Concise International Chemical Assessment Document 27

DIPHENYLMETHANE DIISOCYANATE (MDI)

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The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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FOREWORD

Concise International Chemical Assessment Documents (CICADs) are the latest in a family of publications from the International Programme on Chemical Safety (IPCS) — a cooperative programme of the World Health Organization (WHO), the International Labour Organization (ILO), and the United Nations Environment Programme (UNEP). CICADs join the Environmental Health Criteria documents (EHCs) as authoritative documents on the risk assessment of chemicals.

CICADs are concise documents that provide summaries of the relevant scientific information concerning the potential effects of chemicals upon human health and/or the environment. They are based on selected national or regional evaluation documents or on existing EHCs. Before acceptance for publication as CICADs by IPCS, these documents undergo extensive peer review by internationally selected experts to ensure their completeness, accuracy in the way in which the original data are represented, and the validity of the conclusions drawn.

The primary objective of CICADs is characterization of hazard and dose–response from exposure to a chemical. CICADs are not a summary of all available data on a particular chemical; rather, they include only that information considered critical for characterization of the risk posed by the chemical. The critical studies are, however, presented in sufficient detail to support the conclusions drawn. For additional information, the reader should consult the identified source documents upon which the CICAD has been based.

Risks to human health and the environment will vary considerably depending upon the type and extent of exposure. Responsible authorities are strongly encouraged to characterize risk on the basis of locally measured or predicted exposure scenarios. To assist the reader, examples of exposure estimation and risk characterization are provided in CICADs, whenever possible. These examples cannot be considered as representing all possible exposure situations, but are provided as guidance only. The reader is referred to EHC 170[1] for advice on the derivation of health-based tolerable intakes or guidance values.

[1] International Programme on Chemical Safety (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits.* Geneva, World Health Organization (Environmental Health Criteria 170).

While every effort is made to ensure that CICADs represent the current status of knowledge, new information is being developed constantly. Unless otherwise stated, CICADs are based on a search of the scientific literature to the date shown in the executive summary. In the event that a reader becomes aware of new information that would change the conclusions drawn in a CICAD, the reader is requested to contact IPCS to inform it of the new information.

Procedures

The flow chart shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world — expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing risks to human health and/or the environment.

The first draft is based on an existing national, regional, or international review. Authors of the first draft are usually, but not necessarily, from the institution that developed the original review. A standard outline has been developed to encourage consistency in form. The first draft undergoes primary review by IPCS to ensure that it meets the specified criteria for CICADs.

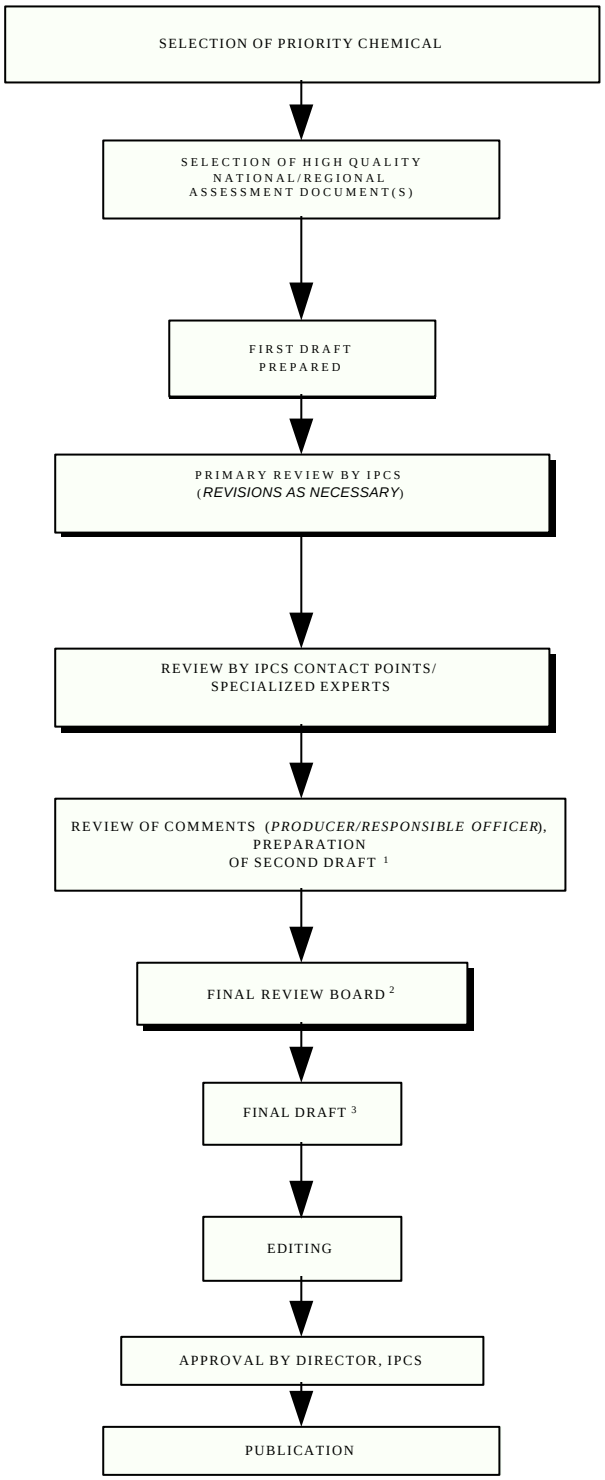
The second stage involves international peer review by scientists known for their particular expertise and by scientists selected from an international roster compiled by IPCS through recommendations from IPCS national Contact Points and from IPCS Participating Institutions. Adequate time is allowed for the selected experts to undertake a thorough review. Authors are required to take reviewers' comments into account and revise their draft, if necessary. The resulting second draft is submitted to a Final Review Board together with the reviewers' comments.

The CICAD Final Review Board has several important functions:

- to ensure that each CICAD has been subjected to an appropriate and thorough peer review;
- to verify that the peer reviewers' comments have been addressed appropriately;
- to provide guidance to those responsible for the preparation of CICADs on how to resolve any remaining issues if, in the opinion of the Board, the author has not adequately addressed all comments of the reviewers; and
- to approve CICADs as international assessments.

Board members serve in their personal capacity, not as representatives of any organization, government, or

CICAD PREPARATION FLOW CHART



1 Taking into account the comments from reviewers.
2 The second draft of documents is submitted to the Final Review Board together with the reviewers' comments.
3 Includes any revisions requested by the Final Review Board.

industry. They are selected because of their expertise in human and environmental toxicology or because of their experience in the regulation of chemicals. Boards are chosen according to the range of expertise required for a meeting and the need for balanced geographic representation.

Board members, authors, reviewers, consultants, and advisers who participate in the preparation of a CICAD are required to declare any real or potential conflict of interest in relation to the subjects under discussion at any stage of the process. Representatives of nongovernmental organizations may be invited to observe the proceedings of the Final Review Board. Observers may participate in Board discussions only at the invitation of the Chairperson, and they may not participate in the final decision-making process.

1. EXECUTIVE SUMMARY

This CICAD on diphenylmethane diisocyanate (MDI) was prepared by the National Institute of Health Sciences, Japan, in collaboration with the National Center for Environmental Assessment, US Environmental Protection Agency (EPA). The CICAD was based principally on the reviews of the Japan Society for Occupational Health (JSOH, 1994) and the US EPA (1998) for the toxicological evaluation and the European Union (EU, 1999) for the environmental assessment. It should be noted that the EU document is still an unapproved draft and that the information presented in the environmental sections is based mainly on unpublished studies. The literature up to November 1998 was searched using MEDLINE to identify any new information relevant to the assessment. The preparation and peer review of the source documents are described in Appendix 1. Information on the peer review of this CICAD is presented in Appendix 2. This CICAD was approved as an international assessment at a meeting of the Final Review Board, held in Stockholm, Sweden, on 25–28 May 1999. Participants at the Final Review Board meeting are listed in Appendix 3. The International Chemical Safety Card (ICSC 0298) for MDI, produced by the International Programme on Chemical Safety (IPCS, 1993), has also been reproduced in this document.

Diphenylmethane diisocyanate (MDI) is the generic name of a product used in industrial settings. Polymeric MDI (PMDI), the primary technical/commercial form of MDI, is actually a mixture that contains 25–80% monomeric 4,4'-MDI as well as oligomers containing 3–6 rings and other minor isomers, such as the 2,2'-isomer. The exact composition of PMDI varies with the manufacturer.

Monomeric 4,4'-MDI is a white to pale yellow solid at room temperature, with a molecular weight of 250. It has a boiling point of >300 °C at 101.3 kPa, a melting point of 39–43 °C, and a vapour pressure of <1 mPa at 20 °C. It has a transient existence in water; thus, its water solubility is only notional. However, monomeric MDI is soluble in octane, benzene, and kerosene. PMDI is a dark reddish brown liquid with an indefinite melting point around 0 °C and a vapour pressure of <1 mPa at 20 °C. MDI is highly reactive in the environment or when taken up by organisms and is rapidly hydrolysed to form 4,4'-methylenedianiline (MDA), which reacts with excess MDI to yield insoluble oligoureas and polyureas.

MDI is used for polyurethane elastomers (rollers, packing, rubber vibration insulators, synthetic leather, etc.), spandex fibres, and rubber shoe soles. PMDI is used to make rigid and flexible foam, foundry resin sand binders, and heat insulating material. The total annual global production of MDI and PMDI was about 1.2 million tonnes in 1991, 1.5 million tonnes in 1993, 1.78 million tonnes in 1994, and 1.95 million tonnes in 1996.

After the appropriate collection of the aerosol form by impingers, bubbles, or filters, high-performance liquid chromatography (HPLC) is used for the analysis of MDI and PMDI. Detection limits of HPLC for MDI and PMDI, which vary depending on the sampling methodology, can be below 0.01 mg/m^3. Free and acetylated MDA are identified in nearly all studies after strongly hydrolysing conditions. These conditions will also form MDA from conjugated MDI. A new method has recently become available for determining the composition of complex mixtures of airborne isocyanates and related compounds formed during the thermal decomposition of polyurethane by derivatization of isocyanates with dibutylamine.

Under normal circumstances, exposure of the general public to MDI is likely only from releases to the atmosphere. High exposures in ambient environments are rare. Where spillage is to soil or water, MDI has a transient existence due to its reaction with the water to produce predominantly insoluble polyureas. MDA concentrations formed in the environment by the reaction of MDI with water are always low. A pond study provides evidence that MDI accumulation through the aquatic food chain is extremely unlikely, as might be expected considering its very low solubility and high reactivity in aqueous solution. The information on occupational exposure is limited; in different industries, 8-h time-weighted average exposures in excess of 50 µg/m^3 have been reported to occur infrequently.

There is very limited information on the toxicokinetics of MDI. Once absorbed, it appears to be predominantly conjugated to protein. With respect to inhalation exposure, only limited studies using rats are available. An inhalation exposure study using radiolabelled MDI indicates that some form or portion of MDI is distributed throughout the body, predominantly in the lungs, muscle, kidneys, and digestive tract. The faecal and urinary elimination of MDI and its metabolites over 4 days was 57% and 13% of the recovered radioactivity, respectively. Less than 1% of the radioactivity was recovered from the major organs, although 23% of the administered dose was recovered in the carcass. In urine, small amounts of free and acetylated MDA were identified.

Studies of workers have identified free MDA, acetylated MDA, and adducts of both with haemoglobin

or albumin in urine and blood. These studies suggest that plasma acid-hydrolysable MDA may be a useful biomarker of long-term exposure to MDI. The half-life of acid-hydrolysable MDA in the urine of a worker exposed to PMDI was 70–80 h, and in serum, 21 days.

MDI is not acutely toxic to laboratory mammals. Animal data provide clear evidence of skin and respiratory sensitization due to MDI. Humoral as well as cellular immunity may be involved in the pathogenesis of hypersensitivity due to isocyanates. Severe respiratory distress and a significant decrease in body weight gain were observed in male and female rats exposed to PMDI aerosol at a concentration of 13.6 mg/m^3 for 6 h per day, 5 days per week, over a period of 2 weeks, with much less severe signs of respiratory distress and only slightly reduced body weight gain in male rats at 4.9 mg/m^3. Based on a marginal increase in lung to body weight ratio at higher doses, it was concluded that 2.2 mg/m^3, which was the lowest dose level examined, was a no-observed-adverse-effect level (NOAEL).

In a 2-year chronic inhalation toxicity/carcinogenicity study, rats that were exposed to PMDI aerosol at concentrations of 0, 0.19, 0.98, or 6.03 mg/m^3 showed changes in the respiratory tract. Pulmonary adenocarcinoma observed in one case was considered as insufficient to identify PMDI as an animal carcinogen; however, *in situ* generation of MDA, which is a known animal carcinogen via drinking-water, could be responsible for the effect. Basal cell hyperplasia in the olfactory epithelium detected at 0.98 and 6.03 mg/m^3 was judged a non-carcinogenic critical end-point. The non-neoplastic information in this study suggests a NOAEL of 0.19 mg/m^3 and a lowest-observed-adverse-effect level (LOAEL) of 0.98 mg/m^3.

Both positive and negative results were obtained when monomeric MDI dissolved in dimethyl sulfoxide (DMSO) was tested *in vitro* with *Salmonella typhimurium*. However, because of the known interaction of DMSO with MDI to yield MDA and possibly other reaction products, these positive results should not be construed as meaningful for human health risk assessment.

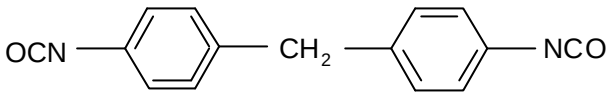
Exposure of gravid Wistar rats to monomeric MDI resulted in an increased incidence of asymmetric sternebrae in fetuses at 9 mg/m^3; however, as the increase was within the limits of biological variability, the NOAEL for developmental toxicity in this study was estimated to be 9 mg/m^3. In another study in which rats were exposed to PMDI, the NOAEL for maternal and fetal toxicity was estimated to be 4 mg/m^3, based on the finding of premature deaths of pregnant females and statistically significant decreases in placental and fetal weights at 12 mg/m^3. There have been no studies that have examined the effect of polymeric or monomeric MDI on reproductive parameters.

The health end-points of most concern are occupationally induced asthma, hypersensitivity pneumonitis, and inflammatory upper respiratory tract diseases through inhalation of polymeric or monomeric MDI. Although not yet well understood, humoral as well as cellular immunological reactions appear to be involved in the allergic reactions. Case reports as well as epidemiological studies have described MDI as a cause of occupational dermatitis, skin sensitization, and asthma. Although limited in various ways, a cohort study and a retrospective study showed no significant association with cancer morbidity. There are no data available for oral exposure, but it is unlikely that humans are exposed to MDI by the oral route.

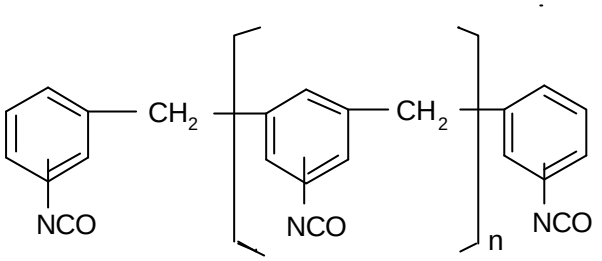
MDI did not show toxicities to fish, aquatic invertebrates, algae, or microorganisms under any acute or long-term exposure testing conditions. However, results of aquatic tests are not meaningful because of MDI's virtual insolubility in water. Similarly, a few tests on terrestrial organisms did not show any effects under the testing conditions. Available data show that there is no need for concern regarding the effects of MDI on organisms in the environment, although more detailed information regarding the formation of MDA in the environment and its effects on organisms is required before any firm conclusions can be drawn.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

MDI is the generic name of a product used in industrial settings. PMDI, the primary technical/commercial form of MDI, is actually a mixture that contains 25–80% monomeric 4,4'-MDI as well as oligomers containing 3–6 rings and other minor isomers, such as the 2,2'-isomer. This composition renders the material semisolid and suitable for aerosol generation. The composition of PMDI varies with the manufacturer and use. The range of variation reflects variations from various sources of information, i.e., from a German review (DFG, 1997), US Toxicological Review (US EPA, 1998), and the EU draft document (EU, 1999). Figure 1 gives chemical structures of 4,4'-MDI and PMDI, and Table 1 provides Chemical Abstracts Service (CAS) registry numbers of several MDI isomers and PMDI.



