

FOREWORD

INTRODUCTION

3,4-DIHYDRO-2METHOXY-2H-PYRAM

CAS N°: 4454-05-1

SIDS Initial Assessment Report

For

SIAM 16

27–30 May 2003, Paris, France

- 1. Chemical Name:** 3,4-Dihydro-2-methoxy-2H-pyran
- 2. CAS Number:** 4454-05-1
- 3. Sponsor Country:** Germany
Contact Point:
BMU (Bundesministerium für Umwelt, Naturschutz und
Reaktorsicherheit)
Contact person:
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- 4. Shared Partnership with:** BASF AG, Germany; Dow Chemical Company, Switzerland
- 5. Roles/Responsibilities of the Partners:**
 - Name of industry sponsor /consortium: BASF AG, Germany
Contact person:
Dr. Hubert Lendle,
GUP/CL - Z570
D-67056 Ludwigshafen
 - Process used: see next page
- 6. Sponsorship History**
 - How was the chemical or category brought into the OECD HPV Chemicals Programme ? by ICCA-Initiative
- 7. Review Process Prior to the SIAM:** Last literature search (update):
18. November 2002 (Human Health): databases medline, toxline;
search profile CAS-No. and special search terms
10. September 2002 (Ecotoxicology): databases CA, biosis;
search profile CAS-No. and special search terms
- 8. Quality check process:** As basis for the SIDS-Dossier the IUCLID was used. All data have been checked and validated by BUA.
- 9. Date of Submission:**

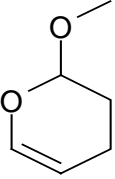
10. Date of last Update:**11. Comments:****OECD/ICCA - The BUA* Peer Review Process**

Qualified BUA personnel (toxicologists, ecotoxicologists) perform a quality control on the full SIDS dossier submitted by industry. This quality control process follows internal BUA guidelines/instructions for the OECD/ICCA peer review process and includes:

- a full (or update) literature search to verify completeness of data provided by industry in the IUCLID/HEDSET
- Review of data and assessment of the quality of data
- Review of data evaluation
- Check of adequacy of selection process for key studies for OECD endpoints, and, where relevant, for non-OECD endpoints by checking original reports/publications
- Review of key study description according robust summaries requirements; completeness and correctness is checked against original reports/publications (if original reports are missing: reliability (4), i.e. reliability not assignable)
- Review of validity of structure-activity relationships
- Review of full SIDS dossier (including SIAR, SIAP and proposal for conclusion and recommendation for further work)
- In case of data gaps, review of testing plan or rationale for not testing

* BUA (GDCh-Beratergremium für Altstoffe): Advisory Committee on Existing Chemicals of the Association of German Chemists (GDCh)

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	4454-05-1
Chemical Name	3,4-Dihydro-2-methoxy-2H-pyran
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

The acute oral LD₅₀ for 3,4-dihydro-2-methoxy-2H-pyran (MDP) in the rat ranged between 1640 and 3740 mg/kg bw. Clinical symptoms included staggering and unsteady gait, lachrymation, apathy, laboured breathing and narcosis. The 4-hr-inhalation LC₅₀ in rat was > 1310 ppm (> 6000 mg/m³) with transient signs of ocular and respiratory irritation. The dermal LD₅₀ in rabbits was 4920 mg/kg bw. Toxicity of the technical product may be influenced by impurities such as acrolein (cf SIAR on acrolein).

Undiluted MDP was irritating to the skin and eyes of rabbits. In acute toxicity studies, high concentrations of vapors were also irritating to the eyes and the respiratory tract. No adequate sensitization data are available.

The main effects following repeated inhalation exposure to MDP in rodents were reduced body weights, sedation, and irritant effects on the respiratory tract. Toxicity may be largely influenced by the presence of toxic impurities, predominantly the highly toxic and irritant acrolein. The results from a limited 14-day repeated inhalation study did not permit the establishment of a NOAEC, since reductions in body weights and signs of respiratory irritation were still present at the lowest tested concentration in the rat (LOAEC: 100 ppm = 480 mg/m³). In mice, bone marrow cytotoxicity of questionable biological significance was still seen at 5 ppm (LOAEC, 5d: 5 ppm = 24 mg/m³). No systemic effects were found up to and including the highest tested dose level of 1000 mg/kg bw/day in a dermal study on rats, limited by its duration of only 14 days.

In vitro, MDP was mutagenic in bacterial and mammalian cell systems (Ames test, HPRT test). In two *in vivo* studies, both of which performed in accordance with contemporary requirements, MDP was not clastogenic in mice dosed by the oral route or repeatedly via inhalation.

There are no experimental data for MDP available for reproduction and developmental toxicity. Since exposure is anticipated to be very low due to its sole use as chemical intermediate with controlled transport to a limited number of locations and because acute and repeated dose toxicity studies are available for the most relevant routes of accidental exposure (inhalation, dermal), no animal tests were performed for these endpoints. No studies concerning the long-term toxicity and/or carcinogenicity of MDP have been conducted.

Environment

The flammable MDP is a colourless-yellowish liquid with an ether-like odour, with a solubility in water of 16 g/l at 25 °C, a density of 1.00 g/cm³ at 20 °C, a vapour pressure of 12.4 hPa at 20 °C and of 16.7 hPa at 25 °C. A Henry's law constant of 31.2 Pa·m³/mol at 25 °C was calculated. Flash point, melting point and boiling point of the substance are 22.8 °C, < -60 °C and 127.1 °C respectively. It is stable at neutral pH, but hydrolyzes at low pH to glutaraldehyde and methanol.

From the physico-chemical properties the compartments air (80.4 %), and to a minor degree water (19.5 %), are identified as target compartments for the substance. However, in air, MDP is expected to be quickly photodegraded by reaction with OH radicals with a half life of 4.5 h. For reaction with O₃ a half-life of 4.8 h can be calculated. The substance is not readily biodegradable according to OECD evaluation criteria (OECD 301 F-Test, 0 % after 28 d). However analytical data from an industrial waste water treatment plant demonstrated that about 60 % of the chemical were eliminated. The log K_{OW} was measured to be 1.3 at 25 °C, hence bioaccumulation is unlikely to

occur. This was confirmed in a bioaccumulation study with fish (BCF = 1.5 – 1.7). The calculated log K_{oc} 0.19 indicates a low potential for adsorption to soil.

The following aquatic effects concentrations are available:

Oryzias latipes: LC₅₀ (96 h) = 232 mg/l (effect concentration; corrected for evaporation, ca. 730 mg/l nominal).

Scenedesmus subspicatus:

EC₅₀ (72 h) > 165 mg/l (effect concentration; corrected for evaporation, > 500 mg/l nominal).

Daphnia magna:

EC₅₀ (48 h) > 100 mg/l (nominal concentration, closed system, measured concentrations > 90 % of nominal values).

Pseudomonas putida: EC₅₀ (17h) = 5991 mg/l (nominal concentration).

Using the aquatic toxic effect on the most sensitive species, *Daphnia magna*, of >100 mg/l a PNEC_{aqua} of 100 µg/l is derived by applying an assessment factor of 1000 according to the EU Technical Guidance Document. No data are available on terrestrial organisms and from prolonged or chronic studies.

Exposure

There are only two known producers in Europe and the U.S. In 2000, the estimates for MDP for the world production amounted to approximately 10,000-25,000 tons. The chemical is exclusively used as an intermediate in the chemical industry for the production of glutaraldehyde. The compound is shipped directly from the production sites to ca. 10 subsidiaries world wide. There the substance is hydrolyzed under strongly acidic conditions (pH 2 – 2.5) to the final product glutaraldehyde and the by-product methanol. The concentration of MDP in the end-use product is below the limit of detection (<50 ppm).

Occupational exposure is well controlled under normal working conditions and may only occur in case of accidental spills via skin contact and the respiratory route. MDP is produced in closed systems at sites open to the environment, and, thus the risk of accumulation in case of accidental spills is minimized. Workers are only close to the production plant during sampling for analytical purpose and control inspections. MDP handling involves quality control sampling and analysis, filling and unfilling of tanks and drums. Personal protective equipment (gloves, face shield, goggles) is used during this work. Technical and organizational means to control exposure comprise the use of closed systems during production, transportation and hydrolysis, and vapor abstraction with encapsulation during filling of tanks or drums. Prior to repair and maintenance work vessels, pipes and other equipment is rinsed to remove MDP.

Acrolein is a minor impurity in the MDP product. Current acrolein concentration in MDP is less than 100 ppm (0.01 %) with a detection limit of 30 ppm. Thus acrolein concentration is considerably lower than it was in the 1980s (0.037%). Reduced acrolein content, natural ventilation at the work place, and the acrolein odor threshold of only ca. 0.1 ppm avoid the potential of unobserved or unintended exposure to acrolein.

MDP is not known to occur in consumer products and is not listed in the product registers of Denmark, Finland, Norway, Sweden and Switzerland (2002).

The exposure of workers at the manufacturing sites and the transport to a limited number of processing sites is effectively controlled. Consumers are generally not exposed to this chemical.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health:

The SIDS data requirement for reproductive toxicity is not fulfilled and the repeated dose toxicity studies are limited, but full studies were not demanded due to very limited and controlled occupational exposure at sites of the two producers. MDP possesses properties indicating a hazard for human health (irritant effects on skin, eye and respiratory system, potential genotoxicity). Exposure to humans is anticipated to be low, because exposure in occupational settings is well controlled by the two producers and because there is no consumer exposure. Therefore this chemical is currently of low priority for further work.

Environment:

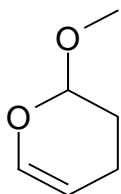
The chemical is currently of low priority for further work because of its low hazard potential.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 4454-05-1
 Chemical Name: 3,4-dihydro-2-methoxy-2H-pyran
 Molecular Formula: C₆ H₁₀ O₂
 Structural Formula:



Molecular Weight: 114.14 g/mol
 Synonyms: 2,3-Dihydro-2-methoxy-4H-pyran
 2-Methoxy-2,3-dihydro-4H-pyran
 2-Methoxy-3,4-dihydropyran
 2H-Pyran, 3,4-dihydro-2-methoxy- (7CI, 8CI, 9CI)
 3,4-Dihydro-2-methoxy-2H-pyran
 3,4-Dihydro-2-methoxypyran
 MDHP
 MDP
 Substance type: organic
 Physical status: liquid

1.2 Purity/Impurities/Additives

Purity: ≥ 99.5 % w/w
 Impurities: water: ≤ 0.2 % (w/w)
 methanol: < 0.2 % (w/w)
 acrylaldehyde: < 0.01 % (w/w)
 glutaraldehyde: < 100 ppm

1.3 Physico-Chemical properties

The flammable 3,4-dihydro-2-methoxy-2H-pyran (MDP) has a flash point of 22.8 °C (manufacturer data without proof). It is a colourless-yellowish liquid with an ether-like odour (BASF 2003). The compound has a water solubility of 16 g/l at 25 °C (BASF 1987), a vapour pressure of 12.4 hPa at 20 °C respectively 16.7 hPa at 25 °C (BASF 1993a) and a measured log Kow of 1.3 at 25 °C (BASF, 1987). A Henry's law constant of 31.2 Pa·m³/mol at 25 °C was calculated via HENRYWIN (v3.1, bond est., BASF, 2002a). Since the density of 3,4-dihydro-2-methoxy-2H-pyran (1.00 g/cm³ at 20 °C; BASF 1993) is nearly identical to that of water, significant flotation or stratification in surface waters in case of accidental losses is not expected. Melting point and boiling

point of the substance are < -60 °C (manufacturer data without proof) (BASF 2003) and 127.1 °C (BASF 1993a) respectively.

2 GENERAL INFORMATION ON EXPOSURE

There are only two known producers of MDP in Europe and the U.S. In 2000, the estimates for the world production amounted to approximately 10,000-25,000 tons.

MDP is exclusively used as an intermediate (precursor; non dispersive use) in the chemical industry for the production of glutaraldehyde. In the sponsor country, MDP is continuously produced in closed systems. The raw materials are fed from storage tanks into the reactor via pipelines, and MDP is then formed under pressure and temperatures of 160 - 190°C by the cycloaddition of methyl vinyl ether and acrolein with acrolein functioning as the 1,3-diene and methyl vinyl ether as the dienophile. The product is collected in closed storage tanks. Most of the produced MDP (about 90%) is pumped via pipelines to other plants on site, where it is hydrolyzed to glutaraldehyde and methanol under strongly acidic conditions (pH 2 – 2.5). Of the remaining about 10%, the majority (ca. 85%) is filled into drums, and about 15% into trucks and trains for transportation to about 10 subsidiaries of the two producers worldwide. All subsidiaries use MDP exclusively as an intermediate to make aqueous glutaraldehyde solutions as described above.

MDP is not known to occur in consumer products and is not listed in the product registers of Denmark, Finland, Norway, Sweden and Switzerland (2002).

2.1 Environmental Exposure and Fate

Releases into the environment may occur during production and further processing of MDP. During production and internal processing at BASF AG, Ludwigshafen (Germany), less than 25 kg/a (limit for notification) were emitted into the air in 2000 (BASF AG 2003a). The measured MDP concentrations in the effluent of the wastewater treatment plant for 10 consecutive days were below the limit of quantitation of 20 µg/l (BASF, 2002c). No further data are available.

MDP rapidly hydrolysed to glutaraldehyde in an aqueous solution at 37 °C and pH 2.5. From the data of the hydrolysis, the half-life of MDP was calculated to be 18.8 minutes under these conditions. In sodium phosphate buffer (50 mM; pH 7.4), no hydrolysis of the compound occurred for up to 4 hours (BASF AG 2000). Hydrolysis at environmental pH conditions is not expected to be a relevant degradation process.

According to OECD criteria the chemical is not readily biodegradable (OECD 301 F, manometric respirometry test, 0 % after 28 days; BASF 2001a). A valid test on inherent biodegradation is not available.

According to the model SIMPLETREAT 3.0, 34.7 % of 3,4-dihydro-2-methoxy-2H-pyran found in waste waters will be distributed into the air and 65 % will be emitted via the effluent of sewage treatment plants. However, when monitoring the substance in influent and effluent of the waste water treatment plant of BASF, Germany (Ludwigshafen) for 10 consecutive days, the measured elimination of the chemical was much higher compared to the model estimation. In 7 out of 10 days, concentrations were below the limit of quantitation (loq = 20 µg/l) in influent as well as in effluent (24 h-mixing samples). For this period the determination of the elimination was impossible. But for the rest of time MDP concentrations in the influent were above the limit of quantitation. In conclusion a mean elimination of about 60 % was measured (BASF 2002c).

Transport and distribution modelling using Mackay Level I (BASF 2003b) indicates air (80.4 %) and to a minor degree water (19.5 %) to be the main target compartments for 3,4-dihydro-2-methoxy-2H-pyran (for input parameter see IUCLID).

MDP in surface water will be subject to rapid volatilization. Using an estimated Henry's law constant of 31.2 Pa·m³/mol, a half-life for volatilization of the chemical from a river one meter

deep flowing 1 m/sec with a wind velocity of 5 m/sec has been estimated to be 3.1 hours. A volatilization half-life from a lake 1 m deep, flowing 0.05 m/sec with a wind velocity of 0.5 m/sec has been calculated to be 5.15 days (BASF 2002b).

In the atmosphere, MDP is quickly degraded by photochemical attack (indirectly photodegraded by reaction with OH-radicals, half life = 4.5 h and by reaction with O₃, half-life = 4.8 h (calculated via AOP v1.51; BASF 1997). MDP is not expected to undergo rapid direct photolytical degradation in the hydrosphere because of the lack of a strong chromophore. A study on bioaccumulation indicates a low potential for bioaccumulation (BCF = 1.5 - 1.7; BASF 1982) and the calculated log K_{oc} of 0.19 a low potential for adsorption to soil (BASF 2001b).

2.2 Human Exposure

2.2.1 Occupational Exposure

As a result from the exclusive use of MDP as an intermediate in the production of glutaraldehyde, only few workers are handling MDP in a very limited number of work processes. Transportation of the chemical is controlled and limited to about 10 subsidiaries of the two manufacturers. Due to its physico-chemical properties, including a high volatility, and the control measures in place during manufacture, processing and transport, exposure may only occur in case of accidental spills with the inhalation and dermal routes being the only relevant routes of exposure. Regular workplace monitoring minimizes the risk of any unforeseen repeated exposures.

During manufacture and processing of MDP, worker exposure is controlled by the use of closed systems, industrial hygiene controls and personal protective equipment. Vapors and spills could theoretically escape from leaks in the piping system, during repair or replacement of the piping system (including tanks and reactors), or during removal of samples for quality control purposes. Prior to repair and maintenance work, vessels, pipes and other equipment is rinsed to remove any residual MDP. In the sponsor country, any risk of accumulation of MDP or its impurities is minimized by natural ventilation, as the chemical is produced in closed systems under conditions open to the environment. At processing sites, the exposure of workers is minimized by vapor abstraction.

Exposure could also theoretically occur during loading, unloading, and transportation of drums and/or tank trucks. However, dedicated systems designed to handle MDP are typically used for loading and unloading purposes and procedures should be in place to prevent spills or leaks during transportation. Drum filling stations are fully encapsulated and vapor abstraction is in place to minimize exposure.

At the production and processing sites, personal protective equipment, including gloves, face shields and safety goggles, has to be used by the workers, also with a view of protecting them against the low pH during processing. During repair and maintenance operations, and during drum emptying operations, respiratory protective equipment is used in addition.

43 exposure measurements at workplace (8 hour t_{wa}) have been performed at the production site at BASF AG, Ludwigshafen (Germany) between 1981 and 2002. By workplace the results were as follows:

- production: n = 31 (range <0.011 - 0.95 mg/m³)
- maintenance/repair: n = 4 (range: 0.047 - 2.5 mg/m³)
- laboratory: n = 7 (range: <0.011 - 0.014 mg/m³)

A value of 52 mg/m³ was also measured in the quality control laboratory. During this work, samples of about 5 ml MDP are handled 2 - 3 times/day under a hood. The air exchange rate of the hood is 100 times per hour (400 m³/h). Personal protective equipment is used (gloves, goggles, laboratory coat). Sampling was performed by personal air sampler. However, the value of 52 mg/m³ must be regarded as an outlier (most probably due to a contamination of the coat near to the personal sampling device). All other measurements in this laboratory were in the range < 0.011 – 0.014 mg/m³ (2.3 - 2.95 ppb) measured over several years, with the most recent value being < 0.0108 mg/m³ (January 2003). Though the reason for the outlier remains unclear it is unlikely that there was a relevant exposure of personnel when preparing minute quantities under the hood for GC quality control analysis.

Today, the filling station is fully encapsulated and vapors are abstracted. Therefore a formerly measured value of 32 mg/m³ in a non encapsulated filling station is outdated (BASF 2003d).

In a simulation of a drum-emptying operation (pumping MDP from a 200 l drum into a reaction vessel) under worst case conditions (32 °C; no ventilation; no personal protective equipment), a value of 36 mg/m³ was measured with a personal sampler over a 30 minutes period (BASF 2003f), confirming the importance of personal protective equipment and good ventilation techniques during these operations.

53 workplace measurements at the production and processing sites of DOW Chemical Company (production: 19, laboratory: 18, maintenance, loading/unloading: 16) between 1997 - 1999 show the following: exposure of operators was below 0.024 mg/m³ (10 ppb) with average exposure of 0.0048 mg/m³ (2 ppb), exposure during maintenance and in laboratory conditions was < 0.024 mg/m³ (< 10 ppb) with average exposure of 0.0024 mg/m³ (1 ppb), exposure during loading and unloading was < 0.024 mg/m³ (< 10 ppb; 8 hour twa) (DOW Chemical Company 2002).

The concentration of MDP in the end-use product, i.e. aqueous glutaraldehyde solutions is below the limit of detection (50 ppm; 0.005%). MDP could also not be detected in a disinfection product containing glutaraldehyde (limit of detection: 10 ppm = 0.001%; BASF 2003f). Exposure of workers to MDP through the use of glutaraldehyde containing products is therefore considered negligible.

