D., D.T.P.H. (Lond.)
Assistant Surgeon General
Director, National Institute for
Occupational Safety and Health
Centers for Disease Control

ABSTRACT

Experimental studies in animals have demonstrated that toluene diisocyanate (TDI) is a carcinogen. When rats and mice were exposed orally to commercial-grade TDI (an 80:20 mixture of 2,4- and 2,6-TDI), tumors were induced in both species. The systemic nature of TDI carcinogenicity was demonstrated by the appearance of tumors at multiple sites (pancreas, liver, skin, mammary glands, and circulatory system). Although not statistically significant, rare brain tumors were found in rats exposed to TDI (two gliomas and one pinealoma). Historical controls have a low incidence of gliomas and no reported incidence of pinealomas.

Experimental studies in animals have also demonstrated that 2,4-toluenediamine (TDA), a hydrolysis product of 2,4-TDI, is a carcinogen. When rats and mice were exposed orally to TDA, tumors were induced in the livers, skin, and mammary glands of both species.

The National Institute for Occupational Safety and Health (NIOSH) concludes that the data on carcinogenicity provide sufficient evidence to warrant concern about the potential consequences of occupational exposure to TDI and TDA. The tumorigenic responses observed in both rats and mice treated with either TDI or TDA meet the criteria of the Occupational Safety and Health Administration (OSHA) Cancer Policy for classifying a substance as a potential occupational carcinogen [29 CFR 1990]. Although the carcinogenic potential of the other TDI and TDA isomers has not been adequately determined, exposure to all TDI and TDA isomers should be reduced. NIOSH therefore recommends that all the isomers of TDI and TDA be regarded as potential occupational carcinogens and that occupational exposures to TDI and TDA be limited to the lowest feasible concentrations. The potential for TDI- or TDA-induced cancer in humans has not been determined, but the risk of developing cancer should be decreased by reducing exposure to TDI and TDA in the workplace.

CONTENTS

CURRENT INTELLIGENCE BULLETIN 53

TOLUENE DIISOCYANATE (TDI) AND TOLUENEDIAMINE (TDA)

Evidence of Carcinogenicity

INTRODUCTION

The purpose of this bulletin is to disseminate recent information on the potential carcinogenicity of toluene diisocyanate (TDI) and toluenediamine (TDA) to humans. Recent studies of chronic effects in animals have produced evidence that cancer is associated with exposure to commercial-grade TDI (an 80:20 mixture of 2,4- and 2,6-TDI) and to 2,4-TDA, a hydrolysis product of TDI. This bulletin describes the results and implications of those animal studies, presents the known human health effects of TDI and TDA, and suggests guidelines for minimizing occupational exposures.

CHEMICAL AND PHYSICAL PROPERTIES

TDI is manufactured by the reaction of TDA with carbonyl chloride (phosgene). TDI is a colorless-to-amber liquid with a pungent odor. Commercial-grade TDI (which represents more than 95% of TDI industrial usage) is an 80:20 mixture of the two chemical isomers 2,4- and 2,6-TDI. Other chemical and physical properties of commercial-grade TDI are listed in Table 1.

TDA is manufactured by nitrating toluene to produce dinitrotoluene, which is then catalytically reduced to TDA. TDA is a colorless solid that tends to darken on storage and exposure to air. Other chemical and physical properties of 2,4-TDA are listed in Table 1.

PRODUCTION, USE, AND POTENTIAL FOR OCCUPATIONAL EXPOSURE

TDI

TDI is one of the most industrially important diisocyanates. In 1986, 650 million pounds of TDI were produced in the United States, and the demand is expected to rise in the future [American Chemical Society 1987]. TDI is widely used in the manufacture of flexible polyurethane foams, elastomers, surface coatings, fibers, sealants, and adhesives. Applications and uses for these products include packaging, insulation materials, upholstery, and shoe soles.

The major route of occupational exposure to TDI is by inhalation of the vapor; exposure may also occur through dermal contact during the handling of liquid TDI. Occupational exposure normally occurs during the production and use of TDI, particularly during the mixing and foaming processes in the polyurethane foam industry. Exposures to airborne TDI may also occur as a result of the melting or burning of polyurethane foams during firefighting. An estimated 34,466 workers were exposed to TDI in the United States during the period 1981 to 1983 [NIOSH 1983]. Representative information on the occurrence of air-

Table 1.—Chemical and physical properties of commercial-grade TDI (80% 2, 4-TDI and 20% 2, 6-TDI)* and 2, 4-TDA†

Chemical identity	TDI	2, 4–TDA
CAS§ registry number	26471-62-5	95-80-7
RTECS** accession number	NQ9490000	XS9625000
Synonyms	Tolylene diisocyanate; isocyanic acid; methyl-meta-phenylene isocyanate	3-Amino-p-toluidine; 1, 3-diamino-4-methyl-benzene; 4-methyl-phenylene-diamine; 2, 4-diamino-toluene
Formula	$CH_3C_6H_3(NCO)_2$	$CH_3C_6H_3(NH_2)_2$
Molecular weight	174.2	122.2
Flash point	135°C (275°F)	149°C (300°F)
Specific gravity of liquid	1.22 at 25°C (77°F)	1.045 at 100°C (212°F)
Boiling point	250°C (482°F)	292°C (558°F)
Freezing/melting point	20° to 22°C (68° to 72°F)	99°C (210°F)
Vapor pressure	0.05 mm Hg at 25°C (77°F)	1.0 mm Hg at 107°C (224°F)
Solubility in:		
Water	Insoluble	Soluble
Alcohol	Soluble	Soluble
Ethyl ether	Soluble	Soluble
Acetone	Soluble	Unspecified
Benzene	Soluble	Soluble
Carbon tetrachloride	Soluble	Unspecified

* Data from Upjohn Company [1970].
† Data from IARC [1978].
§ Chemical Abstracts Service.
** Registry of Toxic Effects of Chemical Substances [NIOSH 1987c].

borne TDI in the work environment is listed in the Appendix.

TDA

In 1984, 187 million pounds of TDA were produced in the United States [USITC 1984]. Nearly all of the TDA produced is used as part of a mixture (80% 2,4-TDA and 20% 2,6-TDA) for the production of TDI. TDA is also used to make dyes for textiles, leathers, furs, wood, and biological stains; 2,4-TDA is no longer used in the United States in any hair dye formulations [Hecht 1978].

Workers may be exposed to TDA by dermal contact and, less frequently, by inhalation. Although solid TDA does not normally present an inhalation hazard, it may also be handled and shipped in the molten state, at which time the vapors may present a hazard. An estimated 8,513 workers were exposed to TDA in the United States during the period 1981 to 1983 [NIOSH 1983]. Potential for worker exposure is minimal because more than 99% of the TDA produced is used captively to produce TDI, usually at the same site [NTP 1985]. During the manufacture of TDA, TDA concentrations have ranged from 0.0002 to 0.1241 parts of TDA per million parts (ppm) of air, or 0.001 to 0.620 milligrams per cubic meter (mg/m^3) [Ahrenholz and Meyer 1980, 1982].

