

# “Diisocianati e metaboliti cancerogeni”

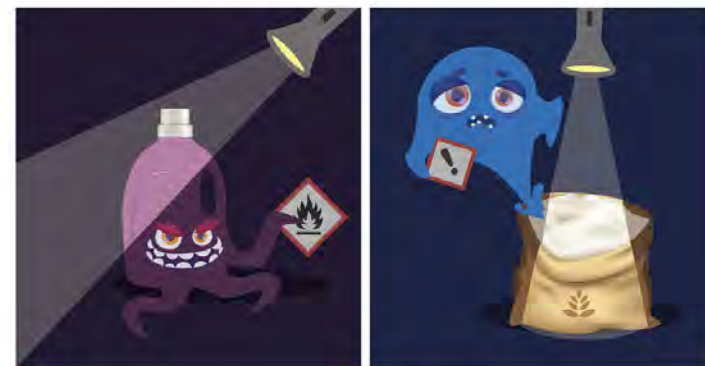
**Lucia Miligi**, Fondazione ISPRO - Istituto per lo Studio, la  
Prevenzione e la Rete Oncologica - Firenze

**20 marzo 2024**

14:00-18:00

**Milano**

Centro Congressi FAST - Aula Morandi



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Review

## Occupational Exposure to Diisocyanates in the European Union

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### DIISOCIANATI E POLIURETANI



## Abstract

**Objectives:** Diisocyanates are a chemical group that are widely used at workplaces in many sectors. They are also potent skin- and respiratory sensitizers. Exposure to diisocyanates is a main cause of occupational asthma in the European Union. To reduce occupational exposure to diisocyanates and consequently the cases of diisocyanate-induced asthma, a restriction on diisocyanates was recently adopted under the REACH Regulation in the European Union.

**Methods:** A comprehensive evaluation of the data on occupational exposure to the most important diisocyanates at workplaces was made and is reported here. The diisocyanates considered are methylene diphenyl diisocyanate (MDI), toluene diisocyanate (TDI), and hexamethylene diisocyanate (HDI), accounting for more than 95% of the market volume in the EU. The exposure assessment is based on data from Chemical Safety Reports (CSRs) of REACH Registration Dossiers, workplace air monitoring data from Germany, from the UK Health and Safety Executive (HSE), and literature data relevant for the EU, and the USA.

**Results:** Occupational exposure to diisocyanates is particularly relevant in: (i) C.A.S.E. applications (Coatings, Adhesives, Sealants, Elastomers), (ii) production of polyurethanes (PUs) (e.g. slab-stock foam), (iii) handling of partly uncured PU products (e.g. cutting, demoulding, spray application of foam), and (iv) when diisocyanates/PUs are heated (e.g. hot lamination, foundry applications/casting forms). Ranking of the reported data on inhalation to diisocyanate exposure at workplaces (maximum values) leads to following order: (i) HDI and its oligomers in coatings, (ii) MDI in spray foam applications, (iii) TDI in manufacture of foam, (iv) TDI in manufacture of PUs and PU composite materials, (v) TDI in adhesives, (vi) MDI in adhesives, (vii) MDI in manufacture of PUs and PU composite materials, (viii) TDI in coatings, (ix) MDI in manufacture of foam, and (x) HDI in adhesives.

**Keywords:** asthma; diisocyanates; occupational exposure; workplace exposure

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**I diisocianati sono un gruppo chimico utilizzato nei luoghi di lavoro trasversalmente a molti settori produttivi**

**L'esposizione a diisocianati è la maggior causa di asma occupazionale in europa.**

**Il toluen diisocianato (TDI), il metilen difenil diisocianato (MDI) e l'esametilen disocianato (HDI) rappresentano il 95% del volume di vendita nella comunita' europea**

**Massimi valori di esposizione inalatoria sono riportati in ordine decrescente per HDI e i suoi oligomeri nelle operazioni di rivestimento**

**MDI nelle operazioni di applicazioni delle schiume spray**

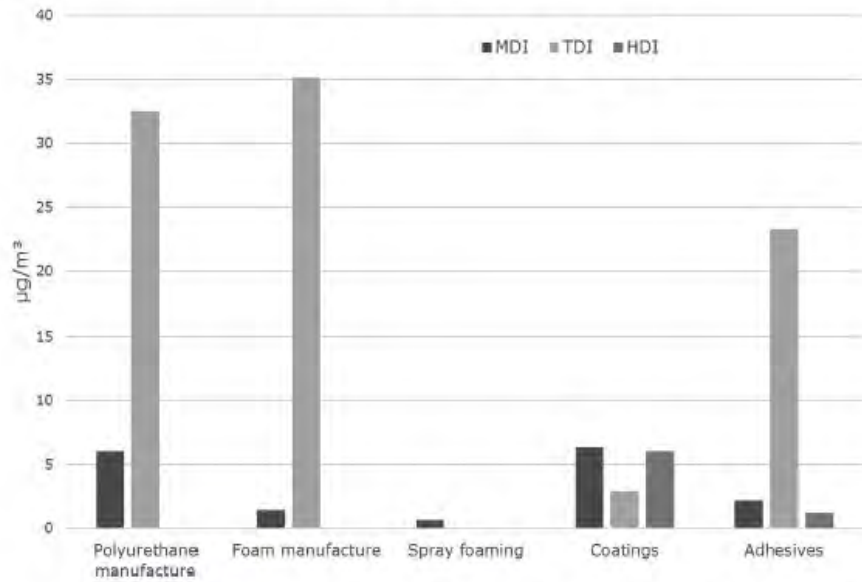
**TDI nella fabbricazione delle schiume**

**TDI nella fabbricazione di poliuretano (PU) e materiali di PU**

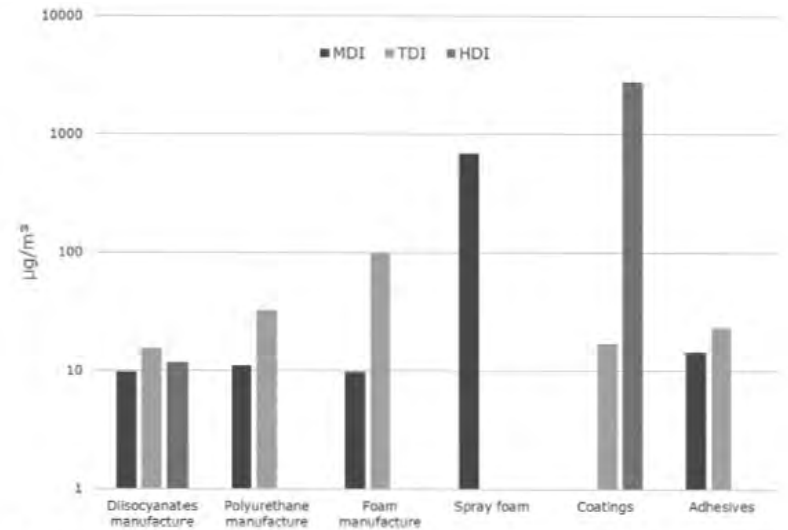
**TDI negli adesivi**

**MDI negli adesivi**

**MDI nella fabbricazione del PUs**



**Figure 3.** 90th percentile values of air concentrations of MDI, TDI, and HDI for work area groups for selected uses from IFA reports (MEGA database; IFA, 2010, 2012, 2013), converted into total NCO units ( $\mu\text{g NCO m}^{-3}$ ).



**Figure 4.** Air concentrations of MDI, TDI, and HDI for uses from all sources presented before, converted into total NCO units ( $\mu\text{g NCO m}^{-3}$ ) (note the logarithmic display of the exposure levels).



Il numero complessivo stimato per gli esposti a diisocianati in Europa:

Sector	Estimated exposed workers
C13 Textiles	4,225
C14 Apparel	7,475
C15 Leather	114,000
C16 Wood	14,427
C20 Chemicals	13,722
C22.21 Rigid foam	4,969
C22.29 Flexible foam	9,750
C22 Other	39,169
C26 Computers	23,438
C27 Electrical equipment	19,990
C28 Machinery	16,226
C29 Motor vehicles	166,373
C30 Transport	58,034
C31 Furniture	16,918
C33 Machinery repair	10,899
F41.2 Construction	1,304,561
F42 Civil engineering	29,990
F43 Specialised construction	1,872,910
F43.29 Other installation	12,469
G45.2 Vehicle repair	471,085
S95 Repairs	15,953
<b>Total</b>	<b>4,226,583</b>

Source: Study team

Attualmente il numero dei monomeri più utilizzati può essere dedotto dai dati ECHA:

Name	EC / List no.	CAS no.
2-methyl-m-phenylene diisocyanate	202-039-0	91-08-7
3,3'-dimethylbiphenyl-4,4'-diyl diisocyanate	202-112-7	91-97-4
4,4'-Methylenediphenyl diisocyanate	202-966-0	101-68-8
Hexamethylene diisocyanate	212-485-8	822-06-0
4-methyl-m-phenylene diisocyanate	209-544-5	584-84-9
4,4'-methylenedicyclohexyl diisocyanate	225-863-2	5124-30-1
m-tolylidene diisocyanate	247-722-4	26471-62-5
2,4,6-trisopropyl-m-phenylene diisocyanate	218-485-4	2162-73-4
2,2'-Methylenediphenyl diisocyanate	219-799-4	2536-05-2
1,3-bis(1-isocyanato-1-methylethyl)benzene	220-474-4	2778-42-9
1,5-naphthylene diisocyanate	221-641-4	3173-72-6
<u>1,3-bis(isocyanatomethyl)benzene</u>	222-852-4	3634-83-1
3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate	223-861-6	4098-71-9
2,4'-Methylenediphenyl diisocyanate	227-534-9	5873-54-1

Source: <https://echa.europa.eu/de/substances-restricted-under-reach/-/dislist/details/0b0236e185347b62>

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Dei 28 diisocianati sottoposti a registrazione per gli obblighi REACH 11 costituiscono oltre il 99% delle tonnellate prodotte, le loro caratteristiche vengono riportate nelle tabelle n.1 e n.2 (pg 2-5) del documento ANNEX 1 TO RAC OPINION ON DIISOCYANATES ECHA/RAC/A77-O-0000006826-64-01/F 11 June 2020

# Le Valutazioni di cancerogenicità:

- **LA IARC**
- **NTP**
- **ECHA**
- **ATSDR**

WORLD HEALTH ORGANIZATION  
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER



# IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

## VOLUME 71 RE-EVALUATION OF SOME ORGANIC CHEMICALS, HYDRAZINE AND HYDROGEN PEROXIDE

1999  
I A R C  
L Y O N  
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### 1.2 Production and use

Worldwide production capacities for toluene diisocyanates in 1987 were reported as (thousand tonnes): western hemisphere, 356; eastern Europe, 46; western Europe, 380; and Japan and the Far East, 88 (Ulrich, 1989). Worldwide production capacities in 1993 were reported as (thousand tonnes): North America, 485; Europe, 530; Pacific region, 308; and Latin America, 102.5 (Anon., 1995).

