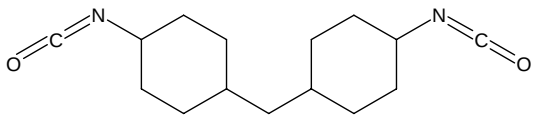
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	5124-30-1
Chemical Name	4,4´-Methylenedicyclohexyl diisocyanate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

4,4´-Methylenedicyclohexyl diisocyanate is of low oral and dermal acute toxicity with an oral LD_{50} (rat) of 9900 mg/kg bw and a dermal LD_{50} (rabbit) > 10,000 mg/kg. Toxic symptoms after oral administration included severe diarrhea, loss of appetite and increasing weakness. Assessment of the acute inhalation toxicity data indicates that exposure to respirable aerosols of 4,4´-methylenedicyclohexyl diisocyanate confined predominantly to the respiratory tract. Clinical signs (salivation, bradypnea, stridor) indicated respiratory distress. A haemorrhagic lung edema was considered to be causative for mortality. An animal study according to OECD TG 403 gives a LC_{50} (4 h, rat) of 434 mg/m^3.

4,4´-Methylenedicyclohexyl diisocyanate is moderately to severely irritant to the skin of rabbits (OECD TG 404). Irritant effects were observed after instillation of 4,4´-methylenedicyclohexyl diisocyanate into the eyes of rabbits (OECD TG 405). The repeated dose studies indicate that 4,4´-methylenedicyclohexyl diisocyanate causes irritation of the respiratory tract.

Animal data are not uniform however they frequently provide evidence of a skin sensitizing potential of 4,4´-methylenedicyclohexyl diisocyanate. Human case reports describe allergic contact dermatitis due to 4,4´-methylenedicyclohexyl diisocyanate exposure. Although no validated animal model is available to assess the potential for respiratory sensitization or asthma in humans animal data support to some extent the hypothesis that respiratory hypersensitivity may be induced by 4,4´-methylenedicyclohexyl diisocyanate.

No results from repeated-dose toxicity tests are available for the oral and dermal route of exposure. A subacute inhalation study (1, 6 and 36 mg/m^3; 6 hours/day on five days/week for 4 weeks) with rats (OECD TG 412) indicates the respiratory tract to be the target organ of respirable 4,4´-methylenedicyclohexyl diisocyanate aerosol. The reported NOAEL for effects governed by respiratory tract irritation is 1 mg/m^3; the LOAEL is 6 mg/m^3 (i.e. histopathological changes in nasal passages, larynx and bronchi). The results of a reproduction/developmental toxicity screening test (OECD TG 421) corresponds to the results of the subacute study.

4,4´-Methylenedicyclohexyl diisocyanate did not induce gene mutations in bacteria (OECD TG 471) and demonstrated no potential to induce chromosome aberrations in Chinese hamster V79 cells *in vitro* (OECD TG 473) either with or without metabolic activation.

Data from an inhalative reproduction/developmental toxicity screening test according to OECD TG 421 with rats (1, 6 and 36 mg/m^3) did not reveal substance related impairment of reproduction up to a 4,4´-methylenedicyclohexyl diisocyanate concentration of 6 mg/m^3. A slightly reduced fertility index was observed at an exposure level (36 mg/m^3) that was associated with parental toxicity. NOAELs were considered to be 1 mg/m^3 in males and females for general toxicity. NOAEL for reproductive toxicity is 6 mg/m^3.

Pre-natal inhalation toxicity testing in rats (OECD°TG°421) indicates the absence of selective toxicity to the development at levels up to 36°mg/m^3. No findings indicate any specific developmental effects such as live birth index, viability index and apparent malformation. The reported $NOAEL_{(developmental)}$ for 4,4´-methylenedicyclohexyl diisocyanate in a developmental toxicity study according to OECD TG 414 (1, 6 and 36 mg/m^3) is 6 mg/m^3/day. At the 36 mg/m^3 level that caused clear maternal respiratory tract toxicity ($NOAEL_{(maternal)}$ = 1 mg/m^3) increased incidences of ventricular septal defects of the heart and slight dilation of lateral brain ventricles were observed, which lay marginally above the upper or within the normal range of scattering of the rat strain used respectively.