EXPOSURE LIMITS

Occupational exposure standards and recommendations for TDI are based on respiratory irritation and sensitization. The current OSHA permissible exposure limit (PEL) for TDI is 0.005 ppm (0.04 mg/m^3) as an 8-hr time-weighted average (TWA) concentration and 0.02 ppm (0.15 mg/m^3) as a short-term exposure limit (STEL) for any 15-minute period [54 FR* 2,662 (1989)]. In two separate criteria documents, NIOSH has recommended that exposure to TDI be limited to 0.005 ppm (0.036 mg/m^3†) as a TWA concentration for up to a 10-hour workday and a 40-hour workweek, with a ceiling concentration of 0.02 ppm (0.14 mg/m^3) for any 10-minute period [NIOSH 1973, 1978]. The NIOSH recommended exposure limit (REL) was intended to prevent acute and chronic irritation and sensitization of workers but not to prevent responses in workers who are already sensitized. Available data do not indicate a concentration at which TDI vapor fails to produce adverse reactions in sensitized persons. The American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV®) for TDI is 0.005 ppm (0.04 mg/m^3) as an 8-hour TWA concentration and 0.02 ppm (0.15 mg/m^3) as a STEL [ACGIH 1988].

No occupational exposure limit for TDA has been established by OSHA, NIOSH, or ACGIH.

STUDIES OF MUTAGENICITY AND CARCINOGENICITY IN ANIMALS

Mutagenic Effects

TDI

At concentrations of 125 to 500 micrograms/plate, commercial-grade TDI§ was mutagenic to *Salmonella typhimurium* strains TA98, TA100, and TA1538 in the presence of a metabolic activator [Andersen et al. 1980]. Commercial-grade TDI and pure 2,6-TDI were tested for mutagenicity in *S. typhimurium* strains in the presence and absence of S-9 liver fractions from male Sprague-Dawley rats or Syrian golden hamsters treated with Aroclor 1254 [NTP 1986]. Only after metabolic activation did the commercial-grade TDI and the pure 2,6-TDI cause dose-dependent mutagenic responses in *S. typhimurium* strains TA98 and TA100.

*Federal Register. See FR in references.

†OSHA, NIOSH, and ACGIH may report slightly different metric equivalents because of differences in rounding.

§Unless otherwise specified, the term "commercial-grade TDI" refers to the 80:20 mixture of the two isomers 2,4- and 2,6-TDI, respectively.

TDA

2,4-TDA, a hydrolysis product of 2,4-TDI, showed mutagenic activity after metabolic activation in S. typhimurium strains TA98, TA100, and TA1538 [Ames et al. 1975; Andersen et al. 1980], whereas 2,6-TDA was mutagenic only in *S. typhimurium* strains TA98 and TA1538 in the presence of a metabolic activator [Pienta et al. 1977; Florin et al. 1980]. 2,5-TDA showed mutagenic activity after metabolic activation in *S. typhimurium* strain TA1538 [Ames et al. 1975]. These findings are consistent with previous reports in the literature in which 2,4-TDA induced sex-linked, recessive, lethal mutations when fed to adult male *Drosophila melanogaster* [Blijleven 1977] and was mutagenic to *S. typhimurium* strain TA1538 following metabolic activation by S9 preparations from rats and mice treated with ß-naphthoflavone [Dybing and Thorgeirsson 1977]. Although 2,4-TDA induced unscheduled DNA synthesis (UDS) in rat hepatocytes, 2,6-TDA did not [Mirsalis et al. 1982]. Four TDA isomers (2,4-, 2,5-, 2,6-, and 3,4-TDA) enhanced the transformation of primary hamster embryo cells (HEC) by Symian adenovirus 7 (SA7) and transformed secondary HEC [Greene and Friedman 1980].

Carcinogenic Effects

TDI

A comprehensive investigation of TDI carcinogenicity has recently been completed as part of the National Toxicology Program (NTP) [NTP 1986]. In this bioassay, F344/N rats (two groups of 50 males and two groups of 50 females) and B6C3F1 mice (two groups of 50 males and two groups of 50 females) received commercial-grade TDI in corn oil by gavage 5 days/week for 105 or 106 weeks. Target doses and estimated average doses received for each group of 50 animals are listed in Table 2. Control groups of 50 males and 50 females of each species received only corn oil on the same schedule as the other groups. Analyses indicated that the TDI had reacted with the corn oil vehicle and produced unidentified reaction compounds, resulting in gavage concentrations that were actually 77% to 90% of theoretical values. The NTP Peer Review Panel concluded that the reactivity of the TDI with corn oil did not compromise the conclusions of the study and that the TDI-dose-related increases in benign and malignant tumors in rats and mice in the 2-year studies [NTP 1986] fit the NTP criteria for clear evidence of carcinogenic activity [NTP 1987]. Under the conditions of these gavage studies, commercial-grade TDI caused pancreatic acinar cell adenomas in male rats ($p<0.05$); pancreatic islet cell adenomas ($p\leq0.01$), neoplastic nodules of the liver ($p<0.05$), and mammary gland fibroadenomas ($p<0.001$) in female rats; and subcutaneous fibromas and fibrosarcomas (combined) in male ($p<0.01$) and female ($p<0.001$) rats. The commercial-grade TDI also caused hepatocellular adenomas ($p\leq0.001$) as well as hemangiomas or hemangiosarcomas (combined) ($p\leq0.01$) in female mice. Commercial-grade TDI was not shown to be carcinogenic for male mice. Although not statistically significant, rare brain tumors were found in male rats exposed to TDI (two gliomas and one pinealoma). Historical controls have a low incidence of gliomas and no reported incidence of pinealomas.

In an inhalation study [Loeser 1983], groups of 126 male and 126 female Sprague-Dawley CD rats and groups of 120 male and 120 female CD-1 mice were exposed to 0, 0.05, or 0.15 ppm of commercial-grade TDI for 6 hours/day, 5 days/week over a 2-year period. The results showed no TDI-induced neoplasms in either species. The exposure levels used by Loeser have been criticized because they did not achieve a maximum tolerated dose (i.e., the highest dose that produces some toxic response without compromising an animal's survival for its full expected life span) [NTP 1986]. Thus the doses may not have been sufficient to produce a carcinogenic response.

Table 2.—Target doses and estimated average doses of TDI received* [NTP 1986]

	Rats				Mice			
	Males		Females		Males		Females	
Item	I†	II	I	II	I	II	I	II
Target dose, mg/kg per day	30	60	60	120	120	240	60	120
Estimated average dose received, mg/kg per day	23	49	49	108	108	202	49	108
% of target dose received	77	82	82	90	90	84	82	90

* Source: NTP [1986].
† Group number.