Toluene diisocyanate is commonly produced as a mixture of the 2,4- and 2,6-isomers, that is used as a monomer in the preparation of polyurethane foams, elastomers and coatings, as a cross-linking agent for nylon-6, and as a hardener in polyurethane adhesives and finishes. Polyurethane elastomers made from toluene diisocyanates are used in coated fabrics and clay-pipe seals. Polyurethane coatings made from toluene diisocyanates are used in floor finishes, wood finishes and sealers, and in coatings for aircraft, tank trucks, truck trailers and truck fleets (United States National Library of Medicine, 1997).

### 1.3 Occurrence

#### 1.3.1 Occupational exposure

According to the 1981–83 National Occupational Exposure Survey (NOES, 1997), approximately 40 000 workers in the United States were potentially exposed to toluene diisocyanates (see General Remarks). Occupational exposures to toluene diisocyanates may occur during their production and in the production of polyurethane foams, elastomers, coatings, adhesives and finishes. Exposure may also occur in the use of some polyurethane products. Data on occupational exposure levels have been presented in a previous monograph (IARC, 1986). More recent exposure levels have been reported in connection with epidemiological (Section 2) and toxicological (Section 4) studies.





# IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

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### 5.2 Human carcinogenicity data

The risk of cancer associated with occupational exposure to isocyanates has been examined in three industrial cohort studies and in a population-based case-control study of several types of cancer. No strong association or consistent pattern has emerged.

### 5.3 Experimental data

Commercial mixtures of 2,4- and 2,6-toluene diisocyanates were tested for carcinogenicity in mice and rats by gavage and by inhalation exposure. Administration by gavage induced a dose-related increase in the incidence of subcutaneous fibromas and fibrosarcomas (combined) in male rats, together with an increase in the incidence of pancreatic acinar-cell adenomas in male rats and in pancreatic islet-cell adenomas, neoplastic nodules of the liver and mammary gland fibroadenomas in female rats. In female mice, dose-related increases in the combined incidence of haemangiomas and haemangiosarcomas and of hepatocellular adenomas were observed; no treatment-related tumour was seen in male mice, possibly due to poor survival. No treatment-related tumour was observed after exposure of mice or rats to commercial toluene diisocyanate by inhalation, although the results of the study with rats have not been reported fully.

### 5.4 Other relevant data

Toluene diisocyanates are metabolized to toluene diamines in humans and rats. Toluene diisocyanates are irritants and respiratory sensitizers in humans and rats.

Toluene diisocyanate did not induce micronuclei in mammalian erythrocytes *in vivo*. It induced DNA damage and chromosomal aberrations but not sister chromatid exchanges in human lymphocytes *in vitro*. It induced gene mutation and sister chromatid exchanges but not DNA damage or chromosomal aberrations in rodent cells *in vitro*. It induced sex-linked mutations in *Drosophila* and in some experiments was mutagenic in bacteria. The presence of an exogenous metabolic activation system led to inconsistent results, sometimes enhancing and at other times eliminating the genotoxic effects of toluene diisocyanate.





# IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

## VOLUME 71 RE-EVALUATION OF SOME ORGANIC CHEMICALS, HYDRAZINE AND HYDROGEN PEROXIDE

### 1.2 Production and use

The world production of methylenediphenyl diisocyanate all types included was 1200 thousand tonnes in 1991. In the European Union, approximately 790 thousand tonnes were manufactured in 1996, compared with 540 thousand tonnes in 1991 and 267 thousand tonnes in 1980; 215 thousand tonnes were processed in 1980 (European Union, 1999).

It is mainly used in the industrial production of rigid polyurethane foams. Many other uses are in the fields of coatings, adhesives, sealants and elastomers such as paints, adhesives, weather-resistant sealing materials and footwear. There is use also in the production of particle board (bonding of wood) and mould cores for the foundry industry (European Union, 1999).

### 1.3 Occurrence

#### 1.3.1 Occupational exposure

Some data on levels of occupational exposure to 4,4'-methylenediphenyl diisocyanate have been presented in a previous *IARC Monograph* (IARC, 1979).

#### 1.3.2 Environmental occurrence

4,4'-Methylenediphenyl diisocyanate can be released to the environment in waste stream emissions from sites of industrial manufacture and use. Toxic Release Inventory reports to the United States Environmental Protection Agency before at least the mid-1990s were subject to serious overestimation of the releases to the environment, because of errors in the way that the figures were calculated by industry. Within the European Union, total emissions from production sites in 1996 were about 43 kg and emissions from processing plants in the same year were about 7100 kg (European Union, 1999).



# IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

## VOLUME 71 RE-EVALUATION OF SOME ORGANIC CHEMICALS, HYDRAZINE AND HYDROGEN PEROXIDE

### 5.5 Evaluation

There is *inadequate evidence* for the carcinogenicity of toluene diisocyanates in humans.

There is *sufficient evidence* for the carcinogenicity of toluene diisocyanates in experimental animals.

#### Overall evaluation

Toluene diisocyanates are *possibly carcinogenic to humans (Group 2B)*.

### 5.5 Evaluation

There is *inadequate evidence* for the carcinogenicity of 4,4'-methylenediphenyl diisocyanate or polymeric 4,4'-methylenediphenyl diisocyanate in humans.

There is *limited evidence* in experimental animals for the carcinogenicity of a mixture containing monomeric and polymeric 4,4'-methylenediphenyl diisocyanate.

#### Overall evaluation

4,4'-Methylenediphenyl diisocyanate (industrial preparation) is *not classifiable as to its carcinogenicity to humans (Group 3)*.

## Toluene Diisocyanates

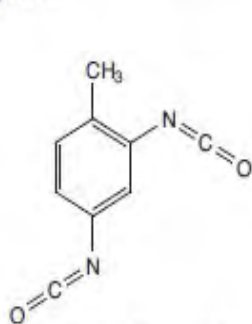
CAS No. 26471-62-5

Reasonably anticipated to be human carcinogens

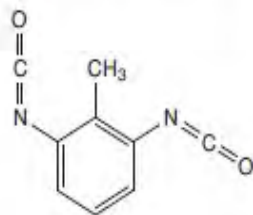
First listed in the *Fourth Annual Report on Carcinogens* (1985)

Also known as TDI; 1,3-diisocyanatomethyl benzene; isocyanic acid, methyl-*m*-phenylene ester; or tolylene diisocyanate

Isomers also known as toluene-2,4-diisocyanate and toluene-2,6-diisocyanate



2,4-Toluene diisocyanate  
CAS No. 584-84-9



2,6-Toluene diisocyanate  
CAS No. 91-08-7

### Carcinogenicity

Toluene diisocyanates are *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals.

NTP  
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COME  
REASONABLE  
ANTICIPATED TO BE  
HUMAN  
CARCINOGENS 2021



# 4-methyl-m-phenylene diisocyanate

# ECHA

Substance description

Scientific properties

Brief Profile - Last updated: 01/12/2023 [Print](#)

**Index number:** 615-006-00-4

**Molecular formula:** C9H6N2O2

chemical Substances) List

## Hazard classification & labelling

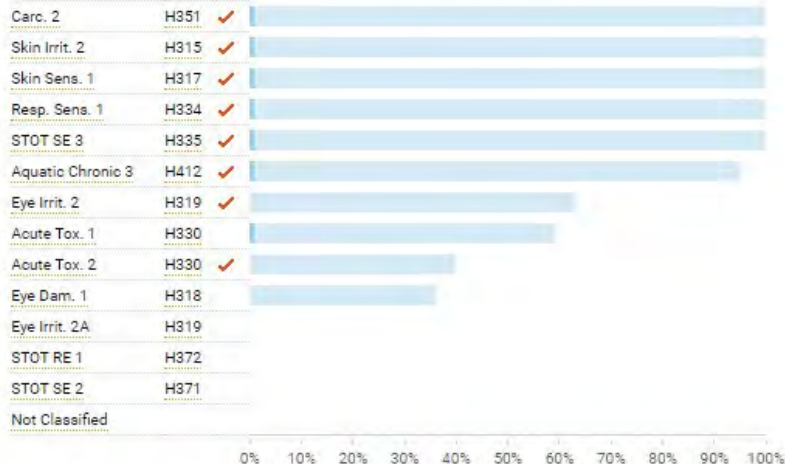


**Danger!** According to the **harmonised classification and labelling** (CLP00) approved by the European Union, this substance is fatal if inhaled, causes serious eye irritation, is suspected of causing cancer, is harmful to aquatic life with long lasting effects, causes skin irritation, may cause an allergic skin reaction, may cause allergy or asthma symptoms or breathing difficulties if inhaled and may cause respiratory irritation.



**Additionally**, the classification provided by companies to ECHA in **CLP notifications** identifies that this substance causes serious eye damage.