Chemical structure of MDI



Chemical structure of PMDI

Figure 1: Chemical structure of 4,4'-MDI and PMDI.

Table 1: Isomers and polymers of MDI.

Name	CAS registry number
4,4'-MDI	101-68-8
2,4'-MDI	5873-54-1
2,2'-MDI	2536-05-2
non-isomer-specific MDI	26447-40-5
PMDI	9016-87-9

Monomeric 4,4'-MDI is a white to pale yellow solid at room temperature, with a molecular weight of 250.26. It has a boiling point of >300 °C at 101.3 kPa, a melting point of 39–43 °C (capillary method) or 40 °C (differential scanning calorimetry or DSC method) (Kelly et al., 1997), and a vapour pressure of <1 mPa at 20 °C (DFG, 1997). It has a transient existence in water; thus, its water solubility is only notional. However, monomeric MDI is soluble in octane, benzene, and kerosene (Chemical Society of Japan, 1989). The conversion factor for MDI is as follows: 1 ppm = 10.4 mg/m^3. Additional properties for MDI are presented in the International Chemical Safety Card (ICSC 0298) reproduced in this document.

PMDI is a dark reddish brown viscous liquid with an indefinite melting point around 0 °C and a vapour pressure of <1 mPa at 20 °C (DFG, 1997).

PMDI is the form produced commercially from aniline and formaldehyde using hydrochloric acid as catalyst. This condensation reaction produces MDA and a complex mixture of polyamines, which are phosgenated to obtain a methylene diphenyl diisocyanate mixture. 4,4'-MDI can be obtained by purifying the diphenylmethane diisocyanate mixture.

3. ANALYTICAL METHODS

Because commercial applications using PMDI generate aerosols (Dharmarajan, 1979), traditional techniques that have been successfully used to measure isocyanate vapours (e.g., the Marcali and paper tape colorimetric methods) are generally not suitable for quantitative measurements of MDI in air. The strengths and limitations of impingers, bubbles, and filters with respect to collection and detection of both MDI aerosols and vapours have been discussed by Streicher et al. (1994). When pure monomeric MDI was heated under laboratory conditions, a 0.5-µm pore size filter blocked more than 87% of the MDI from entering an impinger.

Usually HPLC is used for the analysis of MDI and PMDI (NIOSH, 1985; IARC, 1986; Spanne et al., 1996; Tinnerberg et al., 1997). Detection limits of HPLC for MDI and PMDI, which vary depending on the sampling methodology, can be below 0.01 mg/m^3.

Complex mixtures of airborne isocyanates and related compounds formed during the thermal decomposition of polyurethane were analysed by derivatization of isocyanates in impinger flasks containing dibutylamine with formation of urea derivatives. Derivatives were analysed by reverse-phase liquid chromatography with mass spectrometry or with ultraviolet (UV) detection. The detection limit of MDI with UV detection was 0.5–0.8 µg/m^3 for a 15-litre air sample, and that with mass spectrometry (instrumental detection limit) was 4 fmol of the MDI derivative (Spanne et al., 1996; Tinnerberg et al., 1997).

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

MDI is used for polyurethane elastomers (rollers, packing, rubber vibration insulators, synthetic leather, etc.), spandex fibres, and rubber shoe soles. PMDI is used to make rigid and flexible foam, foundry resin sand binders, and heat insulating material. The total annual global production of MDI and PMDI was about 1.2 million tonnes in 1991, 1.5 million tonnes in 1993, 1.78 million tonnes in 1994, and 1.95 million tonnes in 1996 (Chemical Week, 1998). In Japan, 0.20–0.27 million

tonnes were produced in 1992–1996 (Chemical Daily, 1997).

MDI is usually present in workplace air as vapour, but some aerosol may also co-exist, depending on the type of operation (DFG, 1997). In such atmospheres, exposure may be to unreacted MDI or to a mixture of MDI and polyols, reactants used to convert MDI to polyurethane foams. The range of particle size will vary with the application, and the method of sampling and analysis should be suited to the workplace requirement.

The extent to which MDI, in either monomeric or polymeric form, disperses in air beyond the point of release and exposes general populations is not known.

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

The complex nature of MDI composition and reactions in the environment often makes interpretation difficult.

The observed or likely fates of MDI in air, water, and soil have been described by Brochhagen & Keller (1983) and Gilbert (1988). More recently, comprehensive studies on the behaviour of MDI in the aquatic environment have been carried out by Yakabe et al. (1994) and Heimbach et al. (1996).

5.1 Water

When MDI is added to water, its NCO groups react readily with OH groups of the water to form mixtures of diisocyanates and amines, which then readily react with more MDI to produce inert, solid, insoluble polyurea (EU, 1999). The hydrolysis of isocyanates in aqueous solution is rapid; a half-life of 20 s has been measured for phenyl isocyanate (Castro et al., 1985). However, the subsequent reaction of the formed amine with further isocyanate, to produce a urea, is even faster (Hegarty et al., 1975).

Yakabe et al. (1994) studied the fate of PMDI in water under two conditions — namely, vigorous stirring and static conditions, which simulate two scenarios of accidental spills of PMDI. PMDI used in experiments is complex and composed of 5–6 major constituents having 2–4 aromatic rings. When MDI comes into contact with water, it does not disperse readily, but forms globules or solid masses, which react at their surface. Under such heterogeneous conditions, the disappearance of PMDI shows zero-order kinetics. Production of water-soluble MDA increases gradually with time, and the MDA reaches a nearly constant concentration after 16 h; the amount of MDA formed is less than 0.5% of the nominal concentration of PMDI initially added, and the major products of PMDI breakdown are solid, insoluble polyureas. The polyureas formed from MDI appear to be stable to chemical attack, as would be expected from its insolubility and the stability of ureas.

Support for the chemical stability of MDI is given in one study in which the polyurea formed from the reaction of PMDI with water was stirred at 40 °C in aqueous buffer solutions for 14 days. No soluble products (dissolved organic carbon or MDA) were detected (Yakabe et al., 1994).

A further potential breakdown product of MDI in water is an oligourea. An oligourea was synthesized from 4,4'-MDI and 4,4'-MDA and shown to be mainly diurea. It was insoluble in water and found to be not inherently biodegradable (Yakabe et al., 1994).

In the study by Heimbach et al. (1996), up to 10 g of PMDI was added per litre of water into artificial outdoor ponds, simulating accidental pollution of a pond. Three ponds contained groundwater, above natural lake sediment, to which caged rainbow trout (*Oncorhynchus mykiss*) were added. Following equilibration, PMDI was added to part of the sediment of two ponds at dosages of 1 and 10 g/litre. The third pond served as an untreated control. Water chemistry, MDI and MDA concentrations, and populations and diversity of different trophic levels were monitored over 112 days. The concentrations of MDI and MDA were monitored in the three compartments (water, fish, and sediment) over the duration of the study. No MDI or MDA was detected in the water (detection limits 4 and 10 µg/litre, respectively) or in the fish (detection limits 0.5 and 1.4 mg/kg, respectively). The study provides evidence that MDI accumulation through the aquatic food chain is extremely unlikely, as might be expected considering the very low solubility and high reactivity of MDI in aqueous solution.

5.2 Soil

MDI may come into contact with soil after accidental spillage during transportation or storage.

5.3 Air

The atmospheric concentration of MDI arising from a release is naturally low on account of MDI's very low volatility. It is expected that airborne MDI will have a rather short half-life as a consequence of ready degradation to inorganic compounds by hydroxyl radicals present in the troposphere.

The question of whether MDI vapour or aerosol can hydrolyse in humid air to yield MDA was assessed in a long-term study (Appelman et al., 1986) and a study of chipboard production (Giersig, 1989). In the first study, low concentrations of MDA (not detected to 90 $\mu g/m^3$) were observed in air samples from the subchronic inhalation study in rats exposed to PMDI (Appelman et al., 1986). Detected concentrations were independent of the concentrations of the test atmosphere (0, 0.2, 1, and 5 mg/m^3); thus, it was considered that the detection of MDA was caused by artefacts. In the second study, no MDA was detected, although the PMDI concentrations ranged up to 5 mg/m^3 when polyurethane particleboard was heated up to 80 °C (the detection limit for MDA in air was 10 $\mu g/m^3$) (Giersig, 1989). This result has been accounted for as follows: MDA is formed only slowly at neutral pH and reacts rapidly with excess MDI to yield oligoureas and polyureas; MDI aerosols can form a shell of polyurea on the surface of the droplets, and this shell prevents further reaction of the enclosed MDI (Mann, 1987).

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

6.1 Environmental levels

Commercial synthesis of MDI takes place in closed systems where contact of MDI with water is carefully avoided through production and storage stages, since the NCO group of MDI reacts readily with the OH group of water (EU, 1999). There is no information about levels of various forms of MDI in the ambient air. Where spillage is to soil or water, MDI has a transient existence due to its reaction with the water to produce predominantly insoluble polyureas.

6.2 Human exposure

Under normal circumstances, exposure of the general public is likely only from releases to the atmosphere.

Occupational exposure data from a wide range of applications and processes collected across industry, measured by recent standards and capturing total inhalable MDI (i.e., vapour and aerosol) over a variety of exposure times (0.25–8 h), are available (ISOPA, 1998). Out of 1238 measurements, 138 (11%) were above 0.0125 mg/m^3, and 31 (2.5%) were above 0.05 mg/m^3; these 31 measurements were detected during processes in rigid polyurethane foam preparation for roof panels for thermal insulation or preparation of coatings, adhesives, sealants, and elastomers for spray floor coating, bridge decking primer, or particleboard. Since accidental exposure to MDI in occupational settings may result from incidents such as spillages, split hoses, and leaking drums, the introduction of European Isocyanate Production Association (ISOPA) guidelines for transport, storage, handling, and use of diisocyanate has reduced the potential of accidental exposures over the past 20 years.

Analysis conducted revealed that the environmental MDI concentration was 0.05 mg/m^3 or less in 273 out of 319 samples, and only 2 samples exceeded 0.2 mg/m^3. It is reported, however, that a ventilation duct was installed above the moulding machine several months before the analysis, and that before then samples exceeding 0.2 mg/m^3 had occurred frequently (Diller & Herbert, 1982).

Sepai et al. (1995b) examined biological samples (urine and blood) from 20 workers (as well as 2 unexposed reference workers) exposed to MDI vapour during the manufacture of polyurethane products, together with the levels of MDI in the air of the working environment. In most cases (17 out of 20), the air levels were below detection limits. The blood and urine samples were analysed for the presence of adducts and metabolites using gas chromatography–mass spectrometry methods. The amount of MDA released after acid hydrolysis (in hydrochloric acid at 3 mol/litre, at 100 °C, for 60 min) was on average 6.5 times higher than the amount of free MDA and acetylated MDA present in urine.

The Ontario Ministry of Labour, Canada, assessed the cause of multiple respiratory complaints among workers at a plant that manufactures automotive instrument panels using polyurethane (Liss et al., 1996). Of 137 samples analysed for MDI between 1986 and 1992, 129 (94%) were below the limit of detection (not given). Of the other eight, all but one (with a concentration of 60 $\mu g/m^3$) were below 50 $\mu g/m^3$. Tarlo et al. (1997) reported that 40% of measured MDI concentrations in 1984–1988 in 20 companies with compensated isocyanate asthma claims exceeded 50 $\mu g/m^3$, while the figure was 27% for 203 companies with no compensated isocyanate asthma cases.

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Animal inhalation studies have shown that PMDI exposure (see section 8.4.2 for details of particle size

distribution) results in significant deposition both in the nasal region and in the alveolar region of the lungs (Reuzel et al., 1994a,b). Once absorbed, PMDI appears to be predominantly conjugated to protein, but the role of other biomolecules, such as glutathione, has not been investigated (the role of glutathione has been shown for other isocyanates by Day et al., 1997).

In an unpublished pharmacokinetic study (Istin, 1977), nose-only exposure of male Sprague-Dawley rats to an aerosol (particle sizes less than 5 µm) of radio-labelled (in the methylene group) monomeric MDI for 15 min resulted in the distribution of radioactivity, predominantly to the lungs and a variety of extrarespiratory sites (principally muscle, liver, kidneys, and the digestive tract), after 96 h when the animals were sacrificed. Labelling of the digestive tract was considered to be a result of transference of labelled material from the lungs. After 4 days, 70% of the absorbed dose was eliminated (57% faecal elimination and 13% urinary elimination). There was no attempt to identify the nature of the excreted radioactivity. Twenty-three per cent of the radioactivity administered was found in the carcass; however, less than 1% of the radioactivity was recovered from the major organs. The fate of the other 22% is not known.

Haemoglobin adducts were found after repeated exposure of rats to MDI aerosols for 17 h per day, 5 days per week, over 3 or 12 months in an inhalation chamber (Sepai et al., 1995a). In laboratory animals exposed to PMDI/MDI, MDA in urine and blood formed by strong acid hydrolysis was used as a biomarker for exposure (Sepai et al., 1995a).

When pregnant Wistar rats were exposed for 6 h on gestation day 19 to an aerosol of 20 mg MDI/m^3 (particle size distribution not known), maternal blood, amniotic fluid, fetus, and placenta were measured for MDI and degradation products (as MDA after acid hydrolysis; details of hydrolysis conditions not known) immediately after exposure (Bartsch et al., 1996). The highest level of MDA or degradation products was detected in the maternal blood, followed by the placenta, fetus, and amniotic fluid (at 66.4%, 42.4%, and 13.6% of the maternal blood levels, respectively).

In humans, MDA levels in urine and (after strong acid hydrolysis) in blood were reported to be correlated with exposure to PMDI/MDI (Schuetze et al., 1995; Sepai et al., 1995b; Skarping & Dalene, 1995). The half-life of MDA in the urine of a worker exposed to PMDI was 70–80 h, and in serum, 21 days (Skarping et al., 1995). Other reports also suggest that plasma acid-hydrolysable MDA may be a useful biomarker of long-term exposure to MDI (Sepai et al., 1995b; Dalene et al., 1996). In a recent study of workers occupationally exposed to either PMDI/MDI or MDA, free MDA was detected in urine prior to acid hydrolysis (Schuetze et al., 1995).

Sepai et al. (1995b) reported the formation of adducts of MDA and acetylated MDA with haemoglobin or albumin in the blood of workers exposed to MDI, as described in section 6.2. MDA was detected as a haemoglobin adduct in all 20 subjects, at levels ranging from 70 to 710 fmol/g haemoglobin; this included one case of haemoglobin adduct of acetylated MDA, which was presumably formed by the *in vivo* hydrolysis of MDI. Plasma MDA levels ranged from 3.9 to 70 fmol/mg plasma protein in 20 workers, and up to 120 fmol/mg were found to be covalently bound to albumin. MDI in the air and MDA in the plasma were observed in a study of polyurethane pipe welders (Skarping et al., 1995; Dalene et al., 1996; Tinnerberg et al., 1997). The haemoglobin adduct of acetylated MDI was considered to be formed by *in vivo* hydrolysis.

8. EFFECTS ON LABORATORY MAMMALS AND *IN VITRO* TEST SYSTEMS

8.1 Single exposure

Oral LD_{50}s for MDI (25% in corn oil) and PMDI (undiluted) administered to rats in single gavage doses were reported to be 31.6 g/kg body weight and higher than 10 g/kg body weight, respectively (Mobay Chemical, 1961; Wazeter, 1964a).

PMDI (liquid form; 0, 2.5, 3.9, 6.0, and 9.4 g/kg body weight) was applied to the abraded skin of immobilized albino rabbits (2 per sex per group) whose backs were then covered in rubberized cloth for 24 h (Wazeter, 1964b). After the PMDI was washed off, animals were kept for 14 days for observation. Transiently slight atonia was observed in a few animals at the three highest dose levels. Animals were essentially normal, except for slight oedema observed at the 9.4 g/kg body weight dose.