TDA

Isomers of TDI may be converted to the corresponding isomers of toluenediamine (TDA) on contact with water [Chadwick and Cleveland 1981; Ulrich 1983]. The carcinogenicity of 2,4-TDA was first reported by Ito et al. [1969]. Two groups of 12 male Wistar rats were fed diets containing 0.06% or 0.1% 2,4-TDA for 30 to 36 weeks. A third group of 6 male rats was fed the basal diet alone. Eleven of 12 animals in the group fed 0.06% 2,4-TDA survived for 35 weeks; 7 of these had multiple hepatocellular carcinomas with metastases to the lymph nodes and omentum. Nine of 12 animals in the group fed 0.1% 2,4-TDA survived for 33 weeks, and all 9 had multiple hepatocellular carcinomas. In 6 of the 9 survivors, multiple metastases were present in the lymph nodes, omentum, or epididymis. No tumors were found in any of the controls.

A subsequent National Cancer Institute (NCI) evaluation of 2,4-TDA also showed it to be carcinogenic in F344/N rats and B6C3F$_1$ mice [NCI 1979]. Groups of 50 male and 50 female F344/N rats were given 2,4-TDA in the diet *ad libitum* at concentrations of 125 or 250 ppm for 40 weeks. Because weight gain was excessively depressed in both treated groups, doses were reduced to 50 and 100 ppm, respectively, and the treatment was continued for additional periods of 63 weeks for the low-dose groups, 39 weeks for the high-dose males, and 44 weeks for the high-dose females. Control groups of 20 male and 20 female rats were fed the basal diet. When incidences of hepatocellular carcinomas and neoplastic nodules were combined, dose-related linear trends occurred in males ($p = 0.014$) and females ($p = 0.008$). In addition, the incidence of mammary gland fibroadenomas was dose-related in treated female rats and statistically significant for those on the high dose ($p<0.001$). Furthermore, male rats showed a significantly increased incidence of subcutaneous fibromas ($p = 0.004$).

In another part of the NCI evaluation of TDA [NCI 1979], groups of 50 male and 50 female B6C3F$_1$ mice received 2,4-TDA in the diet *ad libitum* at concentrations of 100 or 200 ppm for 101 weeks. Control groups of 20 male and 20 female mice were fed the basal diet. A statistically significant incidence of hepatocellular carcinomas occurred in low-dose ($p = 0.007$) and high-dose ($p = 0.008$) female mice; a statistically significant increase also occurred in the incidence of lymphomas ($p<0.001$) in the low-dose female mice. No sig-

nificant increase in tumors occurred in male mice treated with 2,4-TDA.

The carcinogenic potential of 2,5-TDA was tested as its sulfate salt in F344 rats and B6C3F1 mice [NCI 1978]. Groups of 50 male and 50 female F344 rats were administered 0.06% or 0.2% 2,5-TDA sulfate in their diets *ad libitum* for 78 weeks followed by 28 to 31 weeks of observation. Groups of 50 male and 50 female B6C3F1 mice were administered 0.06% or 0.1% 2,5-TDA sulfate in their diets *ad libitum* for 78 weeks followed by 16 to 19 weeks of observation. All control groups (25 or 50 animals each) were fed the basal diet. NCI [1978] reported that a statistically significant incidence of lung tumors in high-dose female mice was not considered convincing evidence of a compound-related carcinogenic effect because high-dose and control mice were received in separate shipments and housed in separate rooms. Other flaws in the experimental design of this bioassay included using different mouse strains for the subchronic and chronic toxicity studies and placing the high-dose rats on the 2,5-TDA diet 11 months after the low-dose rats. In addition, low-dose mice began receiving their diet 2 weeks before the control group and 6 months before the high-dose group. Furthermore, the high-dose mice began receiving their diet 2 months after their controls. Under the conditions of this bioassay, 2,5-TDA sulfate was not carcinogenic in F344 rats or B6C3F1 mice [NCI 1978].

The dihydrochloride salt of the 2,6-isomer of TDA was tested for carcinogenicity in F344/N rats and B6C3F1 mice [NCI 1980]. Groups of 50 F344/N rats of each sex were given 2,6-TDA dihydrochloride in the diet *ad libitum* at concentrations of 250 or 500 ppm for 103 weeks; they were then observed for an additional week. Groups of 50 B6C3F1 mice of each sex were given 2,6-TDA dihydrochloride in the diet *ad libitum* at concentrations of 50 or 100 ppm for 103 weeks; they were then observed for an additional week. A dose-related but not statistically significant incidence of liver tumors occurred in treated male rats and female mice. The investigators concluded that under the conditions of this study, 2,6-TDA dihydrochloride was not carcinogenic for F344/N rats or B6C3F1 mice [NCI 1980].

NCI review panels for the 2,5- and 2,6-TDA studies have suggested that both 2,5- and 2,6-TDA be considered for retesting because of deficiencies in experimental design and study conduct and because both compounds were mutagenic in various *S. typhimurium* strains [NCI 1978, 1980].

Independent Evaluations of TDI and TDA Studies

The TDI data [Loeser 1983; NTP 1986] were recently evaluated by the International Agency for Research on Cancer (IARC) and the World Health Organization [IARC 1986; WHO 1987]. The IARC Working Group concluded that the increased incidence of malignant tumors in multiple species was sufficient evidence of the carcinogenicity of TDI in experimental animals. The WHO Task Group concluded that TDI should be treated as a potential human carcinogen and as a known animal carcinogen.

Clement Associates, Inc. [1982] independently reviewed a 1982 draft of the NTP TDI gavage study [NTP 1986] and the TDI inhalation study [Loeser 1983] for the International Isocyanate Institute, Inc. Because inhalation is the normal route of exposure to TDI, Clement Associates considered the Loeser [1983] study the more useful of the two for assessing the carcinogenic potential of TDI for humans, despite the lack of a maximum tolerated dose in the Loeser [1983] study. They further believed that the Loeser [1983] study adequately supported the conclusion that TDI was not carcinogenic to rats and mice under the conditions tested.

On the basis of studies in animals [Ito 1969; NCI 1979], IARC [1978, 1979, 1982] concluded that there is sufficient evidence to demonstrate the

carcinogenicity of 2,4-TDA. IARC assigns a classification of 2B to chemicals for which there is sufficient evidence of carcinogenicity in animals and inadequate data in humans. In addition, NTP lists 2,4-TDA as a substance "which may reasonably be anticipated to be a carcinogen" because there is sufficient evidence of carcinogenicity in experimental animals even though no evidence exists for humans [NTP 1985].

HUMAN HEALTH EFFECTS

TDI

TDI is a powerful irritant to the mucous membranes of the eyes and gastrointestinal and respiratory tracts [Fuchs and Valade 1951; Swensson et al. 1955; Upjohn Company 1970]. Direct skin contact with TDI can also cause a marked inflammatory reaction [Fisher 1967]. The irritant effects on the respiratory tract may progress to a chemical bronchitis characterized by severe bronchospasms [Williamson 1965]. TDI can also sensitize workers so that they are subject to severe asthma attacks, even when they are reexposed at concentrations below the NIOSH REL [NIOSH 1973, 1978]. No data are available on case reports or epidemiologic studies of TDI carcinogenicity to humans. However, NIOSH is currently conducting a cohort mortality study of workers exposed to TDI in the polyurethane foam manufacturing industry [Schnorr et al., in preparation].