2.2.2 Consumer Exposure

MDP is not known to occur in consumer products and is not listed in the product registers of Denmark, Finland, Norway, Sweden and Switzerland (2002).

MDP could not be detected in a disinfection product containing glutaraldehyde (limit of detection: 10 ppm; BASF 2003f).

Due to the lack of bioaccumulation, indirect exposure of the general public via the environment is not considered significant.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

3,4-Dihydro-2-methoxy-2H-pyran (MDP) has not been tested *in vivo*. MDP rapidly hydrolysed to glutaraldehyde and methanol in aqueous HCl at 37 °C and pH 2.5. From the data of the hydrolysis, the half-life of MDP was calculated to be 18.8 minutes under these conditions. In sodium phosphate buffer (50 mM; pH 7.4), no hydrolysis of the compound occurred for up to 4 hours (BASF AG 2000).

3.1.2 Acute Toxicity

The acute oral LD₅₀s in rats range between 1640 and 3740 mg MDP/kg bw, depending on whether the substance was administered in concentrated or diluted form. Clinical symptoms observed included staggering and unsteady gait, lachrymation, apathy, labored breathing, and narcosis (Dodd et al. 1988; BASF AG 1980; Union Carbide 1976, 1986, 1991a, 1991b). The oral LD₅₀ was between 200 and 500 mg/kg body weight in out bred rabbits with both pure and raw MDP. All animals survived 100 mg/kg body weight; 1/3 animals died at 200 mg/kg body weight, and all animals died at 500 and 1000 mg/kg body weight. Deaths occurred within 8 days after dosing at the low dose and within 24 hours at the high dose. Signs of liver injury were noted during necropsy of victims. These were, however, not confirmed in a specific study designed to examine effects on liver. Raw and pure MDP was given by oral gavage at a dose of 200 mg/kg body weight. Incidence of deaths was 1/3 animals with both test substances. Liver in victims was cadaverous and could not be examined. In the surviving animals sGPT (serum glutamate-pyruvate transaminase) and Bromosulphthalein (BST) retention were unchanged and within normal limits at 8 d and 14 d after dosing, and no pathological changes were seen at necropsy in livers from the sacrificed survivors (BASF, 1975).

The inhalation 1-hr-LC₅₀ for rats was determined to be between 8613 and 9076 ppm (40,820 - 43,014 mg/m³) in the absence of acrylaldehyde (acrolein). Signs of toxicity were lachrymation and hypoactivity. The high concentrations of the vapors caused transient irritation to the eyes and respiratory tract (Dodd et al. 1988; Union Carbide 1987). In a dynamic test, the 4-hr LC₅₀ in rat was > 1310 ppm (6000 mg/m³; purity 95 %). Only transient signs of ocular and respiratory irritancy were observed (BASF AG 1979).

The acute inhalation toxicity of MDP depends on the test conditions followed. Under test conditions where acrolein may accumulate, acrolein levels may reach lethal concentrations as was evidenced in acute inhalation toxicity tests using static atmospheres. Acute inhalation studies with dynamic atmospheres did not result in accumulation of acrolein and thus resulted in less toxicity (Dodd et al. 1988; Ballantyne et al. 1989). MDP 'per se' is of low acute inhalation toxicity.

The available inhalation studies showed that exposures to statically generated atmospheres of MDP cause marked signs, principally of an irritant nature, and mortality within a short period of exposure. Both signs and mortality were significantly reduced if MDP was sparged with an inert gas (N₂) before generation of the atmosphere. This suggested that a highly volatile component in MDP was responsible for signs and mortality, and was confirmed by the findings of the dynamic exposure conditions where no mortalities occurred. Under these conditions, highly volatile components will be present in proportion to their concentration in the sample, and thus present in small concentrations only in the vapor phase and not sufficient to cause toxicity. The material to

cause the effects observed was identified as acrolein, which in the static acute inhalation conditions was 240 ppm with the ordinary sample and < 5 ppm with the N₂-sparged sample. The 1hr-LC₅₀ for acrolein is 26 ppm, the 4-hr LC₅₀ is 8.3 ppm (Ballantyne et al. 1989).

The role of acrolein requires special attention because it markedly influenced inhalation toxicity under static test conditions. On one hand this was due to the markedly higher acrolein content (0.037 %) in the particular product tested in the 1980s (Dodd et al. 1988). On the other hand, this type of exposure is not relevant for the workplace under normal work conditions because the processes of production, transportation and hydrolysis are performed in closed systems. Moreover, natural and technical ventilation at the workplace prevents static conditions. The low odor threshold of acrolein (ca. 0.1 to 0.2 ppm) prevents prolonged and unintended acrolein exposure.

The dermal LD₅₀ in rabbits was 4920 mg/kg bw (Dodd et al. 1988; Union Carbide 1986, 1991a). Clinical signs were apathy and atony soon after dosing and 24 hrs thereafter, and labored breathing and emaciated appearance persisting up to 14 d. Skin irritation (erythema, edema, desquamation) was observed at the site of application.

A lower dermal LD₅₀ of 1260 mg/kg bw was observed when a total of 10 rats received 1000, 2000, or 4000 mg/kg bw in a range finding study. Unreported test substance purity, and low number of animals are the restrictions which largely invalidate this study. No signs of toxicity other than erythema, edema, and desquamation at the site of application were noted in treated animals at the end of the 14-d observation period (Union Carbide 1991c).

Conclusion

The oral LD₅₀ of MDP in rats was 1640 - 3740 mg/kg bw. Clinical symptoms observed included staggering and unsteady gait, lachrymation, apathy, labored breathing, and narcosis.

The 4-hr inhalation LC₅₀ in rat was > 1310 ppm (> 6000 mg/m³). Clinical signs observed were lachrymation and hypoactivity, with the high concentrations of the vapors causing transient irritation to the eyes and respiratory tract.

The dermal LD₅₀ in rabbits was 4920 mg/kg bw. Main clinical signs were local skin irritation, labored breathing.

3.1.3 Corrosiveness and irritation

Undiluted MDP (purity 99.1 %) was applied under occlusive conditions for 4 hours to the skin of rabbits. Well-defined erythema (grade 2 of the Draize scoring system) and moderate to severe edema (grade 3 - 4) were seen at the reading at 1 hour. Erythema became more marked overnight and persisted for two days. Edema started to resolve at day 2, and both erythema and edema were absent on day 7. Desquamation was first seen at day 2 and persisted until the end of the observation period on day 7. No animal showed necrosis or ulceration (Dodd et al. 1988; Union Carbide 1991a, 1986).

Under conditions equivalent to the requirements of OECD TG 405, MDP (purity 99.1 %) caused mild to moderate conjunctivitis within 1 hour after instillation. Chemosis and discharge began to subside at 24 hours and disappeared by 48 hours. Erythema started to resolve at 2 days, with only 1/6 animal showing a mild effect still at day 3. Mild iritis was seen in 5/6 animals at 1 and 4 hours after instillation, but was completely reversible by the next day. No corneal injury was found (Union Carbide 1991a). With test material of lesser purity (< 96 %), large size corneal opacity was seen in 3 of 6 animals at day 7 after instillation (BASF AG 1980).

Conclusion

Undiluted MDP was irritating to rabbit skin and eyes. In acute toxicity studies (see 3.1.2) high concentrations of vapors were also irritating to the eyes and the respiratory tract.

3.1.4 Sensitisation

No reliable studies are available pertaining to the sensitizing properties of MDP.

Conclusion

No adequate data available.

3.1.5 Repeated Dose Toxicity

Oral

No oral toxicity study is known to exist for MDP.

Inhalation

As described in the section on acute inhalation toxicity, depending on the atmosphere generation methods, acrolein may interfere with the study results. Therefore the atmosphere concentration of acrolein must be considered during the assessment of the MDP inhalation studies.

Exposure to 4358 ppm MDP (20,640 mg/m³; 9 days, 6 hrs/d) killed 100 % of the rats on the first day. However, the concentration of acrolein in the test atmosphere was 7.8 ppm, which is approximately the LC₅₀ (4 hrs, rat) of acrolein (Ballantyne et al. 1989). Thus, it must be assumed that the animals died from acrolein rather than from MDP. In a 14-day study, 9 exposures at 100 ppm MDP (= 480 mg/m³; < 2 ppm acrolein) caused edema in nasal cavities, mild squamous metaplasia in the respiratory mucosa, and reduced body weight gains. At 984 ppm (= 4660 mg/m³; 3.3 ppm acrolein) the effects on body weight and the respiratory tract were more pronounced (atrophy of the olfactory epithelium, squamous metaplasia of the epithelium of the nasal cavity, trachea and larynx, mucosal cell hyperplasia in some tracheae) (Union Carbide 1993c).

The respiratory tract was also a target organ in mice exposed to MDP (acrolein content < 3 ppm) on 5 consecutive days, 6 hrs/day. Absolute and relative spleen weights were decreased and absolute and relative lung weights were increased in the 50 and 100 ppm groups (240, 480 mg/m³). The epithelium of the respiratory tract from the nasal cavity down to the bronchi/bronchioles was necrotic with occasional ulceration and inflammation resulting from the necrosis. Clinical signs during exposure at concentrations ≥ 10 ppm (48 mg/m³) were hypoactivity, at ≥ 25 ppm (120 mg/m³) lack of startle reflex, and at ≥ 50 ppm (240 mg/m³) spasms of the lids and abdominal breathing. Mortality was 10 % each at 25 and 50 ppm, 60 % at 100 ppm, and 90% at 500 ppm; body weights were reduced at ≥ 25 ppm. At ≥ 5 ppm (24 mg/m³) slight yet non-significant signs of cytotoxicity in bone marrow cells could be demonstrated, which became significant at 50 ppm. Only spleen, respiratory tract and lungs were investigated by light-microscopy (Union Carbide 1995a, b).

Dermal

No 21- or 28-d dermal study according to OECD TG 410 is available. In a 14-day study on rats with 9 exposures, no effect of MDP treatment (purity 99.8 %) on water consumption, hematology, clinical chemistry, and urinalysis was seen up to and including the highest tested dose of 1000 mg MDP/kg bw/day. Food consumption and body weights were slightly reduced in male and female animals receiving 500 and 1000 mg/kg bw/day at the end of the treatment period (body weights

reduced by 8.8 %; 6.4 % in males; 4.1 %; 3.1 % in females in mid-and high dose groups, respectively). Statistical significance was only given in high dose males during scattered days without consistent relation to dose. Therefore these changes were not considered to be relevant. No skin irritation was noted in animals receiving 100 and 500 mg/kg bw/day. Animals at 1000 mg/kg bw/day showed slight erythema and slight desquamation notably during days 5 through 9, but the effect was completely resolved within few days in both genders. A slight, but statistically significant 7.7 % increase in relative liver weight was noted in high dose males. The increase was reversible within the recovery period, and it was not correlated with changes in liver enzyme activities or macroscopical findings. Therefore these findings were not regarded to be of biological significance. The highest tested dose of 1000 mg/kg bw/day was identified as the NOAEL for systemic toxicity (Union Carbide 1999). The lower degree of skin irritation in this (dermal toxicity) study when compared to the acute skin irritation study in rabbits is likely due to the very high sensitivity of rabbit skin to irritants and the 10-fold lower dose per square centimeter at the top dose in the repeated dose study.

Conclusion

No oral toxicity data for this compound is available. Due to its physico-chemical properties, its use as intermediate in closed systems, and regular monitoring of workplaces, repeated exposure via the oral route is unlikely.

In rodents, the main effects following repeated inhalation exposure to MDP were reduced body weights, sedation, and irritant effects on the respiratory tract. Toxicity may be largely influenced by the presence of impurities (acrolein) during static atmosphere generation. The results from the available repeated inhalation studies did not permit the establishment of a NOAEC, since reductions in body weights and signs of respiratory irritation were still present at the lowest tested concentrations in the rat (LOAEC: 100 ppm = 480 mg/m³). In mice, bone marrow cytotoxicity of questionable biological significance was still seen at 5 ppm (LOAEC, 5d: 5 ppm = 24 mg/m³).

No systemic effects were found up to and including the highest tested dose level of 1000 mg/kg bw/day in a dermal study on rats, limited by its short duration of only 14 days.

3.1.6 Genetic Toxicity

In vitro Studies

In an Ames test according to OECD 471 MDP (purity > 99.9 %) was mutagenic in TA 100 only in the presence of S-9 mix from Aroclor 1254 induced rats (BASF AG 1989). In TA 100, the numbers of revertants were dose-dependently increased 1.8 - 2.7-fold in the range 500 to 2500 µg/plate in two independent experiments, and 4.3-fold at 7500 µg/plate. No cytotoxic effects were noted.

In another Ames test with MDP (purity 99.4 %), increased numbers of revertants were obtained with TA 100, both in the absence (2- to 3-fold in the range 300 to 1000 µg/plate) and in the presence (3.5- to 4-fold at 1000 µg/plate) of S-9 mix from Aroclor 1254 induced rats. An apparently dose-related increase in revertants was also seen in TA 98 (2- to 3.3-fold at 1000 and 3000 µg/plate) in the presence of liver S-9 mix. No effect was noted in TA 98 in the absence of S-9 mix (Union Carbide 1993a, 1993b). The substance was cytotoxic at the highest concentration 3000 µg/plate.

MDP was not mutagenic in the HPRT assay with CHO cells, both with and without S-9 mix from Aroclor 1254 induced rats (Union Carbide 1994). The test substance was tested in the range 50 to 2,000 µg/ml. Scattered positive results were not reproducible and showed no dose-relation. Cytotoxicity was seen at 250 µg/ml and above both with and without S-9 mix.

Positive results were obtained in another HPRT assay using V79 Chinese Hamster cells where MDP (purity > 99.9 %) was tested in the range between 50 and 5000 µg/ml (Merck 1997). No increase was seen in the presence of S-9 mix from Aroclor 1254 induced rats. In the absence of S-9 mix, a slight increase was seen at 2810 (2.07 fold) and 5000 µg/ml, i.e. at dose levels, which led to precipitations and cytotoxic effects.

In vivo Studies

In a micronucleus test performed with MDP (purity > 99.9 %) in accordance with OECD guideline 474 under GLP conditions in mice, dosed by gavage with 250, 500 and 1000 mg/kg bw, MDP did not induce micronuclei in bone marrow at any dose level or any harvesting time used in this study (harvesting of cells: 16, 24 and 48 hours after the end of exposure). MDP was considered non-clastogenic and non-aneugenic in this assay. The mean number of normochromatic erythrocytes was not increased after treatment with the test substance as compared to the controls, indicating that MDP had no cytotoxic effect on the bone marrow, but there were clear clinical signs of toxicity at all dose-levels tested (irregular respiration at 250 mg/kg, staggering, squatting posture at 500 mg/kg; gasping, abdominal position, eyelid closure, apathy at 1000 mg/kg). Mortalities had been seen at 1210 mg/kg in the pre-study whereas 1000 mg/kg were survived. The positive control substance induced a distinct increase of micronuclei (BASF 1993b).

MDP was equally negative in a second micronucleus test performed with MDP (purity > 99.9 %) in mice repeatedly dosed for 5 days by inhalation with 5, 10, and 25 ppm (approx. 24, 48, and 120 mg/m³) for 6 hours per day. MDP did not induce micronuclei in peripheral blood polychromatic erythrocytes at any dose level or at any harvesting time used in this study (harvesting of cells: 24 and 48 hours after the end of exposure). MDP was considered non-clastogenic and non-aneugenic in this assay. The mean number of polychromatic erythrocytes was decreased after treatment with the test substance at all dose levels as compared to the controls, indicating that MDP had effects on the bone marrow (Union Carbide 1995a, 1995b).

Conclusion

In vitro MDP was mutagenic in bacterial test systems with *Salmonella typhimurium* TA 100 and TA98, predominantly in the presence of S-9 mix, and mammalian cells (HPRT test).

In two *in vivo* studies, both of which performed in accordance with contemporary requirements, MDP (purity > 99.9 %) did not induce micronuclei in bone marrow red blood cells in mice dosed by the oral route or in peripheral blood cells in mice dosed repeatedly by inhalation and including toxic dose levels.

3.1.7 Carcinogenicity

No studies concerning the long-term toxicity and/or carcinogenic potential of MDP are available.

3.1.8 Toxicity for Reproduction

There is no experimental data for MDP available for this endpoint. Since exposure is anticipated to be very low due to its sole use as chemical intermediate with controlled transport to a limited number of locations and because acute and repeated dose toxicity studies are available for the most relevant routes of accidental exposure (inhalation, dermal), no animal tests were performed for this endpoint.

3.1.9 Developmental Toxicity / Teratogenicity

There is no experimental data for MDP available for developmental toxicity/ teratogenicity. Since exposure is anticipated to be very low due to its sole use as chemical intermediate with controlled transport to a limited number of locations and because acute and repeated dose toxicity studies are available for the most relevant routes of accidental exposure (inhalation, dermal), no animal tests were performed for this endpoint.

3.1.10 Experience with Human Exposure

No other information is available than that described in the human exposure chapter. No accidental exposure is known. No epidemiological data is available.

3.2 Initial Assessment for Human Health

MDP is produced in closed systems, and is solely used as a chemical intermediate with controlled transport to about 10 subsidiaries of the two producers. Occupational exposure is controlled and may only occur in case of accidental spills during manufacture, transportation or processing, with the most likely routes of exposure then being the inhalation and dermal routes. Worker exposure is limited by technical measures such as closed systems, industrial hygiene controls and personal protective measures. Workplace measurements showed that average exposures during manufacture, processing, maintenance and loading/unloading operations are very low.

MDP is not known to occur in consumer products.

The acute oral LD₅₀ of MDP in rats was 1640 - 3740 mg/kg bw. Clinical symptoms observed included staggering and unsteady gait, lachrymation, apathy, labored breathing, and narcosis.

The 4-hr inhalation LC₅₀ in rat was > 1310 ppm (> 6000 mg/m³) with transient signs of ocular and respiratory irritation. The dermal LD₅₀ in rabbits was 4920 mg/kg bw.

Toxicity of the technical product may be influenced by impurities such as acrolein.

Undiluted MDP was irritating to rabbit skin and eyes. In acute toxicity studies high concentrations of vapors were also irritating to the eyes and the respiratory tract.

No adequate sensitization study is available.

The main effects following repeated inhalation exposure to MDP in rodents were reduced body weights, sedation, and irritant effects on the respiratory tract. Toxicity may be largely influenced by the presence of toxic impurities, predominantly the highly toxic and irritant acrolein. The results from a limited 14-day repeated inhalation study did not permit the establishment of a NOAEC, since reductions in body weights and signs of respiratory irritation were still present at the lowest tested concentration in the rat (LOAEC: 100 ppm = 480 mg/m³). In mice, bone marrow cytotoxicity of questionable biological significance was still seen at 5 ppm (LOAEC, 5d: 5 ppm = 24 mg/m³). No systemic effects were found up to and including the highest tested dose level of 1000 mg/kg bw/day in a dermal study on rats, limited by its duration of only 14 days.

In vitro MDP was mutagenic in bacterial test systems with *Salmonella typhimurium* TA 100 and TA98, predominantly in the presence of S-9 mix, and in mammalian cell systems (HPRT test). In two *in vivo* studies, both of which performed in accordance with contemporary requirements, MDP (purity > 99.9 %) was not clastogenic in mice dosed by the oral route or repeatedly via inhalation.

There are no experimental data for MDP available for reproduction and developmental toxicity. Since exposure is anticipated to be very low due to its sole use as chemical intermediate with

controlled transport to a limited number of locations and because acute and repeated dose toxicity studies are available for the most relevant routes of accidental exposure (inhalation, dermal), no animal tests were performed for this endpoint.