Guinea-pigs exposed to monomeric MDI aerosol at concentrations between 0.6 and 350 mg/m^3 (no other details available) for 3 h showed a decrease in respiration rate and an increase in tidal volume at lower concentrations, whereas a concentration-dependent increase in respiration rate was seen above 10.4 mg/m^3 (Thorne et al., 1986). In contrast, the respiration rate was decreased in a dose-dependent manner in mice exposed to MDI aerosol concentrations between 10.2 and 58.5 mg/m^3 (Weyel & Schaffer, 1985).

When rats were exposed to PMDI aerosol (in which more than 99% of particles were smaller than 5 µm) for 4 h at concentrations of 384, 418, 500, or 523 mg/m^3, animals sat quietly with closed eyes during exposure, and their breathing became laboured and nostrils dilated, especially in the highest concentration group (Appelman & de Jong, 1982). Autopsy of the animals immediately after exposure showed haemorrage and oedema in the lungs. The LC_{50} in this study was estimated to be 490 mg/m^3.

8.2 Irritation and sensitization

8.2.1 Irritation

When PMDI (liquid form; 0, 2.5, 3.9, 6.0, or 9.4 g/kg body weight) was applied to the abraded skin of albino rabbits (2 per sex per group) for 24 h (Wazeter, 1964b), one animal at the highest dose exhibited slight oedema during the first and second days. Slight erythema observed initially at all dose levels did not last after 7 days. No desquamation or fissuring was noted with the compound.

8.2.2 Sensitization

There is clear evidence of skin sensitization due to MDI. Humoral as well as cellular immunity may be involved in the pathogenesis of hypersensitivity due to isocyanates.

In a mouse ear-swelling test, which indicates the extent of contact sensitivity, MDI at concentrations ranging between 0.6 and 187 mg/kg body weight was applied to the shaved and depilated abdomens of 4–5 male mice (Thorne et al., 1987). After 4 days, the mice were challenged on the right ear with acetone and on the left ear with acetone containing a dose of MDI that was non-irritating. The thickness of the ears at 24 h after challenge was compared with that immediately before challenge. After calibration of the ear-swelling response with MDI sensitization dose in log scales, an ear thickness increase of more than 0.03 mm was judged to be significant. The challenge with acetone did not produce any ear swelling. The response to MDI challenge indicated a dose–response effect at 0.6–37 mg/kg body weight. Cross-reactivity to toluene diisocyanate (TDI) and other isocyanates was demonstrated.

Using ear thickening as the criterion, transfer of MDI-induced contact sensitivity with or without T-cell deletion by monoclonal anti-Thy-1,2 antibody was studied (Tanaka et al., 1987). A 1% solution of MDI (reagent grade) in ethyl acetate was applied to a group of 7–9 7-week-old male mice. The challenge solution induced ear swelling of delayed onset, with its peak at 24 h. Passive transfer of the MDI-induced contact sensitivity was achieved by injecting lymphocytes from the lymph nodes of MDI-sensitized mice into the caudal vein of syngeneic mice, and the effector cells were found to be T-cells.

8.3 Short-term exposure

Four groups of 10 male and 10 female Wistar rats were exposed, whole body, to PMDI aerosol for 6 h per day, 5 days per week, over a period of 2 weeks (Reuzel et al., 1994a). The overall mean concentrations were 2.2, 4.9, and 13.6 mg/m^3, respectively. Ninety-five per cent of the particles had a mass median aerodynamic diameter (MMAD) below 5 µm. No MDA and no phenyl isocyanate could be detected in the test atmospheres. Severe respiratory distress and a statistically significant decrease (extent not given) in body weight gain were observed in male and female rats exposed to 13.6 mg PMDI/m^3; 7 out of 10 males and 1 out of 10 females died. Male rats exposed to 4.9 mg/m^3 showed much less severe signs of respiratory distress and only slightly reduced body weight gain compared with controls. Lung to body weight ratios were significantly higher only in the mid- and high-concentration groups relative to controls. Gross pathological examination remained essentially negative; no data on histological examination were reported. Based on the marginal increase in lung to body weight ratios, it was concluded that 2.2 mg PMDI/m^3, which was the lowest dose level examined, was a NOAEL. The results show that the toxicity of MDI (which is low after oral exposure) is clearly higher by the inhalation route, with local effects to the lung after repeated dosing.

No short-term study on monomeric MDI and no data from oral or dermal routes were available.

8.4 Long-term exposure

8.4.1 Subchronic exposure

In a subchronic study by Reuzel et al. (1994a), SPF Wistar rats (30 per sex per exposure level) were exposed, whole body, to PMDI (Desmodur 44V20 from Bayer AG, with monomeric MDI 52%, isocyanate content 30%) aerosol at 0, 4.1, 8.4, or 12.3 mg/m^3 for 6 h per day, 5 days per week, for 13 weeks. More than 95% of the particles had an MMAD of less than 5 µm. The highest concentration resulted in 25% mortality (15/60 animals, only during the first 7 weeks), growth retardation, severe respiratory distress, degeneration of nasal tissues, and focal inflammatory changes in the lungs. Signs of less severe respiratory distress were also observed in animals exposed to 8.4 mg/m^3. Body weights in males of the high-concentration group were significantly depressed through week 13. Some body weight depression was observed in males of the mid-concentration group

through week 10. Body weight depression was not observed in females. There was not a clear dose–response trend in macrophage accumulation, although macrophages were increased in incidence in all test groups over controls. Tissues examined by light microscopy included nose, larynx, trachea, lungs, liver, and kidney. The incidence of olfactory atrophy was statistically significant in high-dose males (5/10) and high-dose females (6/10). At 4.1 mg/m^3, olfactory epithelial atrophy occurred infrequently in exposed animals. There was a significant accumulation of macrophages in the lungs and mediastinal lymph nodes of all exposed animals compared with controls. The increase in macrophage accumulation at the level of the alveolar septa was related to exposure, and the difference between treatment groups and controls was statistically significant in males exposed to 4.1 mg/m^3 and in females at 8.4 mg/m^3.

Since the first study found high mortality, probably due to the use of very young animals, another 13-week study was conducted at actual mean concentrations of 0.35, 1.4, and 7.2 mg/m^3 (Reuzel et al., 1994a). Unlike the first study, transient growth retardation and an increased number of pulmonary macrophages were the only effects noted at the highest concentration.

Thus, these studies demonstrated clear adverse pulmonary and nasal effects at 8.4 mg/m^3, and they are statistically significant at 4.1 mg/m^3.

8.4.2 Chronic exposure and carcinogenicity

A 2-year chronic toxicity/carcinogenicity inhalation study was carried out with SPF Wistar rats (60 per sex per exposure level) exposed whole body to PMDI aerosol at 0, 0.19, 0.98, or 6.03 mg/m^3 for 6 h per day, 5 days per week (Reuzel et al., 1994b). An additional satellite group of 10 per sex per exposure level was similarly exposed and used for histopathology at 1 year. Ninety-five per cent of the particles had an MMAD less than 5 µm; the MMAD and geometric standard deviation (in parentheses) corresponding to the exposure levels were 0, 0.68 µm (2.93), 0.70 µm (2.46) and 0.74 µm (2.31), respectively.

Effects at 24 months were confined to the respiratory tract. Compound-related changes were found in the nasal cavity (olfactory degeneration and basal cell hyperplasia), the lungs (fibrosis and interstitial pneumonitis), and the mediastinal lymph nodes; to some degree, they were already present after 1 year of exposure, as indicated in the satellite group. Olfactory epithelial degeneration was elevated significantly at the high concentration in both sexes. Basal cell hyperplasia in the olfactory epithelium was elevated significantly in males only at the mid and high concentrations.

No adverse effects on the distribution and incidence of tumours were found with the exception of tumours in the lungs. Solitary pulmonary adenomas, described as rare in this strain, were observed in males (6/60) and females (2/59) exposed to 6.03 mg/m^3 compared with controls (0/120). The adenomas were only a few millimetres in size and were located adjacent to areas in which haemorrhage, macrophage accumulation, and fibroblastic reactions were observed. Only one pulmonary adenocarcinoma (10 mm in size) was observed in one male exposed to this concentration.

The nasal olfactory and lung lesions indicate a NOAEL of 0.19 mg/m^3 and a LOAEL of 0.98 mg/m^3. Compound-associated yellowish particulate material was found in alveolar luminar macrophages in both sexes at 0.98 and 6.03 mg/m^3. Localized fibrosis was significant in males exposed to 6.03 mg/m^3 and in females at 0.98 and 6.03 mg/m^3. The amount of particulate material accumulated at the level of the alveolar duct increased with time as well as with level of exposure. Macrophages with yellow pigment (a form of MDI within the macrophage) were also found in the alveolar interstitium, and accumulation of these macrophages also occurred in the mediastinal lymph nodes. The accumulation of macrophages and localization of tissue damage in this area suggest that the thoracic effect is due primarily to toxicity to the macrophage, with secondary tissue damage.

A chronic inhalation study (Hoymann et al., 1995, 1997) has also been conducted with 99.5% pure monomeric 4,4'-MDI. Female Wistar rats (80 per exposure group) were exposed (whole body) to MDI in aerosol at 0.23, 0.70, or 2.05 mg/m^3 (MMAD about 1 µm) for 17 h per day, 5 days per week, for up to 24 months. A separate group of 20 per exposure level was examined histopathologically at 12 months. Smaller numbers of animals were assessed at various time points for lung function and for examination of bronchioalveolar lavage (BAL) fluid for cell counts and protein and enzyme determinations. Statistically significant concentration-related pulmonary lesions included (1) an increase in focal/multifocal alveolar and bronchioalveolar hyperplasia, (2) interstitial fibrosis, and (3) an accumulation of particle-laden and pigmented macrophages. Alveolar cell hyperplasia, considered preneoplastic, exhibited a concentration–response trend, with the incidence reaching significance in the high-exposure group. These effects correlated with pulmonary function deficits (FEF_{25} [forced expiratory flow from 25% of the forced vital capacity, or FVC] and carbon monoxide diffusion), particularly in the high-exposure group. All groups exhibited significantly increased relative lung weights at all time periods (more than 60% at 20 months), with significant increases in hydroxyproline in BAL fluid (more than 70% at 12 months). In contrast to the results reported by Reuzel et al. (1994b) for PMDI, there was no

apparent effect of monomeric MDI on nasal tissues at any exposure level. In one high-dose animal, a bronchioloalveolar adenoma was observed. Because of the concentration-related lung effects, 0.23 mg/m^3 is considered a LOAEL. There is no NOAEL in this study.

MDI reacts with water to produce MDA. MDA has also been studied for carcinogenicity by oral administration. Treatment-related increases in the incidences of thyroid follicular cell adenoma and hepatocellular neoplasms were observed in both male and female mice given 150 or 300 mg MDA/litre in drinking-water for 103 weeks. In rats administered MDA in a similar manner, treatment-related increases in the incidences of thyroid follicular cell carcinomas and hepatic nodules were observed in males, and thyroid follicular cell adenomas occurred in females (Weisburger et al., 1984; NTP, 1986). The incidence of thyroid tumours was greater when MDA (1000 mg/kg diet for 19 weeks) was administered orally after a single intraperitoneal injection of 2800 mg *N*-bis(2-hydroxypropyl)-nitrosamine (DHPN)/kg body weight than when DHPN was given alone (Hiasa et al., 1984). The relevance of these results to the evaluation of the carcinogenic response to MDI and its potential metabolite is not certain.

8.5 Genotoxicity and related end-points

When the mutagenicity of isomers and homologues of MDI (4,4'-MDI, 2,4'-MDI, a mixture of monomeric MDI isomers, and PMDI) was determined in the *Salmonella*/microsome test using DMSO and ethyleneglycol dimethyl ether (EGDE) as solvents, positive results were obtained for DMSO solutions of all four diisocyanates in the presence of S9 mix containing 30% S9 fraction. Uniformly negative results were found when the diisocyanates were dissolved in EGDE (Andersen et al., 1980; Herbold, 1980a,b; Woolrich, 1982; Shimizu et al., 1985; Zeiger, 1987; Herbold et al., 1998). MDI is not stable in DMSO, there being many products generated within minutes (Herbold, 1990a,b; Gahlmann, 1993). Thus, it seems that positive test results in any *in vitro* test system are caused by the degradation products of MDI in DMSO, rather than by MDI itself. One of the degradation products of MDI is MDA, which is known to be genotoxic and whose formation was detected when MDI was dissolved in DMSO (Herbold et al., 1998). No MDA could be detected in solutions of MDI in EGDE. It is therefore concluded that the positive results obtained with diisocyanates in DMSO solutions are due to the formation of MDA. The stability of MDI in a model and a real-test environment was studied (Seel et al., 1999). When MDI was dissolved in DMSO, more than 99% of the MDI was degraded before the start of incubation with test ingredients of the *Salmonella* mutagenicity assay, and MDA was detected at 2.1–2.8% of the MDI concentration within 45 s of incubation.

Tests assessing the mutagenic potential of MDI *in vitro* and *in vivo* show no convincing evidence of mutagenic activity.

Female Wistar rats were treated topically (on the back) with ^{14}C-MDI (labelled in the ring) in acetone to investigate the possibility of systemic circulation and DNA-binding potency of MDI (Vock & Lutz, 1997). About 10% of the radioactivity was retained at the site of application. DNA radioactivity in the liver was at the limit of detection. In a second experiment using topical administration, ^{32}P-postlabelling analysis did not reveal isocyanate–DNA adducts in the skin (Vock & Lutz, 1997).

Tissues obtained from female Wistar rats exposed to a 0.9-µm aerosol of MDI for 17 h per day, 5 days per week, for 1 year, at levels of 0, 0.3, 0.7, or 2.0 mg/m^3, were analysed for DNA adducts using a ^{32}P-postlabelling method (Vock et al., 1996). In the lung, neither isocyanate adducts nor the arylamine adduct was detectable. The same negative result was seen in the liver, bladder, kidney, respiratory epithelium, and peripheral lymphocytes. In the olfactory epithelium, on the other hand, the arylamine-derived DNA adduct nucleotides were detected at very low levels (5–10 adducts per 10^{10} nucleotides).

8.6 Reproductive and developmental toxicity

No specific fertility studies are available for MDI.

In a well conducted developmental range-finding study, conducted according to Organisation for Economic Co-operation and Development (OECD) Guideline No. 414, mated female Wistar rats (8 per group) were exposed to PMDI by inhalation (whole body) at exposure levels of 0, 2, 8, or 12 mg/m^3 for 6 h per day from day 6 up to and including day 15 of pregnancy (Waalkens-Berendsen & Arts, 1992). On day 21 of pregnancy, the female rats were sacrificed and a caesarean section was performed. No clinical signs or mortality related to treatment was observed during the study. The mean number of corpora lutea, implantation sites, early and late resorptions, and, consequently, pre- and post-implantation loss showed no statistically significant differences among the control and treated groups. From day 6 to day 9 of pregnancy, maternal body weight gain of the 8 and 12 mg/m^3 groups was slightly decreased (not statistically significant) when compared with the control group. No other differences were observed in body weight and body weight gain, carcass weight, or net weight gain when compared with the control group. Fetal body weights were comparable in all groups, and no external treatment-related abnormalities were observed in the fetuses. The NOAEL of PMDI aerosol

by inhalation for maternal toxicity is 8 mg/m^3, based on the increased lung weights (relative weight increased by 14%) and decreased food intake at 12 mg/m^3. The NOAEL of PMDI aerosol by inhalation for developmental toxicity in this study is 12 mg/m^3.

The prenatal toxicity of PMDI in pregnant Wistar rats was also investigated by aerosol inhalation (whole body) according to OECD Guideline No. 414 by BASF (1994). Twenty-five mated female rats per group were exposed to concentrations of 1, 4, or 12 mg/m^3 (MMAD <2.8 µm) for 6 h per day from day 6 to day 15 of gestation. The study was performed in two replicates comprising about half of the animals each. Exposure to PMDI aerosols at a concentration of 12 mg/m^3 caused premature death in 2 out of 25 animals. In this group, statistically significant decreases in placental (6% decrease compared with control) and fetal weights (10% decrease compared with control) occurred, and fetuses/litters with skeletal variations (irregular shaped sternebra, bipartite sternebra) and retardations (incomplete or missing ossification of skull bones, vertebral column, sternebra, metatarsal bones, and parts of the pelvic girdle) occurred at an increased rate. Mean percentages for skeletal variations were 38.9, 48.7, 47.8, and 63.2% ($p \# 0.05$), and mean percentages for overall variations were 24.6, 34.7 ($p \# 0.05$), 33.4 ($p \# 0.05$), and 40.0% ($p \# 0.01$), at 0, 1, 4, and 12 mg/m^3, respectively. No treatment-related findings in dams and fetuses occurred at 1 and 4 mg/m^3. The NOAEL for maternal and fetal toxicity was 4 mg/m^3, and the NOAEL for developmental effects was 4 mg/m^3.

