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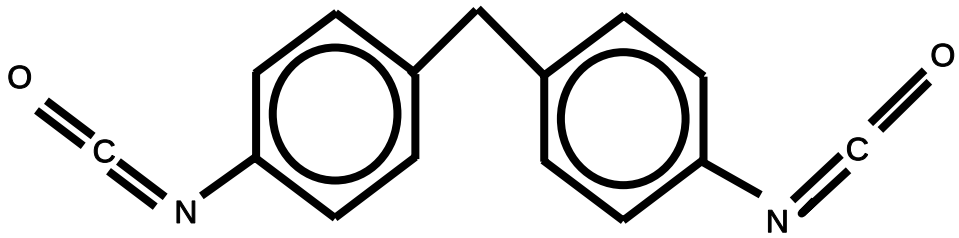
Summary Risk Assessment Report

Existing Substances – 3rd Priority List

CAS: 26447-40-5 EINECS No: 247-714-0

Methylene Diphenyl Diisocyanate



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Contact information
Address: Via E. Fermi 2749 - 21027 Ispra (VARESE) - Italy
E-mail: jrc-ihcp-communication@ec.europa.eu
Tel.: +39 0332 785959
Fax: +39 0332 785730

http://ihcp.jrc.ec.europa.eu/
http://www.jrc.ec.europa.eu/
http://ecb.jrc.ec.europa.eu/

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METHYLENE DIPHENYL DIISOCYANATE

(MDI)

CAS No: 26447-40-5

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SUMMARY RISK ASSESSMENT REPORT

Final report, 2005

Belgium

Rapporteur for the risk assessment of methylenediphenyl diisocyanate is Belgium

Contact point:

BE Rapporteur:

Federal Public Service Health, Food-Chain Safety and Environment
Environment Directorate-general
Mr. R. Moreau, General Director
Risk Management
Place Victor Horta, B 10
1060 Brussels
Contact point:
Linda.debacker@health.fgov.be
Karen.VanMalderen@health.fgov.be

Scientific Expertise:

Environmental part:

University of Liège
Laboratory of Animal Ecology and Ecotoxicology
Quai Van Beneden 22
B-4020 Liège
Belgium

Prof. J.P. Thomé
C. Joaquim-Justo

Human Health part:

Katholieke Universiteit Leuven

Laboratium voor Pneumologie
Eenheid voor Longtoxicologie
Herestraat 49 bus 706
B-3000 Leuven
België
Prof. Dr. B. Nemery
H..Vanhooren

Date of Last Literature Search:	**2003**
Review of report by MS Technical Experts finalised:	**2004**
Final report:	**2005**

PREFACE

This report provides a summary, with conclusions, of the risk assessment report of the substance methylenediphenyl diisocyanate (MDI) that has been prepared by the Belgian Competent Authorities in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances.

For detailed information on the risk assessment principles and procedures followed, the underlying data and the literature references the reader is referred to the comprehensive Final Risk Assessment Report (Final RAR) that can be obtained from the JRC-IHCP website1. The Final RAR should be used for citation purposes rather than this present Summary Report.

[1] Former - European Chemicals Bureau – Existing Chemicals – http://ecb.jrc.ec.europa.eu/

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1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS Number: 26447-40-5

EINECS Number: 247-714-0

IUPAC name: Methylenebis (phenyl isocyanate) (SIDS, 1994)

Methylenediphenyl diisocyanate

Synonyms: MDI (common name)

4,4'-diphenyl methane diisocyanate

2,4'-diphenyl methane diisocyanate

2,2'-diisocyanatodiphenylmethane

Methylene bisphenyl isocyanate

Crude MDI

Polymeric MDI

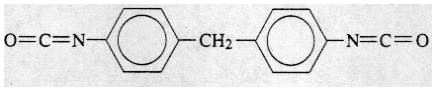
PMDI

Generic MDI

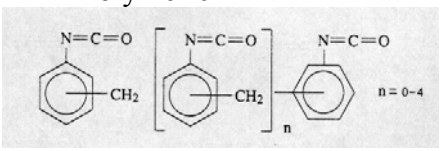
Non isomer specific MDI

Molecular formula: $C_{15}H_{10}N_2O_2$ (monomeric)
$C_{15}H_{10}N_2O_2 \cdot [C_8H_5NO]_n$ (polymeric)

Structural formula: 4,4'-MDI



Polymeric MDI



Molecular weight:
Monomeric MDI: 250.26 Polymeric MDI: 290-400

1.2 PURITY/IMPURITIES, ADDITIVES

Composition of the substance

4,4'-MDI:	4,4'-MDI	> 97%	Polymeric MDI:	4,4'-MDI	40-50%
	2,4'-MDI	1.5-2.5%		2,4'-MDI	2.5-4.0%
	2,2'-MDI	> 0.5%		2,2'-MDI	0.1-0.2%
				Homologues	60-50%

Impurities

monochlorobenzene (max. 80 ppm)
phenylisocyanate (max. 50ppm)
hydrogen chloride

Additives (concentration range 200 - 1000ppm):
triphenyl phosphite (TPP) - dinonyl phthalate (DNP) - triethyl phosphate (TEP) – butyl hydroxy toluene (BHT)

1.3 PHYSICO-CHEMICAL PROPERTIES

Table 1.1 Summary of physico-chemical properties

Property	Value (4.4 MDI)	Value (Polymeric MDI)
Physical state	(at ntp): solid	(at ntp) liquid
Melting point	39-43°C	5°C
Boiling point	(at 101100 Pa): > 300°C	
Relative density	(20°C): 1.325	(20°) 1.2381
Vapour pressure	(20°C): <0.002 Pa	(20°C) < 0.005 Pa
Water solubility	0.02 mg/l (calculated, MDI reacts with water)	
Partition coefficient n-octanol/water (log value)	4.5	
Granulometry	80% on 1.25 mm	

1.4 CLASSIFICATION

Environment

No classification or labelling for the environment.