TDA

Exposure to TDA may result in ataxia, tachycardia, nausea, vomiting, convulsions, and respiratory depression [von Oettingen 1941; Gosselin 1976; Occupational Health Services, Inc. 1987]. TDA can cause chemical cyanosis (i.e., bluish discoloration of the skin) by converting hemoglobin to methemoglobin [Air Products and Chemicals, Inc. 1986]. This compound can also cause fatty degeneration of the liver [von Oettingen 1941]. Repeated or prolonged contact with TDA can result in sensitization dermatitis, which can cause previously exposed individuals to experience redness and blistering of the skin upon reexposure. TDA can also be irritating to the eyes [Gosselin 1976; Occupational Health Services, Inc. 1987]. Data indicate that TDA (unlike TDI) does not induce occupational asthma in workers exposed to polyurethane foams [Candura and Moscato 1984]. No data are available on case reports or epidemiologic studies of TDA carcinogenicity to humans.

CONCLUSIONS

Recent animal studies have demonstrated that commercial-grade TDI and 2,4-TDA are carcinogenic in rats and mice. The pancreas and liver were the principal sites of tumor induction in male and female rats and in female mice treated with TDI. 2,4-TDA induced liver tumors in male and female rats and in female mice, and it induced mammary gland tumors in female rats and mice. Commercial-grade TDI, 2,6-TDI, and four TDA isomers (2,4-, 2,5-, 2,6-, and 3,4-TDA) were mutagenic in various *in vitro* test systems. No conclusion can be drawn about the carcinogenic potential of 2,5-TDA because of the previously mentioned flaws in the experimental design of the bioassay. No conclusion can be drawn about the carcinogenic potential of 2,6-TDA because the dose-related incidence of liver tumors in treated male rats and female mice was not statistically significant.

Currently, there is no epidemiologic evidence that any isomer of TDI or TDA has induced cancer in exposed workers; however, the positive data in other mammalian species suggest that the potential exists. NIOSH therefore concludes that commercial-grade TDI and 2,4-TDA are potential occupational carcinogens.

RESEARCH NEEDS

The following research needs have been identified:

- Development of improved sampling and analytical methods (including field validation) for determining airborne TDI and TDA concentrations
- Development of automated equipment for preventing worker exposure to TDI and TDA
- Identification of less hazardous chemicals that can be used as substitutes for TDI and TDA
- Performance of epidemiologic studies of TDI- and TDA-exposed workers
- Performance of animal studies that include maximum tolerated doses of 2,5- and 2,6-TDA
- Development of a biological monitoring method for TDI and TDA

RECOMMENDATIONS

Exposure to TDI and TDA has been shown to produce benign and malignant tumors in rats and mice. NIOSH therefore recommends that all TDI and TDA isomers or mixtures of isomers be regarded as potential occupational carcinogens* in conformance with the OSHA Cancer Policy [29 CFR 1990]. Though evidence does not exist to demonstrate the carcinogenicity of all TDI and TDA isomers, the NIOSH recommendation applies to all of them and to mixtures of these isomers because of the gravity of the potential health effect (cancer) and because TDI and TDA rarely, if ever, occur as pure isomers in the workplace.

The excess cancer risk for workers exposed to TDI and TDA has not yet been quantified, but the probability of developing cancer should be decreased by minimizing exposure. Employers should therefore assess the conditions under which workers may be exposed to TDI and TDA and reduce exposures to the lowest feasible concentrations.

GUIDELINES FOR MINIMIZING WORKER EXPOSURE TO TDI AND TDA

Because TDI and TDA are regarded by NIOSH as potential human carcinogens in the workplace, appropriate engineering and work practice controls should be used to reduce worker exposures to the lowest feasible concentrations. The guidelines and recommendations that follow are general and should be adapted to specific situations as required.

Exposure Monitoring

Each employer who manufactures, transports, packages, stores, or uses TDI or TDA in any capacity should determine whether a potential exists for any worker to be exposed to these chemicals.

Sampling Strategy

In work areas where exposures may occur, an initial survey should be done to determine the extent of worker exposure. TWA exposures should be determined by collecting samples over a full shift. When the potential for exposure is

*"'Potential occupational carcinogen' means any substance, or combination or mixture of substances, which causes an increased incidence of benign and/or malignant neoplasms, or a substantial decrease in the latency period between exposure and onset of neoplasms in humans or in one or more experimental mammalian species as the result of any oral, respiratory, or dermal exposure, or any other exposure which results in the induction of tumors at a site other than the site of administration. This definition also includes any substance which is metabolized into one or more potential occupational carcinogens by mammals." [29 CFR 1990.103]

periodic, short-term samples may be needed to replace or supplement full-shift sampling. Personal sampling (i.e., sampling conducted in the worker's breathing zone) is preferred over area sampling. Area sampling should be substituted only if the results can be used to approximate the worker's exposure. Sampling should be used to identify the sources of emissions so that effective engineering or work practice controls can be instituted.

If the initial survey indicates that no worker is exposed to TDI or TDA, sampling is recommended annually or whenever there are changes in production, process, controls, work practices, or weather conditions that may affect exposure conditions. If work environments are found to contain measurable concentrations of TDI or TDA, workers must wear respirators, and sampling should be conducted weekly until no measurable concentrations of TDI or TDA are noted in two consecutive surveys. Sampling should be conducted again 6 months after the second negative survey. If no measurable concentrations of TDI or TDA are noted after two consecutive biannual surveys, sampling should be conducted annually or whenever changes in production, process, controls, work practices, or weather conditions may affect exposure conditions.

The NIOSH *Occupational Exposure Sampling Strategy Manual* [Leidel et al. 1977] provides guidance for developing efficient strategies to monitor worker exposure to toxic chemicals. This manual contains information on determining the need for exposure monitoring, the number of samples to be collected, and appropriate sampling times.

Sampling Methods

A recommended sampling and analysis method for 2,4-TDI and 2,6-TDI vapors in air is NIOSH Method 2535 [NIOSH 1987d]. The TDI in a 2- to 170-liter (L) air sample (the volume of air required depends on the anticipated concentration of TDI in the ambient air) is collected at a flow rate of 0.2 to 1 liter/minute (L/min) on reagent-coated glass wool contained in a tube. The reagent *N*-(4-nitrophenylmethyl) propylamine (frequently called "nitro reagent"), reacts with 2,4- and 2,6-TDI to form the corresponding ureas. These ureas are extracted from the glass wool with methanol and quantified using high-performance liquid chromatography with ultraviolet spectrometric detection. The lower limit of TDI quantification for this method is 0.003 mg/m^3 for a 100-L air sample. NIOSH Method 2535 may be used for TDI vapors but not for TDI aerosols because aerosol particles probably are not efficiently trapped by the glass-wool plug, and the TDI in the trapped particles will react incompletely with the nitro reagent.