Gravid Wistar rats were exposed by whole-body inhalation to clean air (control) and to monomeric 4,4'-MDI at 1, 3, or 9 mg/m^3 for 6 h per day from day 6 to day 15 post-conception (Buschmann et al., 1996). The MMAD of the aerosol was 1.1 µm. Rats were sacrificed on day 20. The absolute and relative lung weights in the high-dose group were significantly increased (23%) compared with the sham-treated control animals; this end-point was not examined in the other exposure groups. Treatment did not influence any other maternal or fetal parameters investigated, although a slight but significant increase in litters with fetuses displaying asymmetric sternebra was observed after treatment with the highest dose. Since the number of the effects observed in the 9 mg/m^3 group was within the limits of biological variability, a NOAEL for developmental effects of 9 mg/m^3 was determined in this study.

9. EFFECTS ON HUMANS

It is well documented that isocyanates are a cause of occupational asthma (Vandenplas et al., 1993). Humoral as well as cellular mechanisms are involved in the pathogenesis. Immediate or late allergic reactions or both can occur. The specific humoral immune response can be IgE as well as IgG mediated, but many patients with sensitization to isocyanates have no demonstrative serum antibodies against the isocyanates. Several publications indicate that complex immunological reactions are involved in the process of sensitization to MDI (Pezzini et al., 1984; Tse et al., 1985; Liss et al., 1988; Cartier et al., 1989).

To investigate the immunopathogenesis of diisocyanate-caused asthma, diisocyanate-exposed workers were evaluated for *in vitro* production of antigen-specific mononuclear cell-derived histamine releasing factor (HRF). The mean HRF response to diisocyanate–human serum albumin (HSA) antigens was significantly greater ($p < 0.05$) in patients with occupational asthma than in diisocyanate-exposed asymptomatic subjects. Analysis of HRF production by subpopulations of peripheral blood mononuclear cells showed that lymphocytes and adherent cells were major sources of both spontaneous and antigen-stimulated HRF (cellular immune response) (Herd & Bernstein, 1994).

Plasma albumin conjugates of MDI found in workers exposed to MDI can cause the onset of respiratory disorders in humans (Sepai et al., 1995a). Lushniak et al. (1998) evaluated whether MDI-specific IgG or IgE could be sensitive biological markers of disease or of MDI exposure. The study group consisted of nine MDI-exposed workers and nine non-exposed workers. Air sampling for MDI and PMDI, occupational and medical histories, respiratory physical examinations, pre- and post-shift spirometry, and self-administered peak expiratory flow rates were performed. Serum-specific IgE and IgG antibodies to an MDI–HSA conjugate were assayed by the radioallergosorbent test (RAST) and the enzyme-linked immunosorbent assay, respectively, and compared with nine non-exposed laboratory controls. The mean level of MDI-specific IgG was significantly greater among exposed workers compared with non-exposed workers and laboratory controls ($p = 0.044$). This study demonstrates that serum concentrations of MDI-specific IgG appear to be a moderately sensitive biological marker of MDI exposure, but not an indicator of occupational asthma. Workers with IgG antibodies specific for one diisocyanate–HSA conjugate exhibit cross-reactivity to antigens prepared with other diisocyanates.

9.1 Case reports

A NIOSH (1994a) report noted skin irritation attributed to MDI. Mine workers were exposed to "rock glue" composed of MDI (component A) and a mixture of polyether/polyol blend and tertiary amine catalyst (component B). It was mentioned that the chemical protective gloves were not routinely utilized by miners who were described as having skin contact leading to chronic skin irritation. In another NIOSH (1994b) report, nasal and eye irritation were the two most frequently reported symptoms after MDI exposure.

A hypersensitivity pneumonitis type of reaction has also been reported. Vandenplas et al. (1993) investigated nine subjects who complained of respiratory and general symptoms related to workplace exposure. All the subjects had worked in a plant where a resin based on MDI was used in the manufacture of wood chipboards. They underwent inhalation challenges using the MDI resin for progressively increasing periods of time on separate days. In eight subjects, exposure to subirritant amounts of MDI induced a pattern of reaction consistent with hypersensitivity pneumonitis — i.e., significant decreases in both forced expiratory volume in 1 s (FEV_1: 31%; range 23–40%) and FVC (23%; range 17–35%) associated with a rise in body temperature and an increase in blood neutrophils. Specific IgG and IgE antibodies to MDI–HSA conjugates were present in all subjects. The authors concluded that the MDI resin caused a hypersensitivity pneumonitis type of reaction in at least 8 (4.8%) of the 167 potentially exposed workers employed in the plant.

In a case who had experienced repeated attacks of a work-related pulmonary or systemic disease, association with exposure to MDI was examined because of acute respiratory disorder, rhinoconjunctivitis, and a late systemic reaction after exposure to polyurethane pyrolysis products, including MDI (air level 15 $\mu g/m^3$) (Littorin et al., 1994). Spirometry showed a partly reversible obstructive dysfunction, and a skin-prick test was positive for MDI–HSA. MDA was detected in hydrolysed serum and urine. In serum, specific IgG_1, IgG_4, and IgE antibodies and a very high total IgE were detected. The specific antibodies declined during the 5 years after exposure. *In vitro*, the circulating immune complexes in serum increased after the addition of MDI–HSA. The reactions associated with MDI exposure (in combination with exposure to pyrolysis products) had features compatible with immediate hypersensitivity and with a complement-mediated immune complex respiratory reaction.

Eighteen employees of a single wood products plant using heated MDI in the manufacture of a synthetic wood product with lower respiratory tract symptoms were later confirmed to have occupational asthma after examination of the relationship between onset of symptoms, smoking behaviour, prior experience, and family history of respiratory disorder (Woellner et al., 1997). All cases occurred during a 2.5-year period after exposure to a new manufacturing process using steam-heated MDI resin in a new manufacturing facility. Initially, workers developed symptoms related to the process with possible higher MDI exposures and probable higher resin temperatures. Later, most workers who developed new symptoms were mostly exposed to heated boards. This suggests that MDI sensitization arises at lower temperatures than was previously considered likely for this substance. It is possible that the reaction products of steam and polymers of MDI, alone or in combination with MDI, may be the causative agents.

A foundry worker who died at work had a diagnosis of occupational asthma induced by MDI assessed 5 years earlier, but had had a poor prognosis for occupational asthma and had continued to be exposed to MDI (Carino et al., 1997). Postmortem microscopic examination of the lung showed epithelial desquamation, eosinophilic/neutrophilic infiltration of the mucosa, dilatation of bronchial vessels, oedema, hypertrophy, and disarray of smooth muscle.

The neuropsychological functioning of five men suffering alleged physical, cognitive, and behavioural changes following exposure to MDI was investigated (Reidy & Bolter, 1994). The subjects had been exposed to hydrocarbon solvent as well, but none of them was symptomatic until MDI was introduced to the workplace. Although the duration and severity of exposure varied among patients, formal analysis of MDI levels was not completed during the exposure period. At the time of assessment, four of the five patients remained symptomatic despite having had no contact with MDI for periods ranging from 5 to 9 months. All patients reported experiencing subjective symptoms consisting of respiratory distress, headaches, depression, irritability, forgetfulness, decreased calculating ability, word-finding problems, reduced concentration, and significant emotional distress on an objective personality measure. Despite these data, the small sample size, possible selection bias for workers involved in litigation, possible confounding factors, lack of pertinent matched control, lack of objective exposure data, and lack of knowledge on mechanism preclude the credibility of the findings.

9.2 Epidemiological studies

9.2.1 Irritation and sensitization

Bernstein et al. (1993) reported only three cases of occupational asthma in a cross-sectional study of 243 workers exposed to PMDI in a urethane mould plant that had been designed to minimize exposure; one case was attributable to a spill. Levels were continuously monitored and never exceeded 50 µg/m^3.

In an epidemiological study of occupational dermatitis in five different shoe factories, 246 workers were interviewed, examined, and patch-tested using standard and occupational patch-test procedures of the International Contact Dermatitis Research Group (Mancuso et al., 1996). No information on occupational exposure was reported. In two workers with allergic contact dermatitis, sensitization to MDI was detected. One of two workers reacted simultaneously to both MDI and MDA. The other one reacted only to MDI.

A health study of the 78 workers in an iron and steel foundry in Vancouver, Canada, was carried out, and the results were compared with those found in 372 railway repair yard workers (Johnson et al., 1985). MDI concentrations in the working environment were shown to significantly influence lung function. The foundry workers were exposed to PepSet, which consists of MDI and phenol formaldehyde and their decomposition products, as well as to silica-containing particulate. Compared with the controls, the foundry workers had more respiratory symptoms and a significantly lower mean FEV_1 and forced expiratory flow from 25% to 75% of the FVC ($FEF_{25–75}$, or mid-expiratory flow rate of the FVC). Three workers had radiographic evidence of pneumoconiosis, and 12 had asthma, defined as the presence of bronchial hyperreactivity, cough, and additional respiratory symptoms, such as wheeze, chest tightness, or breathlessness. Sensitization to MDI is probably the cause of asthma in these workers.

A cross-sectional evaluation of workers in a steel foundry in which PMDI was used as a component of a binder system used to make cores and moulds was performed; 26 currently exposed (group I), 6 formerly exposed (group II), and 14 non-exposed workers (group III) were involved (Liss et al., 1988). The mean number of MDI exposure years was 8.6, 1.1, and 0 years for group I, group II, and group III, respectively. Symptoms compatible with occupational asthma were elicited from seven workers of group I, whereas none was found in group III. This study demonstrated that induction of both MDI-specific IgG responses and IgE-mediated respiratory sensitization occurred in a population of workers exposed to MDI in a steel foundry. One worker from group I with asthmatic symptoms exhibited cutaneous reactivity and RAST binding to MDI–HSA (25.5%).

Musk et al. (1982) followed 107 polyurethane manufacturing workers exposed to TDI alone (17), MDI alone (25), or both (6) prospectively for 5 years. MDI was used at the manufacturing plants during only the last 2 years of the study period. Spirometric measurements (e.g., FEV_1) were made on 94 workers at the fifth year over the work shift, on Monday morning after a weekend of no exposure, and after 2-week vacations. There were no statistically significant differences in the total 5-year decrement in FEV_1 among exposed workers versus FEV_1 values in unexposed workers. Because of the relatively low number of workers (25) exposed to MDI (less than 0.04 mg/m^3), the short study duration, confounding from prior exposure to TDI (0.05 mg/m^3) and possibly to amine catalyst, and the uncertainty in the actual duration of MDI exposure, this study offers limited assurance that MDI is without effect on pulmonary function. The investigators discussed the possibility that there may be selection bias, because the study group did not include any subject with symptoms suggesting hypersensitivity to isocyanate; those who were experiencing adverse effects may have been included in the small numbers of subjects who had left and been lost to follow-up.

In 1976 and 1981, Pham et al. (1988) prospectively studied a group of 318 polyurethane foam workers (including 104 women) who were grouped according to their job category as follows: unexposed, indirectly exposed, and directly exposed. At follow-up in 1981, only half of the initial cohort remained (114 males, 45 females), although no reasons were given as to why the other half left. The 5-year longitudinal changes in FEV_1 in exposed groups were stated not to be significantly different from the control population. An increased prevalence of asthma was reported; however, the limitations of the study preclude any meaningful associations. The basis for the diagnosis of asthma was not stated. Whether there was exposure to other substances that could cause asthma or whether there was pre-existing asthma was not reported, and guidelines followed for performing FEV_1 measurements were not stated. Exposure was not well characterized.

Effects on lung function were assessed by DFG (1997) based on the results of nine studies — namely, Cavelier et al. (1977), Pham et al. (1978, 1986, 1988), Martin et al. (1982), Diller & Herbert (1982), Musk et al. (1982), Gee & Morgan (1985), and Sulotto et al. (1990). Although there were many limitations, such as involvement of confounding factors in mixed exposures and lack of knowledge of actual exposure concentrations, it was concluded that significant impairment of lung spirometry values was observed in the collective

exposed to PMDI concentrations up to 0.87 mg/m^3. In the collective at concentrations below 0.2 mg/m^3, no significant changes in lung spirometry were found. However, significantly more frequent respiratory symptoms were sometimes observed at these concentrations, although it is not clear whether they were caused by simultaneous exposure to other compounds. Such symptoms were no longer significantly more frequent at PMDI concentrations of #0.1 mg/m^3. With one exception in which workers were previously exposed to concentrations of up to 0.9 mg/m^3, all the collective exposed to concentrations of 0.05 mg/m^3 or less was without symptoms.

Work-related respiratory diseases were reported in the United Kingdom by almost 800 chest and occupational physicians who participated voluntarily in the SWORD project from 1989 to 1992 (Meredith & McDonald, 1994). Out of 5541 new cases reported between 1989 and 1991, 28% were occupational asthma. Isocyanates were suspected as a causal agent of asthma in 336 cases out of 1528 reported for 1989–1991.

9.2.2 Long-term exposure and carcinogenicity

Cancer incidence and mortality patterns were investigated in a cohort of 4154 workers employed in Swedish polyurethane foam manufacturing plants for at least 1 year (Hagmar et al., 1993a). TDI had been used in all the plants and MDI in all but one, so it was impossible to evaluate their individual effects. Airborne exposure to the isocyanates had been measured on 6–18 occasions at each plant on 7–24 days. The time-weighted average levels of TDI had normally been less than 0.1 µg/m^3 and were currently 0.02 µg/m^3. The corresponding values for MDI had been less than 0.01 µg/m^3. However, much higher values — up to 3 mg/m^3 for TDI and up to 0.35 mg/m^3 for MDI — had been repeatedly measured. There was also ill-defined exposure to blowing agents, mould lubricants, amine accelerators, and various organic solvents. There was no increased risk of death caused by bronchial obstructive disease. The reduced incidence, against control, of all malignant neoplasm was almost statistically significant. The "no exposure" group had fewer rectal cancers than expected, whereas the "apparent exposure" group had more than expected. A similar, smaller difference was seen with non-Hodgkin's lymphoma. When a minimum latency period of 10 years was applied, the increases against control were even higher, but there were very few cases. As the cohort was young with relatively short exposure to the isocyanates, future studies would allow a more conclusive evaluation. A case–reference study within the cohort was made to assess more thoroughly the association between exposure to TDI and MDI and risk of cancer (Hagmar et al., 1993b). It was found that the tentative associations, derived from the previous cohort study, between exposure to isocyanates and excess risk for non-Hodgkin's lymphomas and rectal cancer were not supported. Instead, non-significant associations with prostate cancer and possibly colon cancer were seen.

A retrospective mortality and cancer morbidity study was conducted to investigate associations between health risk and exposures from polyurethane foam production, particularly exposures to diisocyanates (Sorahan & Pope, 1993). The study population (n = 8288) was taken from 11 factories in England and Wales in which TDI was the principal isocyanate (MDI represented 5% of the amount of TDI used). The highest exposure category comprised jobs in which either the 8-h time-weighted average exposure (to isocyanates) during 1978–1986 was greater than 0.04 mg/m^3 or excursions above 0.1 mg/m^3 occurred on most days. The investigators did not find an association (using standardized mortality ratios or SMRs) between exposure to diisocyanates and cancer. The cohort was young, and follow-up was relatively short.