Human Health

Classification:

Classification according to Annex I of the Directive 67/548/EEC (25th ATP, i.e. Dir. 98/98/EC, O.J. 30.12.98):

One entry (Index n° 615-005-00-9) in the Annex I applies to free diphenylmethane diisocyanate isomers:

Xn; R20 Xi; R36/37/38 R42/43

Labelling:

Symbol: St Andrew's Cross Xn

R: 20-36/37/38-42/43

S: (1/2-)23-36/37-45

The following concentration limits are applicable and the label must indicate the presence of the substance:

C ≥ 25 %	Xn: R20-36/37/38-42/43
5 % ≤ C < 25 %	Xn: R36/37/38-42/43
1 % ≤ C < 5 %	Xn: R42/43
0,1 % ≤ C < 1 %	Xn; R42

Note 2 of Annex I (Dir. 67/548/EEC) mentions: The concentration of isocyanate stated is the percentage by weight of the free monomer calculated with reference to the total weight of the preparation.

Note C: Some organic substances may be marketed either in a specific isomeric form or as a mixture of several isomers.

On the label must be stated whether the substance is a specific isomer or a mixture of isomers.

Following the 30th ATP 67/548, a new classification and labelling is proposed:

Classification:

Carc. Cat. 3; R40 Xn; R20-48/20 Xi; R36/37/38 R42/43

Labelling:

Symbol: St Andrew's Cross Xn

R: 20 - 36/37/38 – 40 - 42/43 - 48/20

S: (1/2)-23-36/37-45

C ≥ 25 %	Xn; R20-36/37/38-40-42/43-48/20
10 % ≤ C < 25 %	Xn; R36/37/38-40-42/43-48/20
5 % ≤ C < 10 %	Xn; R36/37/38-40-42/43
1 % ≤ C < 5 %	Xn; R40-42/43
0,1 % ≤ C < 1 %	Xn; R42

Note 2 of Annex I (Dir. 67/548/EEC) mentions: The concentration of isocyanate stated is the percentage by weight of the free monomer calculated with reference to the total weight of the preparation.

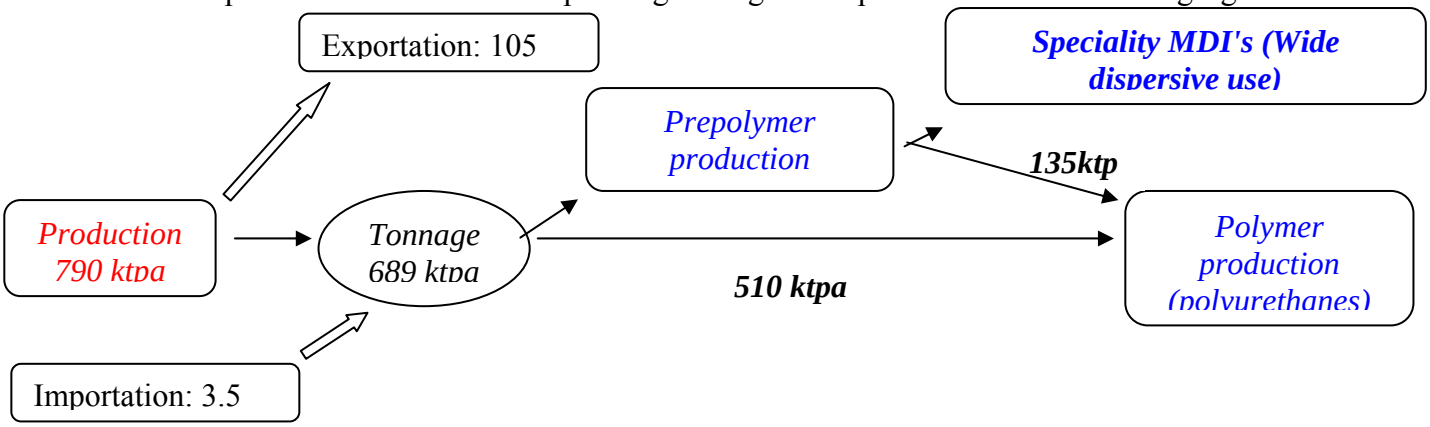
Note C: Some organic substances may be marketed either in a specific isomeric form or as a mixture of several isomers.

On the label must be stated whether the substance is a specific isomer or a mixture of isomers.

2 GENERAL INFORMATION ON EXPOSURE

Production

The life span of MDI and the corresponding tonnage are represented in the following figure:



Production of MDI and further processing to prepolymers take place in closed systems and are carried out in a rather small number of industrial sites (11 sites for total production in EU).

Some prepolymers will contain unreacted MDI in a proportion that will vary according to their intended use. Since no data could be found concerning the accurate proportion of MDI in these products, the total volume of prepolymers produced was used when processing of prepolymers was considered.