When TDI is present as an aerosol, NIOSH investigators determine its concentration by a modification of Method MDHS 25, developed by the Occupational Medicine and Hygiene Laboratory of Her Majesty's Health and Safety Executive [Health and Safety Executive 1987]. Air is sampled at a flow rate of 1 L/min through an impinger containing a solution of toluene and 1-(2-methoxyphenyl) piperazine, which reacts with isocyanates to form ureas. The sample is treated in the laboratory with acetic anhydride and then evaporated to dryness. After the residue is dissolved in methanol, the ureas are quantified by liquid chromatography with electrochemical detection. The lower limit of 2,4-TDI quantification for this method is 0.002 mg/m^3 for a 100-L air sample.

A sampling and analysis method for 2,4- or 2,6-TDA is OSHA Method 65 [Elskamp 1987]. Air is sampled at a flow rate of 1 L/min through a 37-millimeter (mm) glass fiber filter coated with sulfuric acid. Within 10 hours (hr) after sampling, the filter must be transferred to 2 milliliters (mL) of water for storage. The aqueous solution is treated in the laboratory with sodium hydroxide and shaken with

toluene; an aliquot of the resulting toluene solution is then treated with heptafluorobutyryl anhydride. The resulting bis(heptafluorobutyryl)amides formed from the 2,4- and 2,6-TDA are quantified by gas chromatography with electron-capture detection. With a 100-L air sample, the lower limit of quantification is 0.00006 mg/m^3 for 2,4- and 2,6-TDA. In this method, 2,4- and 2,6-TDI are positive interferences to the determination of the corresponding diamine.

Although not validated by NIOSH, other published methods may also be suitable for monitoring TDA in the workplace. Some of these methods yield quantitative data for both the diamines and the diisocyanates [Holdren et al. 1984; Skarping et al. 1985; Dalene et al. 1988], whereas another method quantifies both diamines and diisocyanates as the diamine [Skarping et al. 1981].

Controlling Worker Exposure

Equipment maintenance and worker education are vital aspects of a good occupational health and safety program. Workers must be informed of (1) any materials that may contain or be contaminated with TDI or TDA and (2) the nature of the potential hazard [29 CFR 1910.1200]. Employers must transmit this information by means of a hazard communication program, which is to include container labeling, material safety data sheets (MSDSs), and worker training. Every attempt should also be made to minimize exposure to TDI and TDA by using work practices and controls such as product substitution, closed systems and ventilation, worker isolation, protective clothing and equipment, respiratory protection, decontamination and waste disposal, and medical monitoring. These measures are discussed here briefly.

Product Substitution

When feasible, employers should substitute a less hazardous material for TDI or TDA. However, substitutes must be selected with extreme care, and possible adverse health effects should be evaluated first.

Closed Systems and Ventilation

Engineering controls should be the principal method for minimizing TDI and TDA exposure in the workplace. Achieving and maintaining reduced concentrations of airborne TDI and TDA depend on adequate engineering controls such as properly constructed and maintained closed-system operations and ventilation systems.

Closed-system operations provide the most effective means for reducing worker exposures to TDI and TDA. Closed systems should be used for producing, storing, transferring, packaging, and processing TDI and TDA. Exhaust ventilation systems should be designed to capture and contain vapors and particulates. Guidance for designing local exhaust ventilation systems can be found in *Recommended Industrial Ventilation Guidelines* [Hagopian and Bastress 1976], *Industrial Ventilation: A Manual of Recommended Practice* [ACGIH 1986], and *American National Standard Fundamentals Governing the Design and Operation of Local Exhaust Systems* [ANSI 1979].

Ventilation equipment should be checked at least every 3 months to ensure adequate performance. System effectiveness should also be checked when there are any changes in production, process, or control that might significantly increase TDI and TDA exposures.

Worker Isolation

The areas in which TDI and TDA are produced or used should be restricted to workers who are essential to the process or operation. If feasible, these workers should be isolated from direct contact with these chemicals by the use of automated equipment operated from a closed control booth or room. This room should be maintained at greater

air pressure than that surrounding the process equipment so that air flows out rather than in. When workers must enter the general work area to perform process checks, adjustments, maintenance, assembly line tasks, and related operations, they should take special precautions such as the use of personal protective equipment.

Protective Clothing and Equipment

Workers should be provided with and required to use appropriate personal protective clothing and equipment such as coveralls, footwear, chemical-resistant gloves and goggles, full faceshields, and suitable respiratory equipment. Appropriate coverall materials include Chemrel® and Saranex®-coated Tyvek®; suitable glove materials include butyl rubber, Viton®, Teflon®, and Silver Shield®. Any chemical-resistant clothing that is used should be periodically evaluated to determine its effectiveness in preventing dermal contact. Safety showers and eye wash stations should be located close to operations that involve TDI and TDA.

Respiratory Protection

The use of respirators is the least preferred method of controlling worker exposures. Respirators should not be used as the only control for routine operations, but NIOSH recognizes that they may be required to provide protection under certain situations such as implementation of engineering controls, some short-duration maintenance procedures, and emergencies. NIOSH maintains that only the most protective respirators should be used for situations involving carcinogens. These respirators include

- Any self-contained breathing apparatus with a full facepiece operated in a pressure-demand or other positive-pressure mode, and
- Any supplied-air respirator with a full facepiece operated in a pressure-demand or other positive-pressure mode in combination with an auxiliary self-contained breathing apparatus operated in a pressure-demand or other positive-pressure mode.

Any respiratory protection program must, at a minimum, meet the requirements of 29 CFR 1910.134. Respirators must be approved by NIOSH and the Mine Safety and Health Administration (MSHA). A complete respiratory protection program should include (1) regular training and medical evaluation of personnel and (2) fit testing, periodic environmental monitoring, and maintenance, inspection, cleaning, and storage of equipment. The program should be evaluated regularly. The following publications contain additional information about selection, fit testing, use, storage, and cleaning of respiratory equipment: *Guide to Industrial Respiratory Protection* [NIOSH 1987a] and *NIOSH Respirator Decision Logic* [NIOSH 1987b].

Decontamination and Waste Disposal

Procedures for decontamination, waste disposal, and transport should be established for TDI- and TDA-contaminated materials or equipment. One of the following solutions should be available at the worksite for cleaning up spills of TDI:

- 4% to 8% ammonium hydroxide, 1% to 2% liquid detergent, and 90% to 95% water, or
- 20% nonionic surfactant and 80% water [III 1980].

TDI reacts with either of these decontamination solutions to form polyureas.

The following procedures should be followed if TDI is spilled [III 1980]:

1. Absorb the TDI with sawdust or other absorbent material such as vermiculite or ground clay.
2. Collect the material in an open container and move the container outside.

3. Add the decontamination solution in a ratio of 2 parts decontaminant to 1 part TDI-contaminated material.

4. Collect contaminated waste, place it in sealed containers, and dispose of it in accordance with existing regulations of the U.S. Environmental Protection Agency and the U.S. Department of Transportation. State and local regulations may supersede Federal regulations if they are more restrictive.