10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

10.1 Aquatic environment

Results of most studies available on the toxic effects of MDI on aquatic organisms are based on nominal concentrations of test substance. In all tests summarized in this section, MDI was added to the test solution, and no concentration measurements were performed subsequently during exposure. Although different methods were applied to solubilize the test substance in the test media (e.g., stirring for several hours), the results presented in section 5.1 indicate that only minor amounts of the applied MDI could have been present in the test solution, as the MDI would have rapidly undergone hydrolysis. As a result, due to the virtual unavailability of MDI in water, even for the highest concentrations tested, no adverse effects on the exposed test organisms were observed.

In short-term tests, nominal concentrations in the range of 500–3000 mg MDI/litre caused no lethal effect on freshwater fish (Rhone-Poulenc Chimie, 1977; Nakata, 1983; Caspers et al., 1986). Aquatic invertebrates showed no immobilization after a 24-h exposure to nominal concentrations of up to 1000 mg MDI/litre (Rhone-Poulanc Chimie, 1977; Caspers et al., 1986). After 21 days of exposure to the highest nominal concentration tested (10 mg/litre), PMDI had no effect on the reproduction

rate of *Daphnia magna* (Caspers et al., 1986). Blom & Oldersma (1994) observed no effects on cell multiplication of the freshwater alga *Scenedesmus subspicatus* after a 3-day exposure to a nominal concentration of 1640 mg PMDI/litre. Concerning the impact of PMDI on microorganisms, the highest applied concentrations of up to 100 mg/litre were not inhibitory to cell multiplication of *Escherichia coli* (Fujiwara, 1981) or to the respiration rate of activated sludge (Caspers et al., 1986).

Heimbach et al. (1996) added PMDI at concentrations of 0, 1, and 10 g/litre on top of the sediment of three artificial outdoor ponds, simulating accidental spillage in small standing freshwater ecosystems (see section 5.1). The ponds contained natural lake sediment and groundwater, to which caged fish were added. The fate of the PMDI and ecotoxic effects on the aquatic population were monitored for 112 days.

MDI polymerized to inert polyurea and stayed on top of the sediment, forming a hardened layer at the interface of the compound and water. No MDI was found in the water or in the fish after application. Neither application rate caused any direct toxic effect on the aquatic community, but some significant indirect effects on parts of the macrobenthos were observed. Some of the more immobile populations (Oligochaeta, Bivalvia, Diptera) were almost completely wiped out as a result of physical obstruction by the polyurea layer, lack of oxygen, and toxic carbon dioxide concentrations 7–14 days after application.

Most of the macrobenthos populations regained densities equivalent to the control populations after 2 months of exposure, with the exception of Bivalvia (because of their long generation times). Mobile parts of the macrobenthos (e.g., Gastropoda) remained unaffected. The abundance of some zooplankton species (Cladocera) was clearly reduced in the high-dosed pond 2–8 weeks after application. As a consequence, the rainbow trout in this pond, which were feeding on Cladocera as their main natural food source, lost weight, and three of six fish in this pond died 1 month after the application of MDI.

10.2 Terrestrial environment

Results from an earthworm toxicity test conducted according to OECD Guideline No. 207 and a terrestrial plant growth test conducted according to OECD Guideline No. 208 are presented in Table 2. In these studies, the test substance was initially dissolved in acetone, which was then mixed with sand. The solvent was evaporated and the coated sand mixed with soil. The treated soil was then used for the studies. No toxic effect of MDI on the terrestrial organisms tested was observed.

Table 2: Toxicity of MDI to terrestrial organisms.[a]

Organisms	End-point[b]	Loading (mg/kg)
Eisenia fetida (earthworm)	14-day LC_{50}	>1000
	14-day NOEL (weight increase)	>1000
	14-day NOEL (behaviour, appearance)	>1000
Avena sativa (oats)	NOEL emergence	>1000
	NOEL survival (14 days)	>1000
	NOEL growth (14 days)	>1000
Lactuca sativa (lettuce)	NOEL emergence	>1000
	NOEL survival (14 days)	>1000
	NOEL growth (14 days)	>1000

[a] Source: van der Hoeven et al. (1992a,b).

[b] LC_{50} = median lethal concentration; NOEL = no-observed-effect level.

11. EFFECTS EVALUATION

11.1 Evaluation of health effects

11.1.1 Hazard identification and dose–response assessment

The health end-point of most concern is an association between exposure to airborne polymeric and/or monomeric MDI and occupationally induced asthma. There is abundant evidence not only from epidemiological studies and case-studies, but also from animal studies. However, there is insufficient human evidence to describe (1) the nature of the MDI-containing material, (2) the concentration–response relationship, or (3) the mechanism of isocyanate-induced asthma and sensitization. Although there are no human or animal studies that have examined the oral route of exposure, it is unlikely that humans would be exposed by the oral route. Therefore, it is difficult to quantitatively estimate risk from human exposure.

The available human evidence from cancer incidence and mortality studies of workers exposed to isocyanates is inadequate to describe the carcinogenic potential of polymeric or monomeric MDI. No associations between isocyanates and cancer incidence were demonstrated. The increase in the incidence of mostly benign pulmonary tumours in rats exposed to MDI by inhalation is not considered to be a demonstration of

carcinogenicity. The published studies have a number of limitations (e.g., short duration of exposure, concomitant exposure to other substances), which result in low power to detect cancer occurrence in target organs of interest. The finding of placental transfer of MDI and its degradation product from pregnant rats exposed to aerosol to fetuses demands further study on its relevance to human risk assessment.

11.1.2 Criteria for setting tolerable intakes or guidance values for MDI

An example of a guidance value calculation is given in the US EPA's Integrated Risk Information System (IRIS) (see www.epa.gov/iris for details). The Benchmark Concentration (BMC) analysis described therein is based on the finding of an increase in basal cell hyperplasia in the olfactory epithelium in the chronic inhalation study with male Wistar rats (Reuzel et al., 1990, 1994a). However, it should be noted that this guidance value may not protect against occupational sensitization.

The value considered most appropriate as a basis for development of a tolerable concentration (TC) in air is the lower 95% confidence limit on the BMC at the 10% risk level (BMC_{10}) using the Reuzel et al. (1990, 1994a) data set. The BMC_{10} is first converted to a human equivalent concentration (HEC) by application of the Regional Dose Deposited Ratio (RDDR) calculated using a computer program provided in US EPA (1994). The RDDR adjusts for dosimetric differences between laboratory animals and humans by applying normalizing factors to various areas of the respiratory tract.

Once the BMC_{10} (0.14 mg/m^3) is derived from the Reuzel et al. (1990, 1994a) data set by BMC analysis, it is multiplied by the RDDR (0.453). The resulting value, 0.06 mg/m^3, is the BMC_{10} (HEC). Three uncertainty factors are applied to the BMC_{10} (HEC) — 10 for intraindividual variation (including the possibility of genetic predisposition), $10^{1/2}$ for the lack of reproductive data, and $10^{1/2}$ for interspecies variation — to derive a human TC of 6×10^{-4} mg/m^3.

11.1.3 Sample risk characterization

There are no adequate data available to serve as a basis for estimating risk of occupational asthma. The example given here is a pragmatic approach to reduce occupational exposure to the minimum possible, because a threshold for this effect cannot be established.

In the German study evaluating lung decrement, significant reversible adverse effects on lung function were observed in persons exposed to MDI concentrations above 0.2 mg/m^3. When MDI concentrations were kept largely below this concentration, significant changes in lung spirometry were no longer seen, although the incidence of respiratory symptoms was increased significantly. Such disorders were still observed, but no more frequently than in the group at concentrations below 0.05 mg/m^3. Because of these observations, 0.05 mg/m^3 was established as the MAK (the maximum concentration in the German workplace) value for MDI, to be reasonably practicable under workplace conditions, and there is a continuing remit to reduce exposure levels as far as reasonably practicable with technology that is currently available.

11.2 Evaluation of environmental effects

Under normal circumstances, exposure is likely only from releases to the atmosphere. High exposures involving MDI in ambient environments are expected to be rare. Where spillage is to soil or water, MDI has a transient existence due to its reaction with the water to produce predominantly insoluble polyureas. MDA may be formed only as a minor reaction product and will thus be present at low concentrations. The pond study provides evidence that MDI accumulation through the aquatic food chain is extremely unlikely, as might be expected considering the very low solubility and high reactivity of MDI in aqueous solution.

Available data show that there is no need for concern regarding the effects of MDI on organisms in the environment, although more detailed information regarding the effects of minute amounts of MDA formed in the environment on organisms is required before any firm conclusions can be drawn.

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

IARC (1999) concluded that there is *inadequate evidence* for the carcinogenicity of monomeric or polymeric MDI in humans and *limited evidence* for the carcinogenicity of a mixture containing monomeric and polymeric MDI in experimental animals. Its overall evaluation was that MDI (industrial preparation) is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For MDA, IARC (1986) concluded that there were *no data* in humans and *sufficient evidence for carcinogenicity* in animals. Its overall evaluation was that MDA was *possibly carcinogenic to humans (Group 2B)*.

REFERENCES

Andersen M, Bineru ML, Kiel P, Larsen H, Maxild J (1980) Mutagenic action of isocyanates used in the production of polyurethanes. *Scandinavian journal of work, environment & health*, 6:221–226.

Appelman LM, de Jong AWJ (1982) *Acute inhalation toxicity study of polymeric MDI in rats.* Zeist, CIVO Institute - TNO Toxicology and Nutrition (Report No. 82).

Appelman LM, de Jong AWJ, Keller J (1986) *Additional studies into the presence of MDA in samples of test atmospheres containing polymeric MDI aerosol.* Zeist, CIVO Institute - TNO Toxicology and Nutrition (unpublished; Report No. V84.313/220758).

Bartsch W, Buschmann J, Hoymann HG, Heinrich U (1996) [*Chronic toxicity and carcinogenicity study on MDI.*] Hannover, Fraunhofer Institute for Toxicology and Aerosol Research (unpublished) (in German).

BASF (1994) *Prenatal toxicity of polymeric MDI in rats. Aerosol inhalation*. Prepared by BASF, Ludwigshafen, for US Environmental Protection Agency (unpublished; Project No. 31R0354/93046, 39.09.1994).

Bernstein DI, Korbee L, Stauder T, Bernstein JA, Scinto J, Herd ZL, Bernstein IL (1993) Clinical aspects of allergic disease. The low prevalence of occupational asthma and antibody-dependent sensitization to diphenylmethane diisocyanate in a plant engineered for minimal exposure to diisocyanates. *Journal of allergy and clinical immunology*, 92(3):387–396.

Blom AJM, Oldersma H (1994) *Effect of Desmodur 44 V20-PMDI on the growth of the green alga* Scenedesmus subspicatus. TNO International Isocyanate Institute (Report No.11156).

Brochhagen FK, Keller J (1983) *Accident involving a road tanker carrying tolulene diisocyanate (TDI) — countermeasures and experience*. Leverkusen, Bayer AG.

Buschmann J, Koch W, Fuhst R, Heinfich U (1996) Embryotoxicity study of monomeric 4,4'-methylenediphenyl diisocyanate (MDI) aerosol after inhalation exposure in Wistar rats. *Fundamental and applied toxicology*, 32:96–101.

Carino M, Aliani M, Licitra C, Sarno N, Ioli F (1997) Death due to asthma at workplace in a diphenylmethane diisocyanate-sensitized subject. *Respiration*, 64:111–113.

Cartier A, Grammer L, Malo JL, Lagier F, Ghezzo H, Harris K, Patterson R (1989) Specific serum antibodies against isocyanates: association with occupational asthma. *Journal of allergy and clinical immunology*, 84(4 Pt 1):507–514.

Caspers N, Hamburger B, Kanne R, Klebert W (1986) *Ecotoxicity of toluenediisocyanate (TDI), diphenylmethanediisocyanate (MDI), toluenediamine (TDA), diphenylmethanediamine (MDA).* Prepared by International Isocyanate Institute for Bayer AG, Leverkusen (Report No.10417).

Castro EA, Moodie RB, Sansom PJ (1985) Ecotoxicity of diisocyanates with special reference to controlled exposure of humans. *International archives of occupational and environmental health*, 61(8):495–501.

Cavelier C, Pham QT, Mereau P, Mur JM, Rombach F, Cicolella A, Bui Dinh Long L, Toamain JP, Baudin V, Henquel JC, Poincelot F, Malo JP, Vincent R (1977) [Isocyanates and respiratory function.] *Cahiers de notes documentaires*, 88:315 (in French).

Chemical Daily (1997) *13398 chemical products*. Tokyo, Chemical Daily Co., Ltd., pp. 642–643.

Chemical Society of Japan (1989) [Anti-disaster Guidelines No. 98: 4,4'-Diphenylmethane diisocyanate (MDI).] *Chemistry and industry*, 42:1408–1415 (in Japanese).

Chemical Week (1998) Market & economics/product focus; MDI. *Chemical Week*, April 5, 1998, p. 37.

Dalene M, Jakobsson K, Rannug A, Skarping G, Hagmar L (1996) MDA in plasma as a biomarker of exposure to pyrolysed MDI-based polyurethane: correlations with estimated cumulative dose and genotype for *N*-acetylation. *International archives of occupational and environmental health*, 68:165–169.

Day BW, Basalyga DM, Kramarik JA, Karol MH (1997) Formation, solvolysis and transcarbamoylation reactions of bis(*S*-glutathionyl) adducts of 2,4- and 2,6-diisocyanatotoluene. *Chemical research in toxicology*, 10:424–431.

DFG (1997) Occupational toxicants. Critical data evaluation for MAK values and classification of carcinogens. *Deutsche Forschungsgemeinschaft, VCH*, 8:65–95.

Dharmarajan V (1979) Occupational exposures to methylene bisphenylisocyanate (MDI): gaseous or aerosol? *Journal of environmental pathology, toxicology and oncology*, 2:1–8.

Diller WF, Herbert E (1982) [Lung function and other health parameters measurement by work in an isocyanate plant of MDI-manufacturer.] *Zentralblatt für Arbeitsmedizin*, 32:128–137 (in German).

EU (1999) *Risk assessment for methylenediphenyl diisocyanate.* Brussels, European Union (draft report).

Fujiwara K (1981) *Accumulation of TDI, NDI, TDA, MDA in fish and their toxicity. Aquatic life study, Phase II-2.* Tsukuba, International Isocyanate Institute (Project FE-E-19-II-2).

Gahlmann R (1993) *A critical review for the International Isocyanate Institute*. June 1993. Wuppeltal, Bayer AG, Institute for Toxicology.

Gee JB, Morgan WKC (1985) A 10-year follow-up study of a group of workers exposed to isocyanates. *Journal of occupational medicine*, 27:15–18.

Giersig M (1989) *Polyharnstoff gebundene Spanplatten*. Lecture, University of Bielefeld, Bielefeld, June (unpublished report).

Gilbert DS (1988) Fate of TDI and MDI in air, soil and water. *Journal of cellular plastics*, 24:178–192.

Hagmar L, Welinder H, Mikoczy Z (1993a) Cancer incidence and mortality in the Swedish polyurethane foam manufacturing industry. *British journal of industrial medicine*, 50:537–543.

Hagmar L, Stroemberg U, Welinder H, Mikoczy Z (1993b) Incidence of cancer and exposure to toluene diisocyanate and methylene diphenyldiisocyanate: a cohort based case–referent

study in the polyurethane foam manufacturing industry. *British journal of industrial medicine*, 50:1003–1007.

Hegarty AF, Hegarty CN, Scott FL (1975) The reactivity of phenyl isocyanate in aqueous solution. *Journal of the Chemical Society, Perkin Transactions*, 11:1166–1171.

Heimbach F, Jaeger K, Sporenberg W (1996) Fate and biological effects of polymeric MDI in small artificial ponds. *Ecotoxicology and environmental safety*, 33:143–153.

Herbold B (1980a) [*MDI* Salmonella*/microsome test for investigation of point mutation activity*.] Wuppeltal, Bayer AG (unpublished; Bayer Report No. 9130, 9.5.1980) (in German).

Herbold B (1980b) [*MDI* Salmonella*/microsome test for investigation of point mutation activity*.] Wuppeltal, Bayer AG (unpublished; Bayer Report No. 9341, 1.8.1980) (in German).

Herbold B (1990a) *Special study,* Salmonella*/microsome test with Desmodur 44v20 using TA100.* Wuppeltal, Bayer AG (unpublished; Bayer Report No. 19561, 27.9.1990).

