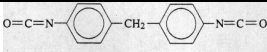
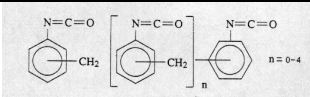
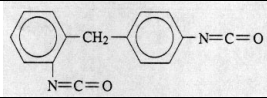
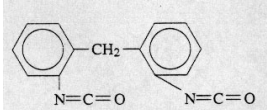


SIDS INITIAL ASSESSMENT PROFILE

CAS No.	26447-40-5		
Chemical Name	Methylenediphenyl diisocyanate ('MDI')		
Structural Formula	Mixture of monomeric, oligomeric and polymeric MDI.		
CAS-No.	101-68-8 (a); 5873-54-1(b); 2536-05-2 (c)	26447-40-5	9016-87-9
Chemical Name	Monomeric MDI a) 4,4'-methylenediphenyldiisocyanate b) 2,4'-methylenediphenyldiisocyanate c) 2,2'-methylenediphenyldiisocyanate	MDI (generic)	Polymeric MDI
Structural formula a)			
b)			
c)			

SUMMARY CONCLUSIONS OF THE SIAR**Category/Analogue Rationale**

The predominant commercial product covered by the term MDI is the liquid reaction mixture produced from methylene di-aniline. It comprises 4,4'-MDI and its oligomers with small amounts of the other monomers 2,4-MDI and 2,2'-MDI. It is commonly termed 'polymeric MDI' also called 'generic', 'crude' or 'non-isomer specific' MDI. A relatively small proportion is converted to monomeric MDI (essentially 4,4'-MDI) by purification. The data-set on this 'generic MDI' covers also the testing results on the other MDI analogues.

The category approach is considered justified since the substances have closely related composition i.e. excess of monomeric MDI as well as comparable -NCO content that are considered as the primary determinants of (eco)toxicity.

Human Health

There are few data available on the toxicokinetics and fate of MDI in humans. Urinary 4,4'-methylenedianiline, measured after acid hydrolysis, has been suggested as a biomarker for short-term exposure to MDI. 4,4'-methylenedianiline (4,4'-MDA), released by hydrolysis of plasma or haemoglobin, has been suggested as a biomarker of intermediate and long-term exposure to MDI. No information is available on the toxicokinetics of MDI following oral exposure in animals.

Contradictory results have been obtained with respect to dermal exposure. Eventually, a dermal absorption of 1% is taken – as reasonable worst case estimate - to use in dermal exposure calculations.

With respect to inhalation exposure, there is reliable data regarding distribution/excretion in experimental animals. In biomonitoring studies haemoglobin adducts and urine metabolites of MDI were determined. From the data generated to date, it is not possible to state categorically that the MDA measured in the majority of studies investigating levels in

blood and plasma represents a metabolite of MDI. The results of the inhalation metabolism / toxicokinetics / distribution study implicate that a proportion of the MDI dose is converted to metabolites via the intermediary formation of an amine group which is rapidly acetylated. However, it is not possible from the current data to elucidate the mechanisms in the biological transport and transformation of MDI. Further studies using biologically relevant *in vitro* systems are ongoing. Additional studies are being designed to investigate metabolism of formed conjugates and any role of free or bound MDA in MDI transformation.

Assessment of the available acute toxicity data indicates that inhalation exposure to respirable aerosols of MDI results in toxicity confined predominantly to the respiratory tract. A well-conducted animal study gives a LC₅₀ (4 h, rat) of 490 mg/m³. The limited data available from animal studies indicate that MDI is of low oral and dermal acute toxicity, with an oral LD₅₀ (rat) > 10,000 mg/kg and dermal LD₅₀ (rabbit) > 10,000 mg/kg.

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

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

No results from repeated-dose toxicity tests are available for the oral and dermal route of exposure. Well-conducted short-term and long-term inhalation animal studies indicate the respiratory tract to be the target organ of respirable MDI aerosol. The reported NOAELs for chronic toxicity (inhalation, rat, 2 years) are 0.23 and 0.2 mg/m³ (final NOAEL = 0.2 mg/m³); LOAEL being 1 mg/m³. The reported NOAEL for short-term toxicity is 1.4 mg/m³; the LOAELs for short-term toxicity being 2 mg/m³ and 1 mg/m³; and a LOEL being 1.1 mg/m³. At present, the NOAEL used for short-term toxicity is 0.5 mg/m³ (for this estimation the LOAEL_(acute, rat) of 0.7 mg/m³, based on a transient dysfunction of the pulmonary epithelial barrier, was taken into account).