No studies concerning the long-term toxicity and/or carcinogenic potential of MDP have been conducted.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Acute Toxicity Test Results

Fish

In a test following Jap. Industrial Standard (JIS) K 0102 Item 55 with *Oryzias latipes* (fresh-water) 6 concentrations, from 147 – 1000 mg/l (nominal) plus control, were tested in unsealed fish tanks. An LC₅₀ (96 h) of ca. 730 mg/l was calculated (BASF AG 1981).

Since no substance specific concentration control analysis was performed, the effect value was related to nominal concentrations. But, due to the vapour pressure of 3,4-Dihydro-2-methoxy-2H-pyran, evaporation from the open test system was likely to have occurred.

To verify this, the volatility was measured under comparable test conditions, but without fish. In the test for volatility, based on MDP-measurements, a recovery rate of 31.7 % (geometric mean of all measured values at test start and after 96 h) was found after 96 h (BASF AG 2003c; Weyers 2003).

An LC₅₀ (96 h) of approximately 232 mg/l could be estimated on the basis of the nominal LC₅₀ (96 h)-value from the acute toxicity test and the recovery rate from the volatility screening test.

Invertebrates

A test on aquatic toxicity to *Daphnia magna* according to OECD 202 was performed, comparing the aquatic toxicity to the invertebrates in both closed and open test systems (BASF AG 2003e).

3 concentrations, of 25 - 100 mg/l (nominal) plus control, were tested in unsealed test tubes and 4 concentrations, from 12.5 – 100 mg/l (nominal) plus control were tested in closed vials.

In the closed system, no immobility was recorded up to the highest test concentration of 100 mg/l, thus the EC₅₀ is > 100 mg/l. Measured concentrations of MDP remained > 90 % of the nominal values throughout the test.

The same result (no immobility) was obtained from the open test system. The test concentration dropped from > 90 % at the start to 21 % after 48 h. The geometric mean of all measured values was 45.5 % of the nominal concentrations (Weyers 2003).

A test following Directive 79/831/EEC, C2 with *Daphnia magna* with 5 nominal concentrations ranging from 31.25 – 500 mg/l, resulted in an EC₅₀ (48 h, immobilisation) of 177 mg/l (nominal concentration) (BASF AG 1988a).

Since the test was performed in unsealed tubes, evaporation from the test system could not be excluded.

An EC₅₀ (48 h) of approximately 81 mg/l could be estimated on the basis of the nominal EC₅₀ (48 h)-value from the acute toxicity test and the geometric mean (45.5 % of nominal concentrations) in the above mentioned *Daphnia* test.

In addition, the volatility of MDP was measured in a test under comparable conditions but without daphnids. Based on TOC measurements a recovery rate of 59.8 % was found after 48 h (geometric mean of all measured values) (BASF AG 2002d; Weyers 2003). With this recovery rate an EC₅₀ (48 h) of approximately 106 mg/l could be estimated. As a test in a closed system with analytical monitoring is available that take precedent over the data obtained in open systems corrected for volatility, the estimated EC₅₀-values are not used for the further effects assessment.

With QSAR estimations (ECOSAR), for daphnia a EC₅₀ (48 h) of 116 mg/l can be obtained providing good support for the experimentally determined data (BASF AG 2002b).

Algae

Acute Toxicity to *Scenedesmus subspicatus* was determined in unsealed flasks in a study, following DIN 38 412 part 9, with 5 nominal concentrations ranging from 31.25 – 500 mg/l. The highest concentration tested did not inhibit growth by 50 %. Therefore, the EC₅₀ (72 h) for the cell density (fluorescence at 685 nm as a size for the biomass) was > 500 mg/l (nominal concentration; BASF AG 1988b).

Again, due to the vapour pressure of 3,4-Dihydro-2-methoxy-2H-pyran, evaporation from the open test system was likely to have occurred.

To verify this, the volatility was measured under comparable test conditions, but without algae. In the test for volatility, based on TOC-measurements, a recovery rate of 33 % was found over 72 h (geometric mean of all measured values) (BASF AG 2002d; Weyers 2003).

An EC₅₀ (72 h) of >165 mg/l could be calculated taking into account the nominal EC₅₀ (72 h)-value from the acute toxicity test and the recovery rate from the volatility screening test.

With QSAR estimations (ECOSAR), for green algae a EC₅₀ (96 h) of 116 mg/l was obtained providing good support for the estimates from recovery data (BASF AG 2002b).

Chronic Toxicity Test Results

No chronic aquatic toxicity data was available.

4.2 Terrestrial Effects

There are no data available on terrestrial organisms.

4.3 Other Environmental Effects

Micro-organisms

Acute Toxicity to *Pseudomonas putida* was determined in a study, following DIN 38 412 part 8, with 8 nominal concentrations ranging from 156.25 – 10,000 mg/l. An EC₅₀ (17 h) of 5991.4 mg/l was calculated (BASF AG 1988c).

The inhibition of the respiration of activated sludge (industrial) was measured, following OECD 209, with three nominal concentrations (150, 750, 1950 mg/l). The EC₂₀ (30 min) was > 1950 mg/l (nominal concentration; BASF AG 1984).

4.4 Initial Assessment for the Environment

Under OECD 301 F test conditions (manometric respirometric test) 3,4-dihydro-2-methoxy-2H-pyran turned out to be not readily biodegradable (0 % after 28 days). A valid test on inherent biodegradation is not available.

According to the model SIMPLETREAT 3.0 65 % of 3,4-dihydro-2-methoxy-2H-pyran will be emitted via the effluent of sewage treatment plants and approx. 35 % will be distributed to the air. But based on monitoring data, the elimination from the industrial waste water treatment plant at BASF was shown to be much higher (about 60 %).

Distribution modelling estimates air and to a minor degree water to be the main target compartments. MDP in surface water will be subject to rapid volatilization, considering an Henry's law constant of 31.2 Pa·m³/mol. A half-life for volatilization from rivers has been estimated to be 3.1 hours, respectively 5.15 days from lakes. Hydrolysis at environmental pH conditions is not expected to be a relevant degradation process. After evaporation to the air, the product will be rapidly degraded by photochemical processes ($t_{1/2} = 4.5$ h, reaction with OH radicals; $t_{1/2} = 4.8$ h, reaction with ozone). A study on bioaccumulation with fish indicates a low potential for bioaccumulation (BCF = 1.5 - 1.7). Due to the low log K_{oc} value of 0.19 adsorption to solid phase is not expected.

The following aquatic effect concentrations are available from tests performed in unsealed test systems, but corrected for losses due to volatility:

Oryzias latipes (fresh water): LC₅₀ (96 h) = approx. 232 mg/l; *Daphnia magna*: EC₅₀ (48 h) = 81 - 106 mg/l; *Scenedesmus subspicatus*: EC₅₀ (72 h) = >165 mg/l.

The low aquatic toxicity of MDP could be confirmed in an acute toxicity test to *Daphnia magna* in a closed system. Based on measured values an EC₅₀ (48 h) of > 100 mg/l was determined (no effects at 100 mg/l).

QSAR estimations (ECOSAR) give the following effect values: daphnia: LC₅₀ (48 h) = 116 mg/l; green algae EC₅₀ (96 h) = 116 mg/l (BASF AG 2002b).

The most sensitive aquatic organism in an acute aquatic ecotoxicity test was *Daphnia magna* with an EC₅₀ (48 h) of >100 mg/l (effective concentration). Applying an assessment factor of 1000 according to the EU Technical Guidance Document, a PNEC_{aqua} of 100 µg/l can be derived.

5 RECOMMENDATIONS

Environment:

The chemical is currently of low priority for further work because of its low hazard potential.

Human Health:

The SIDS data requirement for reproductive toxicity is not fulfilled and the repeated dose toxicity studies are limited, but full studies were not demanded due to very limited and controlled occupational exposure at sites of the two producers.

MDP possesses properties indicating a hazard for human health (irritant effects on skin, eye and respiratory system, potential genotoxicity). Exposure to humans is anticipated to be low, because exposure in occupational settings is well controlled by the two producers and because there is no consumer exposure. Therefore this chemical is currently of low priority for further work.

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I U C L I D

D a t a S e t

Existing Chemical ID: 4454-05-1
CAS No. 4454-05-1
EINECS Name 3,4-dihydro-2-methoxy-2H-pyran
EC No. 224-698-3
Molecular Formula C6H10O2

Producer Related Part
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Creation date: 12-NOV-1992

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Flag: Critical study for SIDS endpoint
06-NOV-2002

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Flag: Critical study for SIDS endpoint
06-NOV-2002

1.0.2 Location of Production Site, Importer or Formulator**1.0.3 Identity of Recipients****1.0.4 Details on Category/Template****1.1.0 Substance Identification**

Mol. Formula: C6 H10 O2
Mol. Weight: 114.142 g/mol

Flag: non confidential, Critical study for SIDS endpoint
08-MAY-2002

1.1.1 General Substance Information

Substance type: organic
Physical status: liquid
Purity: >= 99.5 % w/w
Colour: colourless-yellow
Odour: ether-like

Method: GC
Flag: non confidential, Critical study for SIDS endpoint
14-JAN-2003 (1)

1.1.2 Spectra

1.2 Synonyms and Tradenames

2,3-Dihydro-2-methoxy-4H-pyran

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

2-Methoxy-2,3-dihydro-4H-pyran

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

2-Methoxy-3,4-dihydropyran

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

2H-Pyran, 3,4-dihydro-2-methoxy- (7CI, 8CI, 9CI)

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

3,4-Dihydro-2-methoxy-2H-pyran

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

3,4-Dihydro-2-methoxypyran

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

1.3 Impurities

CAS-No: 111-30-8

EC-No: 203-856-5

EINECS-Name: glutaral

Mol. Formula: C5 H8 O2

Remark: Due to the conditions prevailing at the production process (high pH, low water content), the presence of glutaraldehyde in MDP is very improbable.

Routine analysis carried out for quality control of MDP, would detect glutaraldehyde > 100 ppm; during such analyses however, glutaraldehyde has not been detected so far.

Flag: non confidential, Critical study for SIDS endpoint
14-OCT-2003 (2)

1. GENERAL INFORMATION

SUBSTANCE ID: 4454-05-1

DATE: 16-OCT-2003

CAS-No: 7732-18-5
EC-No: 231-791-2
EINECS-Name: water
Mol. Formula: H₂O
Contents: <= .2 % w/w

Method: GC
Flag: non confidential, Critical study for SIDS endpoint
14-JAN-2003 (1)

CAS-No: 67-56-1
EC-No: 200-659-6
EINECS-Name: methanol
Mol. Formula: CH₄O
Contents: < .2 % w/w

Method: GC
Flag: non confidential, Critical study for SIDS endpoint
14-JAN-2003 (1)

Purity type: measured for specific batch
CAS-No: 107-02-8
EC-No: 203-453-4
EINECS-Name: acrylaldehyde
Mol. Formula: C₃ H₄ O
Contents: = .037 - % w/w

Remark: The value applies to conditions given in previous times. To date the concentration of acrolein in MDP is below the limit of detection.
Flag: non confidential, Critical study for SIDS endpoint
19-FEB-2003 (3)

Purity type: measured for specific batch
CAS-No: 107-02-8
EC-No: 203-453-4
EINECS-Name: acrylaldehyde
Mol. Formula: C₃ H₄ O
Contents: < .01 - % w/w

Remark: The value represents current conditions.
Flag: non confidential, Critical study for SIDS endpoint
19-FEB-2003 (4)

1.4 Additives1.5 Total Quantity

Remark: quantity produced:
> 1000 t/a (year 2000) in Germany

There are only two major producers worldwide:
BASF AG in Germany and DOW Chemical Company in USA.

estimated world production: 10.000 - 25.000 t/a (year 2000)
Flag: Critical study for SIDS endpoint
14-JAN-2003

1.6.1 Labelling

Labelling: provisionally by manufacturer/importer
Symbols: (Xi) irritating
R-Phrases: (10) Flammable
(36) Irritating to eyes
S-Phrases: (23) Do not breathe vapour

Flag: non confidential, Critical study for SIDS endpoint
13-FEB-2003 (5)

1.6.2 Classification

Classified: provisionally by manufacturer/importer
Class of danger: flammable
R-Phrases: (10) Flammable

Flag: non confidential, Critical study for SIDS endpoint
13-FEB-2003 (5)

Classified: provisionally by manufacturer/importer
Class of danger: irritating
R-Phrases: (36) Irritating to eyes

Flag: non confidential, Critical study for SIDS endpoint
13-FEB-2003 (5)

1.6.3 Packaging

1.7 Use Pattern

Type: type
Category: Non dispersive use

Flag: non confidential, Critical study for SIDS endpoint
10-MAR-1994

Type: industrial
Category: Chemical industry: used in synthesis

Remark: Recommended use: initial product for chemical syntheses
Flag: non confidential, Critical study for SIDS endpoint
13-FEB-2003 (5)

1.7.1 Detailed Use Pattern

1.7.2 Methods of Manufacture

Orig. of Subst.: Synthesis
Type: Production

Remark: Acrolein behaves as a 1,3-diene in reactions with dienophiles in which the electron density of the carbon-carbon double bond is increased by electron-releasing substituents. Vinyl ethers and vinylamines react readily with acrolein to form dihydropyrans. The reaction of methyl vinyl ether and acrolein to form 3,4-dihydro-2-methoxy-2H-pyran is a commercially important example. At a reaction temperature of 160-190°C, reported yields are 80-90%.

Flag: non confidential, Critical study for SIDS endpoint
14-JAN-2003 (6)

1.8 Regulatory Measures**1.8.1 Occupational Exposure Limit Values**

Type of limit: MAK (DE)
Limit value: other: not listed in the MAK- and BAT-value list

Flag: non confidential, Critical study for SIDS endpoint
09-DEC-2002 (7)

1.8.2 Acceptable Residues Levels**1.8.3 Water Pollution**

Classified by: other: VwVwS (Germany), Annex 2
Labelled by: other: VwVwS (Germany), Annex 2
Class of danger: 1 (weakly water polluting)

Remark: ID-Number: 1413
Flag: non confidential, Critical study for SIDS endpoint
14-JAN-2003 (8)

1.8.4 Major Accident Hazards**1.8.5 Air Pollution****1.8.6 Listings e.g. Chemical Inventories**

Type: TSCA

Flag: non confidential, Critical study for SIDS endpoint
29-OCT-2001 (9)

Type: DSL

Flag: non confidential, Critical study for SIDS endpoint
29-OCT-2001 (9)

Type: PICCS

Flag: non confidential, Critical study for SIDS endpoint
29-OCT-2001 (9)

Type: ENCS
Additional Info: ENCS-No. 5-5581

Flag: non confidential, Critical study for SIDS endpoint
19-FEB-2002 (9)

Type: EINECS
Additional Info: EINECS No. 224-698-3

Flag: non confidential, Critical study for SIDS endpoint
19-FEB-2002 (9)

Type: ECL
Additional Info: ECL Serial No. KE-23253

Flag: non confidential, Critical study for SIDS endpoint
19-FEB-2002 (9)

Additional Info: SWISS No. G-5953

Flag: non confidential, Critical study for SIDS endpoint
19-FEB-2002 (9)

1.9.1 Degradation/Transformation Products**1.9.2 Components****1.10 Source of Exposure****1.11 Additional Remarks**

Memo: German "Flammable Liquids" classification (VbF): AII

Flag: non confidential, Critical study for SIDS endpoint
12-NOV-2001 (5)

Memo: No hazardous reactions when stored and handled according to instructions.

Flag: non confidential, Critical study for SIDS endpoint
13-FEB-2003 (5)

1.12 Last Literature Search

Type of Search: Internal and External

Chapters covered: 3, 4

Date of Search: 21-JAN-2003

Remark: update 2003, no new data found

Flag: Critical study for SIDS endpoint

24-JAN-2003

Type of Search: External

Chapters covered: 5

Date of Search: 15-NOV-2001

Flag: Critical study for SIDS endpoint

10-DEC-2002

Type of Search: Internal

Chapters covered: 3, 4

Date of Search: 05-APR-2000

Flag: Critical study for SIDS endpoint

10-DEC-2002

Type of Search: Internal

Chapters covered: 5

Date of Search: 05-APR-2000

Flag: Critical study for SIDS endpoint

10-DEC-2002

Chapters covered: 1

Date of Search: 14-JAN-2003

Flag: Critical study for SIDS endpoint

14-JAN-2003

Chapters covered: 8

Date of Search: 14-JAN-2003

Flag: Critical study for SIDS endpoint

14-JAN-2003

Type of Search: Internal and External

Chapters covered: 5.10

Date of Search: 14-NOV-2002

07-FEB-2003

1.13 Reviews

2.1 Melting Point

Value: < -60 degree C

Remark: reason for flagging this data: only value available on this endpoint

Reliability: (4) not assignable
manufacturer/producer data without proof (original report not available)

Flag: Critical study for SIDS endpoint
19-FEB-2002 (5)

2.2 Boiling Point

Value: = 126 degree C

Reliability: (4) not assignable
manufacturer/producer data without proof (original report not available)

14-NOV-2001 (5)

Value: 127.1 degree C at 1013.25 hPa

Decomposition: no

Method: other: dynamic (argon atmosphere); test procedure according to an internal BASF standard, comparable to OECD 104

GLP: no

Test substance: as prescribed by 1.1 - 1.4

Method: The Normal Boiling Temperature was obtained by intrapolation from the vapour pressure curve.