## Breakdown of all 1218 C&L notifications submitted to ECHA



- Substance identity
- Hazard classification & labelling
- Properties of concern
- Regulatory context
- About this substance
- Registrants/suppliers
- Substance names and other identifiers

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# 4,4'-methylenediphenyl diisocyanate

Substance description

Scientific properties

Brief Profile - Last updated: 12/03/2024 [Print](#)

Index number: 615-005-00-9

Molecular formula: C15H10N2O2

chemical Substances) List

## Hazard classification & labelling

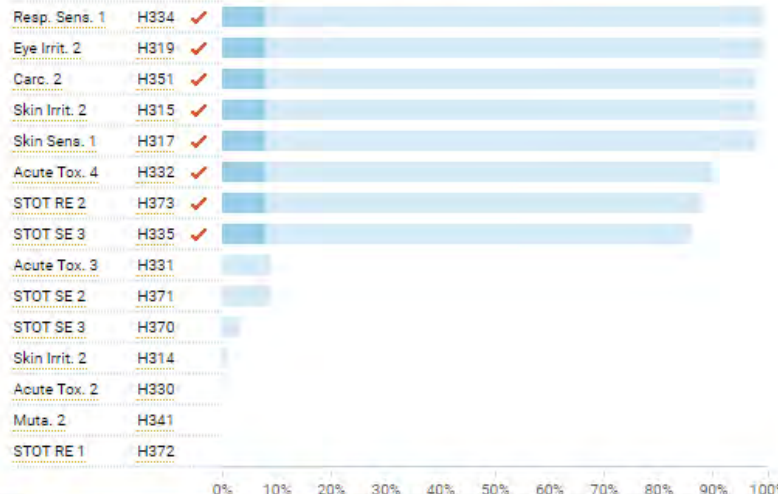


**Danger!** According to the **harmonised classification and labelling (ATP01)** approved by the European Union, this substance causes serious eye irritation, is harmful if inhaled, is suspected of causing cancer, may cause damage to organs through prolonged or repeated exposure, causes skin irritation, may cause an allergic skin reaction, may cause allergy or asthma symptoms or breathing difficulties if inhaled and may cause respiratory irritation.



**Additionally**, the classification provided by companies to ECHA in **CLP notifications** identifies that this substance is toxic if inhaled and may cause damage to organs.

## Breakdown of all 1918 C&L notifications submitted to ECHA



- Substance identity
- Hazard classification & labelling
- Properties of concern
- Regulatory context
- About this substance
- Registrants/suppliers
- Substance names and other identifiers

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# m-tolylidene diisocyanate

Substance description

Scientific properties

Brief Profile - Last updated: 06/01/2024 [Print](#)

Index number: 615-006-00-4

Molecular formula:

## Hazard classification & labelling



**Danger!** According to the **harmonised classification and labelling (CLP00)** approved by the European Union, this substance is fatal if inhaled, causes serious eye irritation, is suspected of causing cancer, is harmful to aquatic life with long lasting effects, causes skin irritation, may cause an allergic skin reaction, may cause allergy or asthma symptoms or breathing difficulties if inhaled and may cause respiratory irritation.



## Breakdown of all 999 C&L notifications submitted to ECHA

Carc. 2	H351	✓	100%
Skin Irrit. 2	H315	✓	100%
Skin Sens. 1	H317	✓	100%
Resp. Sens. 1	H334	✓	100%
STOT SE 3	H335	✓	100%
Aquatic Chronic 3	H412	✓	100%
Eye Irrit. 2	H319	✓	100%
Acute Tox. 2	H330	✓	100%
Acute Tox. 1	H330	✓	100%
Eye Irrit. 2A	H319	✓	100%
Aquatic Chronic 4	H413	✓	100%
Skin Sens. 1A	H317	✓	100%
Resp. Sens. 1A	H334	✓	100%
Not Classified			
Skin Corr. 1B	H314	✓	100%

Substance identity

Hazard classification & labelling

Properties of concern

Regulatory context

About this substance

Registrants/suppliers

Substance names and other identifiers

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Miligi, CIIP 20 Marzo Milano



15:52

15/03/2024

14°C Nuvoloso



# Hexamethylene diisocyanate

Regulatory process names 18 Translated names 22 IUPAC names 20 Trade names 17 Other identifiers 18 | Groups:



## Substance identity

**EC / List no.:** 212-485-8

**CAS no.:** 822-06-0

**Mol. formula:** C<sub>8</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>



## About this substance

This substance is registered under the REACH Regulation and is manufactured in and / or imported to the European Economic Area, at  $\geq 10\,000$  tonnes per annum.

This substance is used by professional workers (widespread uses), in formulation or re-packing, at industrial sites and

## Hazard classification & labelling



**Danger!** According to the **harmonised classification and labelling (CLP00)** approved by the European Union, this substance is toxic if inhaled, causes serious eye irritation, causes skin irritation, may cause an allergic skin reaction, may cause allergy or asthma symptoms or breathing difficulties if inhaled and may cause respiratory irritation.

**Additionally**, the classification provided by companies to ECHA in **REACH registrations** identifies that this substance is fatal if inhaled, causes severe skin burns and eye damage, causes serious eye damage and is harmful if swallowed.

## Properties of concern



Skin sensitising



Respiratory sensitising

[More details](#)

## Important to know

- Some uses of this substance are restricted under [Annex XVII of REACH](#).

## How to use it safely

- ECHA has no data from registration dossiers on the precautionary measures for using this substance.
- [Guidance on the safe use of the substance](#) provided by manufacturers and importers of this substance.



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## TOXICOLOGICAL PROFILE FOR TOLUENE DIISOCYANATE AND METHYLENEDIPHENYL DIISOCYANATE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Agency for Toxic Substances and Disease Registry

Sebbene la cancerogenicità del TDI non sia stata del tutto indagata negli studi di esposizione occupazionali, tre studi epidemiologici di coorte hanno esaminato i lavoratori di aziende di produzione di poliuretano trovando un'associazione tra questa lavorazione e tumore del polmone nelle donne ma non esaminando direttamente l'esposizione a TDI

**TDI.** Studi epidemiologici e studi su animali da laboratorio hanno esaminato la tossicità di TDI e hanno identificato il tratto respiratorio come il bersaglio più sensibile della tossicità. Un'esposizione di 6 ore di adulti sani a 0,005 ppm non ha provocato sintomi respiratori, ma ha comportato un leggero calo della funzionalità polmonare. Gli studi sull'esposizione professionale riportano principalmente tre tipi di effetti respiratorie: asma professionale, sintomi simili all'asma e declino della funzionalità polmonare.

Studi sugli animali hanno riportato lesioni istologiche nella cavità nasale e nei polmoni dopo reazioni acute, intermedie, o esposizione cronica a TDI

**MDI.** Similmente al TDI, il tratto respiratorio è il bersaglio primario della tossicità per gli MDI. Professionale l'esposizione può provocare asma professionale, sintomi simili all'asma e diminuzione dei polmoni funzione.

L'ATSDR come la IARC ha preso in considerazione alcuni studi di coorte per la valutazione dell'evidenza epidemiologica



# **L'evidenza epidemiologica: Gli studi di coorte**

## Cancer incidence and mortality in the Swedish polyurethane foam manufacturing industry

Lars Hagmar, Hans Welinder, Zoli Mikoczy

**Abstract**

**Toluene diisocyanate (TDI) and methylene diphenyldiisocyanate (MDI) are used in large quantities in the polyurethane foam manufacturing industry. Both substances are mutagenic and at least TDI is carcinogenic to animals, but the occupational hazard with respect to cancer is not known. Cancer incidence and mortality patterns were therefore investigated in a cohort of 4154 workers from nine Swedish plants manufacturing polyurethane foam, employed for at least one year. Each workplace and job task in the nine plants was categorically assessed for each calendar year by an experienced occupational hygienist, for "no exposure", "low or intermittent exposure", or "apparent exposure" to TDI and MDI. The observed deficit for all cause mortality (standardised mortality ratio (SMR) 0.78, (95% confidence interval (95% CI) 0.66-0.93) became smaller (SMR 0.92) excluding the first 10 years since the start of exposure and was ascribed to a healthy worker effect. No increased risk for death from bronchial obstructive diseases was found. An almost statistically significant deficit occurred for all malignant neoplasms (standardised incidence ratio (SIR) 0.81, 95% CI 0.63-1.02); slight (not significant) increased risks were found for rectal cancer (SIR 1.66) and non-Hodgkin's lymphoma (SIR 1.53). The SIR for non-Hodgkin's lymphoma increased to 2.80 (95% CI 0.76-7.16) when the first 10 years since first exposure were excluded from the observation period. The corresponding figure for rectal cancer was 1.92 (95% CI 0.52-4.92). Further restricting the analysis to those who had experienced an apparent exposure to TDI or MDI increased the SIR for both rectal cancer (3.19, 95% CI 0.66-9.33), and non-**

**Hodgkin's lymphoma (3.03, 95% CI 0.37-10.9). These estimates were based, however, on few incident cases. As the cohort is still young and little time has elapsed since the start of exposure, future follow ups will enable a more conclusive evaluation.**

**Studio di coorte svedese su 11 aziende in cui c'è stata esposizione a TDI ed MDI , coorte di 4154 soggetti che hanno lavorato nelle aziende di produzione poliuretano. L'esposizione è stata monitorata dal 1985.**

**Concentrazione di TDI generalmente al di sotto di 100 mcg/m3 ma con picchi di 3 mg/m3 e 0,35 mg/m3, concomitanti esposizioni etilendiammina, MOCA, trietilamina, stirene. Mortalità ed incidenza in difetto . Aumenti di rischio per tumore del retto e NHL per chi ha lavorato più di 10 anni.**

*Table 7 Cancer incidence 1959-87 for selected sites in 4154 subjects employed for at least one year by time since first exposure*

Tumour	ICD-7	Year since first exposure							
		1-10				> 10			
		O	E	SIR	(95% CI)	O	E	SIR	(95% CI)
Rectum	154	2	1.5	1.30	(0.16-4.70)	4	2.1	1.92	(0.52-4.92)
Lung	162-164	2	3.3	0.60	(0.07-2.17)	2	4.6	0.44	(0.05-1.58)
Lymphomas, myelomas	200-203	0	2.3	0.00	(0.00-1.59)	6	2.4	2.49	(0.91-5.42)
Non-Hodgkin's lymphoma	200, 202	0	1.2	0.00	(0.00-3.10)	4	1.4	2.80	(0.76-7.16)
All	140-209	32	40.9	0.78	(0.54-1.12)	40	48.6	0.82	(0.59-1.13)

Incidence of cancer and exposure to toluene diisocyanate and methylene diphenyldiisocyanate: a cohort based case-referent study in the polyurethane foam manufacturing industry

Lars Hagmar, Ulf Strömberg, Hans Welinder, Zoli Mikoczy

### Abstract

**Objective**—To assess the association between occupational exposure to toluene diisocyanate or methylene diphenyldiisocyanate and risk of cancer.