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

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

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

No fertility nor multigeneration studies are available for MDI. Data from (sub)chronic toxicity studies (Reuzel et al., 1994b, 1994a) did not reveal clear substance related and/or significant impairment of organs of the reproductive

system of the male and female. Taken altogether, these studies were considered too limited to allow a determination of a NOAEL for fertility. Pre-natal inhalation toxicity testing in rats indicates the absence of selective toxicity to the development (no findings indicate any specific developmental effects at exposure levels below those that caused maternal toxicity). The reported NOAEL_(developmental) for monomeric MDI is 3 mg/m³/day and the NOAEL_(developmental) for polymeric MDI: 4 mg/m³/day. No data on reprotoxicity are available in humans.

Environment

Vapour pressure is < 0.005 Pa; water solubility and log Kow could only be obtained by HPLC method due to high reactivity of the substance with the water; nevertheless, the values yielded are not relevant for predicting environmental fate.

Atmospheric half-life is estimated to be of 1.331 days. Hydrolysis of the isocyanate group under conditions of low dispersion results in the formation of polyureas and polyurethanes (PUs) (i.e. both insoluble and inert compounds) and traces of MDI and methylenedianiline (MDA). Under conditions of high dispersion a substantial amount of MDA may be formed as initial breakdown product. However, MDA in the presence of MDI is rapidly transformed further to polyureas/PUs. Biodegradation tests with MDI and derived oligoureas showed that these substances are not biodegraded by micro-organisms. Two long-term studies showed that MDI is not accumulated by biota (algae, aquatic plants, aquatic invertebrates and fish).

A rather extensive package of environmental tests is available including acute and (sub)chronic tests on fish, aquatic invertebrates, algae, plants, soil dwelling organisms and microorganisms. These tests are however confounded by the rapid hydrolysis of MDI.

In all these tests no effect was observed despite the high loads involved (nominal concentrations range between 100-3000 mg/l or /kg). Absence of effect was observed with all members of substance category tested. This is obviously due to the fact that actual exposure of the test organisms takes place to predominantly polyureas/PUs and only traces MDI and MDA. One exception concerned testing where MDI had been dispersed in test medium by high speed shearing. The observed lethal effects on both fish and cladocerans are assumed to be due to the formation of substantial amounts of MDA and this study is considered irrelevant for the hazard assessment of MDI and the production under field conditions of its breakdown product MDA.

Exposure

MDI is produced in closed, industrial systems. These activities take place in a relatively small number of sites (in total 11 in Europe for the year 1996). MDI is mainly used as industrial intermediate in the manufacture or application of polyurethanes. Smaller amounts are processed to 'prepolymers'. Worldwide production was about 2,500 kilotonnes MDI per annum in 1996 (from which approximately 790 ktpa in Western Europe). MDIs are sold to numerous downstream users (ca. 3,600 in EU).

MDI is used for the production of PU foams (69%) and coatings, adhesives, sealants and elastomers (26%). Other uses are thermoplastic PUs and PU fibers. MDI is also used as grouting agents in rock consolidation or sealing of water leaks in tunnels or geotechnical construction works. There is also use in the production of particle board (bonding of wood) and mould cores for the foundry industry.

In conclusion, human exposure to MDI may occur by inhalation of vapours and aerosols or through skin exposures at workplaces where MDI is produced, or MDI-containing products are used, or at home doing some do-it yourself jobs.

RECOMMENDATION

Human Health: The chemicals in this category are candidates for further work

Environment: The chemicals in this category are currently of low priority for further work

**RATIONALE FOR THE RECOMMENDATION AND
NATURE OF FURTHER WORK RECOMMENDED**

Environment: no further work is needed because MDI is not expected to cause harm to the environment given the absence of any observed effect in ecotoxicity tests.

Human health: The chemical is a candidate for further work. Hazardous properties have been identified for this substance (local effects after repeated inhalation, irritation and sensitisation). In an assessment performed in the European Union in the context of the EU Existing Substances Regulation, both occupational and consumer exposure was identified. Other OECD countries may wish to perform an exposure assessment for humans and if necessary a risk assessment. Based on the outcome, further testing for fertility of MDI could be considered as a post-SIDS activity.

Note: further metabolism/toxicokinetic/distribution studies are currently on-going.