Herbold B (1990b) *Special study,* Salmonella*/microsome test with Desmodur 44M (4,4'-MDI) using TA100*. Wuppeltal, Bayer AG (unpublished; Bayer Report No. 19570, 27.9.1990).

Herbold B, Haas P, Seel K, Walber U (1998) Studies on the effect of the solvents dimethylsulfoxide and ethyleneglycoldimethylether on the mutagenicity of four types of diisocyanates in the *Salmonella*/microsome test. *Mutation research*, 412:167–175.

Herd ZL, Bernstein DI (1994) Antigen-specific stimulation of histamine releasing factors in diisocyanate-induced occupational asthma. *American journal of respiratory and critical care medicine*, 150:988–994.

Hiasa Y, Kitahori Y, Enoki N, Konishi N, Shimoyama T (1984) 4,4'-diaminodiphenylmethane: promoting effect on the development of thyroid tumors in rats treated with *N*-bis(2-hydroxypropyl)nitrosamine. *Journal of the National Cancer Institute*, 72:471–476.

Hoymann HG, Buschmann J, Heinrich U (1995) *Examinations about the chronic toxicity/carcinogenicity of 4,4'-methylene diphenyl diisocyanate (MDI).* Hannover, Fraunhofer Institute for Toxicology and Aerosol Research (Report No. 116-06-084).

Hoymann HG, Creutzenberg O, Ernst H, Hohlfeld J, Heinrich U (1997) Lung function changes in rats after chronic inhalation exposure to 4,4'-methylene diphenyl diisocyanate (MDI). In: Mohr U, ed. *Relationships between respiratory disease and exposure to air pollution*. Washington, DC, International Life Sciences Institute Press, pp. 353–356.

IARC (1986) *4,4'-Methylenedianiline and its dihydrochloride.* Lyon, International Agency for Research on Cancer, pp. 347–365 (IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 39).

IARC (1999) *4,4'-Methylenediphenyl diisocyanate and polymeric 4,4'-methylenediphenyl diisocyanate*. Lyon, International Agency for Research on Cancer, pp. 1049–1058 (IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 71).

IPCS (1993) *International Chemical Safety Card — Methylene bisphenyl isocyanate (MDI)*. Geneva, World Health Organization, International Programme on Chemical Safety (ICSC 0298).

ISOPA (1998) *Submission for the review of the acute inhalation toxicity of MDI.* Brussels, European Isocyanate Production Association (unpublished report).

Istin M (1977) *Pharmacokinetics of MDI after inhalation exposure of rats to labeled MDI.* Unpublished report by Laboratoire d'Études du Métabolisme des Médicaments, Département de Biologie, to the International Isocyanate Institute [cited in DFG, 1997].

Johnson A, Chan-Yeung M, MacLean M, Atkins E, Dybunchio A, Cheng F, Enarson D (1985) Respiratory abnormalities among workers in an iron and steel foundry. *British journal of industrial medicine*, 42:94–100.

JSOH (1994) [Recommendation and the reasoning for the occupational exposure limits on MDI.] *Sangyo Igaku (Japanese journal of industrial health)*, 35:360–363 (in Japanese).

Kelly M, Outterside S, Pemberton D (1997) *Physical properties of MDI and TDI: a review*. Manchester, International Isocyanate Institute (unpublished; III Report No. 11272).

Liss GM, Bernstein DI, Moller DR, Gallagher JS, Stephenson RL, Bernstein IL (1988) Pulmonary and immunologocal evaluation of foundry workers exposed to methylene diisocyanate (MDI). *Journal of allergy and clinical immunology*, 82(1):55–61.

Liss GM, Tarlo SM, Banks DE (1996) Evidence for occupational asthma among compensation claimants at a polyurethane utilizing facility. *Canadian journal of public health*, 87(6):401–403.

Littorin M, Truedsson L, Welinder H, Skarping G, Martensson U, Sjoeholm AG (1994) Acute respiratory disorder, rhinoconjunctivitis and fever associated with the pyrolysis of polyurethane derived from diphenylmethane diisocyanate. *Scandinavian journal of work, environment & health*, 20:216–222.

Lushniak BD, Reh CM, Bernstein DI, Gallagher JS (1998) Indirect assessment of 4,4'-diphenylmethane diisocyanate (MDI) exposure by evaluation of specific humoral immune responses to MDI conjugated to human serum albumin. *American journal of industrial medicine*, 33:471–477.

Mancuso G, Reggiani M, Berdondini RM (1996) Occupational dermatitis in shoemakers. *Contact dermatitis*, 34:17–22.

Mann M (1987) Evidence for the formation of hydrate of MDI [letter to the editor]. *American Industrial Hygiene Association journal*, 48:726.

Martin FD, Fichet D, Arsanian G, Leloup MC (1982) [Epidemiological study on the toxicity of isocyanates in working environment.] *Archives des maladies professionelles de médecine du travail et de sécurité sociale (Paris)*, 43:481 (in French).

Meredith SK, McDonald JC (1994) Work-related respiratory disease in the United Kingdom, 1989–1992: report on the SWORD project. *Journal of occupational medicine*, 44:183–189.

Mobay Chemical (1961) *Toxicity and safety handling of isocyanates* [cited in US EPA, 1998].

Musk AW, Peters JM, DiBerardinis L, Murphy RLH (1982) Absence of respiratory effects in subjects exposed to low concentrations of TDI and MDI. *Journal of occupational medicine*, 24(10):746–750.

Nakata M (1983) *Test report on fish toxicity of polymethylene polyphenyl polyisocyanate: internal communication*. Amagasaki, Sumitomo Bayer Urethane Co. (unpublished report).

NIOSH (1985) *NIOSH manual of analytical methods*, 3rd ed. Vols. 1 and 2 with 1985 supplement and revisions. Cincinnati, OH, US Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. Washington, DC, US Government Printing Office, February 1984, p. 5521-1.

NIOSH (1994a) *Letter from NIOSH to Jim Walter Resources, Inc. with a study report.* Cincinnati, OH, US Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health (Report No. HETA 94-0027, May 24).

NIOSH (1994b) *Letter from NIOSH to Distinctive Designs International Inc. with a study report*. Cincinnati, OH, US Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health (Report No. HETA 91-0386-2427, May).

NTP (1986) *Toxicology and carcinogenesis studies of commercial grade 2,4(80%)- and 2,6(20%)-toluene diisocyanate in F344/N rats and B6C3F$_1$ mice (gavage studies)*. Research Triangle Park, NC, US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program (Technical Report No. 251; NIH Publication No. 86-2507).

Pezzini A, Riviera A, Paggiaro P, Spiazzi A, Gerosa F, Filieri M, Toma G, Tridente G (1984) Specific IgE antibodies in twenty-eight workers with diisocyanate-induced bronchial asthma. *Clinical allergy*, 14:453–461.

Pham QT, Cavelier C, Mereau P, Cicolella A (1978) Isocyanates and respiratory function: a study of workers producing polyurethane foam moulding. *Annals of occupational hygiene*, 21:121.

Pham QT, Meyer-Bisch C, Mur JM (1986) [Study on clinical and respiratory function change of workers exposed to little amount of MDI in 5 years.] *Archives des maladies professionelles de médecine du travail et de sécurité sociale (Paris)*, 47:311 (in French).

Pham QT, Teculescu D, Meyer-Bisch C, Mur JM (1988) Effects of chronic exposure to diisocyanates. *Bulletin européen de physio-pathologie respiratoire*, 23:561–564.

Reidy TJ, Bolter JF (1994) Neuropsychological toxicology of methylene diphenyl diisocyanate: a report of five cases. *Brain injury*, 8(3):285–294.

Reuzel PGJ, Arts JHE, Kuypers MHM, Kuper CF (1990) *Chronic toxicity/carcinogenicity inhalation study of polymeric methylene diphenyl diisocyanate aerosol in rats.* Prepared by the CIVO Institute, Zeist, for the International Isocyanate Institute (Report No. V88.122).

Reuzel, PGJ, Kuper CF, Feron VJ, Appelman L, Loser E (1994a) Acute, subacute, and subchronic inhalation toxicity studies of respirable polymeric methylene diphenyl diisocyanate (polymeric MDI) aerosol in rats. *Fundamental and applied toxicology*, 22:186–194.

Reuzel PGJ, Arts JHE, Lomax LG, Kuijpers MHM, Kuper CF, Gembardt C, Feron VJ, Loser E (1994b) Chronic inhalation toxicity and carcinogenicity studies of respirable polymeric methylene diphenyl diisocyanate (polymeric MDI) aerosol in rats. *Fundamental and applied toxicology*, 22:195–210.

Rhone-Poulenc Chimie (1977) *Biological action of TDI and MDI in water*. Paris (unpublished report; Report No. 770906).

Sakurai H (1997) Brief introduction to occupational exposure limits in Japan. *Journal of occupational health*, 39:246.

Schuetze D, Sepai O, Lewalter J, Miksche L, Henschler D, Sabbioni G (1995) Biomonitoring of workers exposed to 4,4'-methylenediamine and 4,4'-methylenediphenyl diisocyanate. *Carcinogenesis*, 16(3): 573–582.

Seel K, Walber U, Herbold B, Kopp R (1999) Chemical behaviour of seven aromatic diisocyanates (toluenediisocyanates and diphenylmethanediisocyanates) under *in vitro* conditions in relationship to their results in the *Salmonella*/microsome test. *Mutation research*, 438:109–123.

Sepai O, Schuetze D, Heinrich U, Hoymann HG, Henschler D, Sabbioni G (1995a) Hemoglobin adducts and urine metabolites of 4,4'-methylenediamine after 4,4'-methylenediphenyl diisocyanate exposure of rats. *Chemico-biological interactions*, 97:185–198.

Sepai O, Henschler D, Sabbioni G (1995b) Albumin adducts, hemoglobin adducts and urinary metabolites in workers exposed to 4,4'-methylenediphenyl diisocyanate. *Carcinogenesis*, 16(10):2583–2587.

Shimizu H, Suzuki Y, Takemura N, Goto S, Matsushita H (1985) The results of microbial mutation test for forty-three industrial chemicals. *Sangyo Igaku (Japanese journal of industrial health)*, 27:400–417.

Skarping G, Dalene M (1995) Determination of 4,4'-methylene-diphenyldianiline (MDA) and identification of isomers in technical-grade MDA in hydrolysed plasma and urine from workers exposed to methylene diphenyldiisocyanate by gas chromatography–mass spectrometry. *Journal of chromatography B, Biomedical sciences and applications*, 663:209–216.

Skarping G, Dalene M, Lottorin M (1995) 4,4'-methylenedianiline in hydrolysed serum and urine from a worker exposed to thermal degradation products of methylene diphenyl diisocyanate elastomers. *International archives of occupational and environmental health*, 67:73–77.

Sorahan T, Pope D (1993) Mortality and cancer morbidity of production workers in the United Kingdom flexible polyurethane foam industry. *British journal of industrial medicine*, 50:528–536.

Spanne M, Tinnerberg H, Dalene M, Skarping G (1996) Determination of complex mixtures of airborne isocyanates and amines, Part 1. Liquid chromatography with ultraviolet detection of monomeric and polymeric isocyanates as their dibutylamine derivatives. *Analyst*, 121:1095–1099.

Streicher RP, Kennedy ER, Lorberau CD (1994) Strategies for the simultaneous collection of vapors and aerosols with emphasis on isocyanate sampling. *Analyst*, 119:89–97.

Sulotto F, Romano C, Piolatto G, Coggiola M, Polizzi S, Ciacco C, Berra A (1990) Short-term respiratory changes in polyurethane foam workers exposed to low MDI concentrations. *International archives of occupational and environmental health*, 62:521.

Tanaka K, Takeoka A, Nishimura F, Hanada S (1987) Contact sensitivity induced in mice by methylene bisphenyl diisocyanate. *Contact dermatitis*, 17:199–204.

Tarlo SM, Liss GM, Dias C, Banks DE (1997) Assessment of the relationship between isocyanate exposure levels and occupational asthma. *American journal of industrial medicine*, 32:517–521.

Thorne PS, Hillebrand JA, Karol MH (1986) Pulmonary irritation and hypersensitivity in guinea pigs exposed to 4,4'-diphenylmethane diisocyanate (MDI) aerosol. *Toxicologist*, 6:15.

Thorne PS, Hillebrand JA, Lewis DR, Karol MH (1987) Contact sensitivity by diisocyanates; potencies and cross-reactivities. *Toxicology and applied pharmacology*, 87:155–165.

Tinnerberg H, Spanne M, Dalene M, Skarping G (1997) Determination of complex mixtures of airborne isocyanates and amines, Part 3. Methylenediphenyl diisocyanate, methylenediphenylamino isocyanate and methylenediphenylamine and structural analogues after thermal degradation of polyurethane. *Analyst*, 122:275–278.

Tse KS, Johnson A, Chan H, Chan-Yeung C (1985) A study of serum antibody activity in workers with occupational exposure to diphenylmethane diisocyanate. *Allergy*, 40:314–320.

US EPA (1994) *Methods for derivation of inhalation reference concentrations and applications of inhalation dosimetry.* Washington, DC, US Environmental Protection Agency (EPA/600/8-90/066f).

US EPA (1998) *Toxicological review of methylene diphenyl diisocyanate (MDI)*. Washington, DC, US Environmental Protection Agency.

Vandenplas O, Malo JL, Dugas M, Cartier A, Desjardins A, Levesque J, Shaughnessy MA, Grammer LC (1993) Hypersensitivity pneumonitis-like reaction among workers exposed to diphenylmethane diisocyanate (MDI). *American review of respiratory disease*, 147:338–346.

van der Hoeven N, Roza P, Henzen L (1992a) *Determination of the effect of TDI, TDA, MDI, and MDA on the emergence and growth of the plant species* Avena sativa *and* Lactuca sativa *according to OECD Guideline No. 208*. Zeist, International Isocyanate Institute (unpublished; III Report No. 11024).

van der Hoeven N, Roza P, Henzen L (1992b) *Determination of the LC_{50} (14 days) of TDI, TDA, MDI, and MDA to the earthworm* Eisenia fetida *according to OECD Guideline No. 207.* Prepared by TNO, Zeist, for International Isocyanate Institute (unpublished; III Report No. 11025).

Vock EH, Lutz WK (1997) Distribution and DNA adduct formation of radiolabeled methylenediphenyl-4,4'-diisocyanate (MDI) in the rat after topical treatment. *Toxicology letters*, 92:93–100.

Vock EH, Hoymann HG, Heinrich U, Lutz WK (1996) ^{32}P-postlabeling of a DNA adduct derived from 4,4'-methylenedianiline in the olfactory epithelium of rats exposed by inhalation to 4,4'-methylenediphenyl diisocyanate. *Carcinogenesis*, 17(5):1069–1073.

Waalkens-Berendsen DH, Arts JHE (1992) *Report of a developmental toxicity range-finding study of inhaled polymeric MDI aerosol in rats*. Zeist, TNO Nutrition and Food Research (unpublished; TNO Report No. V 92.102).

Wazeter FX (1964a) *Acute inhalation toxicity (LC_{50}) in male albino rats 12.3.64.* International Research and Development Corporation (unpublished report) [cited in EU, 1999].

Wazeter FX (1964b) *Acute dermal toxicity (LD_{50}) in male albino rats 27.01.64.* International Research and Development Corporation (unpublished report) [cited in EU, 1999].

Weisburger EK, Murthy ASK, Lilja HS, Lamb JC (1984) Neoplastic response of F344 rats and B6C3F_1 mice to the polymer and dyestuff intermediates, 4,4'-methylenebis(*N*,*N*-dimethyl)benzenamine, 4,4'-oxydianiline, and 4,4'-methylenedianiline. *Journal of the National Cancer Institute*, 72:1457–1463.

Weyel DA, Schaffer RB (1985) Pulmonary and sensory irritation of diphenylmethane-4,4'-diisocyanate and dicyclohexylmethane-4,4'-diisocyanate. *Toxicology and applied pharmacology*, 77:427–433.

Woellner RC, Hall S, Greaves I, Schoenwetter WF (1997) Epidemic of asthma in a wood products plant using methylene diphenyl diisocyanate. *American journal of industrial medicine*, 31:56–63.