**Design**—A cohort based case-referent study.

**Study base**—7023 subjects employed during the period 1958 to 1987 in nine Swedish polyurethane foam manufacturing plants.

**Main outcome measures**—Odds ratios adjusted with respect to the matching factors (age at risk, calendar year at risk, sex, and plant), calculated from the conditional logistic regression model.

**Results**—A non-significant association was found between high exposure to isocyanates and prostate cancer (OR 2.66, 90% confidence interval (90% CI) 0.39–18.1), which was not enhanced when an induction latency period of 10 years was applied. An association between isocyanate exposure and colon cancer was even weaker. No associations were seen for non-Hodgkin's lymphoma and rectal cancer.

**Conclusions**—The tentative associations, derived from a previous cohort study, between isocyanate exposure and excess risk for non-Hodgkin's lymphoma and rectal cancer were not supported. Instead, non-significant associations with prostate cancer, and possibly colon cancer, were seen.

**Studio caso controllo innestato nella coorte, 7023 soggetti, casi e controlli estratti per stessa azienda, sesso e anno di nascita. Definizione dell'esposizione fatta da igienista industriale e definita come alta media e bassa. Non confermato il rischio per NHL e cancro del retto, una associazione non statisticamente significativa è stata osservata per il tumore della prostata e del colon**

Miligi, CIIP 20 Marzo Milano

Table 2 Odds ratios (ORs) for various malignant tumours with respect to occupational exposure to isocyanates, with and without a 10 year induction latency period

Tumours	Exposure to isocyanates									
	None				Intermediate and high			High		
	No	All*	OR†	(90% CI)	No	OR†	(90% CI)	No	OR†	(90% CI)
No induction-latency period:										
Referents	102	211			155			51		
All tumours	39	75	0.87	(0.55–1.38)	46	0.65	(0.55–1.38)	15	0.76	(0.55–1.38)
Colon cancer	2	6	2.19	(0.48–10.1)	4	3.25	(0.50–21.3)	1	0.69	(0.07–6.91)
Rectal cancer	2	5	0.58	(0.10–3.18)	3	0.44	(0.07–2.82)	1	1.41	(0.08–25.6)
Prostate cancer	2	8	1.62	(0.38–6.90)	7	2.96	(0.45–19.4)	4	2.66	(0.39–18.1)
Lymphoma and leukaemia:	4	8	1.80	(0.45–7.25)	3	0.73	(0.12–4.34)	2	1.09	(0.19–6.18)
Non-Hodgkin's lymphoma	1	3	0.74	(0.09–6.43)	2	0.67	(0.07–6.19)	1	0.52	(0.04–6.20)
10 year induction latency period:										
Referents	65	114			90			38		
All tumours	29	38	0.74	(0.40–1.36)	22	0.56	(0.29–1.12)	6	0.40	(0.15–1.05)
Colon cancer	0	4	∞		3	∞		0	–	
Rectal cancer	2	2	0.75	(0.13–4.29)	1	0.40	(–)	0	–	
Prostate cancer	3	5	1.07	(0.25–4.62)	4	1.73	(0.24–12.3)	2	2.61	(0.28–24.5)
Lymphoma and leukaemia:	4	6	0.51	(0.09–3.00)	3	0.47	(0.07–2.99)	1	0.34	(0.04–2.94)
Non-Hodgkin's lymphoma	1	3	0.88	(0.09–8.36)	2	0.85	(0.09–8.30)	1	0.66	(0.05–8.40)

\*Includes subjects with high, intermediate, and low exposure to isocyanates, and also the subjects for which the reliability of the exposure estimate <2.

†OR adjusted with respect to matching factors (age at risk, calendar year at risk, sex, plant).



## Mortality and cancer morbidity of production workers in the United Kingdom flexible polyurethane foam industry

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Table 3 Cancer mortality 1958-88

Site of cancer	ICD-9	Men			Women			Total study population		
		Exp	Obs	(SMR)	Exp	Obs	(SMR)	Exp	Obs	(SMR)
Lip	140	0.1	0	(0)	0.0	0	(0)	0.1	0	(0)
Tongue	141	0.7	0	(0)	0.1	0	(0)	0.8	0	(0)
Mouth	143-5	0.6	1	(157)	0.1	0	(0)	0.8	1	(134)
Pharynx	146-9	1.4	1	(72)	0.3	2	(610)	1.7	3	(176)
Oesophagus	150	6.4	6	(93)	1.2	0	(0)	7.7	6	(78)
Stomach	151	16.4	12	(73)	2.9	4	(139)	19.3	16	(83)
Small intestine	152	0.4	0	(0)	0.1	0	(0)	0.5	0	(0)
Large intestine	153	11.6	13	(112)	4.6	3	(66)	16.2	16	(99)
Rectum	154	8.2	5	(61)	2.0	0	(0)	10.2	5	(49)
Liver primary	155	1.6	1	(64)	0.3	0	(0)	1.9	1	(53)
Gall bladder	156	1.0	0	(0)	0.5	0	(0)	1.5	0	(0)
Pancreas	157	8.1	8	(99)	2.2	6*	(271)	10.3	14	(136)
Nose, sinuses	160	0.4	0	(0)	0.1	0	(0)	0.5	0	(0)
Larynx	161	1.8	1	(57)	0.2	1	(569)	1.9	2	(103)
Lung	162-3	72.2	65	(90)	9.1	16*	(176)	81.3	81	(100)
Bone	170	0.6	1	(169)	0.2	0	(0)	0.8	1	(134)
Skin	172-3	2.2	2	(93)	0.9	0	(0)	3.0	2	(66)
Breast	175	0.2	0	(0)	16.3	11	(67)	16.5	11	(67)
Prostate	185	8.7	8	(92)				8.7	8	(92)
Testis	186	1.1	1	(90)				1.1	1	(90)
Cervix	180				3.4	2	(59)	3.4	2	(59)
Uterus	182				1.0	0	(0)	1.0	0	(0)
Ovary	183				5.1	6	(119)	5.1	6	(119)
Other genital	184, 187	0.3	0	(0)	0.3	0	(0)	0.6	0	(0)
Bladder	188	6.4	5	(79)	0.8	1	(119)	7.2	6	(83)
Other urinary	189	3.9	1	(26)	0.8	1	(130)	4.6	2	(43)
Brain	191-2	5.9	4	(67)	1.7	1	(59)	7.6	5	(66)
Thyroid	193	0.3	1	(308)	0.2	0	(0)	0.5	1	(186)
Hodgkin's disease	201	1.8	0	(0)	0.4	0	(0)	2.2	0	(0)
Leukaemia	204-8	5.1	4	(78)	1.5	0	(0)	6.7	4	(60)
All neoplasms	140-208	188.0	161*	(86)	63.4	60	(95)	251.4	221	(88)

\*p < 0.05.

**Studio di mortalità ed incidenza su 8288 , lavoratori maschi e femmine, periodo 1958-1979, di 11 aziende, dizionario sulle mansioni riviste da igienista industriale per classificare ogni soggetto per esposizione ad isocianati. L'esposizione nella categoria più alta comprende mansioni nel periodo 1978-86 con concentrazioni maggiori di 4ppb (28.4 mcg/m<sup>3</sup>) o picchi maggiori di 10 ppb (71 mcg/m<sup>3</sup>) su più giorni**

**Aumento di rischio tumore del polmone e pancreas soprattutto nelle donne**

## Abstract

**Objective**—To describe cause specific mortality and site specific cancer morbidity among workers employed in factories that produce polyurethane foams, and to determine if an part of the experience may be due to occupation, and in particular to exposure to diisocyanates.

**Design**—Historical prospective cohort study.

**Setting**—11 factories in England and Wales.

**Subjects**—8288 male and female production employees with some employment in the period 1958–79, and with a minimum period of employment of six months.

**Main outcome measures**—Observed and expected numbers of deaths for the period 1958–88, and corresponding figures for cancer registrations for the period 1971–86.

**Results**—Compared with the general population of England and Wales, standardised mortality ratios (SMRs) for all causes and all neoplasms were 97 (observed deaths (Obs) 816) and 88 (Obs 221) respectively. Statistically significant excesses were found among women for cancer of the pancreas (expected deaths (Exp) 2.2, Obs 6, SMR 271, 95% CI 100–595) and cancer of the lung (Exp 9.1, Obs 16, SMR 176, 95% CI 100–285). Similar excesses were not found among male employees, and the SMRs for cancers of the lung and pancreas among the total study population were 100 (Obs 81) and 136 (Obs 14) respectively. Overall incidence of cancer was also below expectation (SRR 94, Obs 277), although statistically significant excesses among women were found for cancers of the larynx and kidney, based on three and four cases respectively. Incident cancers of the

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lung and pancreas among women were also in excess, although these findings were not independent of the findings for mortality. Poison regression did not indicate that ever having been employed in jobs attracting either higher or lower exposure to isocyanates was a risk factor for the mentioned cancers. A nested case-control design was used to investigate any associations with nine other occupational exposures. No statistically significant association was found.

**Conclusions**—In general, cancer rates in this population were lower than those for the general population. All increased cancer rates among women occurred at sites of cancer known to be related to cigarette smoking, and these excesses are probably due to a combination of cigarette smoking, chance, and factors unrelated to the industry under study.