The following procedures should be followed if TDA is spilled [Air Products and Chemicals, Inc. 1986]:

1. If TDA is in the molten state, evacuate the area until the TDA solidifies.

2. Spills should be cleaned up by personnel wearing complete body protection.

3. Using a clean shovel, place the material into disposal containers constructed of corrosion-protected carbon steel or stainless steel.

4. Waste material may be incinerated or disposed of in accordance with existing regulations of the U.S. Environmental Protection Agency and the U.S. Department of Transportation. State and local regulations may supersede Federal regulations if they are more restrictive.

Medical Monitoring

A medical monitoring program should be established for early detection and prevention of both the acute and chronic effects of exposure to TDI and TDA. Medical and work histories (including previous exposure to TDI, TDA, or other toxic agents) should be taken for each worker before job placement and updated periodically. The worker's physician should be given information about the adverse health effects of exposure to TDI and TDA and an estimate of the worker's potential for exposure. This information should include results of workplace sampling and a description of any protective devices or equipment the worker is required to use. If workers become sensitized to TDI, they should be removed from potential exposure. Complete medical evaluations should also be performed for each worker upon job transfer or termination. The occurrence of disease or other work-related health effects requires immediate evaluation of primary preventive measures (e.g., industrial hygiene monitoring, engineering controls, and personal protective equipment). Medical personnel should ensure that workers and employers are informed about work-related hazards associated with exposure to TDI and TDA.

REFERENCES

ACGIH [1986]. Industrial ventilation: a manual of recommended practice. 19th ed. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

ACGIH [1988]. TLV®s—Threshold limit values and biological exposure indices for 1988–1989. Cincinnati, OH: American Conference of Governmental Industrial Hygienists, p. 36.

Ahrenholz SH, Meyer CR [1980]. Health hazard evaluation report: Olin Chemical Company, Brandenburg, KY. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, HETA 79-113-728, NTIS No. PB-81-167-819/A02.

Ahrenholz SH, Meyer CR [1982]. Health hazard evaluation report: Olin (formerly Allied) Chemical Co., Moundsville, WV. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, HETA 81-295-1155, NTIS No. PB-84-150-465/A03.

Air Products and Chemicals, Inc. [1986]. Toluenediamine—material safety data sheet. Allentown, PA: Air Products and Chemicals, Inc.

Almaguer D, Orris P, Kramkowski R [1982]. Health hazard evaluation report: Janesville Products, Brodhead, WI. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, HETA-81-128-1107, NTIS No. PB84-141845.

American Chemical Society [1987]. Key chemicals, toluene diisocyanate. Chemical and Engineering News *65*(1):12.

Ames BN, Kammen HO, Yamasaki E [1975]. Hair dyes are mutagenic: identification of a variety of mutagenic ingredients. Proc Natl Acad Sci *72*(6):2423-2427.

Andersen M, Binderup ML, Kiel P, Larsen H, Maxild J [1980]. Mutagenic action of isocyanates used in the production of polyurethanes. Scand J Work Environ Health *6*:221-226.

Andersson K, Gudehn A, Levin JO, Nilsson CA [1982]. Analysis of gaseous diisocyanates in air using chemosorption sampling. Chemosphere *11*:3-10.

ANSI [1979]. American national standard fundamentals governing the design and operation of local exhaust systems. New York, NY: American National Standards Institute, Inc., ANSI Z9.2-1979.

Blijleven WG [1977]. Mutagenicity of four hair dyes in *Drosophila melanogaster*. Mutat Res *48*:181-186.

Burroughs GE, Moody PL [1982]. Health hazard evaluation report: Industrial Plastics, Valley City, OH. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, HETA-81-029-1088, NTIS No. PB-83-198390.

Candura F, Moscato G [1984]. Do amines induce occupational asthma in workers manufacturing polyurethane foams? Br J Ind Med *41*:552-553.

CFR. Code of Federal Regulations. Washington, DC: U.S. Government Printing Office, Office of the Federal Register.

Chadwick DH, Cleveland TH [1981]. Organic isocyanates. In: Mark HF, Othmer DF, Overberger CG, Seaborg GT, eds. Kirk Othmer Encyclopedia of Chemical Technology, 3rd edition, Vol. 13. New York, NY: John Wiley and Sons, pp. 789-818.

Chrostek WJ, Cromer JW [1975]. Health hazard evaluation determination report: Trionic Industries, Inc., Harrisburg, PA. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, HHE 74-42-168, NTIS No. PB-246-486/A02.

Clement Associates, Inc. [1982]. Review of the National Toxicology Program carcinogenesis bioassay of toluene diisocyanate. Arlington, VA: International Isocyanate Institute, Inc.

Dalene M, Mathiasson L, Skarping G, Sango C, Sandstrom JF [1988]. Trace analysis of airborne aromatic isocyanates and related aminoisocyanates and diamines using high-performance liquid chromatography with ultraviolet and electrochemical detection. J Chromatogr *435*:469-481.

Daniels W, Almaguer D, Kramkowski R [1987]. Health hazard evaluation report: Sheller Globe (Allen Industries, Inc.), Herrin, IL. Cincinnati,

OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, HETA 86-343-1822.

Diem JE, Jones RN, Hendrick DJ, Glindmeyer HW, Dharmarajam V, Butcher BT, Salvaggio JE, Weill H [1982]. Five-year longitudinal study of workers employed in a new toluene diisocyanate manufacturing plant. Am Rev Respir Dis *126*:420-428.

Dybing E, Thorgeirsson I [1977]. Metabolic activation of 2,4-diaminoanisole, a hair dye component. 1. Role of cytochrome P-450 metabolism in mutagenicity in vitro. Biochem Pharmacol *26*:729-734.

Elskamp CJ [1987]. Benzidine; 3,3′-dichlorobenzidine; 2,4-toluenediamine; 2,6-toluenediamine. Method 65. Salt Lake City, UT: OSHA Analytical Laboratory.

Fisher AA [1967]. Contact dermatitis. Philadelphia, PA: Lea and Febiger, pp. 134-135.

Florin I, Rutberg L, Curvall M, Enzell CR [1980]. Screening of tobacco smoke constituents for mutagenicity using the Ames test. Toxicol *15*:219-232.

45 FR 2,662 [1989]. Air contaminants; final rule. To be codified at 29 CFR 1910.

Fuchs S, Valade P [1951]. Clinical and experimental study of several cases of intoxication by Desmodur T (toluene diisocyanate 1-2-4 and 1-2-6). Arch Mal Prof *12*:191-196.

Glass WI, Thom NG [1964]. Respiratory hazards associated with toluene diisocyanate in polyurethane foam production. NZ Med J *63*:642-647.

Gosselin RE [1976]. Clinical toxicology of commercial products. 4th edition. Baltimore, MD: The Williams and Wilkins Co., p. 141.

Greene EJ, Friedman MA [1980]. In vitro cell transformation screening of 4 toluene diamine isomers. Mutat Res *79*:363-375.

Gunter BJ [1975]. Health hazard evaluation determination report: Lange Company, Broomfield, CO. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, HHE 74-148-239, NTIS No. PB-249-419/A02.