Remark: reason for flagging this study: intrapolation based on measured data

Test substance: 3,4-dihydro-2-methoxy-2H-pyran, purity 99.8 %

Reliability: (2) valid with restrictions
scientifically acceptable method

Flag: Critical study for SIDS endpoint
10-JAN-2003 (10)

2.3 Density

Type: density

Value: = 1 g/cm³ at 20 degree C

Reliability: (4) not assignable
manufacturer/producer data without proof (original report not available)

14-NOV-2001 (5)

Type: density

Value: = 1.0004 g/cm³ at 20 degree C

Method: other: German Industrial Standard DIN 51 757 (25 cm³ glas pycnometer, multiple determination)

GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: reason for flagging this data: most reliable data available on this parameter

Result:

temperature (°C)	density (kg/m3)
20.0	1000.4
40.0	979.5
60.0	958.6
80.0	936.5
100.0	914.5

Test condition: measured range: 20.0 to 100.0 degree C, average deviation: 0.01 %

Test substance: 3,4-dihydro-2-methoxy-2H-pyran, purity 99.95 %

Reliability: (2) valid with restrictions
test procedure following National Standard

Flag: Critical study for SIDS endpoint

14-JAN-2003 (11)

2.3.1 Granulometry2.4 Vapour Pressure

Value: 13 hPa at 20 degree C

Reliability: (4) not assignable
manufacturer/producer data without proof (original report not available)

18-FEB-2002 (5)

Value: = 20 hPa at 28 degree C

Decomposition: no

Method: other (measured): dynamic (argon atmosphere); test procedure according to an internal BASF standard, comparable to OECD 104

GLP: no

Test substance: as prescribed by 1.1 - 1.4

Remark: reason for flagging this data: experimentally derived data

Result:

temperature (°C)	vapour pressure (hPa)
28.04	20.00
35.50	30.00
45.57	50.00
52.70	70.00
60.62	100.0
77.52	200.0
88.63	300.0
103.48	500.0
114.27	700.0
126.48	1000.0
129.96	1102
155.39	2101
171.60	3013
197.21	5002
214.7	7050

2.6.1 Solubility in different media

Solubility in: Water
Value: = 13 g/l at 30 degree C
pH value: 7 - 8
Conc.: 5 g/l at 20 degree C

Remark: reason for flagging this information: only value available on this parameter [pH value of an aqueous solution]
Reliability: (4) not assignable
 manufacturer/producer data without proof (original report not available)
Flag: Critical study for SIDS endpoint
 14-JAN-2003 (5)

Solubility in: Water
Value: = 1.527 other: weight% at 30 degree C

Method: other: titration to the point of turbidity; test procedure according to an internal BASF standard
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: ca. 15.27 g/l at 30 °C
Result: temperature (°C) water solubility (weight%)
 30 1.527
 50 1.379
 60 1.670
 70 2.806
 72.4 4.317
 75.6 7.080

Test substance: 3,4-dihydro-2-methoxy-2H-pyran, purity 99.64 weight%
Reliability: (2) valid with restrictions
 scientifically acceptable method
 14-JAN-2003 (13)

Solubility in: Water
Value: 16 g/l at 25 degree C

Method: other: test procedure according to an internal BASF standard, comparable to OECD 105
GLP: no
Test substance: other TS
Stable: yes

Method: gas chromatographic determination of 3,4-dihydro-2-methoxy-2H-pyran in the saturated aqueous solution

Remark: mean value of 3 determinations each of 3 solutions
 reason for flagging this study: experimentally derived data
Test substance: 3,4-dihydro-2-methoxy-2H-pyran, purity 98.8 %
Reliability: (2) valid with restrictions
 study meets generally accepted scientific principles
Flag: Critical study for SIDS endpoint
 14-JAN-2003 (12)

2.6.2 Surface Tension

2.7 Flash Point

Value: 22.8 degree C
Type: closed cup

Method: other: DIN 51 755

Remark: reason for flagging this data: only information available on this parameter

Reliability: (4) not assignable
manufacturer/producer data without proof (original report not available)

Flag: Critical study for SIDS endpoint
14-NOV-2001 (5)

2.8 Auto Flammability

Value: 210 degree C

Method: other: DIN 51 794

Remark: Ignition temperature
reason for flagging this study: only information available on this parameter

Reliability: (4) not assignable
manufacturer/producer data without proof (original reference not available)

Flag: Critical study for SIDS endpoint
14-NOV-2001 (5)

2.9 Flammability

Result: flammable

Remark: reason for flagging this information: only information available on this parameter

Reliability: (4) not assignable
manufacturer/producer data without proof (original report not available)

Flag: Critical study for SIDS endpoint
14-NOV-2001 (5)

2.10 Explosive Properties

Result: not explosive

Remark: not explosive due to the chemical structure
reason for flagging this data: only information available on this parameter

Reliability: (2) valid with restrictions
expert judgement

Flag: Critical study for SIDS endpoint
19-FEB-2002 (14)

2.11 Oxidizing Properties

Result: no oxidizing properties

Remark: no oxidizing properties due to the chemical structure
reason for flagging this data: only information available on
this parameter

Reliability: (2) valid with restrictions
expert judgement

Flag: Critical study for SIDS endpoint
25-JUN-2001 (14)

2.12 Dissociation Constant**2.13 Viscosity**

Value: = 1.11 mPa s (dynamic) at 20 degree C

Method: other: measured: German Industrial Standard DIN 51 562
GLP: no

Test substance: as prescribed by 1.1 - 1.4

Remark: reason for flagging this information: experimentally derived
data

Result:	temperature (°C)	viscosity (mPa.s)
	20	1.11
	50	0.73
	80	0.52
	100	0.41
	120	0.35

Test substance: 3,4-dihydro-2-methoxy-2H-pyran, purity 99.9 %

Reliability: (2) valid with restrictions
test procedure following National Standard

Flag: Critical study for SIDS endpoint
14-JAN-2003 (15)

2.14 Additional Remarks

Remark: Explosion limits: 1 - 7.6 vol.-%
reason for flagging this information: important information on
this endpoint

Reliability: (4) not assignable
manufacturer/producer data without proof (original report not
available)

Flag: Critical study for SIDS endpoint
10-JUL-2000 (5)

3.1.1 Photodegradation

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: O3

Method: other (calculated): AOP v1.9

Remark: - overall ozone rate constant = 5.6875E-17 cm³/molecule*sec
 - half life = 0.201 d (at 7E11 mol/cm³)
 - half life = 4.836 h

Reliability: (2) valid with restrictions
 scientifically acceptable method

17-FEB-2003 (16)

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 500000 molecule/cm³
Rate constant: .000000000085445 cm³/(molecule * sec)
Degradation: 50 % after 4.5 hour(s)

Method: other (calculated): AOP v1.5.1

Remark: calculation based on the following assumptions: 24 h day,
 0.5E6 OH/cm³
 reason for flagging this data: important information on this
 parameter; model accepted by US-EPA

Reliability: (2) valid with restrictions
 scientifically acceptable method

Flag: Critical study for SIDS endpoint

13-JAN-2003 (17)

Type: other

Remark: K=9.07E-11 cm³/mol*s; calculated with AOP according to
 Meylan

Reliability: (4) not assignable
 document not available

20-JAN-2003 (18)

3.1.2 Stability in Water

Type: abiotic
t1/2 pH4: = 12.9 hour(s) at 50 degree C

Method: other: gas chromatographic determination of
 3,4-dihydro-2-methoxy-2H-pyran as a function of time; test
 procedure according to an internal BASF standard

GLP: no

Test substance: other TS

Method: - test was performed at pH 4.0
 - t1/2 and k were calculated from the regression equation

Remark: reason for flagging this data: experimentally derived value

Result: k = 14.9 10e-5 s-1

Test substance: 3,4-dihydro-2-methoxy-2H-pyran, purity 98.8 %

Reliability: (2) valid with restrictions

Flag: scientifically acceptable method
Critical study for SIDS endpoint
16-JUN-2003 (19)

Type: abiotic

Remark: rates of hydrolysis:
in aqueous hydrochloric acid solutions at 25 Grad Celcius:
 $k(H^+) = (1.67 \pm 0.02) \cdot 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$
in cyanoacetic acid:
 $k(H^+) = (1.66 \pm 0.02) \cdot 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$
in formic acid:
 $k(H^+) = (1.64 \pm 0.04) \cdot 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$
Reliability: (2) valid with restrictions
acceptable publication which meets basic scientific principles
14-JAN-2003 (20)

Type: abiotic

Deg. products: yes

Method: other: measured: hydrolysis of 3,4-dihydro-2-methoxy-2H-pyran
under simulated physiological conditions; test procedure
according to an internal BASF standard

GLP: yes

Test substance: as prescribed by 1.1 - 1.4

Remark: Hydrolysis at environmental pH conditions is not expected to
be a relevant degradation process

Result: In order to check whether and at which rate
2-Methoxy-2,3-dihydro-4H-pyran hydrolyzes to glutaraldehyde
under simulated physiological conditions,
2-Methoxy-2,3-dihydro-4H-pyran (1 mg/ml) was incubated either
in aqueous hydrochloric acid (pH 2.5) or sodium phosphate
buffer (50mM; pH 7.4) at 37 °C for up to 4 hours. These media
should simulate conditions in stomach and blood plasma.

The results of the study demonstrated that
2-Methoxy-2,3-dihydro-4H-pyran rapidly hydrolysed to
glutaraldehyde in aqueous HCl at 37 °C and pH 2.5. Within 15
min after start of the incubation, almost 50 % of
2-Methoxy-2,3-dihydro-4H-pyran are already hydrolyzed. After 1
and 2 hour, 90 % and 99 % of 2-Methoxy-2,3-dihydro-4H-pyran
are hydrolyzed, respectively. At each timepoint, the
concentration of glutaraldehyde formed virtually corresponds
to the decrease of the concentration of
2-Methoxy-2,3-dihydro-4H-pyran. From the data of the
hydrolysis, the half-life of 2-Methoxy-2,3-dihydro-4H-pyran
was calculated to be 18.8 minutes under these conditions.

In sodium phosphate buffer (50 mM; pH 7.4), no hydrolysis of
2-Methoxy-2,3-dihydro-4H-pyran occurred.

Test substance: 3,4-dihydro-2-methoxy-2H-pyran, purity 99.87 % (w/w)

Reliability: (1) valid without restriction
Fully reliable study, performed under GLP. Meets
generally accepted scientific standards and is described in
sufficient detail.

16-JUN-2003 (21)

3.1.3 Stability in Soil**3.2.1 Monitoring Data (Environment)****3.2.2 Field Studies****3.3.1 Transport between Environmental Compartments**

Type: adsorption
Media: water - soil
Method: other: calculated with PCKOCWIN v1.63

Remark: reason for flagging this calculation: only information available on this endpoint; model accepted by US-EPA

Result: Koc = 1.53; log Koc = 0.1856

Reliability: (2) valid with restrictions
scientifically acceptable method

Flag: Critical study for SIDS endpoint
13-JAN-2003 (22)

Type: volatility
Media: water - air
Method: other: calculated: HENRYWIN v3.1

Remark: reason for flagging this model calculation: scientifically acceptable method; model accepted by US-EPA

Result: Henry's law constant at 25 °C:
Bond Est: 31.21 Pa*m3/mol
Group Est: 6.22 Pa*m3/mol

Reliability: (2) valid with restrictions
scientifically acceptable method

Flag: Critical study for SIDS endpoint
31-JAN-2003 (23)

Type: volatility
Media: water - air
Method: other: calculated

Result: Henry's law constant at 25 °C:
Input parameter:
vapour pressure: 1670 Pa at 25 °C
water solubility: 16000 g/m3 at 25 °C
molecular weight: 114.15 g/mol

$H = \text{vapour pressure} * \text{molecular weight} / \text{water solubility}$
 $H = 1670 \text{ Pa} * 114.15 \text{ g/mol} / 16000 \text{ g/m3}$
 $H = 11.9 \text{ Pa} * \text{m3} * \text{mol}^{-1} \text{ at } 25 \text{ °C}$

Reliability: (2) valid with restrictions
scientifically acceptable method

24-JAN-2003 (24)

Type: other: volatilization from surface water
Method: other: EPIWIN v3.1

Remark: reason for flagging this model calculation: important information on this parameter (volatilization of MDP from surface water)

Result: MDP in surface water will be subject to rapid volatilization. Using an estimated Henry's law constant of 31.2 Pa*m³/mol, a half-life for volatilization of the chemical from a river one m deep flowing 1 m/sec with a wind velocity of 5 m/sec has been estimated to be 3.1 hours. A volatilization half-life from a lake one meter deep, flowing 0.05 m/sec with a wind velocity of 0.5 m/sec has been calculated to be 5.15 days

Reliability: (2) valid with restrictions
scientifically acceptable method

Flag: Critical study for SIDS endpoint
31-JAN-2003 (16)

3.3.2 Distribution

Media: air - biota - sediment(s) - soil - water

Method: Calculation according Mackay, Level I

Method: Level 1, V 2.1 model

Remark: calculation is based on the following physico-chemical properties of the substance:

- temperature (°C):	25
- molecular mass (g/mol):	114.15
- vapour pressure (Pa):	1670
- melting point (°C):	-60
- water solubility (g/m ³):	16000
- Henry's law constant (Pa*m ³ /mol; 25 °C):	11.9
- log Kow:	1.33

reason for flagging this calculation: scientifically acceptable method

Result: over time, the substance will preferentially distribute into the compartments air and water:

- air:	80.4 %
- water:	19.5 %
- soil:	0.03 %
- sediment:	0.03 %

Reliability: (2) valid with restrictions
scientifically acceptable method

Flag: Critical study for SIDS endpoint
24-JAN-2003 (25) (26)

3.4 Mode of Degradation in Actual Use

3.5 Biodegradation

Type: aerobic

Inoculum: activated sludge, domestic

Concentration: 100 mg/l related to Test substance

Degradation: 0 % after 28 day(s)

Result: other: poorly biodegradable

Method: OECD Guide-line 301 F "Ready Biodegradability: Manometric

Respirometry Test"

Year: 1993

GLP: yes

Test substance: other TS: 3,4-dihydro-2-methoxy-2H-pyran; purity: 99.87 %

Remark: reason for flagging this study: most reliable study available on this endpoint

test device:

- Sapromat-system

number of replicates:

- test substance (TS): 7
- reference substance (RS): 1
- blank (BC): 2
- inhibition control (IH): 1
- assay to examine physico chemical (abiotic) elimination (PC): 1

inoculum:

- source: municipal activated sludge from laboratory wastewater treatment plants fed with municipal sewage
- concentration: 30 mg/L dry weight

reference control:

- reference substance: aniline
- concentration: 100 mg/L related to reference substance
- kinetic of reference substance: 3 day(s) -2 % BOD/ThOD
4 day(s) 57 % BOD/ThOD
5 day(s) 61 % BOD/ThOD
15 day(s) 84 % BOD/ThOD
20 day(s) 100 % BOD/ThOD
28 day(s) 105 % BOD/ThOD
- coloured dip sticks indicated that NO₃⁻ and NO₂⁻ ions had been produced in the reference assay. A quantitative determination of the concentration of these ions was not performed

inhibition control:

- substances: aniline + 3,4-dihydro-2-methoxy-2H-pyran
- concentration: aniline: 100 mg/L related to substance
test subst.: 98.4 mg/L related to substance
- kinetic of inhibition control: 3 day(s) -1 % BOD/ThOD
4 day(s) 17 % BOD/ThOD
5 day(s) 33 % BOD/ThOD
7 day(s) 35 % BOD/ThOD
14 day(s) 44 % BOD/ThOD
21 day(s) 46 % BOD/ThOD
28 day(s) 45 % BOD/ThOD

assay to examine physico-chemical (abiotic) elimination:

- concentration: 103.6 mg/L related to test substance
- w/o inoculum, w mercury chloride to avoid biodegradation
- kinetic of physico-chemical elimination:
7 day(s): 0 % BOD/ThOD
14 day(s): 2 % BOD/ThOD
21 day(s): 3 % BOD/ThOD
28 day(s): 4 % BOD/ThOD

pH values at test start and test end (after 28 day(s)):

- assay	pH day 0	pH day 28
BC1	7.5	7.4
BC2	7.5	7.4
RS	7.5	6.8
IH		8.7
PC		7.3
TS1		7.7
TS2		7.7
TS3		7.7
TS4		7.7
TS5		7.7
TS6		7.7
TS7		7.7

DOC-elimination (%) at test end (after 28 day(s)):

- assay	DOC-elimination (%)
RS	100
IH	78
PC	-19
TS1	46
TS2	35
TS3	38
TS4	40
TS5	40
TS6	45
TS7	33

- remark: DOC-elimination was suggested to be due to stripping

Reliability:

(1) valid without restriction
guideline study

Flag:

20-FEB-2003

Critical study for SIDS endpoint

(27)

Type:

aerobic

Inoculum:

activated sludge, industrial

Concentration:

400 mg/l related to DOC (Dissolved Organic Carbon)

Degradation:

90 - 100 % after 7 day(s)

Result:

other: easily eliminated from water

Method:

other: following OECD 302 B

GLP:

no

Test substance:

as prescribed by 1.1 - 1.4

Method:

OECD Guideline 302 B "Inherent biodegradability: static test according to Zahn-Wellens"

Result:

- the following elimination kinetic was observed (inoculum: activated sludge, industrial [1000 mg/l dry weight], test concentration: 400 mg/L DOC):

DOC-elimination	time
28 %	3 hours
62 %	1 day
97 %	3 days
97 %	7 days

- the physio-chemical (abiotic) elimination was examined in a flask containing the test substance and mercury chloride

to avoid biodegradation but no inoculum. The following kinetic was observed:

DOC-elimination	time
17 %	3 hours
22 %	1 day
32 %	3 days
29 %	6 days
27 %	9 days
34 %	13 days
31 %	18 days
34 %	20 days

- conclusion:

the test clearly demonstrated that the chemical was easily eliminated. But for relevant methodological deficiencies (test substance flask and abiotic control did not run at the same period) it remains unclear which process was involved in the elimination of the substance (evaporation into the air and/or adsorption and/or biodegradation)

Reliability:

(3) invalid
relevant methodological deficiencies

20-FEB-2002

(28)

3.6 BOD5, COD or BOD5/COD Ratio

Method: other: BOD-test according to DIN 38409/51

C O D

Method: other: COD-test according to DIN 38409/41

Year:

COD: 1945 mg/g substance

R A T I O B O D 5 / C O D

BOD5/COD: .001

Method:

Remark: inoculum: activated sludge, industrial

Result: BOD5 < 2 mg/g

Reliability: (1) valid without restriction

test procedure according to National Standard

14-JAN-2003

(29)

3.7 Bioaccumulation

Species: Cyprinus carpio (Fish, fresh water)

Exposure period: 56 day(s)

BCF: 1.5 - 1.7

Elimination: no

Method: other: Law No. 117, 1973, Order of the Japanese Prime Minister, the Minister of Health and Welfare and the Minister of Int. Trade and Industry, No.1, Promulgated July 13, 1974

Year: 1974

GLP: yes

Test substance: other TS: 3,4-dihydro-2-methoxy-2H-pyran (MOP), purity: 99.75 %

Method: OECD Guideline for testing of Chemicals, "Bioaccumulation: Test for the Degree of Bioconcentration in fish" (305 C). Adopted May 12, 1981

Remark: reason for flagging this study: only reliable study available on this endpoint
test procedure:

- fish:
Cyprinus carpio L. (carp; Central European variety; scattered carp, i.e. mirror carp)
mean body weight at the beginning of the test: 30.9 g
20 carp were put in each aquarium
- decontamination (1)/acclimatization (2):
(1) 24 h treatment in a 10 ppm solution of tetracycline hydrochloride once
(2) adaption from 18 °C to 25 °C within approx. 3 weeks, further adaption at 25 °C for approx. 2 months
- test vessels:
glass vessels (capacity 100 L)
flow rate: 60 L/h (1440 L/d), ratio of stock solution to water: 2:1000
- method of disposal of compound:
stock solution: to reach 1 mg/L and 0.1 mg/L in the test vessels, concentration of the stock solution fed into test vessels was 0.05 % (500 mg/L) and 0.005 % (50 mg/L), respectively
the stock solutions were changed twice a week. Before the test started, it had been demonstrated that the concentrations in the aquaria could be kept constant for at least 4 days without exchanging the stock solutions
- aeration:
because of the relatively high volatility no additional aeration was possible in the aquaria. Thus the oxygen values were not as high as usual in this kind of test. The extremely high flow rate of 60 l of water saturated with oxygen could not fully compensate for the missing aeration in the aquaria. Nevertheless the carp were healthy and did not show any signs of oxygen deficiency
dissolved oxygen in the aquaria (mg/L; time span: day 0-day 56):
exposed to 1 mg/L test compound: range: 3.1 mg/L - 5.7 mg/L
exposed to 0.1 mg/L test compound: range: 3.3 mg/L - 6.0 mg/L
control group: 4.2 mg/L - 5.9 mg/L
- temperature:
25 °C +/- 2°C
- test concentrations:
1.0 mg/L test compound
0.1 mg/L test compound

0.0 mg/L control group

- analytical monitoring:

concentration (nominal, mg/L)	concentration (mg/L) after n weeks	start	2 weeks	4 weeks	6 weeks	8 weeks
1.0			0.97	1.0	1.03	1.03
0.1			0.108	0.106	0.102	0.102
0.0	n.d.					n.d.