**Coorte inglese su 11 aziende, 8288 lavoratori maschi e femmine periodo 1958-1979, un igienista industriale definì un dizionario sulle mansioni e classificò in base all'esposizione allocando le esposizioni al di sopra di 4 ppb quelle mansioni a più alta esposizione nel periodo 1978-86, ed a più bassa esposizione quelle con esposizione minore di 4 ppb**

Table 4 Mortality from lung cancer and cancer of pancreas by type of cohort and by period from first employment, 1958-88

Years from first employment*	Lung cancer						Cancer of pancreas					
	Survivor population		Entry cohort		Total		Survivor population		Entry cohort		Total	
	Obs	(SMR)	Obs	(SMR)	Obs	(SMR)	Obs	(SMR)	Obs	(SMR)	Obs	(SMR)
Men:												
0-4	2	(176)	2	(48)	4	(76)	0	(0)	0	(0)	0	(0)
5-9	4	(108)	6	(92)	10	(98)	0	(0)	0	(0)	0	(0)
10-14	5	(75)	9	(126)	14	(101)	0	(0)	1	(117)	1	(64)
≥15	29	(83)	8	(104)	37	(86)	5	(129)	2	(215)	7	(146)
Total	40	(86)	25	(98)	65	(90)	5	(98)	3	(100)	8	(99)
Women:												
0-4	0	(0)	1	(214)	1	(168)	0	(0)	1	(857)	1	(672)
5-9	0	(0)	3	(347)	3	(233)	0	(0)	2	(954)	2	(633)
10-14	1	(127)	2	(174)	3	(155)	0	(0)	1	(361)	1	(214)
≥15	4	(125)	5	(241)	9	(170)	0	(0)	2	(406)	2	(156)
Total	5	(110)	11	(241)	16	(176)	0	(0)	6	(548)	6	(271)

\*Irrespective of how long any worker remains in employment.

Table 9 Cancers of the lung. Results of fitting multiplicative model with the factors: \* attained age, calendar year, period of follow up and sex

Follow up (y)	Level of exposure to isocyanates		
	Always minimal/zero	Ever lower	Ever higher
	<b>Men</b>		
0-9	O 11 F 12-12	2 2-00	1 0-42
10-19	O 21 F 21-61	7 5-13	1 1-08
≥20	O 18 F 17-11	3 4-65	1 0-89
Total	O 50 F 50-84	12 11-78	3 2-38
	<b>Women</b>		
0-9	O 4 F 3-44	0 0-03	0 0-01
10-19	O 7 F 8-10	0 0-07	0 0-01
≥20	O 5 F 4-23	0 0-11	0 0-02
Total	O 16 F 15-77	0 0-20	0 0-03

O = Observed; F = fitted.

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Mortality and cancer morbidity of production workers in the United Kingdom flexible polyurethane foam industry

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**Aumento di rischio per pancreas laringe, polmone soprattutto nelle donne**

Table 6 Incidence of cancer among total study population, 1958-88

Site of cancer	ICD-9	Exp	Obs	(SRR)
Lip	140	0.6	0	(0)
Tongue	141	1.1	0	(0)
Salivary gland	142	0.7	0	(0)
Mouth	143-5	1.3	3	(225)
Pharynx	146-9	2.0	1	(50)
Oesophagus	150	5.7	3	(53)
Stomach	151	16.4	17	(104)
Small intestine	152	0.6	0	(0)
Large intestine	153	17.6	17	(97)
Rectum	154	13.2	8	(60)
Liver	155	1.5	1	(68)
Gall bladder	156	1.4	1	(73)
Pancreas	157	7.5	10	(133)
Peritoneum + other dig.	158-9	0.9	0	(0)
Nose, sinuses	160	0.7	0	(0)
Larynx	161	3.9	7	(178)
Lung	162-3	65.6	76	(116)
Bone	170	0.8	0	(0)
Connective tissue	171	1.6	4	(255)
Malignant melanoma	172	4.1	2	(49)
Other skin	173	31.6	25	(79)
Breast	174, 175	24.3	23	(95)
Cervix	180	6.1	3	(49)
Chorionepithelioma	181	0.0	0	(0)
Uterus	179, 182	3.9	3	(77)
Ovary	183	5.0	6	(121)
Prostate	185	11.0	10	(91)
Testis	186	3.8	3	(79)
Other genital	184, 187	1.4	1	(71)
Bladder	188	14.3	9	(63)
Kidney	189	5.4	8	(149)
Eye	190	0.6	1	(167)
Brain	191-2	6.6	7	(106)
Thyroid	193	1.3	1	(78)
Other endocrine	194	0.4	1	(257)
Unspecified	195-9	12.2	11	(90)
Lymphosarcoma	200, 202	6.6	5	(75)
Hodgkin's disease	201	3.5	2	(57)
Multiple myeloma	203	2.6	5	(193)
Leukaemia	204-8	5.9	4	(68)
Total	140-208	294.3	277	(94)



# Mortality and cancer morbidity of production workers in the UK flexible polyurethane foam industry: updated findings, 1958–98

T Sorahan, L Nichols

*Occup Environ Med* 2002; **59**: 751–758

**Table 3** Mortality in UK polyurethane foam workers (5824 men, 2464 women), 1958–98

Cause of death	ICD-9	Males			Females		
		Obs	Exp	SMR (95% CI)	Obs	Exp	SMR (95% CI)
<b>Cancers</b>							
Lip	140	0	0.1	0.0 (0 to 3630)	0	0.0	0.0 (0 to 49214)
Tongue	141	0	1.3	0.0 (0 to 279)	0	0.3	0.0 (0 to 1491)
Salivary gland	142	0	0.5	0.0 (0 to 718)	0	0.1	0.0 (0 to 3062)
Mouth	143–145	2	1.3	151 (18 to 544)	0	0.2	0.0 (0 to 1623)
Pharynx	146–149	6	2.7	227 (83 to 493)	2	0.5	367 (44 to 1326)
Oesophagus	150	18	14.7	122 (72 to 314)	3	2.6	107 (22 to 314)
Stomach	151	23	27.3	84 (53 to 136)	6	5.0	120 (44 to 262)
Small intestine	152	2	0.7	285 (35 to 1029)	0	0.2	0.0 (0 to 1738)
Large intestine	153	30	23.6	127 (86 to 182)	7	8.9	78 (32 to 162)
Rectum	154	10	15.3	65 (31 to 120)	2	3.8	53 (6 to 192)
Liver	155.0, 155.1	3	3.4	88 (18 to 256)	0	0.8	0.0 (0 to 482)
Gallbladder	156	0	1.6	0.0 (0 to 232)	0	0.8	0.0 (0 to 446)
Pancreas	157	20	15.1	132 (81 to 204)	9	4.6	194 (89 to 368)
Peritoneum	158	1	0.7	144 (4 to 801)	1	0.2	469 (12 to 2611)
Other digestive	159	3	1.8	169 (35 to 493)	0	0.5	0.0 (0 to 656)
Nose and sinuses	160	0	0.6	0.0 (0 to 598)	0	0.2	0.0 (0 to 2432)
Larynx	161	4	3.5	116 (32 to 297)	1	0.3	291 (7 to 1624)
Lung and bronchus	162	134	125.0	107 (90 to 127)	35	19.4	181** (126 to 251)
Pleura	163	0	2.1	0.0 (0 to 175)	0	0.2	0.0 (0 to 2341)
Bone	1	1	0.9	117 (3 to 651)	0	0.2	0.0 (0 to 1681)
Connective tissue	171	3	1.5	202 (42 to 589)	2	0.5	376 (46 to 1358)
Melanoma	172	2	3.4	59 (7 to 215)	0	1.4	0.0 (0 to 262)
Skin, other	173	2	1.0	205 (25 to 742)	0	0.2	0.0 (0 to 1800)
Breast	175	2	0.4	466 (56 to 1684)	27	29.6	91 (60 to 133)
Cervix	180	–	–	–	7	5.1	137 (65 to 288)
Uterus	182	–	–	–	0	1.9	0.0 (0 to 197)
Ovary	183	–	–	–	8	9.3	86 (37 to 170)
Other genital	184, 187	0	0.5	0.0 (0 to 702)	1	0.6	159 (4 to 888)
Prostate	185	26	22.9	114 (74 to 156)	–	–	–
Testis	186	1	1.3	75 (2 to 417)	–	–	–
Bladder	188	8	12.8	63 (27 to 123)	2	1.8	109 (13 to 395)
Kidney	189.0	8	7.6	106 (46 to 208)	3	1.6	187 (39 to 547)
Other urinary	189.1–189.9	0	0.4	0.0 (0 to 966)	0	0.1	0.0 (0 to 4158)
Eye	190	0	0.4	0.0 (0 to 926)	0	0.1	0.0 (0 to 2551)
Brain	191–192	7	10.5	67 (27 to 138)	3	3.1	98 (20 to 287)
Thyroid	193	1	0.6	173 (4 to 961)	0	0.4	0.0 (0 to 962)
Other endocrine glands	194	1	0.3	305 (8 to 1701)	0	0.1	0.0 (0 to 2990)
Secondary and other cancers	195–199	25	23.0	109 (70 to 160)	13	7.9	164 (87 to 280)
Hodgkin's disease	201	1	2.3	44 (1 to 243)	0	0.5	0.0 (0 to 702)
Non-Hodgkin's lymphoma	200, 202	6	9.2	65 (24 to 142)	3	2.7	110 (23 to 321)
Multiple myeloma	203	7	4.7	148 (59 to 304)	0	1.5	0.0 (0 to 239)
Leukaemia	204–208	8	9.2	87 (37 to 171)	2	2.8	108 (22 to 317)
Lymphoid leukaemia	204	1	2.7	37 (1 to 208)	0	0.6	0.0 (0 to 641)
Myeloid leukaemia	205	3	5.6	54 (11 to 158)	2	1.9	106 (13 to 382)
Monocytic leukaemia	206	0	0.2	0.0 (0 to 1915)	1	0.1	1759 (45 to 9799)
Other leukaemia	207, 208	4	0.8	507* (138 to 1298)	0	0.2	0.0 (0 to 1523)
All neoplasms	140–239	374	359.2	104 (94 to 115)	139	12.0	113 (95 to 133)
<b>Non-cancers</b>							
Infectious and parasitic diseases	1–139	10	7.6	132 (63 to 243)	0	1.9	0.0 (0 to 191)
Endocrine nutritional and metabolic diseases	240–279	19	15.5	122 (74 to 191)	9	5.7	157 (72 to 298)
Diseases of blood	280–289	3	3.0	100 (21 to 298)	2	1.1	176 (21 to 636)
Mental disorders	290–319	4	7.6	53 (14 to 135)	3	3.1	98 (20 to 286)
Diseases of nervous system	320–389	15	18.7	80 (45 to 133)	3	6.7	45 (9 to 131)
Diseases of circulatory system	390–459	612	568.1	108 (99 to 117)	137	125.9	109 (91 to 129)
Diseases of respiratory system	460–519	140	116.9	120* (101 to 141)	35	28.4	123 (86 to 171)
Diseases of digestive system	520–579	34	35.0	97 (67 to 136)	19	11.2	192 (97 to 253)
Diseases of genitourinary system	580–629	7	10.8	65 (26 to 133)	4	3.8	106 (29 to 271)
Diseases of skin	680–709	0	0.6	0.0 (0 to 588)	0	0.4	0.0 (0 to 938)
Diseases of musculo skeletal system	710–739	7	3.5	203 (82 to 418)	4	2.9	139 (38 to 356)
Accidents	800–949	32	30.8	83 (57 to 117)	5	7.0	115 (60 to 227)
Suicide	950–959	25	20.1	124 (81 to 184)	1	3.9	26 (1 to 143)
<b>All causes</b>		1298	1218.2	107* (101 to 113)	364	329.7	110 (99 to 122)