Gunter BJ, Lucas JB [1975]. Health hazard evaluation determination report: Gates Rubber Company, Denver, CO. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, HHE 74-73-233, NTIS No. PB-249-413/A02.

Hagopian JH, Bastress EK [1976]. Recommended industrial ventilation guidelines. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, DHEW (NIOSH) Publication No. 76-162.

Health and Safety Executive [1987]. Organic isocyanates in air. In: Methods for the determination of hazardous substances. London, United Kingdom: Health and Safety Executive, MDHS 25.

Hecht A [1978]. Hair dyes—a look at safety and regulation. FDA Consumer, June.

Hervin R, Thoburn TW [1975]. Health hazard evaluation/toxicity determination report: Trans World Airlines Main Overhaul Facility, Kansas City International Airport, Kansas City, MO. Cin-

cinnati, OH: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, HHE 72-96-237, NTIS No. PB-249-417.

Hobara T, Kobayashi H, Higashihara E, Kawamoto T, Iwamoto S, Shimazu W, Sakai T [1984]. Health hazard by exposure to toluene diisocyanate in the shipyard. Bull Environ Contam Toxicol *32*:134-139.

Holdren MW, Spicer CW, Riggin RM [1984]. Gas phase reaction of toluene diisocyanate with water vapor. Am Ind Hyg Assoc J *45*:626-633.

Hosein HR, Farkas S [1981]. Risk associated with the spray application of polyurethane foam. Am Ind Hyg Assoc J *42*:663-665.

IARC [1978]. IARC monographs on the evaluation of the carcinogenic risk of chemicals to man: some aromatic amines and related nitro compounds, hair dyes, colouring agents and miscellaneous industrial chemicals. IARC Monograph 16. Lyon, France: World Health Organization, International Agency for Research on Cancer, pp. 83-95.

IARC [1979]. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans: polynuclear aromatic compounds; chemicals and industrial processes associated with cancer in humans. IARC Monographs, Volumes 1–20, Supplement 1. Lyon, France: World Health Organization, International Agency for Research on Cancer, pp. 3-5.

IARC [1982]. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans: chemicals, industrial processes and industries associated with cancer in humans. IARC Monographs 1–29, Supplement 4, Appendix 2. Lyon, France: World Health Organization, International Agency for Research on Cancer.

IARC [1986]. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans: some chemicals used in plastics and elastomers. IARC Monograph 39. Lyon, France: World Health Organization, International Agency for Research on Cancer, pp. 287-323.

III [1980]. Recommendations for the handling of toluene diisocyanate (TDI): Bulletin No. 1. New Canaan, CT: International Isocyanate Institute, Inc.

Ito N, Hiasa Y, Konishi Y, Marugami M [1969]. The development of carcinoma in liver of rats treated with m-toluylenediamine and the synergistic and antagonistic effects with other chemicals. Cancer Res *29*:1137-1145.

Lee SA, Bennett D [1986]. Health hazard evaluation report: Schlegel, Inc., Rochester, NY. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, HETA 84-458-1733, HETA 84-489-1733, NTIS No. PB-87-174-199.

Leidel NA, Busch KA, Lynch JR [1977]. Occupational exposure sampling strategy manual. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, DHEW (NIOSH) Publication No. 77-173, NTIS No. PB-274-792/A07.

Loeser E [1983]. Long-term toxicity and carcinogenicity studies with 2,4/2,6-toluene diisocyanate (80/20) in rats and mice. Toxicol Lett *15*:71-81.

Markel HL, Shama SK [1974]. Health hazard evaluation report: Whirlpool Corporation, Ft. Smith, Arkansas. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, Na-

tional Institute for Occupational Safety and Health, HHE 72-100-121, NTIS No. PB-232-721/A02.

Maxon FC Jr. [1964]. Respiratory irritation from toluene diisocyanate. Arch Environ Health *8*:755-758.

Mirsalis C, Tyson CK, Butterworth BE [1982]. Detection of genotoxic carcinogens in the in vivo-in vitro hepatocyte DNA repair assay. Environ Mutagen *4*:553-562.

Musk AW, Peters JM, DiBerardinis L, Murphy RLH [1982]. Absence of respiratory effects in subjects exposed to low concentrations of TDI and MDI. J Occup Med *24*:746-750.

NCI [1978]. Bioassay of 2,5-toluenediamine sulfate for possible carcinogenicity. Bethesda, MD: U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, TR 126, DHEW (NIH) Publication No. 79-1718.

NCI [1979]. Bioassay of 2,4-diaminotoluene for possible carcinogenicity. Bethesda, MD: U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, TR 162, DHEW (NIH) Publication No. 78-1381.

NCI [1980]. Bioassay of 2,6-toluenediamine dihydrochloride for possible carcinogenicity. Bethesda, MD, and Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, NTP-80-20, DHHS (NIH) Publication No. 80-1756.

NIOSH [1973]. Criteria for a recommended standard: occupational exposure to toluene diisocyanate. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, HSM 73-11022.

NIOSH [1978]. Criteria for a recommended standard: occupational exposure to diisocyanates. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, DHEW (NIOSH) Publication No. 78-215.

NIOSH [1983]. National occupational exposure survey (NOES), 1981-1983: estimated total and female employees, actual observation and trade-named exposure to toluene diisocyanate and methyl benzene diamine. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluations and Field Studies, Surveillance Branch. Unpublished data base.

NIOSH [1987a]. Guide to industrial respiratory protection. Morgantown, WV: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 87-116.

NIOSH [1987b]. NIOSH respirator decision logic. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 87-108.

NIOSH [1987c]. Registry of toxic effects of chemical substances: 1985-86 edition. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 87-114.

NIOSH [1987d]. Toluene-2,4-diisocyanate—NIOSH Method 2535. In: Second supplement to NIOSH manual of analytical methods, 3rd edition. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 84-100.

NTP [1985]. Fourth annual report on carcinogens: summary. Washington, DC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program, NIH Publication No. NTP 85-002, pp. 69-70.

NTP [1986]. NTP technical report on the toxicology and carcinogenesis studies of commercial grade 2,4(80%)- and 2,6(20%)-toluene diisocyanate (CAS No. 26471-62-5) in F344/N rats and B6C3F$_1$ mice (gavage studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program, NTP TR 251, NIH Publication No. 86-2507.

NTP [1987]. NTP technical report on the toxicology and carcinogenesis studies of methyl carbamate (CAS No. 598-55-0) in F344/N rats and B6C3F$_1$ mice (gavage studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program, NTP TR 328, NIH Publication No. 88-2584.

Occupational Health Services, Inc. [1987]. Toluenediamine—material safety data sheet. New York, NY: Occupational Health Services, Inc.

Peters JM, Murphy RLH, Pagnotto LD, Van Ganse WF [1968]. Acute respiratory effects in workers exposed to low levels of toluene diisocyanate (TDI). Arch Environ Health *16*:642-647.

Peters JM, Murphy RLH, Ferris BG Jr. [1969]. Ventilatory function in workers exposed to low levels of toluene diisocyanate: a six-month follow-up. Br J Ind Med *26*:115-120.