Some speciality MDI's (i.e. coatings, paintings, adhesives, sealants and cast elastomers) products may contain free MDI that will react immediately with air when used. Even if most of these products will be used in industrial structures, a certain amount will be sold to the public at large in do-it-yourself products. Consequently, the processing of prepolymers to speciality MDI's was attributed to the main category V (wide dispersive use) as a worst case assumption.

Categories considered in the risk assessment are as follow:

Table 3.1 Life span stages, categories and volumes used for estimation of MDI releases

Life span stage	Industry category	Use category	Main category	Volume (ktpa)
Production	11 Polymers industry	43 Process regulators (dry monomers)	Ic Isolate intermediates with controlled transport	790
Processing to PU	11 Polymers industry	43 Process regulators (dry monomers)	III Non dispersive use	511
Processing to prepolymers	11 Polymers industry	43 Process regulators (dry monomers)	III Non dispersive use	179
Processing of prepolymers – speciality MDI's	11 Polymers industry	43 Process regulators (dry monomers)	V Wide dispersive use	44
Processing of prepolymers other than speciality MDI's	11 Polymers industry	43 Process regulators (dry monomers)	III Non dispersive use	135

Uses

MDI's are sold to many downstream users (ca 3600 in EU). Main applications for MDI are:

polyurethane foams (69%) e.g. in refrigerators, boilers, spray foams, roofing, automotive seating, carpet backing, office furniture,…;

coatings, adhesives, sealants and elastomers (26%) e.g. in sport surfaces, windscreens, containers, aircraft, wheels, tyres, electrical joints,…;

Other uses are thermoplastic polyurethanes (tubes, hoses, cable sheatings for electrical applications, sports shoes and ski boots) and polyurethane fibres. MDI is also used as grouting agent in rock consolidation or sealing of water leaks in tunnels or geotechnical construction works.

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

Synthesis of MDI takes place in closed systems; since the NCO groups[2] of MDI react readily with OH groups, contact of MDI with water is carefully avoided through production and storage stages. Consequently releases of MDI to effluents are expected to be virtually null at the production sites. Likewise releases to sediment and soil are also expected to be negligible. Indeed, although releases of MDI to atmosphere might occur during production, they are expected to be low. Moreover exhaust gazes produced during the MDI formation reaction are treated by incineration or scrubbing of MDI vapours.

As far as transport and storage are concerned, waste water resulting from cleaning and decontamination of road tankers and tank containers is not considered to contain any MDI but rather polyurethanes and polyureas which are insoluble and inert compounds.

The MDI produced is mainly directly processed for the synthesis of polyurethanes products in which all di-isocyanates are reacted. Emissions of MDI to soil, waste water and thus sediment linked to this processing stage are expected to be negligible and polyurethane products neither contain generic isocyanates nor biologically available isocyanate group. Since the reaction of MDI and OH groups is exothermic, it is possible that some MDI might evaporate near the exit of the device where MDI and polyols are mixed (mixing head). Nevertheless the proportion of MDI which indeed reaches the atmosphere is likely to be low because of the low vapour pressure of MDI and the further treatment of the vapours collected at this stage.

Part of the MDI produced is processed in prepolymers that are mainly processed in big plants. Nevertheless, some applications of MDI concern small companies or may even be sold to the public at large in do-it-yourself products. So releases relevant for processing of these latter types of applications, which essentially concern coatings, adhesives, sealants and cast elastomers, are not well controlled or defined. This aspect was tackled by allocating prepolymer processing for such kind of products to the main category “wide dispersive use” as a worst case approach.

A somewhat particular use of MDI is its utilisation as grouting agent in tunnels; a laboratory scaled study conducted in the frame of the Romeriksporten tunnel construction (Norway) where MDI has been used to reduce water leaks from the tunnel indicated that the levels of MDI and MDA released from the foam to surrounding water were negligible.

PECs presented in table 3.2 and 3.3 were calculated with the European Union System for the Evaluation of Substances program (EUSES 1.00) on the basis of emission factors as included in release tables of TGD and on the basis of specific release information provided by industry when available.

[2] Nitrogen, Carbon, Oxygen –group (added to the aromatic ring)

Table 3.2 Local PECs

Environmental compartment	Production	Processing to PU	Processing to prepolymers	Processing of prepolymers speciality MDI's	Processing of prepolymers other than speciality MDI's
Air *(mg/m³)*	$8.14\ 10^{-7}$	$2.35\ 10^{-5}$	$7.71\ 10^{-6}$	$5.25\ 10^{-6}$	$1.\ 05\ 10^{-5}$
Surface water *(mg/l)*	$1.37\ 10^{-6}$	$1.37\ 10^{-6}$	$1.37\ 10^{-6}$	$1.37\ 10^{-6}$	$1.37\ 10^{-6}$
Agricultural soil (mg/kg wwt)	$5.38\ 10^{-5}$	$4.85\ 10^{-4}$	$1.85\ 10^{-4}$	$1.38\ 10^{-4}$	$2.38\ 10^{-4}$
Grassland *(mg/kg wwt)*	$6.00\ 10^{-7}$	$7.22\ 10^{-4}$	$2.61\ 10^{-4}$	$1.89\ 10^{-4}$	$3.43\ 10^{-4}$
Sediment *(mg/kg wwt)*	$1.66\ 10^{-4}$	$1.66\ 10^{-4}$	$1.66\ 10^{-4}$	$1.66\ 10^{-4}$	$1.66\ 10^{-4}$