(n.d. = not detectable)

Result:

- bioaccumulation factor (BCF):

concentration (nominal, mg/L)	concentration factor after n weeks	2 weeks	4 weeks	6 weeks	8 weeks
1.0		1.3/1.5	1.7/1.3	1.2/1.2	1.6/1.7
0.1		1.4/1.6	0.9/1.1	1.3/1.3	1.5/1.5
0.0	n.d./n.d. (duplicate determinations)				n.d./n.d.

the results of the investigations show that the compound is not accumulating

- mortality and symptoms:

no deaths occurred. All carp in the three aquaria were healthy during the whole test and did not show any symptoms

the compound is not accumulating

Reliability:

(1) valid without restriction

guideline study

Flag:

Critical study for SIDS endpoint

16-JUN-2003

(30)

3.8 Additional Remarks

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Species: Oryzias latipes (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** no
NOEC: 147
LC50: ca. 730

Method: other: following: Jap. Ind. Standard (JIS) K 0102 Item 55, Acute Toxicity Test by Fishes (1974) and Proposal on Standard Tlm Test with Orange-Red Killifish. Kenji Tabata, Yosui To Haisui, 14, 1297-1303 (1972)

Year: 1974
GLP: no

Test substance: other TS: 3,4-dihydro-2-methoxy-2H-pyran, purity: 99.75 %

Remark:

- closely followed the Japanese Industrial Standard K 0102 item 55 (1974) and Kenji Tabata, Yosui to haisui (available water and waste water), 14, 1297-1303 (1972):
- animal species: Oryzias latipes Schlegel
- test water: reconstituted freshwater was prepared from fully demineralized tap water according to Josui to Haisui (available water and waste water), 14, 1297-1303 (1972) that was resalted by the addition of 26.1 mg/L CaCl₂.2H₂O, 17.7 mg/L MgSO₄.7H₂O, 1.1 mg/L K₂SO₄, 25.0 mg/L NaHCO₃
- volume of water: 10 L
- aeration: none
- No. of animals per test concentration: 10
- loading (G fish / L test water): 0.5
- test vessels: all-glass aquarium (30 * 22 * 24 cm)
- test was performed in unsealed aquaria
- temperature: 25 °C +-2°C
- duration of adaptation to test water and test temperature: 10 days
- body length: 3.5 cm (range: 2.7 - 3.7 cm)
- body weight: 0.5 g (range: 0.4 - 0.8 g)
- positive control of animals conducted with chloracetamide: LC50 (48 h): approx. 0.5 mg/L
- test concentration: 147, 215, 316, 464, 681, 1000 mg/L (nominal)
- preparation to test substance: The test substance was added into the aquaria. Subsequently the fish were placed into the aquaria
- pH values at the beginning of the experiment and after 96 h:

concentration (mg/L)	pH (0 h)	pH (96 h)
147	7.2	6.8
215	7.2	6.8
316	7.2	6.8
464	7.2	6.8
681	7.2	6.7
1000	7.2	
control	7.2	6.7

- oxygen values at the beginning of the experiment and after 96 h:

concentration (mg/L)	oxygen (0 h)	oxygen (96 h)
147	8.5	5.7
215	8.2	6.3
316	8.2	5.7
464	8.4	6.1
681	8.3	4.7
1000	8.5	
control	8.6	5.9

- the control was the test water without the test substance

- median lethal concentration (LC50) was estimated using Probit Analysis (Finney D.J., Probit Analysis, Cambr. Univ. Press, 3. edition, 1971)

- volatility screening test (for details see chapter 4.9): due to the vapour pressure of 3,4-Dihydro-2-methoxy-2H-pyran, evaporation from the open test system was likely to have occurred. To verify this, the volatility was measured under comparable test conditions, but without fish. In the test for volatility, based on MDHP-measurements, a recovery rate of 31.7 % (geometric mean of all measured values at test start and after 96 h) was found after 96 h
reason for flagging this study: only study available on this endpoint

Result:

- observed symptoms:

concentration time (mg/L)	1 h	4 h	24 h	48 h	72 h	96 h
147						
215		l				
316		l	l		l	l
464		l	l,s	l,s	l,s	l,s
681		l,s,t	l,s,t	l,n,s,t	l,n,s,t	l,n,s,t
1000		k,n,s	n,s	n,s		
control						

k=convulsions, l=gasping, n=narcotic-like state, t=tumbling, s=lateral position

- maximum concentration causing no effect: 147 mg/L

- total No. of living fish at the beginning and after 96 h:

concentration (mg/L)	No. of living fish (0 h)	(96 h)
147	10	10
215	10	10
316	10	10
464	10	10
681	10	7
1000	10	0
control	10	10

- an LC50 (96 h) of approximately 232 mg/l could be estimated on the basis of the nominal LC50 (96 h)-value from the acute toxicity test and the recovery rate from the volatility screening test

Reliability:

(2) valid with restrictions
test procedure according to National Standard (with restrictions: no concentration control analysis)

Flag: Critical study for SIDS endpoint
13-FEB-2003 (31) (32) (33)

4.2 Acute Toxicity to Aquatic Invertebrates

Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** yes
EC0: >= 100
EC50: > 100
EC100: > 100

Method: OECD Guide-line 202
Year: 1984
GLP: yes
Test substance: other TS: 2-methoxy-2,3-dihydro-4H-pyran (MOP), purity: 99.9 %

Remark: reason for flagging this study: in contrast to other tests on aquatic toxicity (fish, daphnia [BASF AG, 1/0012/2/88-0012/88, 05.02.1988], algae), this study was performed in a closed system

test conditions:

- water composition: a synthetic fresh water was used for culture and test purposes. For composition of the M4-medium see ISO 10706. Properties of the M4-medium: total hardness: 2,58 mmol/L; alkalinity up to pH 4.3: 0.89 mmol/L; molar ratio Ca:Mg: ca. 4:1; pH value: 8.1; conductivity: 630 µS/cm. After preparation the M4-medium was aerated for ca. 24 h until saturation with oxygen was reached
- illumination: artificial light, type warm white (OSRAM L58 W 31); day-night rhythm = 16 : 8 h
- light intensity: ca. 1-8 µE/(m²*s) at a wave length of 400-750 nm
- temperature: 18-22 °C (max. difference: 2 °C)
- test volume: ca. 20 ml
- test vessels: vials sealed with teflon caps and aluminium rings (nominal volume: 20 ml)
- test was performed in sealed vials
- replicates: 4 per concentration
- loading (animals/ml): 0.25 ml
- number of animals/vessel: 5
- total number of animals/conc.: 20
- age of animals: 2-24 h
- observation times: visually after 0, 24 and 48 h
- observation parameters: swimming ability, pH, oxygen
- test concentrations: 12.5 mg/L, 25 mg/L, 50 mg/L, 100 mg/L

Result: - number of mobile test animals after exposure (48 h) to various test concentrations:

concentration (mg/L)	mobile Daphnids
12.5	20
25	20
50	20
100	20
control	20

- effect values after 48 h:
EC0 (48 h) >= 100 mg/L

EC50 (48 h) > 100 mg/L
EC100 (48 h) > 100 mg/L

- effect values after 24 h:
EC0 (24 h) >= 100 mg/L
EC50 (24 h) = 100 mg/L
EC100 (24 h) = 100 mg/L

- analytical monitoring:
the measured concentration of MDP remained >90 % of the nominal values throughout the test

- pH values:
concentration time
(mg/L) 0 h 48 h
12.5 8.0 7.9
25 8.0 7.9
50 8.0 7.9
100 8.0 7.9
control 8.0 8.0

- O2 values:
concentration time
(mg/L) 0 h 48 h
12.5 9.1 8.1
25 9.1 8.5
50 9.0 8.2
100 8.9 8.1
control 9.0 8.5

- symptoms at test start:
narcotic like effects at 100 mg/L and 50 mg/L

Reliability: (1) valid without restriction
guideline study

Flag: Critical study for SIDS endpoint

13-FEB-2003 (34)

Type: static

Species: Daphnia magna (Crustacea)

Exposure period: 48 hour(s)

Unit: mg/l **Analytical monitoring:** yes

Method: OECD Guide-line 202

Year: 1984

GLP: yes

Test substance: other TS: 2-methoxy-2,3-dihydro-4H-pyran (MOP), purity: 99.9 %

Remark: reason for flagging this study: test was performed in an unsealed test system including analytical monitoring
test conditions:
- water composition: a synthetic fresh water was used for culture and test purposes. For composition of the M4-medium see ISO 10706. Properties of the M4-medium: total hardness: 2,58 mmol/L; alkalinity up to pH 4.3: 0.89 mmol/L; molar ratio Ca:Mg: ca. 4:1; pH value: 8.1; conductivity: 630 µS/cm. After preparation the M4-medium was aerated for ca. 24 h until saturation with oxygen was reached
- illumination: artificial light, type warm white (OSRAM L58 W 31); day-night rhythm = 16 : 8 h

- light intensity: ca. 1-8 $\mu\text{E}/(\text{m}^2\cdot\text{s})$ at a wave length of 400-750 nm
- temperature: 18-22 °C (max. difference: 2 °C)
- test volume: ca. 10 ml
- test vessels: test tubes (glass) with a flat bottom (nominal volume: 20 ml)
- test was performed in unsealed tubes
- replicates: 4 per concentration
- loading (animals/ml): 0.5 ml
- number of animals/vessel: 5
- total number of animals/conc.: 20
- age of animals: 2-24 h
- observation times: visually after 0, 24 and 48 h
- observation parameters: swimming ability, pH, oxygen
- test concentrations: 25 mg/L, 50 mg/L, 100 mg/L
- number of mobile test animals after exposure (48 h) to various test concentrations:

Result:

concentration (mg/L)	mobile Daphnids
25	20
50	20
100	20
control	20

- effect values after 48 h:
EC0 (48 h) \geq 100 mg/L
EC50 (48 h) $>$ 100 mg/L
EC100 (48 h) $>$ 100 mg/L
(values related to nominal concentrations)
 - effect values after 24 h:
EC0 (24 h) \geq 100 mg/L
EC50 (24 h) $>$ 100 mg/L
EC100 (24 h) $>$ 100 mg/L
(values related to nominal concentrations)
 - analytical monitoring:
time minimum maximum
(h) (%) (%)
0 92.8 96.6
24 45.8 46.9
48 21.2 21.8
(values are given in percent of the nominal concentrations)
- recovery rate (geometric mean of all values): 45.5 %

- pH values:
concentration time
(mg/L) 0 h 48 h
25 8.1 7.9
50 8.1 8.1
100 8.0 8.1
control 8.1 8.0

- O2 values:
concentration time
(mg/L) 0 h 48 h
25 9.0 9.2
50 9.1 9.4
100 9.2 9.3

control 9.1 9.6

- symptoms at test start:
narcotic like effects at 100 mg/L and 50 mg/L

Reliability: (1) valid without restriction
guideline study

Flag: Critical study for SIDS endpoint
20-FEB-2003 (34)

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC0: 125
EC50: 176.78
EC100: 250

Method: other: Directive 79/831/EEC, Annex V, Part C
Year: 1984
GLP: no
Test substance: other TS: 3,4-dihydro-2-methoxy-2H-pyran, purity: >=99 %

Method: procedures to determine EC-values after 48 h:
- EC50: according to Spearman-Kärber
- EC0: highest concentration tested at which <= 10 % of the animals were immobile
- EC100: lowest tested concentration at which 100 % of the animals were immobile

static acute toxicity test

analysis according: Sachs L., Angewandte Statistik, Springer Verlag, Berlin, Heidelberg, New York, 4. edition, 1974

Remark: reason for flagging this study: important data available on this endpoint
test conditions:
- dilution water: source: tap water; pretreatment steps: (1) 6 µm- and charcoal-filtration; (2) H₂SO₄ was added to reduce alkalinity up to pH 4.3; (3) distilled water was added to reduce water-hardness; (4) water was aerated (oil-free air) until saturated with oxygen; (5) water was stored for at least 24 h for stabilization. Specifications measured at test start: water-hardness: 2.51 mmol/L, alkalinity up to pH 4.3: 0.86 mmol/L, pH: 7.9, conductivity: 610 µSiemens/cm
- water solubility: >500 mg/L at 21 °C (293 K)
- O₂-content: > 2 mg/L
- illumination: diffuse light
- temperature: 20-22 °C (292-294 K)
- test volume: 10 ml
- test vessels: test tubes (glass) with flat bottom (nominal volume 20 ml)
- test was performed in unsealed tubes
- replicates: 4 per concentration
- volume/animal: 2 ml
- number of animals/vessel: 5
- total number of animals/conc.: 20
- age of animals: 2-24 h
- observation times: visually after 0, 3, 6, 24 and 48 h
- observation parameters: swimming ability, pH, oxygen
- test concentrations: 31.25, 62.5, 125, 250, 500 mg/L mg/L,

100 mg/L

- volatility screening test (BASF AG, 00/0598-2, 25.11.2002; for details see chapter 4.9):
since the test was performed in unsealed tubes, evaporation from the test system could not be excluded. Therefore the volatility was measured under comparable test conditions, but without Daphnia magna. Based on TOC measurements, a recovery rate of ca. 59.8 % of the nominal concentrations was calculated after 48 h (geometric mean of all values)

Result:

- number of mobile test animals after exposure (48 h) to various test concentrations:

concentration (mg/L)	mobile Daphnids
31.25	20
62.5	20
125.0	20
250.0	0
500.0	0
control	20

- effect values after 48 h:

EC0 = 125 mg/L
EC50 = 176.78 mg/L
EC100 = 250 mg/L
(values related to nominal concentrations)

- effect values after 24 h:

EC0 = 125 mg/L
EC50 = 176.78 mg/L
EC100 = 250 mg/L
(values related to nominal concentrations)

- range of pH at start: 7.97 (500 mg/L) - 8.16 (control)
- range of pH after 48 h: 8.0 (250 mg/L) - 8.08 (control)

- range of O₂ (mg/L) at start: 8.59 (control) - 8.66 (250 mg/L)
- range of O₂ (mg/L) after 48 h: 8.33 (250 mg/L) - 8.64 (control)

- an EC50 (48 h) of approximately 81 mg/l could be estimated on the basis of the nominal EC50 (48 h)-value from the acute toxicity test and the recovery rate from the acute toxicity test to Daphnia magna (= 45.5 %, BASF AG, 00/0598/50/2, February 2003)

- an EC50 (48 h) of approximately 106 mg/l could be estimated on the basis of the nominal EC50 (48 h)-value from the acute toxicity test and the recovery rate from the volatility screening test (=59.8 %; BASF AG, 00/0598-2, 25.11.2002)

Reliability:

(2) valid with restrictions
test procedure according to guideline study with restrictions (no concentration control analysis)

Flag:

20-FEB-2003

Critical study for SIDS endpoint

(35) (36) (34) (33)

4.3 Toxicity to Aquatic Plants e.g. Algae

Endpoint: other: cell density (fluorescence at 685 nm as a size for the biomass)

Exposure period: 72 hour(s)

Unit: mg/l **Analytical monitoring:** no

EC50: > 500

EC20 : = 322.9

Method: other: German National Standard: DIN 38412, Part 9, Determination of inhibitory effect on the cell multiplication

Year: 1984

GLP: no

Test substance: other TS: 3,4-dihydro-2-methoxy-2H-pyran, purity: >=99 %

Remark: reason for flagging this study: only study available on this endpoint
test was performed according to the German National Standard DIN 38412, Part 9:

pre-culture:

- species: *Scenedesmus subspicatus*, SAG 86.81
- medium: OECD-medium
- temperature: 20 °C
- test flasks: 250 ml-Erlenmeyer flasks plugged with gas permeable silicon-sponge caps
- test volume: 100 ml
- flasks were incubated in an incubation chamber for 72 h
- flasks were shaken once a day to hold cells in suspension
- illumination: permanent artificial light
- light intensity: approx. 120 µE/(m2*s)

test conditions:

- No. of algae in test flasks at test start: 10000 exponentially-growing cells
- stock solution of test substance: conductivity: 7 µS/cm, pH 6.9); stock solution was diluted in test medium to reach the final test concentrations
- test concentrations: 31.25, 62.5, 125, 250, 500 mg/L
- test vessels: 20 ml tubes plugged with gas permeable silicon-sponge caps
- test was performed in unsealed vessels
- replicates: per concentration and control: 4, blank per concentration (w/o cells): 2
- test volume: 10 ml
- tubes were incubated in an incubation chamber for 96 h at 23 °C
- tubes were shaken once a day to hold cells in suspension
- illumination: permanent artificial light
- light intensity: approx. 120 µE/(m2*s)
- samples were taken at regular intervals (0, 24, 48, 72, 96 h)
- measurements: fluorescence (in vivo chlorophyll-a fluorescence at 685 nm as a size for the biomass (pulsed excitation with light flashes having a wavelength of 435 nm)), pH
- the EC values are calculated (linear regression analysis) from the concentration-response relationship

- volatility screening test (for details see chapter 4.9):
due to the vapour pressure of 3,4-Dihydro-2-methoxy-2H-pyran,
evaporation from the open test system was likely to have
occurred. To verify this, the volatility was measured under
comparable test conditions, but without algae. In the test for
volatility, based on TOC-measurements, a recovery rate of 33 %
was found (geometric mean of all measured values over 72 h)

Result: - the highest concentration (500 mg/L) tested did not inhibit
growth by 50 %

- effect values after 96 h:
EC20 = 387 mg/L
EC50 > 500 mg/L
EC90 > 500 mg/L
(values related to nominal concentrations)

- pH range at start: 8.3 (control, 500, 250, 125, 62.5 mg/L)
- 8.4 (31.25 mg/L)
- pH range after 96 h: 10.1 (all assays)

- an EC50 (72 h) of >165 mg/l could be calculated taking into
account the nominal EC50 (72 h)-value from the acute toxicity
test and the recovery rate from the volatility screening test

Reliability: (2) valid with restrictions
test procedure according to National Standard with
restrictions (no concentration control analysis)

Flag: Critical study for SIDS endpoint
16-JUN-2003 (37) (36) (33)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: aquatic
Species: activated sludge, industrial
Exposure period: 30 minute(s)
Unit: mg/l **Analytical monitoring:**
EC20 : > 1950

Method: other: Activated Sludge Respiration Inhibition Test following
to OECD 209
Year: 1984
GLP: no

Remark: - test concentrations: 150 mg/l, 750 mg/l, 1950 mg/l
(nominal).

- No inhibitory effects were observed even at the highest test
concentration of 1950 mg/l.