Woolrich PF (1982) Toxicology, industrial hygiene and medical control of TDI, MDI and PMPPI. *American Industrial Hygiene Association journal*, 43:89–97.

Yakabe Y, Mori E, Tadokoro H (1994) *Study on the fate of polymeric MDI in water.* Kurume, International Isocyanate Institute (unpublished; III Report No. 11122).

Zeiger E (1987) *Salmonella* mutagenicity test: III. Result from testing of 225 chemicals. *Environmental mutagenesis*, 9(9):1–110.

APPENDIX 1 — SOURCE DOCUMENTS

JSOH (1994)

The original review in Japanese was translated into English by the National Institute of Health Sciences (NIHS) and is available from the Division of Chem-Bio Informatics of NIHS at the following address:

National Institute of Health Sciences
1-18-1 Kamiyoga, Setagayaku
Tokyo, Japan

The Japan Society for Occupational Health (JSOH, formerly the Japan Association of Industrial Health) is an academic organization consisting of experts in occupational health, including scientists in universities and institutions, industrial physicians, occupational health nurses, industrial hygienists, management staff from health and safety departments, and government officials in occupational health sectors.

The Committee for the Recommendation of Occupational Exposure Limits of JSOH reviews scientific information on the health effects of chemical substances and physical agents with special reference to exposure–effect and exposure–response relationships and applies its research to the creation of an Occupational Exposure Limit (OEL) and to the documentation of the reasoning behind the OEL. The Committee submits the OEL as a provisional OEL to a meeting of JSOH councillors and to an annual general meeting of JSOH for temporary approval, after which the provisional OEL and documentation are published in JSOH's official journal, *Sangyo Eiseigaku Zasshi* (formerly *Sangyo Igaku* [*Japanese Journal of Industrial Health*]. The Committee accepts opinions based on scientific aspects of the provisional OEL until the next annual general meeting. If no opinions contrary to the provisional OEL are filed with the Committee, it is adopted as the formal OEL recommended by JSOH. If opinions contrary to the provisional OEL are filed with the Committee and deemed valid, the Committee then proceeds to reexamine the provisional OEL and the documentation (Sakurai, 1997). Dr Sakurai, who chairs the Committee, peer-reviewed and assisted in the preparation of the draft of the CICAD for MDI.

US EPA (1998)

The report entitled *Toxicological review of methylene diphenyl diisocyanate (MDI)* and summary information on IRIS (Integrated Risk Information System) have received peer review both by EPA scientists and by independent scientists external to EPA. Subsequent to external review and incorporation of comments, this assessment has undergone an agency-wide review process whereby the IRIS Program Manager has achieved a consensus approval among the Office of Research and Development, Office of Air and Radiation, Office of Prevention, Pesticides, and Toxic Substances, Office of Solid Waste and Emergency Response, Office of Water, Office of Policy Planning and Evaluation, and the Regional Offices. The author and reviewers are listed below.

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New Jersey Department of Environmental Protection
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William E. Brown, Ph.D.
Professor and Head
Department of Biological Sciences
Carnegie Mellon University
Pittsburgh, PA

EU (1999)

The EU *Risk assessment for methylenediphenyl diisocyanate* has not yet been peer reviewed or published. However, this is the only source of environmental information and extensive review available at present to the Final Review Board.

APPENDIX 2 — CICAD PEER REVIEW

The draft CICAD on diphenylmethane diisocyanate (MDI) was sent for review to institutions and organizations identified by IPCS after contact with IPCS national Contact Points and Participating Institutions, as well as to identified experts. Comments were received from:

A. Aitio, WHO, Switzerland

M. Baril, Institut de Recherche en Santé et en Sécurité du Travail du Québec, Canada

R. Benson, US EPA Region VIII, USA

T. Berzins, National Chemicals Inspectorate (KEMI), Sweden

R. Cary, Health and Safety Executive, United Kingdom

Chemical Industries Association (CIA) Isocyanate Producers Sector Group (IPSG), United Kingdom

M. Collins, Gilbert International Limited, United Kingdom

P. Edwards, Department of Health, United Kingdom

T. Fortoul, National University of Mexico, Mexico

R. Hertel, Bundesinstitut für Gesundheitlichen Verbraucherschutz und Veterinärmedizin, Germany

J. Lesage, Institut de Recherche en Santé et en Sécurité du Travail du Québec, Canada

H. Nagy, National Institute for Occupational Safety and Health, Cincinnati, USA

D. Willcocks, National Industrial Chemicals Notification and Assessment Scheme, Australia

P. Yao, Chinese Academy of Preventive Medicine, People's Republic of China

K. Ziegler-Skylakakis, GSF-Forschungszentrum für Umwelt und Gesundheit GmbH, Germany

APPENDIX 3 — CICAD FINAL REVIEW BOARD

Stockholm, Sweden, 25–28 May 1999

Members

Mr H. Abadin, Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention, Atlanta, GA, USA

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Dr H. Gibb, National Center for Environmental Assessment, US Environmental Protection Agency, Washington, DC, USA

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Dr G. Koennecker, Chemical Risk Assessment, Fraunhofer Institute for Toxicology and Aerosol Research, Hannover, Germany

Dr A. Löf, National Institute of Working Life, Solna, Sweden

Dr A. Nishikawa, National Institute of Health Sciences, Division of Pathology, Tokyo, Japan

Professor K. Savolainen, Finnish Institute of Occupational Health, Helsinki, Finland

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Professor P. Yao, Institute of Occupational Medicine, Chinese Academy of Preventive Medicine, Ministry of Health, Beijing, People's Republic of China

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Dr A. Poole (representing CEFIC), Dow Europe S.A., Horgen, Switzerland

Dr K. Ziegler-Skylakakis, GSF Forschungszentrum für Umwelt und Gesundheit, Institut für Toxikologie, Neuherberg, Oberschleissheim, Germany

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Dr P. Toft, Division of Health and Environment, World Health Organization, Regional Office for the Americas/Pan American Sanitary Bureau, Washington, DC, USA

Dr M. Younes, Programme for the Promotion of Chemical Safety, World Health Organization, Geneva, Switzerland

METHYLENE BISPHENYL ISOCYANATE

0298
March 1999

CAS No: 101-68-8
RTECS No: NQ9350000
EC No: 615-005-00-9

Diphenylmethane-4.4'-diisocyanate
bis(1,4-Isocyanatophenyl)methane
MDI
4,4'-Methylenediphenyldiisocyanate
$C_{15}H_{10}N_2O_2$ / $OCNC_6H_4CH_2C_6H_4NCO$
Molecular mass: 250.3

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/SYMPTOMS	PREVENTION	FIRST AID/FIRE FIGHTING
FIRE	Combustible. Gives off irritating or toxic fumes (or gases) in a fire.	NO open flames.	Powder, carbon dioxide.
EXPLOSION			

EXPOSURE		**AVOID ALL CONTACT!**	**IN ALL CASES CONSULT A DOCTOR!**
Inhalation	Headache. Nausea. Shortness of breath. Sore throat.	Local exhaust or breathing protection.	Fresh air, rest. Artificial respiration if indicated. Refer for medical attention.
Skin	Redness.	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse skin with plenty of water or shower. Refer for medical attention.
Eyes	Pain.	Safety goggles or face shield.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion		Do not eat, drink, or smoke during work.	Rinse mouth. Do NOT induce vomiting. Refer for medical attention.

SPILLAGE DISPOSAL	**PACKAGING & LABELLING**	
Evacuate danger area! Consult an expert! Sweep spilled substance into sealable containers. Carefully collect remainder, then remove to safe place. Chemical protection suit including self-contained breathing apparatus.	Xn Symbol R: 20-36/37/38-42/43 S: (1/2-)23-3 Note: C6/37-45	Unbreakable packaging; put breakable packaging into closed unbreakable container. Do not transport with food and feedstuffs.

EMERGENCY RESPONSE	**STORAGE**
	Separated from incompatible materials (see Chemical Dangers), food and feedstuffs. Cool. Dry. Keep in the dark.

IPCS
International Programme on Chemical Safety

Prepared in the context of cooperation between the International Programme on Chemical Safety and the European Commission

SEE IMPORTANT INFORMATION ON THE BACK.

IMPORTANT DATA

Physical State; Appearance
WHITE TO PALE YELLOW CRYSTALS OR FLAKES.

Chemical dangers
The substance may polymerize under the influence of temperatures above 204°C. On combustion, forms toxic and corrosive fumes including nitrogen oxides and hydrogen cyanide (see ICSC 0492). Reacts readily with water to form insoluble polyureas. Reacts violently with acids, alcohols, amines, bases and oxidants causing fire and explosion hazard.

Occupational exposure limits
TLV: 0.005 ppm as TWA (ACGIH 1998).

Routes of exposure
The substance can be absorbed into the body by inhalation.

Inhalation risk
Evaporation at 20°C is negligible; a harmful concentration of airborne particles can, however, be reached quicklywhen dispersed.

Effects of short-term exposure
Tear drawing. The substance irritates the eyes, the skin and the respiratory tract. The substance may cause effects on the lungs, resulting in impaired functions.

Effects of long-term or repeated exposure
Repeated or prolonged contact may cause skin sensitization. Repeated or prolonged inhalation exposure may cause asthma (see Notes).

PHYSICAL PROPERTIES

Boiling point at 100 kPa: 314°C
Melting point: 37°C
Relative density (water = 1): 1.2
Solubility in water: reaction

Vapour pressure, Pa at 20°C: negligible
Relative vapour density (air = 1): 8.6
Flash point: 196°C c.c.
Auto-ignition temperature: 240°C

ENVIRONMENTAL DATA

NOTES

The symptoms of asthma often do not become manifest until a few hours have passed and they are aggravated by physical effort. Rest and medical observation are therefore essential.
Anyone who has shown symptoms of asthma due to this substance should avoid all further contact with this substance.
MDI may sensitize workers so that they react to other isocyanates (asthma).
Do NOT take working clothes home.
Caradate 30, Desmodur 44, Hylene M 150, Isonate, Nacconate 300, NCI-C50668, Rubinate 44 are trade names.

ADDITIONAL INFORMATION

RÉSUMÉ D'ORIENTATION

Ce CICAD sur le diisocyanate de diphénylméthane (MDI) a été préparé par l'Institut national japonais des sciences de la santé en collaboration avec le National Center for Environmental Assessment de l'Environmental Protection Agency des États-Unis (EPA). Il repose essentiellement sur des mises au point de la Société japonaise de médecine du travail (JSOH, 1994) et de l'EPA (US EPA, 1998) pour l'évaluation toxicologique et de l'Union européenne (EU, 1999) pour les effets sur l'environnement. Il est à noter que le document de l'Union européenne n'a pas encore été définitivement approuvé et que les données présentées dans les paragraphes relatifs à l'impact écologique de ce produit proviennent pour l'essentiel d'études non publiées. Le dépouillement bibliographique a été poursuivi jusqu'à novembre 1998 à l'aide du système MEDLINE, à la recherche de toute information nouvelle susceptible d'être utile à l'évaluation. La préparation des sources documentaire et leur examen par des pairs sont exposés à l'appendice 1. Des renseignements sur l'examen par des pairs du présent CICAD sont par ailleurs donnés à l'appendice 2. Ce CICAD a été approuvé en tant qu'évaluation internationale lors d'une réunion du Comité d'évaluation finale qui s'est tenue à Stockholm (Suède) du 25 au 28 mai 1999. La liste des participants au Comité d'évaluation finale figure à l'appendice 3. La fiche internationale sur la sécurité chimique (ICSC 0298) du MDI, établie par le Programme international sur la sécurité chimique (IPCS, 1993), est également reproduite dans le présent document.

On désigne sous le nom générique de diisocyanate de diphénylméthane (MDI) un produit utilisé dans l'industrie. Le MDI polymérisé (PMDI), qui est la forme technique et commerciale principale de ce composé est en fait un mélange contenant 25 à 80 % de 4,4'-MDI monomère et des oligomères à 3-6 cycles plus quelques isomères comme l'isomère 2,2'. La composition exacte du PMDI varie selon les producteurs.

Le 4,4'-MDI se présente sous la forme d'un solide jaune pâle à la température ambiante, dont la masse moléculaire est de 250. Son point d'ébullition est de > 300 °C à 101,3 kPa et son point de fusion, de 39-43 °C. Sa tension de vapeur est inférieure à 1 mPa à 20 °C. Comme il ne subsiste que peu de temps dans l'eau, sa solubilité dans ce solvant est purement théorique. Il est toutefois soluble dans l'octane, le benzène et le kérosène. Le PMDI est un liquide brun-rouge foncé dont le point de fusion, mal défini, se situe autour de 0 °C. Sa tension de vapeur est inférieure à 1 mPA à 20 °C. Le MDI est très réactif dans l'environnement ou lorsqu'il est absorbé par des organismes vivants et il est rapidement hydrolysé en 4,4'-méthylènedianiline (MDA), laquelle réagit à son tour sur le MDI en excès pour donner des oligo-urées et des polyurées insolubles.

Le MDI est utilisé pour la fabrication d'elastomères à base de polyuréthane (roulements, emballages, amortisseurs de vibrations, cuirs synthétiques, etc.), de fibres (spandex) et de semelles de chaussures. Le PMDI sert à la confection de mousses rigides ou souples, de liants pour sable de moulage et d'isolants thermiques. La production annuelle totale de MDI et de PMDI a été d'environ 1,2 millions de tonnes en 1991, de 1,5 millions en 1993, de 1,78 millions en 1994 et de 1,95 millions de tonnes en 1996.

Une fois le produit recueilli sous forme d'aérosol sur un impacteur, dans un barboteur ou sur des filtres, on fait appel à la chromatographie en phase liquide à haute performance (CLHP) pour le dosage du MDI ou du PMDI. La limite de détection de la CLHP pour ces deux produits, qui varie en fonction de la méthode d'échantillonnage, peut être inférieure à 0,01 mg/m^3. Selon toutes les études disponibles, on trouve de la MDA libre ou acétylée en milieu fortement hydrolytique. En pareil cas, il se forme également de la MDA aux dépens du MDI conjugué. On dispose depuis peu d'une nouvelle méthode pour déterminer la composition des mélanges complexes aéroportés d'isocyanates et de composés apparentés qui prennent naissance au cours de la décomposition thermique du polyuréthane. Elle consiste à faire réagir la butylamine sur les isocyanates et à doser les dérivés formés.

Dans les conditions normales, l'exposition de la population générale au MDI devrait provenir uniquement des émissions de ce composé dans l'atmosphère. Il est rare que l'on soit fortement exposé dans le milieu ambiant. Répandu sur le sol ou déversé dans l'eau, le MDI ne subsiste que brièvement en raison de sa réaction avec l'eau qui conduit principalement à la formation de polyurées insolubles. Il se forme également de la MDA mais sa concentration est toujours faible. Une étude sur un étang a montré que l'accumulation du MDI le long de la chaîne alimentaire aquatique est extrêmement peu probable, comme on peut s'y attendre du fait de sa très faible solubilité et de sa forte réactivité en solution aqueuse. On ne dispose que de données limitées sur l'exposition professionnelle; des valeurs supérieures à 50 µg/m^3 (en moyenne pondérée par rapport au temps sur 8 h) ont été signalées de temps à autre.

Les données toxicocinétiques relatives au MDI sont très limitées. Une fois absorbé, il semble se conjuguer principalement aux protéines. Pour ce qui est de l'exposition par la voie respiratoire, on ne dispose que d'études limitées sur le rat. L'une de ces études, basée sur l'utilisation de MDI radiomarqué, a montré qu'une

certaine proportion de MDI se répartit dans l'organisme sous une forme ou sous une autre, essentiellement dans les poumons, les reins, les muscles et les voies digestives. Le composé est ensuite éliminé avec ses métabolites, 57 et 13 % de la radioactivité étant respectivement récupérés dans les matières fécales et les urines au bout de 4 jours. Moins de 1 % de la radioactivité a été récupéré dans les principaux organes, mais 23 % de la dose initiale ont été retrouvés dans la carcasse. Dans les urines, on a mis en évidence une petite quantité de MDA sous les deux formes : libre et acétylée.