Environment

4,4'-Methylenedicyclohexyl diisocyanate is a slightly yellowish, moisture/water sensitive liquid with a melting point of 15 °C. 4,4'-Methylenedicyclohexyl diisocyanate has a relative density of 1.07 at 25 °C, a boiling point of 167 - 168 °C (at 2 hPa), and a vapor pressure of 2.13 x 10^{-5} hPa at 25 °C [Directive 92/69/EEC, A.4]. A water solubility and a log K_{OW} are not determinable due to the instability of 4,4'-methylenedicyclohexyl diisocyanate in water. The flash point of 4,4'-methylenedicyclohexyl diisocyanate is 200 °C [DIN 51758], the ignition point is 225 °C and the viscosity is approximately 30 mPa x s at 25 °C [DIN ISO EN 3219/A.3]. The calculated half-life of 4,4'-methylenedicyclohexyl diisocyanate in air due to indirect photodegradation is about 15.0 h.

4,4'-Methylenedicyclohexyl diisocyanate hydrolyses rapidly in the presence of water, the major product in the aqueous phase is methylene bis(4-cyclohexylamine). In water, a half-life for 4,4'-methylenedicyclohexyl diisocyanate of approximately 2 hours was determined experimentally. Due to the rapid hydrolysis of 4,4'-methylenedicyclohexyl diisocyanate, a transport of the substance between environmental compartments is unlikely. Consequently, a calculation of the Henry Law Constant and of the distribution between the environmental compartments according to the Mackay fugacity model level 1 is not suitable.

However, several aquatic toxicity tests have been undertaken with 4,4'-methylenedicyclohexyl diisocyanate and its hydrolysis products. Because of the rapid hydrolysis the assessment of the substance should be based on the hydrolysis products and not on 4,4'-methylenedicyclohexyl diisocyanate. The hydrolysis product methylenebis-p-cyclohexylamine was assessed by the EU PBT Working Group. The hydrolysis product was not classified as a PBT substance.

4,4'-Methylenedicyclohexyl diisocyanate is not readily biodegradable.

Due to the rapid hydrolysis 4,4'-methylenedicyclohexyl diisocyanate is neither persistent in the water compartment nor bioaccumulative. The calculated K_{oc}-value indicates that 4,4'-methylenedicyclohexyl diisocyanate may strongly adsorb to soil but due to its rapid hydrolysis any emission to the terrestrial compartment would be affected by humidity and therefore, geoaccumulation of 4,4'-methylenedicyclohexyl diisocyanate is not expected to occur.
Concerning the toxicity of 4,4'-methylenedicyclohexyl diisocyanate and its hydrolysis products towards aquatic species, reliable experimental results of tests with fish, *Daphnia*, and algae are available (* = determined as TOC and back-calculated to parent substance, n = nominal concentration).

Danio rerio (fish):	96 h-LC_{50} > 8.1 mg/l*,	[Directive 92/69/EEC, C.1]
Daphnia magna (aq. invertebrate):	48 h-EC_{50} > 8.3 mg/l*,	[Directive 92/69/EEC, C.2]
Scenedesmus subspicatus (algae):	72 h-E_rC_{50} > 5 mg/l*,	[Directive 92/69/EEC, C.3]
Activated sewage sludge (bacteria):	3 h-EC_{50} = 191 mg/l (n),	[Directive 88/302/EEC, Part C (corresponds to the OECD TG 209)].

It has to be considered that the toxicity observed in the reported aquatic studies was caused both by the 4,4'-methylenedicyclohexyl diisocyanate as well as by the hydrolysis products due to the instability of the test substance.
Based on the acute aquatic toxicity data on three trophic levels (fish, *Daphnia*, algae), the Predicted No Effect Concentration ($PNEC_{aqua}$) can be calculated with an assessment factor of 1000 applied to the lowest acute effect concentration. The lowest 72 h-E_rC_{50}-value of > 5 mg/l obtained for the alga species *Scenedesmus subspicatus* was used to derive a $PNEC_{aqua}$ of > 5 µg/l.