- The inhibition of the degradation activity of activated
sludge is not anticipated when introduced in appropriate low
concentrations.
reason for flagging this study: only study available on this
endpoint

Result: - EC20 (10 min) >1950 mg/L
- EC20 (30 min) >1950 mg/l

Reliability: (2) valid with restrictions
comparable to guideline study with acceptable restrictions
(activated sludge from industrial wwtp instead of municipal

wwtp)
Flag: Critical study for SIDS endpoint
14-JAN-2003 (38)

Type: aquatic
Species: Pseudomonas putida (Bacteria)
Exposure period: 17 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC10: = 3806.4
EC50: = 5991.4
EC90 : = 8903.7

Method: other: German National Standard: DIN 38412, Part 8,
Determination of the inhibitory effect on the cell
multiplication
GLP: no
Test substance: other TS: 3,4-dihydro-2-methoxy-2H-pyran, purity: >=99 %

Remark: pre-culture:
- species: Pseudomonas putida, DSM 50026
- incubated at 24 °C (297 K +/- 1 K), 150 rpm for 7+-1 h
- medium: AK-medium according to DIN 38412, Part 8 (draft)
- test vessel: 300 ml-Erlenmeyer flasks, 1 baffle
- liquid volume: 100 ml

test conditions:
- test vessel: Penicillium glass vessel
- liquid volume: 10 ml
- inoculum: 1 ml pre-culture (adjusted to 10 TE/F)
- test medium: AK-medium according to DIN 38412, Part 8
(draft)
- test concentrations (nominal): 156.25, 312.5, 625, 1250,
2500, 5000, 7500, 10000 mg/L
- replicates: inoculated: 4 per concentration and control;
non-inoculated: 1 per concentration and control
- incubated at 20°C (292 K), 150 rpm for 17 h
- measurements: photometric determination at 436 nm and pH
at test start and after 17 h
reason for flagging this study: only study available on this
endpoint

Result: range of pH:
- at test start: 7.0 (156.25 mg/L, non-inoculated) - 7.1
(all other assays)
- after 17 h: 4.8 (control, 156.25 mg/L) - 6.9 (10000 mg/L)

inhibition (%) after 17 h:
- test concentration inhibition
(mg/L) (%)
control --
156.25 0.06
312.5 +3.57 (1)
625 +10.76 (1)
1250 +15.68 (1)
2500 +13.65 (1)
5000 31.61
7500 77.98
10000 99.38

(1) no inhibition of growth, but growth promotion
Reliability: (1) valid without restriction

Flag: test procedure following National Standard
13-JAN-2003 Critical study for SIDS endpoint

(39)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

4.5.2 Chronic Toxicity to Aquatic Invertebrates

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Sediment Dwelling Organisms

4.6.2 Toxicity to Terrestrial Plants

4.6.3 Toxicity to Soil Dwelling Organisms

4.6.4 Toxicity to other Non-Mamm. Terrestrial Species

4.7 Biological Effects Monitoring

4.8 Biotransformation and Kinetics

4.9 Additional Remarks

- Memo:** screening test (w/o algae) to determine the evaporation of 2-methoxy-2,3-dihydro-4H-pyran closely following the test conditions of the acute toxicity test to algae (BASF AG, Department of Ecology, 2/0012/88, 15.07.1988)
- Method:** a screening test w/o algae was performed to determine the evaporation of 2-methoxy-2,3-dihydro-4H-pyran closely following the test conditions of the acute toxicity test to the algae (BASF AG, Department of Ecology, unpublished study, 2/0012/88, 15.07.1988):
- test flask:
Erlenmeyer flask (nominal volume 250 ml) plugged with gas permeable silicon sponge caps
 - test volume:
100 ml liquid
 - medium:
OECD-Medium T 9
 - incubation:
 - incubator: Ecophyt (air conditioned)
 - temperature: 23 °C ± 2 °C
 - liquid was not mixed during the test period
 - illumination: artificial light, type universal white, continuous illumination
 - light intensity: ca. 120 µE/(m².s) at a wave length of 400 - 700 nm
 - No. of test vessels at test start:
four flasks
 - target test substance concentration at test start:
125 mg/l 2-methoxy-2,3-dihydro-4H-pyran
 - analytical method:
TOC (total organic carbon)
 - sampling and measurements:
at test start, after 24 h, 48 h and 72 h one of the flasks was taken to measure the TOC
- Result:**
- calculated test concentration at test start:
125 mg/l 2-methoxy-2,3-dihydro-4H-pyran ~ 78,8 mg/l TOC
(calculation based on the following ThOC-value: 630 mg

carbon/1000 mg 2-methoxy-2,3-dihydro-4H-pyran)

- measurements:

time [h]	TC [mg/l]			TIC [mg/l]			TOC [mg/l]	recovery rate [%]
	1.	2.	mean	1.	2.	mean		
0	81.1	80.9	81	6.4	6.3	6.35	74.65	95
24	47.7	47.7	47.7	6.5	6.3	6.4	41.3	52.4
48	32.5	32.4	32.5	6.4	6.2	6.3	26.2	33.2
72	27.9	27.4	27.7	6.8	7	6.9	20.8	26.3

(TC = total carbon, TIC = total inorganic carbon, TOC = total organic carbon)

- recovery rates:

ca. 26.3 % (based on measured TOC-value after 72 h)
ca. 60.7 % (arithm. mean: based on measured TOC-values after 0 h and 72 h)
ca. 51.7 % (arithm. mean: based on all measured TOC-values over 72 h)

Reliability:

(2) valid with restrictions
screening test meets basic scientific principles

17-JAN-2003

(36)

Memo:

screening test (w/o algae) to determine the evaporation of 2-methoxy-2,3-dihydro-4H-pyran closely following the test conditions of the acute toxicity test to algae (BASF AG, Department of Ecology, 2/0012/88, 15.07.1988)

Method:

a screening test w/o algae was performed to determine the evaporation of 2-methoxy-2,3-dihydro-4H-pyran closely following the test conditions of the acute toxicity test to the algae (BASF AG, Department of Ecology, unpublished study, 2/0012/88, 15.07.1988):

- test flask:

Erlenmeyer flask (nominal volume 250 ml) plugged with gas permeable siliconsponge caps

- test volume:

100 ml liquid

- medium:

OECD-Medium T 9

- incubation:

- incubator: Ecophyt (air conditioned)

- temperature: 23 °C ± 2 °C

- liquid was continuously mixed on a laboratory shaker: ca. 85 rpm

- illumination: artificial light, type universal white, continuous illumination

- light intensity: ca. 120 µE/(m².s) at a wave length of 400 - 700 nm

- No. of test vessels at test start:

four flasks

- target test substance concentration at test start:

125 mg/l 2-methoxy-2,3-dihydro-4H-pyran

- analytical method:

TOC (total organic carbon)

- sampling and measurements:

at test start, after 24 h, 48 h and 72 h one of the flasks was taken to measure the TOC
Remark: reason for flagging this screening test: important data to evaluate the acute toxicity test to algae (BASF AG, Department of Ecology, 2/0012/88, 15.07.1988)

Result: - calculated test concentration at test start:
125 mg/l 2-methoxy-2,3-dihydro-4H-pyran ~ 78,8 mg/l TOC (calculation based on the following ThOC-value: 630 mg carbon/1000 mg 2-methoxy-2,3-dihydro-4H-pyran)

- measurements:

time [h]	TC [mg/l]			TIC [mg/l]			TOC [mg/l]	recovery rate [%]
	1.	2.	mean	1.	2.	mean		
0	83.1	83.1	83.1	6.3	6.3	6.3	76.8	98
24	37.5	37.4	37.5	6.7	6.6	6.7	30.8	39.1
48	22.5	22.5	22.5	6.5	6.5	6.5	16	20.3
72	18.2	18.5	18.4	6.3	6.2	6.3	12.1	15.4

(TC = total carbon, TIC = total inorganic carbon, TOC = total organic carbon)

- recovery rates:

ca. 15.4 % (based on measured TOC-value after 72 h)
ca. 56.7 % (arithm. mean: based on measured TOC-values after 0 h and 72 h)
ca. 43.2 % (arithm. mean: based on all measured TOC-values over 72 h)

33.08 % (geometric mean: based on all measured TOC-values over 72 h)

Reliability: (2) valid with restrictions
screening test meets basic scientific principles

Flag: Critical study for SIDS endpoint

31-JAN-2003

(36) (33)

Memo: screening test (w/o daphnia) to determine the evaporation of 2-methoxy-2,3-dihydro-4H-pyran closely following the test conditions of the acute toxicity test to *Daphnia magna* (BASF AG, Department of Ecology, 1/0012/2/88-0012/88, 05.02.1988)

Method: a screening test w/o daphnia was performed to determine the evaporation of 2-methoxy-2,3-dihydro-4H-pyran closely following the test conditions of the acute toxicity test to the *Daphnia magna* (BASF AG, Department of Ecology, unpublished study, 1/0012/2/88-0012/88, 05.02.1988):

- test flask:
test tubes with flat bottom (nominal volume 20 ml), unsealed
- test volume:
10 ml liquid
- medium:
M4 medium
- incubation:
 - temperature: 20 °C ± 2 °C
 - liquid was not mixed during the test period
 - illumination: artificial light, day/night rhythm = 16:8 h
- No. of test tubes at test start:
three tubes
- target test substance concentration at test start:

100 mg/l 2-methoxy-2,3-dihydro-4H-pyran
- analytical method:
TOC (total organic carbon)
- sampling and measurements:
at test start, after 24 h and 48 h one of the tubes was taken to measure the TOC

Remark: reason for flagging this screening test: important data to evaluate the acute toxicity test to *Daphnia magna* (BASF AG, Department of Ecology, 1/0012/2/88-0012/88, 05.02.1988)

Result: - calculated test concentration at test start:
100 mg/l 2-methoxy-2,3-dihydro-4H-pyran ~ 63.0 mg/l TOC (calculation based on the following ThOC-value: 630 mg carbon/1000 mg 2-methoxy-2,3-dihydro-4H-pyran)

- measurements:

time [h]	TC [mg/l]			TIC [mg/l]			TOC [mg/l]	recovery rate [%]
	1.	2.	mean	1.	2.	mean		
0	73.7	73.5	73.6	9.9	10	9.95	63.7	101
24	47.6	47	47.3	9.9	9.8	9.85	37.5	59.4
48	32.4	32.2	32.3	9.7	10	9.85	22.5	35.6

(TC = total carbon, TIC = total inorganic carbon, TOC = total organic carbon)

- recovery rates:
ca. 35.6 % (based on measured TOC-value after 48 h)
ca. 68.3 % (arithm. mean: based on measured TOC-values after 0 h and 48 h)
ca. 65.3 % (arithm. mean: based on all measured TOC-values over 48 h)

59.8 % (geometric mean: based on all measured TOC-values over 48 h)

Reliability: (2) valid with restrictions
screening test meets basic scientific principles

Flag: Critical study for SIDS endpoint

16-JUN-2003 (36) (33)

Memo: screening test (w/o fish) to determine the evaporation of 2-methoxy-2,3-dihydro-4H-pyran closely following the test conditions of the acute toxicity test to *Oryzias latipes* (BASF AG, Department of Toxicology, 81/233, 10.12.1981)

Method: a screening test w/o fish was performed to determine the evaporation of 2-methoxy-2,3-dihydro-4H-pyran closely following the test conditions of the acute toxicity test to the *Oryzias latipes* (BASF AG, Department of Toxicology, unpublished study, 81/233, 10.12.1981):

- test vessels:
all-glass aquarium

- test volume:
10 L liquid

- medium:
synthetic freshwater, resalted by the addition of 26.1 mg/L CaCl₂*2H₂O, 17.7 mg/L MgSO₄*7H₂O, 1.1 mg/L K₂SO₄, 25.0 mg/L NaHCO₃

- incubation temperature: 25 °C ± 2 °C

- aeration: no aeration
- preparation of test substance: the chemical was added into the aquaria without any pretreatment
- No. of aquaria:
1 per concentration
- target test substance concentrations at test start:
100 mg/L, 464 mg/L and 1000 mg/L 2-methoxy-2,3-dihydro-4H-pyran
- analytical method:
(1) TOC (total organic carbon)
(2) substance specific analysis
- sampling and measurements:
(1) TOC: samples were taken at test start, after 24 h, 48 h, 72 h and 96 to determine the TOC content
(2) substance specific analysis: samples were taken at test start and at the end of the test to determine 2-methoxy-2,3-dihydro-4H-pyran

Remark: reason for flagging this screening test: important data to evaluate the acute toxicity test to *Oryzias latipes* (BASF AG, Department of Toxicology, 81/233, 10.12.1981)

Result:

- calculated MDHP-test concentrations at test start:
100 mg/L (nominal) ~ 63.0 mg/l TOC
464 mg/L (nominal) ~ 292.3 mg/L TOC
1000 mg/L (nominal) ~ 630.0 mg/l TOC
(calculation based on the following ThOC-value: 630 mg carbon/1000 mg 2-methoxy-2,3-dihydro-4H-pyran)

- TOC-measurements:

TS [mg/L]	time: 0 h		time: 24 h		time: 48 h	
	DOC [mg/L]	recovery rate [%]	DOC [mg/L]	recovery rate [%]	DOC [mg/L]	recovery rate [%]
100	59.1	93.7	37.5	59.5	25.4	40.2
464	262.2	89.7	126.5	43.3	71.8	24.5
1000	556.8	88.4	384	61.0	270	42.9

TS [mg/L]	time: 72 h		time: 96 h	
	DOC [mg/L]	recovery rate [%]	DOC [mg/L]	recovery rate [%]
100	17.5	27.8	10.2	16.3
464	37.6	12.8	18.8	6.4
1000	172.4	27.4	107	16.9

(TS = test substance, related to nominal concentrations; TC = total carbon, TIC = total inorganic carbon, TOC = total organic carbon)

- recovery rates (based on TOC measurements):
ca. 13.2 % (based on measured TOC-values after 96 h)
ca. 51.9 % (arithm. mean: based on measured TOC-values after 0 h and 96 h)
ca. 43.4 % (arithm. mean: based on all measured TOC-values over 96 h)

- MDHP measurements (substance specific analysis):

TS [mg/L]	time: 0 h		time: 96 h	
	MDHP [mg/L]	recovery rate [%]	MDHP [mg/L]	recovery rate [%]
100	99.8	99.8	15.7	15.7

464	379.0	81.7	30.6	6.6
1000	661.7	66.2	182	18.2

- recovery rates (based on MDHP measurements):
 ca. 13.5 % (arithm. mean: based on measured MDHP-values
 after 96 h)
 ca. 48.0 % (arithm. mean: based on all measured MDHP-values
 over 96 h)

31.7 % (geometric mean: based on all measured MDHP-values
 over 96 h)

Reliability:

(2) valid with restrictions
 screening test meets basic scientific principles

Flag:

Critical study for SIDS endpoint

16-JUN-2003

(31) (33)

5.0 Toxicokinetics, Metabolism and Distribution

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Strain: Sprague-Dawley
Sex: male/female
No. of Animals: 38
Vehicle: other: none
Doses: 0.5, 1, 1.4, 2, 4 ml/kg; i.e. 500, 1000, 1400, 2000, 4000 mg/kg
Value: ca. 1640 mg/kg bw
Method: other
GLP: no data
Test substance: other TS

Method: Similar to OECD test guideline 401 "Acute Oral Toxicity"
Result: MORTALITY

Deaths occurred within 1.5 hrs to 3 d after dosing, with higher doses being associated with shorter times. Dose-mortality data are given below.

Dose (ml/kg)	Males	Females
4.0	5/5	3/3
2.0	3/5	4/5
1.4	na	2/5
1.0	0/5	1/5
0.5	na	0/5

From these data LD50 values (with 95% confidence intervals) were calculated:

Male rats= 1.87 (1.26-2.76) mg/kg

Female rats= 1.41 (0.8-2.49) mg/kg

CLINICAL SIGNS

At 1 ml/kg and above, signs of toxicity were seen which included sluggishness, prostration, moribund appearance, lachrymation (within 0.5 to 5 hr), and unsteady gait and tremors at 1 d. Survivors recovered within 1 to 2 d after dosing and gained weight over the 14 d observation period.

NECROPSY FINDINGS

Necropsy of animals that died revealed dark red or dark pink lungs as a consistent finding. Survivors showed no gross pathology at necropsy.

Test condition: TEST ORGANISMS

Dose groups contained 5 male and 5 female rats, except for one group of 3 females. Mean group body weights ranged between 210-262 g.

ADMINISTRATION

MDP was given by gavage undiluted as received, i.e. without vehicle. Animals were fasted overnight before dosing.

EXAMINATIONS

Animals were inspected twice daily for signs of pharmacologic or toxicologic effects during a 14 day observation period. Body weight was measured before dosing, and at 7 and 14 d thereafter. At the end of the observation period survivors were sacrificed and necropsied as were animals that died. LD50 values were calculated by the moving average method described by Weil.

Test substance: Purity of the TS was 99.105% MDP, 0.643% of the MDP dimer and 0.037% acrolein (AC)

Reliability: (1) valid without restriction
(1d) Meets generally accepted scientific standards and is described in sufficient detail.

Flag: Critical study for SIDS endpoint
28-AUG-2003 (40) (3) (41) (42) (43)

Type: LD50
Species: rat
Strain: Sprague-Dawley
Sex: male/female
No. of Animals: 60
Vehicle: CMC
Doses: 1000, 2150, 3160, 3830, 4640, 6810, 10 000 mg/kg
Value: = 3740 mg/kg bw

Method: other
GLP: no data
Test substance: other TS

Method: In compliance with test guideline OECD 401 "Acute Oral Toxicity"

Remark: Very steep dose-mortality curve.
Low purity of TS.

Result: MORTALITY
No deaths occurred at the lower doses up to 2.15 g/kg. All animals died at 4.64 g/kg and above. Details are given in the table below.

Dose (g/kg)	deaths		Deaths	total
	Males	Females	in 1 hr	within 24 hr
1.0	0/5	na	0	0
2.15	na	0/5	0	0
3.16	0/5	1/5	0	1
3.83	2/5	3/5	3	4
4.64	5/5	5/5	4	9
6.81	5/5	5/5	3	10
10.0	5/5	5/5	8	10

Typically deaths occurred within the first 24 hr after dosing.

From these data LD50 values (with 95% confidence intervals) were calculated:

Male rats = 3890 (3660-4140) mg/kg
Female rats = 3600 (3280-3950) mg/kg
both sexes = 3740 (3530-3740) mg/kg

CLINICAL SIGNS

At 1 g/kg apathy, ataxia and closed eyes were seen. At 2.15 g/kg and above clinical signs included apathy, mild to strong ataxia, prostration, reduced or no reflexes (toe and tail pinching; upright surface; eye and ear reflexes), and labored breathing. Most of survivors showed no signs at 4 d post treatment.

NECROPSY FINDINGS

Necropsy of animals that died revealed red and hardened stomach lining, one animal of the 6.81 g/kg group showing signs of gastric hemorrhage. Dark red lungs were seen in some animals. Marble pattern was seen in liver from 2 animals at 10 g/kg.

Test condition:

TEST ORGANISMS

5 SD rats per sex and dose group, mean weight 147 g (males) and 133 g (females), were used. Except from the lowest doses where only 5 males (1 g/kg) or 5 females (2.15 g/kg) were used.

ADMINISTRATION

TS was given by gavage in a constant volume of 10 ml/kg. Accordingly, TS was diluted with 0.5% CMC to give the desired concentrations. These were 100, 215, 316, 383, 464, and 681 mg/ml for the respective doses, and undiluted for the highest dose used in this study.

EXAMINATIONS

Animals were inspected for signs of pharmacologic or toxicologic effects at 15 and 30 min, at 1, 2, 4, 5, and 24 hr after application, and daily during a 14 d observation period after dosing.

At the end of the observation period survivors were sacrificed and necropsied as were animals that died.

Test substance:

MDP (<96%), dimer acrolein (4%). Traces of acrolein and methylvinylether.

Reliability:

(1) valid without restriction
(1d) Meets generally accepted scientific standards and is described in sufficient detail.

Flag:

20-FEB-2002

Critical study for SIDS endpoint

(44) (45)

Type:

LD50

Species:

rat

Strain:

Wistar

Sex:

male

No. of Animals:

15

Vehicle:

other: none

Doses:

2000, 4000, 8000 mg/kg

Value:

ca. 3730 mg/kg bw

Method:

other

GLP:

no

Test substance:

other TS: MDP from UCC

Method:

Similar to OECD 401

Result:

Findings after 14 days observation period:

Animals at 2000 mg/kg

No deaths seen (0/5 animals). Body weight change 87 to 113

gm. Unsteady gait was seen 3 min after dosing.
Animals at 4000 mg/kg
3/5 animals died at 1, 1, 3 days after dosing. Body weight change 87 to 97 gm. Unsteady gait was seen 5 min after dosing. Heavy breathing, prostrate at 20 min.
Animals at 8000 mg/kg
5/5 animals died at 0, 0, 1, 1, 1 days after dosing.
Erythema and edema. Unsteady gait 1 min after dosing. Heavy breathing, prostrate 3 min. Death of 2 animals in 1.75 to 4 hrs.

Gross pathology
Victims: livers mottled and pale, acini prominent. Kidneys and adrenals slightly congested. Stomachs transparent, fluid-filled, glandular portions pink. Intestines transparent, fluid-filled, pink to yellow.
Nothing remarkable in survivors.

Test condition: TEST ANIMALS
5 male Wistar rats per dose level. Age 3-4 weeks, 90-120 gm body weight.
ADMINISTRATION
Stomach intubation. Undiluted MDP as delivered.
Test substance: MDP from UCC, US; charge no.03118
Conclusion: Calculated oral LD50, rat: 3730 (2520-5520) mg/kg.
Reliability: (2) valid with restrictions
(2a) Guideline study without detailed documentation.

25-JAN-2003

(46)

Type: LD50
Species: rabbit
Strain: other: outbred
Sex: male/female
No. of Animals: 27
Vehicle: water
Doses: 100, 200, 500, 1000 mg/kg bw
Value: 200 - 500 mg/kg bw

Method: other
GLP: no data
Test substance: other TS

Method: Similar to OECD 401 (1987). Additionally a specific target organ study was performed (hepatotoxicity).

Remark: Hepatotoxicity was tested upon customer request. The hypothesis was that glutaraldehyde might be involved in formation of hepatotoxicity observed in a number of the customer's employees. Study results did not support this hypothesis

Result: Preliminary study
All rats survived (2/2) a dose of 100 mg/kg bw of either raw or pure MDP. During necropsy after terminal sacrifice no changes in any organ were noted.
All rats receiving 500 or 1000 mg/kg bw of either raw or pure MDP died within 2-6 days at 500 mg/kg bw (2/2 animals) or within 24 hours at 1000 mg/kg bw (2/2 animals). Pathology revealed signs of liver injury in victims.