Table 3.3 Regional PECs

Environmental compartment	Regional PEC
Surface water	$1.38\ 10^{-6}$ mg/l
Air	$2.06\ 10^{-7}$ mg/m³
Agricultural soil	$4.21\ 10^{-5}$ mg/kg wwt
Natural soil	$4.23\ 10^{-5}$ mg/kg wwt
Sediment	$6.94\ 10^{-5}$ mg/kg wwt

3.2 EFFECTS ASSESSMENT

In all tests performed, MDI had to be either added to water or to some moistened material; considering the high reactivity of MDI with water, it is most probable that it was the breakdown products that were being tested and not MDI. The hydrolysis products of MDI and water are dependent on the conditions of the mixing of the MDI with water. Under conditions of low dispersion the immediate products are insoluble, solid and inert polyureas. Under conditions of high dispersion, some MDA as an initial hydrolysis product may be formed, however, given its extreme reactivity with MDI, MDA is rapidly transformed.

Consequently, PNECs have been calculated on the basis of nominal concentrations even though the amount of MDI in test media was always most probably well below these values. Nominal values have been considered as representative of the amount of product that can be added per volume of media above which an effect will not occur. The reader should thus be forewarned that designation of the following effect thresholds by PNEC is not consistent with the approach adopted for non-reactive chemicals.

Effect data are summarised in the following table.

Table 3.4 Summarised effect data available

Test organism	Endpoint	Value
Fish	Acute/short-term: EC_{50}	from > 1000 to > 3000 mg/l
Daphnid	Acute/short-term: EC_{50}	> 1000 mg/l
	Reproduction/long-term: NOEC	>10 mg/l
Algae	72 hours: EC50	>1640 mg/l
	NOEC	>1640 mg/l
Earthworm	14 days: EC_{50}	> 1000 mg/kg
Plant	14 days: EC_{50}	> 1000 mg/kg
E. coli	10 days inhibition growth: EC_0	≥ 100 mg/l
Activated sludge	Respiration inhibition test:EC_{50}	> 100 mg/l

Since all tests performed were limit tests, no concentration-effect relationship could be established. Consequently NOECs were not considered for calculating the PNEC as advised in the TGD.

$PNEC_{water}$ was calculated as : > 1000 $mg.l^{-1}/1000$ = > **1 mg/l;**

$PNEC_{soil}$ as: > 1000 $mg.kg^{-1}/1000$ = > **1 mg/kg** and,

$PNEC_{micro}$ as: >100 mg/l/100: > **1 mg/l.**

$PNEC_{sediment}$ was estimated by the equilibrium partitioning approach and resulted in a value of **108 mg/kg W.W.**

3.3 RISK CHARACTERISATION

As shown in table 3.5, all PEC/PNEC ratios calculated are below 1 (conclusion ii).

Table 3.5: Calculated PEC/PNEC ratios

Compartment	Production	Processing to PU	Processing to prepolymers	Processing of prepolymers speciality MDI's	Processing of prepolymers other than speciality MDI's	Regional
Water	$<1.37\ 10^{-6}$	$<1.37\ 10^{-6}$	$<1.37\ 10^{-6}$	$<1.37\ 10^{-6}$	$<1.37\ 10^{-6}$	$<1.37\ 10^{-6}$
Soil	$<5.36\ 10^{-5}$	$<4.78\ 10^{-4}$	$<1.83\ 10^{-4}$	$<1.37\ 10^{-4}$	$<2.35\ 10^{-4}$	$<4.21\ 10^{-5}$
Sediment	$<1.54\ 10^{-6}$	$<1.54\ 10^{-6}$	$<1.54\ 10^{-6}$	$<1.54\ 10^{-6}$	$<1.54\ 10^{-6}$	$<6.4510^{-7}$
Sewage treatment plants	0	0	0	0	0	-

The EUSES program predicts that MDI will not induce perturbations to **sewage treatment plants.** This conclusion is obvious since releases of MDI by production and big processing plants (> 76% of tonnage) to STP are virtually non-existent. Moreover, any traces of MDI rejected into the water would undergo hydrolysis and disappear from effluent water very rapidly.

The **atmospheric compartment** was not included in the quantitative risk assessment because of the lack of information relevant to this compartment

Secondary poisoning is very unlikely to occur considering the physico-chemical characteristics of MDI, assumption which is confirmed by the results of accumulation studies with MDI.

Possible hazard due to MDA formation when MDI enters the water compartment was also assessed through calculation of local MDA PECs associated with MDI hydrolysis on the basis of a 2% yield. PECs estimated through this approach were negligible compared to the local PECs stated in the MDA risk assessment report (local MDA PECs from MDI: $2.8\ 10^{-8}$ compared to $69\ 10^{-3}$ for MDA generic approach and $0.4\ 10^{-3}$ for MDA site-specific approach).

It can thus be concluded that MDA amounts yielded by the hydrolysis of MDI will not lead to environmental hazards for aquatic organisms and will not influence the hazard due to production and use of MDA.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

Occupational exposure

Occupational exposure may occur by inhalation of vapours and aerosols or through skin exposure at workplaces where MDI is produced or used. Inhalation can theoretically also occur with dust arising from the handling of pure crystals of MDI.

For the occupational exposure assessment the exposure situations can be clustered into 2 scenarios:

Scenario 1: Production of MDI and prepolymers in almost completely closed systems

Scenario 2: Use of MDI as an intermediate by the downstream users. This scenario considers the use of almost completely closed systems but also the use of MDI as an aerosol in spraying applications.

An overview of the conclusions of the occupational exposure assessment is given in Table 4.1.