\*p<0.05, \*\*p<0.01.

**Aggiornamento del follow up al 1998 della coorte dei 8288 lavoratori nelle 11 aziende, nuovamente osservato un eccesso di tumore del polmone nelle donne, ma gli autori nonostante quanto osservato non ritengono che questi aumenti siano dovuti all'esposizione a TDI**

**Table 4** Mortality in UK polyurethane foam workers (5824 men, 2464 women) by time since first employment, 1958–98

Time since first employment (years)	Males			p value for trend†	Females			p value for trend†
	Obs	Exp	SMR (95% CI)		Obs	Exp	SMR (95% CI)	
<b>All causes</b>								
0–9	125	162.3	77** (64 to 92)		36	42.1	86 (60 to 118)	
10–19	391	339.9	115** (104 to 127)	0.16	108	93.6	115 (95 to 139)	0.63
20–29	450	389.5	116** (105 to 127)		151	124.6	121* (103 to 142)	
≥30	332	326.6	102 (91 to 113)		69	69.4	99 (77 to 126)	
<b>Total</b>	1298	1218.2	107* (101 to 113)		364	329.7	110 (99 to 122)	
<b>Lung cancer‡</b>								
0–9	16	15.3	105 (60 to 170)		4	1.9	215 (59 to 550)	
10–19	41	35.0	117 (84 to 159)	0.60	11	5.5	201* (100 to 359)	0.76
20–29	44	40.9	107 (78 to 144)		12	7.9	152 (79 to 266)	
≥30	33	33.8	98 (67 to 137)		8	4.1	193 (83 to 380)	
<b>Total</b>	134	125.0	107 (90 to 127)		35	19.4	181** (126 to 251)	
<b>Non-malignant diseases of the respiratory system§</b>								
0–9	11	14.1	78 (39 to 139)		1	3.2	32 (1 to 177)	
10–19	38	30.3	125 (89 to 172)	0.79	6	7.1	84 (31 to 183)	0.02
20–29	55	36.7	150** (113 to 195)		15	10.9	137 (77 to 227)	
≥30	36	35.9	100 (70 to 139)		13	7.2	180 (96 to 308)	
<b>Total</b>	140	116.9	120* (101 to 141)		35	28.4	123 (86 to 171)	

\*p<0.05, \*\*p<0.01, ( ) indicates deficit.

†Linear component of trend over four time periods.

‡ICD-9 162.

§ICD-9 460–519.



## ORIGINAL ARTICLE

## Cancer incidence and mortality of isocyanate exposed workers from the Swedish polyurethane foam industry: updated findings 1959–98

Z Mikoczy, H Welinder, H Tinnerberg, L Hagmar

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**Aims:** To assess whether cancer incidence and mortality in chronic obstructive lung diseases were increased in the Swedish polyurethane foam industry cohort, updated with 11 more years of follow up.

**Methods:** The mortality and cancer incidence (1959–98) experienced by a cohort of 4175 male and female employees employed for at least one year in the period 1959–87 at one of nine Swedish polyurethane foaming plants were investigated. Comparisons were based on calendar year, sex, and five-year age group specific mortality and incidence rates for Sweden. Workplaces and job tasks were categorically assessed for exposure to toluene diisocyanate (TDI) and methylene diphenyldiisocyanate (MDI) by occupational hygienists.

**Results:** Fewer cancer cases than expected were observed, but the lung cancer incidence was enhanced in women. Women with “apparent exposure” to TDI or MDI did not, however, have a higher lung cancer incidence than those with “no or low exposure”. Moreover, a nested case referent study did not find that polyurethane dust exposure had been more prevalent among the female lung cancer cases than among referents. No increased mortality in chronic obstructive lung diseases was observed in the cohort.

**Conclusions:** Results support the findings from two other cohort studies of an increased lung cancer risk among female workers in the polyurethane foam manufacturing industry. Chance or confounding from smoking are not obvious explanations for the coherent findings. However, the study was not able to link isocyanate exposed employment with lung cancer risk.

**Studio di mortalità e l'incidenza di tumori (1959–98) sperimentate da una coorte di 4.175 uomini e donne impiegati per almeno un anno nel periodo 1959-87 presso uno di nove impianti svedesi. I luoghi di lavoro e le attività lavorative sono stati valutati categoricamente per l'esposizione al toluen diisocianato di (TDI) e al difenil diisocianato di metilene (MDI) da parte di igienisti industriali.**

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Table 2 Mortality 1958–99 in subjects employed for at least one year by gender

Causes of death	ICD-8	All (n=4175)				Men (n=2639)				Women (n=1536)			
		O	E	SMR	95% CI	O	E	SMR	95% CI	O	E	SMR	95% CI
Malignant tumours	140–209	100	106	0.94	0.77 to 1.15	63	71.6	0.88	0.68 to 1.13	37	34.5	1.07	0.75 to 1.48
lung cancer	1620–1621	17	17.1	0.99	0.58 to 1.59	7	14.2	0.49	0.20 to 1.01	10	2.84	3.52	1.69 to 6.48
Cardiovascular diseases	390–458	145	176	0.82	0.70 to 0.97	129	145	0.89	0.74 to 1.05	16	30.6	0.52	0.30 to 0.85
Respiratory diseases	460–519	14	20.6	0.68	0.37 to 1.14	10	16.1	0.62	0.30 to 1.15	4	4.51	0.89	0.24 to 2.27
Asthma, bronchitis, emphysema	490–493	5	8.13	0.62	0.20 to 1.44	4	6.22	0.64	0.18 to 1.65	1	1.90	0.53	0.01 to 2.93
Accidents, poisonings, and violence	800–999	46	53.4	0.86	0.63 to 1.15	39	43.8	0.89	0.63 to 1.22	7	9.64	0.73	0.29 to 1.50
All causes	000–999	337	403	0.84	0.75 to 0.93	266	312	0.85	0.75 to 0.96	71	90.8	0.78	0.61 to 0.99

Table 3 Cancer incidence 1959-98 in subjects employed for at least one year by gender

Tumour site	ICD-7	All (n=4175)				Men (n=2639)				Women (n=1536)			
		O	E	SIR	95% CI	O	E	SIR	95% CI	O	E	SIR	95% CI
Colon	153	8	15.1	0.53	0.23 to 1.05	7	9.81	0.71	0.29 to 1.47	1	5.26	0.19	0.00 to 1.06
Rectum	154	11	17.7	0.62	0.31 to 1.11	8	6.77	1.18	0.51 to 2.33	3	2.86	1.05	0.22 to 3.07
Pancreas	157	3	6.09	0.48	0.10 to 1.44	3	4.28	0.70	0.14 to 2.05	0	1.81	0	0.00 to 2.04
Lung	1620-1621	18	19.0	0.95	0.56 to 1.50	6	15.0	0.40	0.15 to 0.87	12	4.00	3.00	1.55 to 5.24
Breast	170	23	30.0	0.77	0.49 to 1.15	1	0.24	4.17	0.11 to 23.2	22	29.8	0.74	0.46 to 1.12
Prostate	177	23	26.7	0.86	0.55 to 1.29	23	26.7	0.86	0.55 to 1.29	-	-	-	-
Urinary bladder, ureter	181	11	11.9	0.92	0.46 to 1.65	10	10.3	0.98	0.47 to 1.79	1	1.68	0.60	0.02 to 3.32
Melanoma	190	9	11.3	0.80	0.36 to 1.51	9	6.71	1.34	0.61 to 2.55	0	4.59	0.00	0.00 to 0.80
Brain and nervous system	193	15	10.1	1.49	0.83 to 2.46	10	6.37	1.57	0.75 to 2.89	5	3.70	1.35	0.44 to 3.16
Non-Hodgkin's lymphoma	200, 202	6	8.31	0.72	0.27 to 1.57	5	6.35	0.79	0.26 to 1.84	1	2.35	0.43	0.01 to 2.37
Leukaemia	204-207	7	5.61	1.25	0.50 to 2.57	4	4.31	0.93	0.25 to 2.38	3	1.45	2.07	0.43 to 6.05
All	140-209	209	241	0.87	0.75 to 0.99	130	147	0.88	0.74 to 1.05	79	94.2	0.84	0.66 to 1.04

**Questo studio conferma quanto osservato nei precedenti studi : un aumento di rischio per tumore del polmone nelle donne. Gli autori però fanno osservare non c'è un associazione dose risposta con esposizione a TDI e MDI. Un risultato dovuto al caso o al confondimento dovuto al fumo di sigaretta non è una spiegazione sufficiente per questo rischio osservato da approfondire**

Table 5 Exposure to TDI or MDI and cancer incidence in polyurethane foam industry workers with stable exposure classification over their employment period

Tumour	Constantly apparent exposure (n=1679)†											
	None or constantly low exposure (n=1394)*				>5 years employment				All employment periods			
	O	E	SIR	95% CI	O	E	SIR	95% CI	O	E	SIR	95% CI
Lung cancer (women)	6	1.50	4.00	1.47 to 8.71	3	0.63	4.76	0.98 to 13.9	5	1.53	3.27	1.06 to 7.64
Brain cancer (men and women)	6	3.68	1.63	0.60 to 3.55	1	1.32	0.76	0.02 to 4.22	5	3.90	1.28	0.42 to 3.00
All (men and women)	80	92.2	0.87	0.69 to 1.08	27	36.9	0.73	0.48 to 1.06	82	93.4	0.88	0.70 to 1.09

\*582 women.  
†566 women.