Main study - liver injury
At a dose of 200 mg/kg bw both raw and pure MDP caused 1/3

deaths in either test substance group within 8 days after dosing.

In survivors serum GPT and Bromosulphthalein (BST) retention were within normal limits at 8 d and 14 d after dosing with either TS.

No pathological changes were seen in livers from sacrificed survivors. Livers from victims were cadaverous and could not be examined.

Test condition: TEST ORGANISMS
Outbred rabbits, bodyweight ca, 3.5 kg, were used; additionally, 3 animals were used as controls for the liver function tests.

ADMINISTRATION
Preliminary studies
The test substances were given to 2 animals per dose group by single gavage. Substances were given as aqueous solutions in a constant dose volume of 10 ml/kg bw and varying concentrations of 0.1 ml/kg bw (1%), 0.5 ml/kg bw (5%) and 1 ml/kg bw (10%), which is equivalent to 100, 500, and 1000 mg/kg bw of the Test Substance, respectively. Value in brackets gives the concentration of MDP in the aqueous solution that was given to the animals.

Main Study
Based on the preliminary study results all substances were given at 0.2 ml/kg bw (2%) to 3 animals per substance (equivalent to 200 mg/kg bw). Dose volume was 10 ml/kg bw as in the preliminary study. 3 control animals were left untreated.

EXAMINATIONS
Animals of the preliminary study were observed for signs of toxicity for 14 days. Survivors were sacrificed and subjected to necropsy as were animals that died. The same examinations were performed in the main study. Additionally liver function tests were carried out before and 8 d and 14 d after dosing (BST retention, sGPT; definition: BST= bromosulphthaleine; sGPT= serum glutamate-pyruvate transaminase).

Test substance: The following substances were tested:
1. MDP
2. raw MDP; raw product
3. Solution of 25% glutaraldehyde in water, contained ca. 8% methanol

Conclusion: Acute oral toxicities of raw and pure MDP were identical with respect to mortalities, biochemical parameters, and pathological findings. No animal died at 100 mg/kg bw; 1/3 animals died at 200 mg/kg bw, and all animals died at 500 and 1000 mg/kg bw. Therefore the oral LD50 in rabbits was between 200 and 500 mg/kg bw in this study. No signs of hepatic injury were seen in animals that survived a single dose of raw or pure MDP, or of 25% glutaraldehyde solution at 200 mg/kg bw, as substantiated by biochemical parameters (BST retention and sGPT at 8 and 14 days after dosing), and by the lack of liver changes during pathological examination after terminal sacrifice.

Reliability: (2) valid with restrictions
The study was conducted similar to OECD TG 401 (1987).
Restrictions: small number of animals; cadaverous victims

did not allow liver examination during necropsy of the main study.

Flag: Critical study for SIDS endpoint
05-SEP-2003 (47)

5.1.2 Acute Inhalation Toxicity

Type: LC50
Species: rat
Strain: Sprague-Dawley
No. of Animals: 20
Doses: 6.1 mg/l (= 6100 mg/m³ = 1310 ppm)
Exposure time: 4 hour(s)
Value: > 6100 mg/m³

Method: OECD Guide-line 403 "Acute Inhalation Toxicity"
Year: 1981
GLP: no
Test substance: other TS

Method: Limit test
Result: MDP concentration was 6.1 mg/l (=1310 ppm). No death seen (0/20) within the observation period. Clinical signs which included perinasal discharge, closed eye lids, labored breathing were resolved at 8 d. Weight gain was not affected. No gross pathological findings at necropsy.

Test substance: MDP ca. 95% grade.
Test condition: TEST ORGANISMS
10 rats of either sex

ADMINISTRATION
Inhalation chamber; dynamic generation of atmosphere.

EXAMINATIONS
Observation for clinical signs for 14 d and necropsy of animals that died or were sacrificed at the end of the observation period.

Reliability: GC analysis of MDP concentration.
(1) valid without restriction
(1b) Comparable to guideline study.

Flag: Critical study for SIDS endpoint
20-JAN-2003 (48)

Type: LC50
Species: rat
Strain: Sprague-Dawley
Sex: male/female
Vehicle: other: air
Doses: target concentrations: 1000 ppm (4739 mg/m³) and near vapor saturation
Exposure time: 1 hour(s)
Value: >= 40820 - 43014 mg/m³

Method: other: see Test condition
GLP: no data
Test substance: other TS: MDP, Purity 99.105% (MDP dimer 0.643 % and acrolein (AC) 0.037% according to GC)

Method: Similar to OECD guideline 403. Whole body inhalation chamber

Remark:

exposure at 1000 ppm and at near vapor saturation. A series of separate experiments was undertaken to investigate influence of Acrolein impurities on the acute inhalation toxicity of MDP. The LC50 value reported here relates to pure MDP.

The study was initially reported by UCC report No. 49-158 and 41-37 (submitted to US EPA TSCATS: OTS0534601, Doc. I.D. 88-920000152, Bushy Run Res Ctr, Report no. 49-158, sponsored by Union Carbide Corp., 04 Feb 1987) and subsequently published: Dodd DE et al. (1988) Vet Hum Toxicol 30: 545-550. It was also reported to USEPA: TSCATS: OTS0534601, Doc. I.D. 88-920000083, Union Carbide Corp., amended summaries to Reports 41-37 (14 Mar 1976), 49-174 (16 Dec 1986), and 49-158 (04 Feb 1987). Letter to USEPA dated 22 Nov 1991.

TSCATS: OTS0534601, Doc. I.D. 88-920000152, Bushy Run Res Ctr, Report no. 41-37, sponsored by Union Carbide Corp., 14 Mar 1976

TSCATS: OTS0534601, Doc. I.D. 88-920000152, Bushy Run Res Ctr, Report no. 49-158, sponsored by Union Carbide Corp., 04 Feb 1987

Result:

MORTALITY, CLINICAL SIGNS, NECROPSY FINDINGS

Results for the 4 experiments using different methods of atmosphere generation were as follows:

1. Static atmosphere, using MDP as supplied, concentration near saturation

In 2 separate experiments all animals (10/10 each) died during exposure at an average MDP concentration of 8070 ppm(measured value), or within 24 hr. AC concentration analysis was not carried out in the first experiment; in the second AC concentration was 240 ppm. Signs of toxicity included lachrymation, perioral and perinasal wetness, mouth breathing, hypoactivity, absence of reflexes (toe and tail pinch, surface righting). Lesions at necropsy included lung discoloration and clear fluid in trachea and pleural cavity.

2. Static atmosphere, MDP treated with a stream of N2 to remove AC, concentration near saturation

One experiment resulted in 50% mortality (5/10 animals, sexes combined). The measured concentration of MDP was 9076 ppm. AC was not determined. Time to death was 1 to 3 d. Signs of toxicity were similar as described above. Survivors recovered by day 5 after exposure and lost weight during the first postexposure week. Necropsy of animals that died revealed dark red discoloration of the lung, and perinasal and periocular encrustation. Survivors showed no gross pathology at necropsy.

In a second experiment, no deaths were seen (0/10 animals, sexes combined). MDP concentration was 8613 ppm; AC was below the detection limit (< 5 ppm). Lachrymation, perioral and perinasal wetness, mouth breathing, prostration, absence of toe and tail pinch reflexes were seen. These effects disappeared the next day. No gross pathology was seen at

necropsy.

3. Dynamic atmosphere, MDP near saturation.
No mortality (0/10 animals) was seen at a measured vapor concentration of 7748 ppm MDP. Concentration of AC was below the limit of detection (< 5ppm). Signs of toxicity were initial hyperactivity, followed by hypoactivity and lachrymation during exposure. Hypoactivity and periorcular wetness persisted on the day of exposure but disappeared by the next day.

4. Dynamic atmosphere, MDP at 1000 ppm
No mortality (0/20 animals) was seen at ca. 1070 ppm MDP. No acrolein was detected (< 5ppm). Lachrymation and hypoactivity was seen during exposure. Animals gained weight over the 14-d observation period, and no gross pathology was seen at necropsy.

Attached doc.:

Table: Mortalities and Vapor Concentrations for Various Exposures of Sprague-Dawley Rats to Vapor from 2-Methoxy-3, 4-Dihydro-2H-Pyran (Dodd et al. 1988)

Generation Method	Target Concentration	Sample ^A	Sex	Vapor Concentration (ppm)		
				Mortality ^B	MDP	Acrolein ^C
Static	Saturated	Untreated	M	5/5	8098 ± 269	NM
Static	Saturated	Untreated	F	5/5	8098 ± 269	NM
Static	Saturated	Untreated	M	5/5	8098 ± 269	240 ± 41
Static	Saturated	Untreated	F	5/5	8098 ± 269	240 ± 41
Static	Saturated	Sparged	M	3/5	9076 ± 560	NM
Static	Saturated	Sparged	F	2/5	9076 ± 560	NM
Static	Saturated	Sparged	M	0/5	8613 ± 422	<MLD
Static	Saturated	Sparged	F	0/5	8613 ± 422	<MLD
Dynamic (bubbler)	Saturated	Untreated	M	0/5	7748 ± 524	<MLD
Dynamic (bubbler)	Saturated	Untreated	F	0/5	7748 ± 524	<MLD
Dynamic (bubbler)	1000 ppm	Untreated	M	0/5	1064 ± 19	<MLD
Dynamic (bubbler)	1000 ppm	Untreated	F	0/5	1064 ± 19	<MLD
Dynamic (bubbler)	1000 ppm	Untreated	M	0/5	1095 ± 15	<MLD
Dynamic (bubbler)	1000 ppm	Untreated	F	0/5	1095 ± 15	<MLD

^A Untreated= as received; sparged= attempted removal of Acrolein with N₂ stream

^B Expressed as [No. Dying]/[No. Dosed]

^C NM= not measured; MLD= minimum level of detection (5 ppm)

Conclusion:

In some experiments, mortalities were observed that were attributable to AC impurities and occurred under conditions which favour AC accumulation, i.e. low ventilation and confined spaces. This is due to the high toxicity of AC (LC50, rat, inhal: 26 ppm (1 hr), 8.3 ppm (4 hr)). More details (Ballantyne et al.) are contained in chapter 5.11 of this document. It was concluded that a highly toxic impurity, acrolein (AC), accumulated under static

conditions, but not under dynamic conditions.

This is supported by the findings:

1. AC was present at 0.037% in the liquid MDP
2. AC concentration in the static exposure averaged 240 ppm. This is approx. 10-fold the 1 hr LC50 of 26 ppm for AC to rats.
3. Under dynamic conditions for high MDP concentrations (7748 ppm), AC was not detected (< 5 ppm), and no deaths did occur.
4. Attempts to remove volatile AC by sparging MDP prior to vaporization largely reduced (50%) or abolished mortality. AC was not detected (< 5 ppm) in the second study.

Thus toxic signs are limited to lachrymation and hypoactivity where exposure is only to, or nearly only to, MDP vapor. This indicates that MDP is irritant, but of a lower order of intrinsic toxicity by exposure to vapor.

Test condition:

TEST ORGANISMS

5 SD rats per sex and dose, of weight range 200-300g, were used per group. A total of 70 animals was used for this study. No untreated control animals were included. date: 16-OCT-2003

ADMINISTRATION

Animals were placed in a 120 L whole body exposure chamber. Animals were exposed for 1 hr. In four subexperiments different methods were used to produce the inhalation atmospheres:

1. Two studies with static atmosphere generation near saturation; MDP as supplied.
2. Two studies with atmosphere as above, but sparging of MDP prior to atmosphere generation with N2 to remove AC.
3. Two studies with dynamic atmosphere generation near saturation and at 1000 ppm MDP.
4. One study with vaporization of MDP in an air stream to yield 1000 ppm MDP.

For static atmosphere generation, a MDP sample (130-210 g) was allowed to evaporate overnight in the exposure chamber. For the dynamic atmosphere generation compressed air was passed through MDP in a wash bottle. Vapor was either passed directly to the chamber or diluted with filtered air to produce the target 1000 ppm concentration.

EXAMINATIONS

During the exposure samples of chamber air were taken for measurement of MDP and AC. Animals were observed during exposure and during a 14 d observation period for signs of pharmacologic or toxicologic effects. Body weight was measured before exposure, and at 7 and 14 d thereafter. At the end of the observation period survivors were sacrificed and necropsied as were animals that died.

Reliability:

- (1) valid without restriction
- (1b) Comparable to guideline study.

Flag:

Critical study for SIDS endpoint

21-FEB-2003

(49) (3) (41) (42) (50)

Type: other: IRT
Species: rat
Strain: no data
Sex: no data
No. of Animals: 24
Vehicle: other: air
Exposure time: 3 hour(s)

Method: other
GLP: no
Test substance: other TS

Method: Inhalation Risk Test, IRT; according to Smyth et al. (1962)
Remark: IRT provides toxicity information at or near vapor saturation concentration, i.e. at a fixed concentration that usually is not analyzed. Thus rather than LC50 estimation this test system is suitable for a more practical approach, i.e. to estimate inhalation toxicity risks after spills in confined spaces with low ventilation.

Result: MORTALITY
No deaths (0/12) were observed after 1 hr. After 3 hrs 10/12 animals had died.

CLINICAL SIGNS
Closed eyes, perinasal discharges, salivation, loss of pain reflexes, labored breathing, loss of upright surface reflex, narcosis were observed. 2 animals showed opalescent corneae.

FINDINGS AT NECROPSY
In animals that died: right heart dilatation, both sided congestion. Lung: congestion and moderate oedema. No pathological findings in sacrificed animals.
Test substance: MDP (<96%), acrolein dimer (4%). Traces of acrolein and methylvinylether.
Test condition: TEST ORGANISMS
12 rats were used.

ADMINISTRATION
Animals were placed in an exposure chamber and exposed to an atmosphere at near vapor saturation, generated by bubbling air through TS (layer of 5 cm) at a rate of 200 L/min at 20°C. Time of exposure was 3 hr.

EXAMINATIONS
Animals were observed for signs of toxicity for a period of 3 hr. Dead animals were necropsied as were survivors which were sacrificed at the end of the exposure period.
Reliability: (3) invalid
Concentration of test substance in atmosphere not measured.

05-SEP-2003

(44) (51)

5.1.3 Acute Dermal Toxicity

Type: LD50
Species: rabbit
Strain: New Zealand white
Sex: male/female
No. of Animals: 30
Vehicle: other: none

Doses: 2, 4, 8 ml/kg (=2000, 4000, 8000 mg/kg)
Value: = 4920 mg/kg bw

Method: other
GLP: no data
Test substance: other TS

Method: Similar to OECD Guideline 402

Result: MORTALITY
Deaths occurred within 1.5 hrs to 3 d after dosing, with higher doses being associated with shorter times. Dose-mortality data are given below.

Dose (ml/kg)	Males	Females
8.0	5/5	5/5
4.0	1/5	1/5
2.0	0/5	0/5

From these data dermal LD50 value (with 95% confidence intervals) of 4920 (3580-6750) mg/kg was calculated for both male and female rabbits.

CLINICAL SIGNS

Signs of toxicity were seen at all doses and included comatose appearance at 15 to 25 min, sluggishness during 24 hr contact period, and labored breathing and emaciated appearance at 7 and 14 d. Body weight loss was seen in the survivors.

Erythema and oedema were seen in some animals after removal of the occlusive dressing, with erythema persisting in a few animals for 7 d. A few animals that died from 8 ml/kg had ecchymoses. Desquamation was seen at 7 and 14 d.

NECROPSY FINDINGS

Necropsy of animals that died revealed dark red lungs and red patches in the trachea. Survivors showed red or pink discoloration of the lungs.

Test condition: TEST ORGANISMS

5 rabbits, bodyweight ca. 2.56 kg, were used per sex and dose group. No control animals were included.

ADMINISTRATION

Undiluted MDP was applied to the clipped trunk skin and held in place for 24 hr by an occlusive sheeting. After removal of the occlusion the skin was cleaned .

EXAMINATIONS

Animals were inspected twice daily for signs of toxicity and local effects. Body weight was measured before dosing, and at 7 and 14 d thereafter. At the end of the observation period survivors were sacrificed and necropsied as were animals that died.

LD50 values were calculated by the moving average method described by Weil.

Test substance: Purity of the TS was 99.105% MDP, 0.643% of the MDP dimer and 0.037% acrolein (AC)

Attached doc.:

Table: Mortalities and Body Weights for Rats and Rabbits Used to Determine the Acute Peroral and Percutaneous Toxicity of Undiluted 2-Methoxy-3,4-Dihydro-2H-Pyran

Route	Species	Sex	Dose (ml/kg)	Mortality *	Body Weight (g) as Mean ±S.D.		
					Pre dosing	7 Days	14 Days
Peroral	Rat	Male	4.0	5/5	246 ±14.1	258 ± 5.7	306 ± 2.1
			2.0	3/5	254 ± 8.0	293 ± 19.1	316 ± 20.7
		Female	4.0	3/3	209 ± 3.2	-----	-----
			2.0	4/5	222 ± 23.9	236	240
			1.4	2/5	226 ±13.9	244 ± 23,6	257 ± 21.4
Percutaneous	Rabbit	Male	8.0	5/5	2564 ± 144	-----	-----
			4.0	1/5	2574 ± 100	2108 ± 254	2226 ± 198
			2.0	0/5	2565 ± 127	2394 ± 230	2367 ± 154
		Female	6.0	5/5	2538 ± 249	----	-----
			4.0	1/5	2522 ± 150	201 ± 158	2145 ± 106

Mortality expressed as (No. Dying)/(No. Dosed)

Reliability: (1) valid without restriction
(1d) Meets generally accepted scientific standards and is described in sufficient detail.

Flag: Critical study for SIDS endpoint
20-JAN-2003 (40) (3) (41) (43)

Type: LD50
Species: rabbit
Strain: no data
Sex: male/female
No. of Animals: 10
Vehicle: other: none
Doses: 200 mg/kg
Value: > 200 mg/kg bw

Method: other
GLP: no data
Test substance: other TS

Method: Single dose dermal toxicity
Result: No deaths observed. Skin was hardened at the site of application at 5 d post treatment in 2/10 animals.
Test condition: TEST ORGANISMS
5 rabbits per sex and dose, weight 2-3 kg.

ADMINISTRATION
Undiluted TS was applied to the shaved dorsal rabbit skin in a volume of 0.2 ml/kg. Exposure under an occlusive cover was 24 hr.

EXAMINATIONS

Animals were observed for deaths to occur for a 3 d period. Necropsies were planned for animals that died.

Test substance: MDP (<96%), dimer acrolein (4%). Traces of acrolein and methylvinylether.

Reliability: (3) invalid
(3a) Significant methodological deficiencies. Method used does not comply with test guideline OECD 402 which requires 3 doses to produce mortalities and a 14 d observation period which allows LD50 calculation to be performed. The dose was chosen in order to evaluate classification according to DOT regulations at that time.

20-FEB-2002 (44) (52)

Type: LD50
Species: rabbit
Strain: no data
Sex: male
No. of Animals: 10
Vehicle: other: none
Doses: 1000, 2000, 4000 mg/kg
Value: = 1260 mg/kg bw

Method: other
GLP: no data
Test substance: other TS: MDP from UCC

Method: Similar to OECD 402
Remark: Range finding study. Purity of TS not reported. Deviations from OECD 402: number of animals.
Result: Findings after 14 days observation period:

Animals at 1000 mg/kg
1/4 animals died at day 14. Weight change -282 to 102 gm. Erythema and edema. Desquamation at 14 days. No other clinical signs of toxicity reported.

Animals at 2000 mg/kg
4/4 animals died at 5, 9, 11 and 12 days after dosing. Erythema and edema, desquamation. No other clinical signs of toxicity reported.

Animals at 4000 mg/kg
2/2 animals died at 2 and 3 days after dosing. Erythema and edema. Unsteady gait at 24 hrs.