Des études portant sur des ouvriers ont permis de mettre en évidence de la méthylènedianiline sous diverses formes dans leur sang et leurs urines : MDA libre, MDA acétylée et adduits MDA-hémoglobine et MDA-albumine. Ces travaux donnent à penser que la MDA plasmatique acido-hydrolysable pourrait constituer un biomarqueur intéressant d'une exposition de longue durée au MDI. Chez un ouvrier exposé au PMDI, on a constaté que la demi-vie de la MDA acido-hydrolysable était de 70 à 80 h dans l'urine et de 21 jours dans le sérum.

Le MDI ne provoque pas d'intoxications aiguës chez l'animal. L'expérimentation animale apporte cependant des preuves indiscutables d'une sensibilisation cutanée et respiratoire provoquée par le MDI. Il est possible que l'immunité cellulaire et l'immunité humorale jouent un rôle dans la pathogénèse de l'hypersensibilité provoquée par les isocyanates. Chez des rats mâles et femelles exposés à un aérosol de PMDI à la concentration de 13,6 mg/m^3, 6 h par jour, 5 jours par semaine, pendant 2 semaines, on a observé une intense détresse respiratoire et une réduction sensible du gain de poids, les signes de détresse respiratoire étant beaucoup moins marqués et le gain de poids juste un peu réduit chez les mâles à la concentration de 4,9 mg/m^3. En se basant sur une augmentation marginale du rapport poids du poumon/poids du corps aux doses les plus élevées, on a conclu que la concentration de 2,2 mg/m^3 - la plus faible étudiée - correspondait à la dose sans effet nocif observable (NOAEL).

Lors d'une étude de 2 ans visant à évaluer la toxicité respiratoire chronique et la cancérogénicité du PMDI, des rats exposés à des aérosols de PMDI à des concentrations de 0, 0,19, 0,98 et 6,03 mg/m^3, ont présenté des anomalies au niveau des voies respiratoires. On n'a pas considéré que les adénocarcinomes pulmonaires observés dans un cas constituaient une preuve suffisante de la cancérogénicité du PMDI pour l'animal; en revanche, la formation *in situ* de MDA, composé cancérogène bien connu par l'intermédiaire de l'eau de boisson, pourrait être à l'origine de cet effet. On a également considéré que l'hyperplasie des cellules basales de l'épithélium olfactif constatée aux doses de 0,98 et 6,03 mg/m^3 constituait un point d'aboutissement très important de l'action toxique, mais de nature non cancérogène. Les résultats de cette étude, permettent de retenir - en dehors de tout effet cancérogène - la valeur de 0,19 mg/m^3 pour la dose sans effet nocif observable (NOAEL) et de 0,98 mg/m^3 pour la dose la plus faible produisant un effet nocif observable (LOAEL).

Du MDI monomère dissous dans le diméthylsulfoxyde (DMSO) et mis en présence *in vitro* de *Salmonella typhimurium*, a donné des résultats tantôt positifs, tantôt négatifs. Toutefois, sachant que le DMSO réagit sur le MDI pour donner de la MDA et peut-être d'autres produits, on ne peut pas considérer ces résultats comme significatifs en vue d'une évaluation du risque pour l'Homme.

L'exposition de rattes Wistar gravides à du MDI monomère a entraîné une incidence accrue de sternèbres asymétriques chez les foetus à la concentration de 9 mg/m^3; toutefois, étant donné que cet accroissement se situait dans les limites de la variabilité biologique, on a estimé pouvoir prendre la valeur de 9 mg/m^3 comme représentant la NOAEL relative aux effets toxiques sur le développement. Dans une autre étude sur le PMDI, la NOAEL relative à la toxicité pour les mères et les foetus a été estimée à 4 mg/m^3, en se basant sur la mort prématurée d'un certain nombre de rattes gravides et sur la diminution statistiquement significative du poids placentaire et du poids foetal à la dose de 12 mg/m^3. Il n'y a pas eu d'études consacrées aux effets du MDI ou du PMDI sur les paramètres génésiques.

Les points d'aboutissement toxicologiques les plus préoccupants sont l'asthme d'origine professionnelle, les pneumopathies d'hypersensibilité et les affections inflammatoires des voies respiratoires supérieures consécutives à l'inhalation de MDI ou de PMDI. Même si on en voit encore mal le mécanisme, il semble que des réactions immunitaires humorales et cellulaires jouent un rôle dans les manifestations allergiques. Un certain nombre de cas ont été décrits qui, à l'instar de diverses études épidémiologiques, mettent en cause le MDI dans certaines dermatites et dans des problèmes de sensibilisation ou d'asthme d'origine professionnelle. Une étude sur cohorte et une étude rétrospective, présentant il est vrai un certain nombre de limitations, ont montré qu'il n'y avait aucune association entre le MDI et la morbidité cancéreuse. On ne dispose d'aucune donnée sur l'exposition par la voie orale, mais il est peu probable que l'Homme soit exposé au MDI par cette voie.

Le MDI ne présente aucune toxicité pour les poissons, les invertébrés aquatiques, les algues ou les microorganismes dans des conditions d'exposition

susceptibles de générer une intoxication aiguë ou chronique. Toutefois, les résultats des tests pratiqués dans le milieu aquatique ne sont guère significatifs étant donné que le MDI est pratiquement insoluble dans l'eau. De même, un certain nombre de tests pratiqués sur des organismes terricoles n'ont donné aucun résultat positif dans les conditions expérimentales. Il n'y a, à la lumière des données disponibles, aucune préoccupation à avoir quant aux effets du MDI sur les êtres vivants dans leur milieu naturel, encore qu'il faille obtenir davantage de renseignements concernant la formation de MDA dans l'environnement et ses effets sur les organismes vivants avant de tirer des conclusions définitives.

RESUMEN DE ORIENTACIÓN

El presente CICAD sobre el diisocianato de difenilmetano (MDI) se preparó en el Instituto Nacional de Ciencias de la Salud, Japón, en colaboración con el Centro Nacional para la Evaluación del Medio Ambiente, la Agencia para la Protección del Medio Ambiente de los Estados Unidos (EPA). Se basó principalmente en los exámenes de la Sociedad Japonesa de Salud Ocupacional (JSOH, 1994) y de la US EPA (1998) para la evaluación toxicológica y de la Unión Europea (EU, 1999) para la evaluación ambiental. Hay que señalar que el documento de la UE es todavía un borrador pendiente de aprobación y que la información que presenta en las secciones relativas al medio ambiente se basa fundamentalmente en estudios no publicados. Se buscó la bibliografía hasta noviembre de 1998 mediante MEDLINE, para localizar cualquier información nueva pertinente a la evaluación. La preparación de los documentos originales y su examen colegiado se describen en el apéndice 1. La información sobre el examen colegiado de este CICAD figura en el apéndice 2. Este CICAD se aprobó en una reunión de la Junta de Evaluación Final celebrada en Estocolmo, Suecia, los días 25-28 de mayo de 1999. En el apéndice 3 figura la lista de participantes en esta reunión. La Ficha internacional de seguridad química (ICSC 0298) para el MDI, preparada por el Programa Internacional de Seguridad de las Sustancias Químicas (IPCS, 1993), también se reproduce en el presente documento.

El diisocianato de difenilmetano (MDI) es el nombre genérico de un producto utilizado en la industria. El MDI polimérico (PMDI), forma técnico/comercial primaria del MDI, es en realidad una mezcla que contiene un 25%-80% de 4,4'-MDI monomérico, así como oligómeros con 3-6 anillos y otros isómeros secundarios, como el isómero 2,2'. La composición exacta del PMDI varía de un fabricante a otro.

El 4,4'-MDI monomérico es una sustancia sólida de un color entre blanco y amarillo pálido a temperatura ambiente, con un peso molecular de 250. Tiene un punto de ebullición >300 °C a 101,3 kPa, un punto de fusión de 39-43 °C y una presión de vapor <1 mPa a 20 °C. Su presencia en el agua es fugaz; así pues, su solubilidad en agua es puramente teórica. Sin embargo, el MDI monomérico es soluble en octano, benceno y queroseno. El PMDI es un líquido de color oscuro entre rojizo y marrón, con un punto de fusión indefinido alrededor de 0 °C y una presión de vapor <1 mPa a 20 °C. El MDI es muy reactivo en el medio ambiente o cuando lo absorben los organismos y se hidroliza con rapidez, formando 4,4'-metilendianilina (MDA), que reacciona con el MDI en exceso para producir oligoureas y poliureas insolubles.

El MDI se utiliza en la fabricación de elastómeros de poliuretano (rodillos, embalaje, aislantes de caucho contra las vibraciones, piel sintética, etc.), fibras expandidas y suelas de goma para zapatos. El PMDI se utiliza para fabricar espuma rígida y flexible, aglutinantes de arena y resina de fundición y aislantes térmicos. La producción anual total de MDI y PMDI en todo el mundo fue de alrededor de 1,2 millones de toneladas en 1991, 1,5 millones de toneladas en 1993, 1,78 millones de toneladas en 1994 y 1,95 millones de toneladas en 1996.

Una vez recogida de manera adecuada la forma aerosol mediante interceptadores, burbujas o filtros, el MDI y el PMDI se analizan mediante cromatografía líquida de alto rendimiento. Los límites de detección de esta técnica para el MDI y el PMDI, que varían en función de la metodología de muestreo, pueden ser inferiores a 0,01 mg/m^3. En casi todos los estudios se identifica MDA libre y acetilada después de mantener unas condiciones muy hidrolizantes. En estas condiciones también se forma MDA a partir del MDI conjugado. Desde hace poco se dispone de un nuevo método que permite determinar la composición de mezclas complejas de isocianatos y compuestos afines suspendidos en el aire formados durante la descomposición térmica del poliuretano mediante la producción de derivados de los isocianatos con dibutilamina.

En circunstancias normales, la exposición del público general al MDI probablemente se limitará a los casos de liberación en la atmósfera. Son raras las exposiciones altas en el medio ambiente. Cuando se produce un vertido al suelo o al agua, el MDI tiene una existencia fugaz, debido a que reacciona con el agua para producir de manera predominante poliureas insolubles. Las concentraciones de MDA que se forman en el medio ambiente por la reacción del MDI con el agua son siempre bajas. En un estudio de un estanque se comprobó que es muy poco probable que se produzca acumulación de MDI a lo largo de la cadena alimentaria acuática, como cabría esperar considerando que tiene una solubilidad muy baja y una elevada reactividad en solución acuosa. La información sobre la exposición ocupacional es limitada; en diferentes industrias se ha notificado que no son frecuentes las exposiciones medias ponderadas por el tiempo de ocho horas superiores a 50 µg/m^3.

Hay una información muy limitada sobre la toxicocinética del MDI. Una vez absorbido, parece estar predominantemente conjugado a proteína. Con respecto a la exposición por inhalación, solamente se dispone de estudios limitados en ratas. Un estudio de exposición por inhalación con MDI radiomarcado indica que alguna forma o parte del MDI se distribuye por todo el organismo, sobre todo en los pulmones, los músculos, los riñones y el aparato digestivo. La eliminación fecal y

urinaria del MDI y sus metabolitos durante cuatro días fue el 57% y el 13% de la radiactividad recuperada, respectivamente. Se recuperó menos del 1% de la radiactividad de los órganos principales, aunque el 23% de la dosis administrada se recuperó en la canal. En la orina aparecieron pequeñas cantidades de MDA libre y acetilada.

En estudios con trabajadores se han identificado MDA libre, MDA acetilada y aductos con hemoglobina o albúmina en la orina y la sangre. Estos estudios parecen indicar que la MDA hidrolizable ácida del plasma puede ser un biomarcador útil de la exposición prolongada al MDI. La semivida de la MDA hidrolizable ácida en la orina de un trabajador expuesto al PMDI fue de 70-80 horas, y en el suero de 21 días.

El MDI no tiene una toxicidad aguda para los mamíferos de laboratorio. Los datos obtenidos en animales proporcionan indicios claros de sensibilización cutánea y respiratoria debida al MDI. En la patogénesis de la hipersensibilidad debida a los isocianatos podría intervenir la inmunidad humoral, así como la mediada por células. Se observaron trastornos respiratorios graves y una disminución significativa del aumento del peso corporal en ratas machos y hembras expuestas a un aerosol de PMDI con una concentración de 13,6 mg/m^3 durante seis horas al día, cinco días a la semana, durante un período dos semanas, con síntomas mucho menos graves de trastornos respiratorios y sólo una ligera reducción del aumento del peso corporal en ratas machos con 4,9 mg/m^3. Tomando como base un aumento marginal de la razón peso del pulmón: peso corporal con dosis más elevadas, se llegó a la conclusión de que 2,2 mg/m^3, el nivel de dosis más bajo examinado, era una concentración sin efectos adversos observados (NOAEL).

En un estudio de toxicidad/carcinogenicidad por inhalación crónica de dos años, las ratas expuestas a un aerosol de PMDI en concentraciones de 0, 0,19, 0,98, y 6,03 mg/m^3 mostraron cambios en el aparato respiratorio. Se consideró que el adenocarcinoma pulmonar observado en un caso no era suficiente para identificar al PMDI como carcinógeno humano; sin embargo, la causa de ese efecto podría ser la generación *in situ* de MDA, que es un carcinógeno conocido de los animales a través del agua de bebida. Se consideró que la hiperplasia celular basal en el epitelio olfatorio detectada con 0,98 y 6,03 mg/m^3 era un efecto final crítico no carcinogénico. La información no neoplásica de este estudio parece indicar una NOAEL de 0,19 mg/m^3 y una concentración más baja con efectos adversos observados (LOAEL) de 0,98 mg/m^3.

Se obtuvieron resultados tanto positivos como negativos cuando se realizaron pruebas *in vitro* con MDI monomérico disuelto en dimetilsulfóxido en *Salmonella typhimurium*. Sin embargo, debido a la interacción conocida del dimetilsulfóxido con el MDI para producir MDA y posiblemente otros productos de la reacción, estos resultados positivos no deberían considerarse válidos en la evaluación del riesgo para la salud humana.

La exposición de ratas Wistar preñadas a MDI monomérico dio lugar a una mayor incidencia de esternebras asimétricas en fetos con 9 mg/m^3; sin embargo, como el aumento quedaba dentro de los límites de la variabilidad biológica, la NOAEL para la toxicidad en el desarrollo en ese estudio se estimó en 9 mg/m^3. En otro estudio en el cual se expusieron ratas a PMDI, la NOAEL para la toxicidad materna y fetal se estimó en 4 mg/m^3, basada en el resultado de las muertes prematuras de hembras preñadas y en la reducción estadísticamente significativa del peso de la placenta y del feto con 12 mg/m^3. No se han realizado estudios en los que se haya examinado el efecto del MDI polimérico o monomérico en los parámetros reproductivos.

Los efectos finales en la salud más preocupantes son el asma de origen ocupacional, la neumonitis por hipersensibilidad y las enfermedades inflamatorias de las vías respiratorias superiores mediante la inhalación de MDI polimérico o monomérico. Aunque aún no se conocen bien, en las reacciones alérgicas parecen intervenir reacciones inmunitarias de carácter humoral, así como de las mediadas por células. En notificaciones de casos, así como en estudios epidemiológicos, se ha descrito el MDI como causante de dermatitis ocupacional, sensibilización cutánea y asma. En un estudio de cohortes y un estudio retrospectivo, aunque eran limitados en varios aspectos, se puso de manifiesto que no había una asociación significativa con la morbilidad del cáncer. No hay datos disponibles para la exposición oral, pero es poco probable la exposición de las personas al MDI por esta vía.

El MDI no mostró toxicidad para los peces, los invertebrados acuáticos, las algas o los microorganismos en ninguna de las condiciones de prueba de exposición aguda o prolongada. Sin embargo, los resultados de las pruebas acuáticas carecen de valor, debido a que el MDI es prácticamente insoluble en agua. Análogamente, en un pequeño número de pruebas realizadas con organismos terrestres no se observaron efectos en las condiciones de la prueba. Los datos disponibles indican que no hay que preocuparse por los efectos del MDI en los organismos del medio ambiente, aunque para llegar a conclusiones definitivas se necesitaría información más detallada sobre la formación de MDA en el medio ambiente y sus efectos en los organismos.

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