Table 4. 1 Summary on the occupational exposure assessment

Scenario	Exposure		Estimated inhalation exposure level (mg/m³)						Estimated skin exposure	
			Full shift (8 hour time weighed average)				Short-term			
	Duration (h/day)	Frequency (day/year)	Typical	Method	Reasonable Worst Case	Method	Level	Method	mg/day	mg/kg.day
1 Chemical industry: MDI production Prepolymer production	Continuous (8-hour-shifts) and batch-synthesis	continuous	0.007	Meas.[1]	0.053 1	Meas.[2] EASE	0.1	Expert	650	9.29
2 Industrial and skilled trade sectors: Breached closed systems, partially open and manual processes			Not estimated		0.05 1	Meas.[2] EASE	0.1	Expert	1,300	18.57
Spraying					>10,000	EASE			3,500	50
Specialist contractor foam applicators					0.40	literature	0.57	literature	3,500	50

Meas.[1]: data taken from industry measurements; median value
Meas.[2]: data taken from industry measurements; 95 percentile
EASE: calculated with the EASE model
Expert: expert judgement; short-term exposure estimate = 2x Reasonable Worst Case
Literature: data found in the literature

Consumer exposure

Four scenarios are considered for consumer exposure:
Scenario 1: Spray painting (liquid roof coating, outdoors)
Scenario 2: Use of spray foam or One Component Foam (OCF)
Scenario 3: Gluing, and the use of putty/filler in cartridge, painting with brush
Scenario 4: Use of Hot Melt Adhesives

The frequency of exposure is expected to be low i.e. to occur occasionally for short-term events.

The main results of the consumer exposure assessment which are used in the risk characterisation are gathered in Table 4.2.

Table 4. 2 External acute exposure for consumers

		Acute Exposure Levels (External)		
Scenario	free MDI (%)	Inhalation (mg/m³)	Dermal	
			(mg/d)	(mg/kg bw)
(1) Spray painting	0.1	-	5.35	0.076
(2) Use of OCF	10	0.0061	535	7.6
(3) Gluing, putty/filler cartridge, brush painting	35	-	2,940	42
(4) Hot melt adhesives	2	0.025	168	2.4

Humans exposed via the environment

The EUSES model has been used to calculate the MDI human daily dose through food, air, and drinking water. The main results are gathered in Table 4.3. Daily doses linked with releases in the local environment are expressed as a range of intake when considering all use patterns of MDI.

Table 4. 3 Estimated human daily intake of MDI via the environment

	Regional	Local
Daily dose through air (mg/kg.d)	$4.41\ 10^{-8}$	$1.74\ 10^{-7} – 5.04\ 10^{-6}$
Daily dose through drinking water (mg/kg.d)	$1.95\ 10^{-8}$	$1.95\ 10^{-8} – 1.41\ 10^{-7}$
Daily dose through fish (mg/kg.d)	$2.99\ 10^{-6}$	$2.99\ 10^{-6}$
Daily dose through leaf crop (mg/kg.d)	$8.78\ 10^{-8}$	$3.47\ 10^{-7} – 1\ 10^{-5}$
Daily dose through root crop (mg/kg.d)	$6.35\ 10^{-7}$	$8.11\ 10^{-7} – 7.31\ 10^{-6}$
Daily dose through meat (mg/kg.d)	$1.46\ 10^{-9}$	$5.23\ 10^{-9} – 1.47\ 10^{-7}$
Daily dose through milk (mg/kg.d)	$8.62\ 10^{-10}$	$3.09\ 10^{-9} – 8.66\ 10^{-8}$
Total daily intake for humans (mg/kg.d)	$3.78\ 10^{-6}$	$4.\ 35\ 10^{-6} – 2.57\ 10^{-5}$

At the regional level, intake from fish is the most important source of MDI; on the local scale, man is mainly exposed via fish and vegetable consumption and via the air.

However, given the reactivity with water and the information available on the absence of accumulation of MDI in organisms, it is very unlikely that MDI becomes available in the food chain.

Combined exposure

On the basis of the exposure estimates given, humans can be exposed to MDI as a result of combined exposure. However, indirect exposure via the environment can be considered to be negligible for the calculation of the combined exposure.

As a reasonable worst-case (RWC), someone who works in the industrial and skilled trade sector, and is exposed at home doing some 'D.I.Y[3].' (e.g. use of OCF[4]) will receive a maximum dose of MDI which can be quantified as is shown in Table 4.4.

Table 4. 4 Calculated combined exposure

Exposure pathway	Acute exposure	Lifetime exposure[1]
Inhalative	Workplace[2] WC 0.05 mg/m³ Consumer[3] WC 0.0061 mg/m³	Workplace[2] WC 68.57 mg/kg bw Consumer[3] WC 0.14 mg/kg bw
Dermal	Workplace[4] WC exposure 1,300 mg/d, WC uptake 13 mg/d Consumer[5] WC exposure 535 mg/d WC uptake 5.35 mg/d	Workplace[4] WC exposure 178.3 g/kg bw, WC uptake 1,783 mg/kg bw Consumer[5] WC exposure 1.2 g/kg bw, WC uptake 12 mg/kg bw

[1] for the calculation of lifetime doses following parameters were used: 70 kg bw (adult), 1.25 m³/h inhaled air for a consumer doing D.I.Y.-jobs for working 8h/d, 4 days/y for 40 years (consumer), 10 m³/8 h workshift inhaled air, 5 days/week 48 weeks/y and 40 years working period (worker), dermal absorption 1%.