Pienta RJ, Mukund JS, Lebherz WB III, Andrews AW [1977]. Correlation of bacterial mutagenicity and hamster cell transformation with tumorigenicity induced by 2,4-toluenediamine. Cancer Lett *3*:45-52.

Porter CP, Higgins RL, Scheel LD [1975]. A retrospective study of clinical, physiologic and immunologic changes in workers exposed to toluene diisocyanate. Am Ind Hyg Assoc J *36*:159-168.

Roper CP, Cromer JW Jr. [1975]. Health hazard evaluation/toxicity determination report: General Tire and Rubber Company, Marion, IN. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, HHE 74-118-218, NTIS No. PB-249398.

Schnorr TM, Egilman D, Boeniger MF [in preparation]. Mortality study of workers exposed to toluene diisocyanate. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluations, and Field Studies, Industrywide Studies Branch.

Skarping G, Sango C, Smith B [1981]. Trace analysis of isocyanates in industrial atmospheres using gas chromatography and electron-capture detection. J Chromatogr *208*:313-321.

Skarping G, Penman L, Sango G, Mathiasson L, Dalene M [1985]. Capillary gas chromatographic method for the determination of complex mixtures of isocyanates and amines. J Chromatogr *346*:191-204.

Swensson A, Holmquist CE, Lundgren KD [1955]. Injury to the respiratory tract by isocyanates used in making lacquers. Br J Ind Med *12*:20-33.

Ulrich H [1983]. Urethane polymers. In: Mark HF, Othmer DF, Overberger CG, Seaborg GT, eds. Kirk Othmer Encyclopedia of Chemical Technology. 3rd edition, Vol. 23. New York, NY: John Wiley and Sons, pp. 576-608.

Upjohn Company [1970]. Urethanes—engineering, medical control and toxicologic considerations. Kalamazoo, MI: Upjohn Company, Technical Bulletin-105.

USITC [1984]. Synthetic organic chemicals: United States production and sales (Investigation No. 332-135). Washington, DC: United States International Trade Commission, Publication 1745, pp. 25-26.

Vandervort R, Shama SK [1973]. Health hazard evaluation determination report: King Seely Thermos Company, Macomb, IL. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, HHE 73-30-90, NTIS No. PB-232-565/A02.

von Oettingen WF [1941]. The aromatic amino and nitro compounds: their toxicity and potential dangers. A review of the literature. Federal Security Agency, U.S. Public Health Service, Public Health Bulletin No. 271, p. 61.

Walworth HT, Virchow WE [1959]. Industrial hygiene experiences with toluene diisocyanate. Am Ind Hyg Assoc J *20*:205-210.

Wegman DH, Pagnotto LD, Fine LJ, Peters JM [1974]. A dose-response relationship in TDI workers. J Occup Med *16*:258-260.

Wegman DH, Musk AW, Main DM, Pagnotto LD [1982]. Accelerated loss of FEV-1 in polyurethane production workers: a four-year prospective study. Am J Ind Med *3*:209-215.

White GL, Wegman DH [1978]. Health hazard evaluation determination report: Lear Siegler, Inc., Marblehead, MA. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, HHE 78-68-546, NTIS No. PB-81-150-534/A03.

White WG, Sugden E, Morris MJ, Zatata E [1980]. Isocyanate-induced asthma in a car factory. Lancet *i*:756-760.

WHO [1987]. Environmental Health Criteria No. 75: Toluene Diisocyanate. International Programme on Chemical Safety (IPCS). Geneva, Switzerland: World Health Organzation.

Williamson KS [1965]. Studies of diisocyanate workers (2). Trans Assoc Ind Med Off *15*:29-35.

Appendix.—Concentrations of Toluene Diisocyanate (TDI) in the Workplace*

Source of exposure and year of study	Air concentration† No. of samples	Air concentration† Mean or range of means (mg/m^3)	Reference
TDI production:			
1956–1974	Unspecified	<0.028–0.43	Porter et al. [1975]
1973–1978	1949	0.0142§	Diem et al. [1982]
Polyurethane foam production (pouring and molding):			
1955	>10	0.28–2.71	Walworth and Virchow [1959]
1956	>130	ND**–3.13	Walworth and Virchow [1959]
1957	>20	ND–19.95	Walworth and Virchow [1959]
1964	28	0.05–0.239	Glass and Thom [1964]
1965	Unspecified	0.142–0.214	Peters et al. [1968]
1966	24	ND–0.214	Peters et al. [1969]
1967	8	ND–0.085	Peters et al. [1969]
1972	Unspecified	0.142–0.085	Wegman et al. [1974]
1972–1974	286	0.142–0.036	Wegman et al. [1982]
1974–1976	138	0.007–0.050	Wegman et al. [1982]
1973	11	0.005–0.007§	Vandervort and Shama [1973]
1973	21	0.053–0.356	Markel and Shama [1974]
1973	418	0.009–0.016§	Musk et al. [1982]
1974 (2, 4-isomer)	6	0.021§	Chrostek and Cromer [1975]
1974	540	0.010–0.011§	Musk et al. [1982]
1974	8	0.123§	Gunter and Lucas [1975]
1975	6	0.379§	Gunter [1975]
1975	10	0.004–0.017§	Roper and Cromer [1975]
1975	624	0.006–0.011§	Musk et al. [1982]
1976	461	0.003–0.009§	Musk et al. [1982]
1978	21	0.036–0.041§	White and Wegman [1978]
1981	12	0.002–0.004§	Burroughs and Moody [1982]
1981	7	0.003§	Almaguer et al. [1982]
1981	4	0.054–0.140	Andersson et al. [1982]
1984 (2, 4-isomer)	20	0.007–0.011§	Lee and Bennett [1986]
1984 (2, 6-isomer)	20	0.004–0.004§	Lee and Bennett [1986]

See footnotes at end of table.

(Continued)

Appendix (Continued).—Concentrations of Toluene Diisocyanate (TDI) in the Workplace*

Source of exposure and year of study	Air concentration† No. of samples	Air concentration† Mean or range of means (mg/m^3)	References
Polyurethane foam spray application:			
1979	12	0.121–0.199§	Hosein and Farkas [1981]
Polyurethane spray paint use:			
1960	3	0.712	Maxon [1964]
1974	13	0.015–0.021§	Hervin and Thoburn [1975]
Heating of polyurethane foam:			
1987	6	0.015§	Daniels et al. [1987]
TDI release from insulation (1 meter from polyurethane floor in a ship's hold):			
1983	6	0.138	Hobara et al. [1984]
TDI release from coated fabric (in a seat cover factory):			
1979	Unspecified	0.002–0.021	White et al. [1980]

* Unidentified mixtures primarily containing 2, 4- and 2, 6-TDI (unless the particular isomer is listed).

† Concentrations are reported as milligrams of TDI per cubic meter of ambient air (mg/m^3) in work areas, except for those figures marked with an asterisk (*), which were personal samples.

§ Personal samples.

** None detected.

☆U. S. GOVERNMENT PRINTING OFFICE: 1990/749-578