Exposure

Commercial 4,4'-methylenedicyclohexyl diisocyanate manufacturing starts with hydrogenated methylenedianiline (methylenebis-p-cyclohexylamin) which is phosgenated. The global production capacity of 4,4'-methylenedicyclohexyl diisocyanate is 10 000 - 20 000 tonnes/a, with most of it in the USA. In Germany, the only producer has a manufacturing capacity of 1000 - 5000 tonnes/a of 4,4'-methylenedicyclohexyl diisocyanate.

4,4'-Methylenedicyclohexyl diisocyanate is an intermediate in the chemical industry, used for the manufacture of binders or hardeners for coating materials or adhesives (60 %), prepolymers (20 %), and for other applications, e.g. for the production of elastomers (20 %). 4,4'-Methylenedicyclohexyl diisocyanate is not used for "Do It Yourself" applications or in other consumer products. 4,4'-Methylenedicyclohexyl diisocyanate is registered as a component in approximately 50 industrial products listed in the Danish, Finnish, and Swedish Product Registers with a consumption of about 30 tonnes/a in 2000 and 2001 (last years of record). 4,4'-Methylenedicyclohexyl diisocyanate is confidentially listed in the Norwegian Product Register. There is no registration for a consumer product. The main use category is "non-dispersive use". For 4,4'-methylenedicyclohexyl diisocyanate the Swiss Product Register lists 34 industrial products (with concentrations of up to 100 % 4,4'-methylenedicyclohexyl diisocyanate), but no consumer product.

By the producer in Germany, 4,4'-methylenedicyclohexyl diisocyanate is manufactured and processed (including filling) in closed systems at the same industrial site. To the customers most of the 4,4'-methylenedicyclohexyl diisocyanate is transported in ISO containers, and to a minor part, in drums.

During 4,4'-methylenedicyclohexyl diisocyanate manufacturing and processing, virtually no 4,4'-methylenedicyclohexyl diisocyanate (< 25 kg/a) is emitted into the atmosphere from the Bayer plants. Waste from the manufacturing and processing of 4,4'-methylenedicyclohexyl diisocyanate is disposed off in an incinerator for hazardous wastes. Due to wastewater-free manufacturing and processing, and to rapid hydrolysis, no emissions into the aquatic environment are expected.

Surveys of the workplaces have been performed also according to German Technical Guidance TRGS 402, TRGS 430, and TRGS 900 by the producer in Germany. To protect workers from exposure, several precautionary and protective measures are taken, e.g., sampling takes place in a widely closed system. In Germany for occupational settings, the maximum permissible concentration for 4,4'-methylenedicyclohexyl diisocyanate is 0.054 mg/m³. At the producer in Germany, all exposure data were below the maximum permissible concentration.

No environmental monitoring data have been identified. Traces of 4,4'-methylenedicyclohexyl diisocyanate (up to 2 µg/m^3) were detected as a thermolytic degradation product during joint welding of polyurethane floor covering in a small room with no ventilation.

The exposure of consumers to 4,4'-methylenedicyclohexyl diisocyanate is unlikely to occur, because no consumer product is known to contain 4,4'-methylenedicyclohexyl diisocyanate. An exposure via the environment is also unlikely to occur because there are virtually no emissions of 4,4'-methylenedicyclohexyl diisocyanate, and 4,4'-methylenedicyclohexyl diisocyanate released to environment would rapidly be degraded by photooxidants and water.

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

Human Health: The chemical possesses properties indicating a hazard for human health (severe irritation of skin, eye and respiratory tract, sensitization of skin and predicted to be a respiratory tract sensitizer because it is a diisocyanate). Based on data presented by the Sponsor country (relating to production by one producer which accounts for approximately 5 % to 50 % of global production and relating to the use pattern in several OECD countries), occupational exposure is anticipated to be low and there are no known consumer uses. Therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment: The chemical (including its hydrolysis products) possesses properties indicating a hazard for the environment. Based on data presented by the Sponsor country (relating to production by one producer which accounts for approximately 5 % to 50 % of global production and relating to the use pattern in several OECD countries), exposure to the environment is anticipated to be low, and therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.