[2] worst case inhalation exposure for the occupational scenarios 1 and 2 is 0.05 mg/m³.
[3] worst case inhalation exposure for consumer scenario 2 (use of OCF) is 0.0061 mg/m³.
[4] worst case dermal exposure for almost all applications in the occupational scenario 2 (industrial and skilled trade sector) is 1300 mg/d.
[5] worst case dermal exposure for consumer scenario 2 (use of OCF) is 535 mg/d.

4.1.2 Effects assessment

Toxicokinetics, metabolism and distribution

There are few data available on the toxicokinetics and fate of MDI in humans. Urinary 4,4'-methylenedianiline, measured after acid hydrolysis, has been suggested as a biomarker for the short-term exposure to MDI. 4,4'-methylenedianiline (4,4'-MDA), released by hydrolysis of plasma or haemoglobin, has been suggested as a biomarker of intermediate and long-term

[3] Do it yourself
[4] One component foam

exposure to MDI. No information is available on the toxicokinetics of MDI following oral exposure in animals.

Contradictory results have been obtained with respect to dermal exposure. Eventually, as reasonable worst-case estimate, a dermal absorption of 1% was taken forward to the risk characterisation.

With respect to inhalation exposure, there is reliable data regarding distribution/excretion in experimental animals. In biomonitoring studies haemoglobin adducts and urine metabolites of MDI were determined. From the data generated to date, it is not possible to state categorically that the MDA measured in the majority of studies investigating levels in blood and plasma represents a metabolite of MDI. The results of the inhalation metabolism/toxicokinetics/distribution study indicate that a proportion of the MDI dose is converted to metabolites via the intermediary formation of an amine group which is rapidly acetylated. However, the current data do not allow entire elucidation of the mechanisms involved in the biological transport and transformation of MDI. Further studies using biologically relevant *in vitro* systems are ongoing. Additional studies are being designed to investigate metabolism of formed conjugates and any role of free or bound MDA in MDI formation.

Acute toxicity

Assessment of the available acute toxicity data indicates that inhalation exposure to respirable aerosols of MDI results in toxicity confined predominantly to the respiratory tract. A well-conducted animal study gives a LC_{50} (4 h, rat) of 490 mg/m³. The limited data available from animal studies indicate that MDI is of low oral and dermal acute toxicity, with an oral LD_{50} (rat) > 10,000 mg/kg bw and dermal LD_{50} (rabbit) > 10,000 mg/kg bw.

Irritation

MDI is a known skin and eye irritant. The toxicity studies, mechanistic studies, and human data indicate that MDI causes irritation of the respiratory tract. A RD50 (mice), due to pulmonary irritation, of 32 mg/m³ was found. An acute irritant threshold concentration of 0.5 mg/m³ was estimated from rat studies based on the most sensitive (and reversible) endpoints in bronchoalveolar lavage fluid.

Sensitisation

MDI has also a skin sensitising potential. Animal studies indicate that MDI is a strong allergen. A few human case reports describe allergic contact dermatitis due to MDI exposure. MDI is a well-established respiratory sensitiser in animals and humans. Animal studies have shown that respiratory sensitisation can be induced by skin contact with MDI. The quantitative relationships between exposure (concentration, duration, rate of exposure, route of exposure) and incidence of sensitisation have not been established. No threshold level for sensitisation could be determined. Extensive information is available on the mechanism of hypersensitivity. Cross-reactivity with other isocyanates has been described in several publications.

Repeated dose toxicity

No results from repeated-dose toxicity tests are available for the oral and dermal route of exposure.

Well-conducted short-term and long-term inhalation animal studies indicate the respiratory tract to be the target organ of respirable MDI aerosol.

The most reliable NOAEL of short-term toxicity is 1.4 mg/m³; LOAEL being 2 mg/m³ (based on increased lung weights). However, mechanistic studies revealed a LOEL of 1.1 mg/m³ (based on changes in the phospholipid content of alveolar macrophages and non-specific cell proliferation of Type II pneumocytes). These findings are consistent with the sub-acute LOAEL of 1 mg/m³ found for effects on the surfactant homeostasis. In an acute rat inhalation study a LOAEL of 0.7 mg/m³ was found for transient dysfunction of the pulmonary epithelial barrier (NOAEL being estimated at 0.5 mg/m³). For the risk characterisation, the NOAEL = 0.5 mg/m³ is used for acute irritation after short-term inhalation (consumers).

The reported NOAELs for chronic toxicity (inhalation, rat, 2 years) are 0.23 mg/m³ and 0.2 mg/m³; LOAEL being 1 mg/m³. For the risk characterisation, the most reliable NOAEL = 0.2 mg/m³ is used for inflammatory and other non-neoplastic pulmonary changes after long-term inhalation exposure (workers).

The effect of long-term exposure of MDI on the respiratory system of humans has been described in several studies. Long-term exposure of MDI tends to cause restriction of pulmonary function and decline on pulmonary diffusing capacity. In addition to reports of cases of asthma, hypersensitivity pneumonitis, pleuritis, and progressive fibrosing alveolitis it may be concluded that chronic exposure to even low levels (mostly undetermined or below 0.05 mg/m³) of MDI carries a risk of respiratory disease.