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### **Mortality Among Workers Exposed to Toluene Diisocyanate in the US Polyurethane Foam Industry: Update and Exposure-Response Analyses**

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#### **Abstract**

**Background**—Mortality among 4,545 toluene diisocyanate (TDI)-exposed workers was updated through 2011. The primary outcome of interest was lung cancer.

**Methods**—Life table analyses, including internal analyses by exposure duration and cumulative TDI exposure, were conducted.

**Results**—Compared with the US population, all cause and all cancer mortality was increased. Lung cancer mortality was increased but was not associated with exposure duration or cumulative TDI exposure. In post hoc analyses, lung cancer mortality was associated with employment duration in finishing jobs, but not in finishing jobs involving cutting polyurethane foam.

**Conclusions**—Dermal exposure, in contrast to inhalational exposure, to TDI is expected to be greater in finishing jobs and may play a role in the observed increase in lung cancer mortality. Limitations include the lack of smoking data, uncertainty in the exposure estimates, and exposure estimates that reflected inhalational exposure only.

TABLE II  
Mortality Among a Cohort of TDI-Exposed Workers (1960–2011, U.S. Referent Rates)<sup>a</sup>

	Men (n = 2,871)			Women (n = 1,874)			Overall (n = 4,545)		
	OBS	SMR	95% CI	OBS	SMR	95% CI	OBS	SMR	95% CI
All deaths	750	1.12	1.04–1.20	376	1.26	1.14–1.39	1,126	1.16	1.10–1.23
All cancers	193	1.18	1.02–1.36	140	1.43	1.21–1.69	333	1.27	1.14–1.42
Buccal and pharyngeal cancer	2	0.41	0.05–1.50	0	0.00	0.00–3.57	2	0.34	0.04–1.23
All digestive cancer	44	0.99	0.72–1.33	24	1.26	0.81–1.88	68	1.07	0.83–1.36
Esophagus	3	0.45	0.09–1.30	1	0.95	0.02–5.27	4	0.51	0.14–1.31
Stomach	5	0.97	0.31–2.26	1	0.56	0.01–3.14	6	0.86	0.32–1.88
Intestine (except rectum)	14	1.11	0.61–1.86	13	1.81	0.96–3.09	27	1.36	0.90–1.98
Rectum	5	1.67	0.54–3.90	0	0.00	0.00–2.68	5	1.14	0.37–2.67
Liver and biliary	6	0.81	0.30–1.76	4	1.65	0.45–4.22	10	1.01	0.49–1.87
Pancreas	11	1.23	0.61–2.20	3	0.63	0.13–1.83	14	1.02	0.56–1.71
Peritoneum, other, and unspecified	0	0.00	0.00–7.75	2	5.39	0.65–19.5	2	2.36	0.29–8.53
All respiratory cancer	78	1.36	1.07–1.69	57	2.38	1.80–3.09	135	1.66	1.39–1.96
Larynx	7	2.93	1.18–6.04	4	11.1	3.03–28.4	11	4.00	1.99–7.16
Trachea, bronchus, and lung	71	1.30	1.01–1.64	53	2.27	1.70–2.96	124	1.59	1.32–1.89
Breast cancer	1	4.33	0.11–24.1	22	1.08	0.68–1.64	23	1.12	0.71–1.68
Female genital cancer	—	—	—	14	1.21	0.66–2.02	14	1.21	0.66–2.02
Cervix	—	—	—	6	2.02	0.74–4.40	6	2.02	0.74–4.40
Uterus	—	—	—	4	1.54	0.42–3.95	4	1.54	0.42–3.95
Ovary	—	—	—	3	0.53	0.11–1.55	3	0.53	0.11–1.55
Other	—	—	—	1	2.65	0.07–14.8	1	2.65	0.07–14.8
Male genital cancer	10	0.98	0.47–1.80	—	—	—	10	0.98	0.47–1.80
Prostate	10	1.02	0.49–1.88	—	—	—	10	1.02	0.49–1.88
All urinary cancer	9	1.20	0.55–2.27	3	1.23	0.25–3.61	12	1.21	0.62–2.11
Kidney	6	1.34	0.49–2.92	2	1.30	0.16–4.71	8	1.33	0.58–2.63
Bladder	3	0.99	0.20–2.88	1	1.11	0.03–6.21	4	1.02	0.28–2.60
Lymphatic and hematopoietic cancer	17	1.07	0.62–1.72	8	1.02	0.44–2.02	25	1.06	0.68–1.56
Hodgkin disease	2	2.21	0.27–7.99	2	5.57	0.67–20.1	4	3.17	0.86–8.10

**La coorte include 4595 lavoratori di tre aziende, definizione dell' esposizione tramite matrice basata sulla concentrazione del TDI nell'aria startificata per azienda , reparto e operazione. Trend in diminuzione negli ultimi anni Le donne hanno lavorato di più degli uomini nelle mansioni di rifinizione Mortalità generale e per tumori significativamente in eccesso, così per tumore della laringe e polmone**



	Men (n = 2,871)			Women (n = 1,874)			Overall (n = 4,545)		
	OBS	SMR	95% CI	OBS	SMR	95% CI	OBS	SMR	95% CI
Non-Hodgkin lymphoma	10	1.65	0.79-3.04	3	1.03	0.21-3.00	13	1.45	0.77-2.48
Multiple myeloma	1	0.32	0.01-1.80	2	1.21	0.15-4.39	3	0.63	0.13-1.85
Leukemia and aleukemia	4	0.69	0.19-1.76	1	0.35	0.01-1.93	5	0.57	0.19-1.34
All other and unspecified cancer	32	1.39	0.95-1.96	12	1.05	0.54-1.83	44	1.27	0.93-1.71
Melanoma	3	1.11	0.23-3.23	0	0.00	0.00-3.18	3	0.77	0.16-2.26
Non-melanoma skin	1	1.05	0.03-5.85	0	0.00	0.00-19.5	1	0.88	0.02-4.88
Connective tissue	2	1.72	0.21-6.22	0	0.00	0.00-4.56	2	1.01	0.12-3.66
Brain	6	1.29	0.47-2.80	2	0.83	0.10-2.98	8	1.13	0.49-2.22
Thyroid	0	0.00	0.00-11.9	1	3.90	0.10-21.7	1	1.76	0.04-9.82
Other and unspecified (excludes cancers of the bone and eye and mesothelioma)	19	1.55	0.93-2.42	9	1.42	0.65-2.70	28	1.51	1.00-2.18
Benign/unspecified neoplasms	1	0.50	0.01-2.79	3	2.35	0.49-6.88	4	1.22	0.33-3.13
Tuberculosis and HIV related diseases	14	0.69	0.38-1.16	3	1.00	0.21-2.91	17	0.73	0.42-1.17
Diseases of the blood	2	0.73	0.09-2.64	2	1.24	0.15-4.47	4	0.92	0.25-2.35
Diabetes mellitus	29	1.56	1.05-2.24	12	1.12	0.58-1.95	41	1.40	1.00-1.90
Mental disorders	6	0.49	0.18-1.06	3	0.60	0.12-1.75	9	0.52	0.24-0.99
Alcoholism	4	0.58	0.16-1.49	0	0.00	0.00-3.16	4	0.50	0.14-1.28
Nonmalignant nervous system diseases	16	1.38	0.79-2.24	7	0.80	0.32-1.64	23	1.13	0.71-1.69
Heart diseases	186	1.10	0.95-1.27	66	1.09	0.84-1.38	252	1.10	0.97-1.24
Ischemic heart disease	136	1.09	0.91-1.28	44	1.08	0.78-1.45	180	1.08	0.93-1.25
Circulatory system diseases	49	1.12	0.83-1.48	22	0.86	0.54-1.30	71	1.02	0.80-1.29
Nonmalignant respiratory diseases	53	1.36	1.02-1.78	36	1.61	1.13-2.23	89	1.45	1.17-1.79
Chronic obstructive pulmonary disease	31	1.66	1.13-2.35	28	2.37	1.57-3.42	59	1.93	1.47-2.49
Asthma	1	0.75	0.02-4.18	0	0.00	0.00-2.90	1	0.38	0.01-2.14
Nonmalignant digestive diseases	26	0.76	0.50-1.12	19	1.41	0.85-2.20	45	0.94	0.69-1.26
Cirrhosis and other chronic liver diseases	12	0.61	0.31-1.06	5	0.83	0.27-1.93	17	0.66	0.38-1.06
Other (excludes diseases of stomach and duodenum, hernia, and intestinal obstruction)	10	0.85	0.41-1.57	12	1.97	1.02-3.44	22	1.24	0.77-1.87
Musculoskeletal and connective tissue diseases	1	0.55	0.01-3.06	7	2.72	1.09-5.60	8	1.82	0.79-3.59
Nonmalignant genitourinary diseases	12	1.08	0.56-1.89	7	1.06	0.43-2.19	19	1.08	0.65-1.68
Acute glomerulonephritis, nephrotic syndrome and acute renal failure	2	1.74	0.21-6.28	3	4.79	0.99-14.0	5	2.81	0.91-6.57
Chronic/unspecified nephritis and renal failure and other renal sclerosis	6	0.83	0.31-1.81	2	0.50	0.06-1.82	8	0.71	0.31-1.41