Mutagenicity

From the body of available data it is concluded that MDI does not have genotoxic properties. Conflicting results were obtained in *in vitro* test systems. The results from the requested *in vivo* micronucleus test indicate that aerosolized, inhaled MDI at concentrations as high as 118 mg/m³ air (a concentration high enough to produce portal-of-entry-specific toxic effects, including statistically significantly increased lung weights) did not induce cytogenetic damage *in vivo*.

Carcinogenicity

In a well-conducted chronic toxicity/carcinogenicity animal inhalation study, tumours in the lungs were found, without adverse effect on the distribution and incidence of tumours apart from these lung tumours. In another long-term animal inhalation study a single bronchio-alveolar adenoma was found at 2.05 mg/m³ MDI. There are two hypotheses concerning the oncogenesis of MDI: 1° oncogenesis on the basis of irritation through epigenetic mechanisms, 2° oncogenesis resulting from the formation of MDA (4,4'-methylenedianiline). A NOAEL of 0.2 mg/m³ is established for inflammatory and other non-neoplastic pulmonary changes. No carcinogenicity studies are available using the oral or dermal route of exposure. There is inadequate evidence of carcinogenicity in humans and limited evidence in experimental animals.

Toxicity for reproduction

No fertility or multigeneration studies are available for MDI. Data from (sub)chronic toxicity studies did not reveal clear substance related and/or significant impairment of organs of the reproductive system of the male and female. Taken together, these studies were considered too limited to allow a determination of a NOAEL for fertility. Pre-natal inhalation toxicity

testing in rats indicated the absence of selective toxicity to the development (no findings indicated any specific developmental effects at exposure levels below those that caused maternal toxicity). The reported NOAEL(developmental) for monomeric MDI is 3 mg/m³/day and the NOAEL(developmental) for polymeric MDI is 4 mg/m³/day. No data on reprotoxicity are available in humans.

4.1.3 Risk characterisation

Workers

The risk characterisation for workers is limited to the dermal and respiratory routes of exposure. Because it its generally known that MDI is a harmful, irritating, and sensitising agent, high inhalation and dermal exposure levels are avoided in practice and the use of protective measures have been taken into account on the exposure estimates.

Table 4.5 provides an overview of the conclusions reached in the risk characterisation for workers for different exposure scenarios and different toxicological endpoints.

Table 4. 5 Overview of conclusions with respect to occupational risk characterisation

End point and outcome of the key study used in risk characterisation (between brackets)	Conclusions valid for the occupational scenarios			
	Scenario 1: Chemical Industry		Scenario 2: Downstream users	
	MOS	Conclusion	MOS	Conclusion
Acute toxicity				
- oral (LD_{50} rat >10,000 mg/kg bw)	-	ii	-	ii
- dermal (LD_{50} rabbit >10,000 mg/kg bw)	1,076	ii	-539 (200 for specialist contractor foam applicators)	ii
- inhalation (LC_{50}, 4h, rat: 490 mg/m3)	4,900	ii	4,900 (860 for specialist contractor foam applicators)	ii
Irritation				
dermal (irritant)	-	ii	-	ii (exception: unprotected workers on building sites: iii)
eyes (irritant)	-	ii	-	ii (exception: unprotected workers on building sites: iii)
respiratory tract	9.4	iii	10 1.3 (specialist contractor	iii iii

End point and outcome of the key study used in risk characterisation (between brackets)	Conclusions valid for the occupational scenarios			
	Scenario 1: Chemical Industry		Scenario 2: Downstream users	
	MOS	Conclusion	MOS	Conclusion
			foam applicators)	
Sensitisation - dermal (sensitising) - inhalation (sensitizing)	 - -	 iii iii	 - -	 iii iii
Repeated dose toxicity, systemic effects, including possible carcinogenicity - dermal (no studies) - inhalation (NOAEL rat, 0.2mg/m³) - combined	 - 3.77 0.6	 ii iii iii	 - 4 0.3 0.1 (specialist contractor foam applicators)	 ii iii iii iii
Mutagenicity (no evidence for mutagenicity)	-	ii	-	ii
Reproductive toxicity - inhalation Fertility (database not adequately enough)	 -	 i on hold	 -	 i on hold
Developmental toxicity ($NOAEL_{dev}$, rat, 3 mg/m³/d)	57	ii	60 7.5 (specialist contractor foam applicators), but PPE	ii ii

Consumers

Table 4.6 provides an overview of the conclusions reached in the risk characterisation for consumers for different exposure scenarios and different toxicological endpoints. Scenario 1: Spray painting; Scenario 2: Use of spray foam 'OCF'; Scenario 3: Gluing, putty/filler adhesives, painting with brush/roller; Scenario 4: Hot melt adhesives.

Table 4. 6 Overview of conclusions with respect to consumer characterisation

Endpoint	Conclusions valid for the consumer scenarios			
	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Acute toxicity (oral, dermal, inhalation)	ii	ii	ii	ii
Irritation (skin, eyes)	iii	iii	iii	iii
Irritation (respiratory tract)	ii	iii	ii	iii
Sensitisation (dermal, inhalation)	iii	iii	iii	iii
Lung effects induced by short-term repeated exposure	ii	iii	ii	iii
Chronic toxicity / carcinogenicity	ii	ii	ii	ii
Mutagenicity	ii	ii	ii	ii
Reproductive toxicity (fertility)	i on hold	i on hold	i on hold	i on hold
Reproductive toxicity (developmental)	ii	ii	ii	ii
Physicochemical properties	ii	ii	ii	ii

Humans exposed via the environment

The human exposure from the indirect exposure in local and regional scenarios is presented in Table 4.7. The estimations were performed according to EUSES.

Table 4. 7 Estimated human exposure via the environment and MOS[5]

	MOS Total	MOS Air
Local scale:		
Production	$1.32\ 10^4$	$3.28\ 10^5$
Processing to polyurethanes	$2.24\ 10^3$	$1.13\ 10^4$
Processing of prepolymers – speciality MDI'S	$6.75\ 10^3$	$5.05\ 10^4$
Processing of prepolymers – other than speciality MDI'S	$4.27\ 10^3$	$2.54\ 10^4$
Processing to prepolymers	$5.33\ 10^3$	$3.46\ 10^4$
Regional scale	$1.52\ 10^4$	$1.30\ 10^6$

Given that exposure levels are most probably much lower than calculated by the model on account of the very high reactivity of MDI with water and the worst case assumptions upon which the calculations were based, and in view of the MOS obtained (minimum 2,240), it can be concluded that exposure of humans to MDI through the environment is not expected to lead to any health hazard: Conclusion (ii).

[5] Margin of safety

Combined exposure

Combining occupational, consumer and indirectly via the environment exposure will not materially influence the characterisation of the risks associated with occupational exposure alone.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

With regard to the physico-chemical properties and with regard to the occupational, consumer, indirect and combined exposure, MDI is not expected to cause specific concern relevant to human health.

5 RESULTS

5.1 ENVIRONMENT

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

The risk assessment shows that risks are not expected

5.2 HUMAN HEALTH (TOXICITY)

Workers

Conclusion (i) There is a need for further information and/or testing.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (i) on hold applies to the current database which does not adequately cover the toxicity for fertility. The collection of additional better information to adequately characterise the risks regarding this endpoint should, however, not delay the implementation of appropriate control measures needed to address the concerns related to other endpoints.

Conclusion (iii) applies to

- skin and eye irritation for workers on building sites, as in this case occupational hygiene standards are often low and PPE might not be worn.
- respiratory tract irritation as a consequence of inhalation exposure arising from all investigated occupational exposure scenarios.
- skin and respiratory sensitisation as a consequence of dermal and inhalation exposures arising from all investigated occupational exposure scenarios.
- respiratory toxicity as a consequence of repeated inhalation exposure arising from all investigated occupational exposure scenarios.

Consumers

Conclusion (i) There is a need for further information and/or testing.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (i) on hold applies to the current database which does not adequately cover the toxicity for fertility. The collection of additional better information to adequately characterise the risks regarding this endpoint should, however, not delay the implementation of appropriate control measures needed to address the concerns related to other endpoints.

Conclusion (iii) applies to

- skin and eye irritation as a consequence of exposure arising from the use of all types of MDI-containing consumer products.
- respiratory tract irritation as a consequence of inhalation exposure arising from the use of MDI-containing one component foams (OCFs) and hot melt adhesives.
- skin and respiratory sensitisation as a consequence of dermal and inhalation exposures arising from the use of all types of MDI-containing consumer products.
- lung effects as a consequence of inhalation by short-term repeated exposure arising from the use of MDI-containing one component foams (OCFs) and hot melt adhesives.

Humans exposed via the environment

Conclusion (**ii)** There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

The risk assessment shows that risks are not expected. Risk reduction measures already being applied are considered sufficient.

Combined exposure

Conclusion (i) There is a need for further information and/or testing.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (i) on hold applies to the current database which does not adequately cover the toxicity for fertility. The collection of additional better information to adequately characterise the risks regarding this endpoint should, however, not delay the implementation of appropriate control measures needed to address the concerns related to other endpoints.

Conclusion (iii) applies to

- eye, skin, respiratory tract irritation as a consequence of exposure arising from combined occupational and consumer exposure.
- skin and respiratory sensitisation as a consequence of dermal and inhalation exposures arising from combined occupational and consumer exposure.
- respiratory toxicity as a consequence of repeated inhalation exposure arising from combined occupational and consumer exposure.

5.3 HUMAN HEALTH (RISKS FROM PHYSICO-CHEMICAL PROPERTIES)

Conclusion (**ii)** There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

The risk assessment shows that no concern is expected related to the physico-chemical properties of MDI. Risk reduction measures already being applied are considered sufficient.

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Abstract

The report provides the summary of the substance Methylenediphenyl diisocyanate (MDI). It has been prepared by Belgium in the frame of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances, following the principles for assessment of the risks to humans and the environment, laid down in Commission Regulation (EC) No. 1488/94.

Part I - Environment
This part of the evaluation considers the emissions and the resulting exposure to the environment in all life cycle steps. Following the exposure assessment, the environmental risk characterisation for each protection goal in the aquatic, terrestrial and atmospheric compartment has been determined. The environmental risk assessment concludes that there is no concern.

Part II – Human Health
This part of the evaluation considers the emissions and the resulting exposure to human populations in all life cycle steps. The scenarios for occupational exposure, consumer exposure and humans exposed via the environment have been examined and the possible risks have been identified. The human health risk assessment concludes that there is concern for workers and consumers with regard to irritation of skin, eye and respiratory tract, skin sensitisation and lung effects induced by repeated inhalation exposure. There is a need for further information and for testing (on hold) on the toxicity for fertility for workers and consumers. For humans exposed via the environment and for human health (physico-chemical properties) there is no concern. The conclusions of this report will lead to risk reduction measures to be proposed by the Commission's committee on risk reduction strategies set up in support of Council Regulation (EEC) N. 793/93.

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