**Aumenti di rischio non significativo per hodgkin disease, non hodgkin linfoma, cancro intestino e del retto, tumore mammella utero, cervice uterina, tumore cerebrale e tiroide.**

**Tumore del polmone e laringe aumentati soprattutto nelle donne**

## 3. HEALTH EFFECTS

**Table 3-4. Results of Cohort Studies of Diisocyanate Exposure and Mortality from Specific Cancers**

	U.S. cohort		U.K. cohort		Swedish cohort	
Reference	Schnorr et al. 1996		Sorahan and Nichols 2002		Mikoczy et al. 2004	
Cohort size (number of plants)	4,611 (4)		8,288 (11)		4,175 (9)	
Time period of follow-up	1958–1993		1958–1998		1959–1998	
Person-years at risk	90,393		200,262		83,023	
Cancer site	Number of cases	SMR (95% CI)	Number of cases	SMR (95% CI)	Number of cases	SMR (95% CI)
<b>Females</b>						
Lung	8	173	35	181 <sup>a</sup> (126–251)	10	352 <sup>a</sup> (169–648)
Rectum	0	NA	2	53 (6–192)	–	–
Non-Hodgkin's lymphoma	–	–	3	110 (23, 321)	–	–
Hodgkin's disease	–	–	0	NA	–	–
<b>Males</b>						
Lung	12	79	134	107 (90–127)	7	49 (20–101)
Rectum	3	390	10	65 (31–120)	–	–
Non-Hodgkin's lymphoma	–	–	6	65 (24–142)	–	–
Hodgkin's disease	–	–	1	44 (1–243)	–	–
<b>Females and males (combined)</b>						
Lung	20 <sup>b</sup>	101 (62–156)	–	–	17	99 (58–159)
Rectum	3	278 (57–813)	–	–	–	–
Non-Hodgkin's lymphoma	4	154 (42–395)	–	–	–	–
Hodgkin's disease	2	232 (28–838)	–	–	–	–

<sup>a</sup>Significantly different from null hypothesis at  $p < 0.05$ .

<sup>b</sup>Includes tumors of the lung, trachea, and bronchus.

– = not reported; CI = confidence interval; SMR = standardized mortality ratio

**La IARC esaminò anche uno Studio caso controllo del 1991 condotto da Siemiatycki in Canada, che aveva stimato l'associazione tra 293 luoghi di lavoro e vari tipi di tumore , gli isocianati furono presi in considerazione in particolare il toluen diisocianato, trovati soprattutto nelle aziende di rifinizione veicoli motori ma solo lo 0,8 die soggetti totali risulta esposto. Non furono trovate associazioni con i diversi tipi di tumore ma per il tumore del polmone fu trovato nella sottopopolazione canadese un RR non significativo di 2.2 ma basato di un numero basso di casi esposti**





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# Carcinogenic Risk of Toluene Diisocyanate and 4,4'-Methylenediphenyl Diisocyanate: Epidemiological and Experimental Evidence

Claudia Bognesi, Xaver Baur, Boleslaw Marczynski, Hannu Norppa, Ovnair Sepai & Gabriele Sabbioni

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## Abstract

Diisocyanates are highly reactive compounds widely used, for example, in the production of polyurethane foams, elastomers, paints, and adhesives. The high

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I diisocianati sono composti altamente reattivi ampiamente utilizzati, ad esempio, nella produzione di schiume poliuretatiche, elastomeri, vernici e adesivi. L'elevata reattività chimica di questi composti si riflette anche nella loro tossicità: i diisocianati sono una delle più importanti cause di asma professionale ma nei soggetti esposti sono stati descritti anche altri effetti avversi, come irritazioni e reazioni tossiche. Una delle questioni aperte è se l'esposizione professionale agli isocianati costituisca un pericolo cancerogeno. I pochi studi epidemiologici disponibili si basano su coorti giovani e un breve follow-up e non sono conclusivi. Il **toluene diisocianato (TDI)** è stato classificato come cancerogeno negli animali sulla base di studi di somministrazione tramite sonda gastrica, ma non sono disponibili conclusioni sull'esposizione per inalazione. Per il **4,4'-metilene difenildiisocianato (MDI)** esistono prove suggestive di cancerogenicità nei ratti. Il possibile meccanismo cancerogeno di TDI e MDI non è chiaro. Entrambe le sostanze chimiche sono risultate positive in una serie di test a breve termine che hanno indotto mutazioni genetiche e danni cromosomici. La forma reattiva potrebbe essere il diisocianato stesso oppure potrebbe derivare dall'attivazione metabolica dei derivati diamminici aromatici formati per idrolisi. TDI e MDI reagiscono con il DNA in vivo e in vitro. Tuttavia, la struttura degli addotti non è stata identificata. Soprattutto dall'esperimento in vivo non è noto se gli addotti siano un prodotto della reazione con l'isocianato o con l'ammina corrispondente. In conclusione, sia il TDI che l'MDI sono sostanze chimiche altamente reattive che si legano al DNA e sono probabilmente genotossiche. La presunta cancerogenicità sugli animali di TDI e MDI suggerirebbe che l'esposizione professionale a questi composti costituisca un rischio cancerogeno. I pochi studi epidemiologici disponibili non sono però riusciti a chiarire se TDI e MDI siano cancerogeni professionali



Article  
**Exposure of Toluene Diisocyanate Induces DUSP6 and p53 through Activation of TRPA1 Receptor**

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**Abstract:** Toluene diisocyanate (TDI), a major intermediate agent used in the manufacturing industry, causes respiratory symptoms when exposed to the human body. In this study, we aimed to determine the molecular mechanism of TDI toxicity. To investigate the impact of TDI exposure on global gene expression, we performed transcriptomic analysis of human bronchial epithelial cells (BEAS-2B) after TDI treatment. Differentially expressed genes (DEGs) were sorted and used for clustering and network analysis. Among DEGs, dual-specificity phosphatase 6 (DUSP6) was one of the genes significantly changed by TDI exposure. To verify the expression level of DUSP6 and its effect on lung cells, the mRNA and protein levels of DUSP6 were analyzed. Our results showed that DUSP6 was dose-dependently upregulated by TDI treatment. Thereby, the phosphorylation of ERK1/2, one of the direct inhibitory targets of DUSP6, was decreased. TDI exposure also increased the mRNA level of p53 along with its protein and activity which trans-activates DUSP6. Since TRPA1 is known as a signal integrator activated by TDI, we analyzed the relevance of TRPA1 receptor in DUSP6 regulation. Our data revealed that up-regulation of DUSP6 mediated by TDI was blocked by a specific antagonist against TRPA1. TDI exposure attenuated the apoptotic response, which suggests that it promotes the survival of cancerous cells. In conclusion, our results suggest that TDI induces DUSP6 and p53, but attenuates ERK1/2 activity through TRPA1 receptor activation, leading to cytotoxicity.

**Keywords:** toluene diisocyanate; DUSP6; p53; ERK1/2; TRPA1; cytotoxicity



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**Toluene diisocyanato (TDI), provoca sintomi respiratori . In questo studio, hanno cercato di determinare il meccanismo molecolare della tossicità del TDI. Studiare l'impatto dell'esposizione al TDI sull' espressione globale del gene, hanno eseguito l'analisi trascrittomiche delle cellule epiteliali bronchiali umane (BEAS-2B) dopo il trattamento TDI. I geni differenzialmente espressi (DEG) sono stati ordinati e utilizzati per il clustering e analisi di rete. Tra i DEG, la fosfatasi 6 a doppia specificità (DUSP6) era uno dei geni significativamente modificato dall'esposizione TDI. Verificare il livello di espressione di DUSP6 e il suo effetto sul polmone cellule, sono stati analizzati i livelli di mRNA e proteine di DUSP6. I risultati hanno mostrato che DUSP6 lo era sovraregolato in modo dose-dipendente dal trattamento TDI. Pertanto, la fosforilazione di ERK1/2, uno dei bersagli inibitori diretti di DUSP6, erano diminuiti. L'esposizione al TDI ha anche aumentato il livello di mRNA di p53 insieme alla sua proteina e all'attività che transattiva DUSP6. Poiché TRPA1 è noto come integratore di segnale attivato da TDI, è stata analizzato la rilevanza del recettore TRPA1 nella regolazione di DUSP6. Questi dati hanno rivelato che la sovraregolazione di DUSP6 mediata da TDI è stata bloccata da un antagonista specifico contro TRPA1. L'esposizione al TDI ha attenuato la risposta apoptotica, il che suggerisce che essa promuova l'apoptosi sopravvivenza delle cellule cancerose. In conclusione, i nostri risultati suggeriscono che TDI induce DUSP6 e p53, ma attenua l'attività di ERK1/2 attraverso l'attivazione del recettore TRPA1, portando a citotossicità.**

Miligi, CIIP 20 Marzo Milano



## Qualche considerazione conclusiva

**L'Esposizione a diisocianati è una delle cause principali di asma nell'Unione europea. Per ridurre l'esposizione occupazionale a diisocianati e i possibili conseguenti casi di asma una restrizione nei prodotti contenenti più del 0,1% in peso di diisocianati è stata recentemente adottata con il regolamento REACH in UE.**

**Gli studi epidemiologici condotti ad oggi non danno un supporto importante alla cancerogenicità di queste sostanze anche per mancanza di controllo di fattori confondenti come il fumo o l'esposizione concomitante ad altri cancerogeni. L'aumento di tumore del polmone osservato nelle donne andrebbe maggiormente indagato**

**Gli studi su animali di laboratorio hanno fornito indicazioni importanti di cancerogenicità e sono stati alla base della valutazione di cancerogenicità espresse sino ad ora.**

**GRAZIE PER L'ATTENZIONE!**