Gross pathology revealed congested livers and kidneys in victims but nothing remarkable in survivors.

Test condition: 10 male albino rabbits, age 3 to 5 months, were used. Animals were immobilized during the 24-hr exposure period. Undiluted TS was applied to the clipped intact skin under impervious sheeting. Thereafter, TS was washed off.

Test substance: MDP from UCC, US; charge no.03118
Conclusion: Dermal LD50, rabbit: 1260 (0.772-2060) mg/kg
Reliability: (2) valid with restrictions
Small number of animals and immobilization are not regarded as significant restrictions.

Flag: Critical study for SIDS endpoint

17-SEP-2003 (46)

5.1.4 Acute Toxicity, other Routes

Type: LD50
Species: mouse
Strain: NMRI
Sex: male/female
No. of Animals: 70
Vehicle: CMC
Doses: 215, 316, 464, 681, 1000, 1470, 3160 mg/kg
Route of admin.: i.p.
Value: = 525 mg/kg bw

Method: other
GLP: no data
Test substance: other TS

Method: Intraperitoneal injection to mice
Result: LD 50, ip, mus=525 mg/kg; calculated for both sexes.
Test condition: TEST ORGANISMS
5 mice per sex and dose.

ADMINISTRATION
I.p. injection at 10 ml/kg.

EXAMINATIONS
Observation for 14 d with necropsy of animals that died or sacrificed at the end of the observation period.

Test substance: MDP (<96%), dimer acrolein (4%). Traces of acrolein and methylvinylether.

Reliability: (3) invalid
(3b) Unsuitable test system. Unphysiological route of exposure.

14-DEC-2001

(44) (53)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Concentration: undiluted
Exposure: Occlusive
Exposure Time: 4 hour(s)
No. of Animals: 6
Result: irritating

Method: other
GLP: no data
Test substance: other TS

Method: Similar to OECD 404, except from the use of occlusive exposure. May be regarded as worst case compared with semioclusive exposure.

Remark: The publication of Dodd et al. is cited in RTECS. There, however, exposure time is incorrectly cited as being 24 hr (instead of 4 hr), and MDP is reported to be moderately irritating.

Other than the publication of Dodd et al. the BRRC study report does not unequivocally identify TS and impurities.

In an early range finding study MDP was applied in a volume dose of 0.01 ml at concentrations of 10, 1, 0.1, and 0.01% to the clipped uncovered bellies of 5 rabbits. No irritancy was observed in this experiment.

Result: Well defined erythema and moderate to severe oedema were seen at 1 hr after removal of the occlusive dressing. Erythema became more marked overnight and persisted for 2 d. At 3 d oedema began to resolve, and both erythema and oedema were absent at 7 d. Desquamation was first seen at 2 d postapplication and persisted to 7 d. No animals showed necrosis or ulcerati

Test condition: TEST ORGANISMS
3 New Zealand white rabbits, bodyweight between 2.0-3.0 kg, were used per sex.

ADMINISTRATION

Undiluted MDP was applied to the clipped dorsal skin and covered for 4 hr by an occlusive dressing. After removal of the occlusion excess material was removed and the skin was cleaned.

EXAMINATIONS

The application site was inspected for local signs of inflammation at 1 hr and at 1, 2, 3, and 7 d after removal of the occlusive material.

Erythema and oedema were scored according to the method of Draize:

Score	Erythema	Oedema
0	not present	not present
1	slight	slight (barely visible)
2	well defined	mild (well defined margin)
3	moderate	moderate (ca. 1 mm raised)
4	severe	severe (raised > 1mm)

Test substance: Purity of the TS was 99.105% MDP, 0.643% of the MDP dimer and 0.037% acrolein (AC).

Attached doc.: Table: Summary for cutaneous irritation after 4 hr occluded application of MDP to rabbits.
Scored as described in text

Observation time (post application)	Effect as average (and range)		
	Erythema	Oedema	Desquamation
1 hr	2.0 (all 2)	3.5 (2-4)	-
1 d	2.0 (2-3)	3.3 (2-4)	-
2 d	2.5 (2-3)	2.7 (1-4)	D
3 d	2.5 (2-3)	2.3 (1-3)	D
4 d	0.0	0.0	D

Conclusion: Moderate erythema on 6/6 rabbits, moderate to severe oedema and desquamation 6 from 0.5 ml. Irritation subsided within 7 d except desquamation.

Reliability: (2) valid with restrictions
(2e) Meets generally accepted scientific standards, well documented and acceptable for assessment.

Flag: Critical study for SIDS endpoint

20-JAN-2003

(40) (3) (41) (42) (43)

Species: rabbit
Concentration: undiluted
Exposure: Semiocclusive
Exposure Time: 20 hour(s)
No. of Animals: 2
Result: irritating

Method: other
GLP: no
Test substance: other TS

Result: 1. MDP; moderate erythema was seen at 24 hr (2/2 animals) and peeling at 8 d (1/2).
2. Raw MDP caused moderate erythema (24 hr) followed by peeling in 1 animal (8 d); in the other, moderate erythema and strong oedema (24 hr) was followed by pronounced peeling and necrosis at 8 d.
3. Regular (25% glutaraldehyde) caused moderate necrosis and oedema (2/2) at 24 hr. Stronger necrosis and hardening of the skin was seen at 8 d.

Test condition: TEST ORGANISMS
2 rabbits, ca. 3.5 kg body weight

ADMINISTRATION
TS applied to the dorsal rabbit skin and covered with an gauze patch for 20 hr.

EXAMINATIONS
The application sites were inspected after removal of the dressings and at 24 hr and 8 d thereafter.

Test substance: The following substances were tested:
1. MDP
2. raw MDP; raw product
3. Regular GT; 25% glutaraldehyde in water (water ca. 67%), contains ca. 8% methanol

Conclusion: MDP was less irritating than the raw MDP, and much less irritating than 25% glutaraldehyde containing Regular.

Reliability: (3) invalid
(3a) Significant methodological deficiencies. Test procedure deviates from current test procedures in time of exposure (20 hr instead of 4 hr) and times of inspection. Applied volumes of TS not reported.

14-DEC-2001

(47)

Species: rabbit
Concentration: undiluted
Exposure: Occlusive
Exposure Time: 24 hour(s)
No. of Animals: 6
Vehicle: other: none
Result: not irritating

Method: other
GLP: no data
Test substance: other TS

Method: Draize test. Skin irritation according to Federal Register

38 no. 178 § 1500.41 p. 27019 (1973) using both intact and scarified skin.

Remark: The Draize test cannot be regarded as a valid test procedure from today's standpoint. It is evaluating scarified skin too, and its exposure time exaggerates the OECD exposure time 6-fold (24 hr) using occlusive dressing instead of semioclusive dressing. Other than in current test guidelines no readings were made at 1 and 48 hr after treatment. According to the Draize scheme the substance is not irritant. However, due to findings at necropsy it was recommended to regard the Test Substance as slightly irritating.

Result: FINDINGS
No mortalities were seen. No erythema and no oedema were observed at any time according to the score by Draize (1959), neither at the intact nor at the scarified rabbit skin.

FINDINGS AT NECROPSY
At day 7 post treatment skin of the sites of application was found thickened compared to surrounding and hardened (leather-like). Muscles not affected.

Test condition: TEST ORGANISMS
6 rabbits were used.

ADMINISTRATION
0.5 ml of the TS was applied to the shaved intact and scarified rabbit skin and covered by an occlusive dressing for 24 hr.

EXAMINATIONS
At 24 and 72 post treatment sites of application were examined for development of erythema or oedema. Animals were sacrificed at 7 d after dosing and skin at the site of application was examined.

Test substance: MDP (<96%), acrolein dimer (4%). Traces of acrolein and methylvinylether.

Reliability: (3) invalid
(3b) Unsuitable test system with respect to exposure time, scarified skin, and occlusive dressing.

14-DEC-2001 (44) (54)

5.2.2 Eye Irritation

Species: rabbit
Concentration: undiluted
Dose: .1 ml
Comment: not rinsed
No. of Animals: 18
Vehicle: other: none
Result: irritating

Method: OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year: 1987
GLP: no data
Test substance: other TS

Remark: OECD guideline 405 requires a volume of 0.1 ml of the TS.

Observation period was only 7 days and sufficient to evaluate reversibility of the effects.

In an early a range finding study MDP was found to cause moderate eye injury.

Other than the publication of Dodd et al. the underlying study report does not unequivocally identify TS and impurities.

Result:

1. After instillation of 0.1 ml MDP a mild to moderate conjunctivitis developed within 1 hr. Chemosis and discharge began to subside at 24 hr and had disappeared by 48 hr. Erythema began to resolve at 2 d, with only 1 animal showing a mild effect at 3 d. Conjunctivae of this animal were normal at 7 d. Mild iritis was seen in 5/6 animals by 1 to 4 hr which had resolved the day after. No corneal injury developed.

2. Following 0.01 ml there was still a mild to moderate conjunctivitis. Conjunctivae of all rabbits were normal by 3 d. Mild iritis was seen in 4/6 animals at 1 hr, but only 1/6 at 4 hr which resolved by 24 hr. No corneal injury was seen.

3. 0.005 ml led to mild conjunctivitis in 2/6 within 1 hr which resolved by 24 hr. All conjunctivae were normal at 48 hr. Transient iritis was seen at 4 hr in 1/6 animals. No corneal injury was seen.

Test condition:

TEST ORGANISMS

6 New Zealand white rabbits, bodyweight between 2.0-3.0 kg, were used per volume dose group.

ADMINISTRATION

0.1 ml of undiluted MDP was instilled into the inferior conjunctival sac of one eye of each of 6 rabbits. 0.01 or 0.005 ml MDP was placed directly on the surface of the cornea of 2 further groups of 6 rabbits.

EXAMINATIONS

The eyes were inspected for signs of ocular and periocular injury and inflammation at 1 and 4 hr and at 1, 2, 3, and 7 d.

Particular attention was paid to the development of hyperemia of the conjunctiva and nictating membrane, chemosis, discharge, iritis, and corneal injury. Effects were scored according to Draize.

Test substance:

Purity of the TS was 99.105% MDP, 0.643% of the MDP dimer and 0.037% acrolein (AC).

Attached doc.:

Table: Summary of Scores for Eye Lesions After the Application of Various Volumes of 2-Methoxy-3,4-Dihydro-2H-Pyran to the Eyes of Rabbits. Six Animals for Each Volume Group. Scored According to the Scheme in Table 3. (Dodd et al. 19988)

Volume (ml)	Observation time	Effects as Average (and Range)					
		Cornea		Iris	Conjunctiva		
		Opacity	Area		Hyperemia	Chemosis	Discharge
0.1	1 Hr	0.0	0.0	0.5(0-1)	1.0 (All)	1.3(1-2)	2.8 (2-3)
	4 Hrs	0.0	0.0	0.8 (0-1)	1.0 (All)	1.3(1-2)	2.7 (2-3)
	1 Day	0.0	0.0	0.0	1.0 (All)	0.3(0-1)	0.8 (0-1)
	2 Days	0.0	0.0	0.0	0.8 (0-1)	0.0	0.0
	3 Days	0.0	0.0	0.0	0.2(0-1)	0.0	0.0
	7 Days	0.0	0.0	0.0	0.0	0.0	0.0
0.01	1 Hr	0.0	0.0	0.7 (0-1)	1.0 (All)	1.2 (1-2)	1.5 (1-2)
	4 Hrs	0.0	0.0	0.2 (0-1)	1.0 (All)	0.3 (0-1)	1.5 (1-2)
	1 Day	0.0	0.0	0.0	0.7(0-1)	0.0	0.3 (0-2)
	2 Days	0.0	0.0	0.0	0.2 (0-1)	0.0	0.0
	3 Days	0.0	0.0	0.0	0.0	0.0	0.0
	7 Days	0.0	0.0	0.0	0.0	0.0	0.0
0.005	1 Hr	0.0	0.0	0.0	1.0 (All)	0.3 (0-1)	1.5 (1-2)
	4 Hrs	0.0	0.0	0.2 (0-1)	1.0 (All)	0.3 (0-1)	1.2 (0-2)
	1 Day	0.0	0.0	0.0	0.3 (0-1)	0.0	0.0
	2 Days	0.0	0.0	0.0	0.0	0.0	0.0
	3 Days	0.0	0.0	0.0	0.0	0.0	0.0
	7 Days	0.0	0.0	0.0	0.0	0.0	0.0

Conclusion: Splashes of liquid MDP in the eye may be expected to cause conjunctivitis for several days, but not corneal lesions.

Reliability: (1) valid without restriction
(1d) Meets generally accepted scientific standards and is described in sufficient detail.

Flag: Critical study for SIDS endpoint
20-JAN-2003 (40) (3) (41) (42) (43)

Species: rabbit
Concentration: undiluted
Dose: .1 ml
Comment: not rinsed
No. of Animals: 6
Result: irritating
EC classificat.: risk of serious damage to eyes

Method: other
GLP: no data
Test substance: other TS

Method: Draize test; eye irritation according to Federal Register 38 no. 178 § 1500.42 p. 27019 (1973). Not in compliance with OECD 405 "Acute Eye Irritation/Corrosion" which requires a observation period sufficient to evaluate reversibility or irreversibility of the lesions, up to a maximum of 21 days.

Result: FINDINGS
Cornea: At 24 hr in 5/6 animals diffuse areas (score 1) covering large areas of the eye (score 4) were seen. Mean score (ms) was 17 of the theoretical maximum of 80 for cornea. The

following 2 d opacity slightly aggravated (ms=23 and ms=27 at 48 and 72 hr, resp.). At each time of inspection the affected area of the cornea represented three-quarters or more.

Iris: Not affected in any animal at any time of inspection. Accordingly, ms=0 throughout the experiment.

Conjunctivae: Slight redness in all animals at 24, 48, 72 hr (ms=1)

Chemosis obvious (ms=2) at 24 hr, aggravated (ms=2.8) at 48 hr and at subsiding (ms=2.5) at 72 hr.

Secretion was moderate (ms=2 to 2.5) at 24, 48 and 72 hr.

Taking all scores together resulted in ms=27 at 24 hr, ms=36 at 48 hr, and ms=38 at 72 hr. This compares with the theoretical maximum of ms=110.

At 7 d post treatment opacity of the cornea persisted in 3/6 animals (ms=45); the corneae of the other 3 animals were judged ms=7. As no reversibility was noted after 8 days with respect to corneal opacity in 3 out of 6 rabbits a severe effect is assumed.

Test condition:

TEST ORGANISMS

6 rabbits were used.

ADMINISTRATION

0.1 ml of the TS was instilled to the conjunctival sac of one eye of each rabbit.

EXAMINATIONS

At 24, 48 and 72 post treatment cornea, iris and conjunctivae were examined for development signs of irritation or inflammation. Further observation until 7 d if there were signs of irritation at 72 hr.

Findings were scored according to DRAIZE

Test substance:

MDP (<96%), dimer acrolein (4%). Traces of acrolein and methylvinylether.

Conclusion:

According to the rating scheme the TS was classified as "moderately irritating". This attributes to a ms=26 to ms=55 on the ms scale from 0 to 110.

The observed persisting cornea opacity indicates the potential of severe eye injuries after contact with TS. Degree of injury, the large area affected and the persistence of the injury need to be taken into account for safety measures.

Reliability:

(2) valid with restrictions

(2c) Comparable to guideline study with acceptable restrictions.

Flag:

Critical study for SIDS endpoint

09-FEB-2003

(44) (55)

5.3 Sensitization

5.4 Repeated Dose Toxicity

Type: Sub-acute
Species: rat **Sex:** male/female
Strain: Sprague-Dawley
Route of administration: inhalation
Exposure period: 6 hr/d
Frequency of treatment: 9 d within 2 weeks
Post exposure period: 14 d
Doses: 0, 100, 984 and 4358 ppm (0.48, 4.66 or 20.64 mg/l)
Control Group: yes
NOAEL: < 100 ppm

Method: other
GLP: yes
Test substance: other TS

Method: Similar to OECD 412. Repeated inhalation, 9 exposures/2 wks, 6 hr each.

Remark: Only 10-page report summary available.

Result: Mean MDP and acrolein concentrations:
Low dose: MDP 100 ppm, Acrolein < 2 ppm
Mid dose: MDP 984 ppm, Acrolein 3.3 ppm
High dose: MDP 4358 ppm, Acrolein 7.8 ppm

Mortalities

Low and medium dose group: no mortalities reported.
High dose group: 100%; 13/15 m and 11/15 f were found dead, and 2 males and 4 females were killed for humane reasons on the first exposure day.

Signs and necropsy observations

Low dose group animals had decreased body weight gain. Increased spleen weight in females. Oedema in nasal cavities and mild squamous metaplasia in the respiratory mucosa. Intermediate group animals showed decreased food consumption, decreased body weight and body weight gain. Increased organ weights: lung and spleen (both sexes); liver, kidney, brain, adrenal glands, testes in males. Mild to moderate rhinitis. Cell degeneration or atrophy of the olfactory epithelium. Squamous metaplasia in the epithelium of the nasal cavity and to a lesser degree in larynges and trachea. Mucosal cell hyperplasia in some tracheae. High dose animals showed signs of respiratory distress and histological examination showed respiratory tract injury.

Test condition: A NOEL was not determined.
TEST ORGANISMS
10 animals per dose and sex. Another 5 animals per sex were assigned to 4 wk-recovery groups in the control and the high dose group. Body weight ranged between 287 to 400 g for males and 186 to 258 for females.

ADMINISTRATION

Whole body inhalation chamber, volume 1330 l. Dynamic atmosphere generation. Air flow 300 l/min. Exposure was for 6 hours/day, for 5 days in wk 1 and 4 days in wk 2.

EXAMINATIONS

Observation for signs of toxicity for 14 d. Necropsy of animals that died or that were sacrificed at the end of the

observation period. Observations included clinical signs, bodyweights, food and water consumption, ophthalmological parameters, hematological and clinical chemical parameters, macroscopical pathology, microscopical pathology of 10 organs, organ weights of liver, kidneys, brain, adrenals, lungs, spleen and testes.
MDP concentration was analyzed twice/6 hr exposure by CG/FID.

Test substance: MDP from UCC; purity 99.5% as revealed by GC analysis; data contained in report, Appendix 1

Conclusion: No NOAEL was determined, based on observed changes in body weight gain and microscopic findings in the 100 ppm group. Acrolein concentration of 7.8 ppm in the high dose group was just below the 4-hr LC50 value and thus probably contributed to death of the animals.

Reliability: (2) valid with restrictions
(2c) Comparable to guideline study with acceptable restrictions.

Flag: Critical study for SIDS endpoint

25-JAN-2003

(56) (57)

Type: Sub-acute
Species: rat **Sex:** male/female
Strain: Sprague-Dawley
Route of administration: dermal
Exposure period: 6 hr/d (occluded)
Frequency of treatment: 9 d within 2 weeks
Post exposure period: With and without
Doses: 100, 500, 1000 mg/kgxday
Control Group: yes
NOAEL: 1000 mg/kg bw

Method: other: see test condition

GLP: yes

Test substance: other TS: MDP, 99.8%

Method: Repeated dermal, 9 days occluded

Result: Mortalities: None.

Clinical signs and necropsy observations: No effect of MDP dosing was seen on water consumption, hematology, clinical chemistry or urinalysis. A slight, but statistically significant increase in relative liver weight was seen in sacrificed high dose males (+7.7% vs control, $p < 0.1$), but was not found in animals sacrificed at the end of the recovery period.

No liver changes were seen macroscopically, and no changes in liver enzyme activities were found. Therefore the increase in liver weight was not considered of biological relevance. No weight changes were observed for any of the other organs. All animals were free of treatment related macroscopic changes at necropsy, and no test material microscopic lesions were seen in the tissue sections examined. The neurobehavioral observation in treated animals was comparable with control animals.

Topical administration of MDP to rats for 9 days did result in reduced food consumption and slightly reduced body weights at the 500 and 1000 mg/kg/day dose groups (body

weights at the end of the dosing period: males: -8.8%; -6.4%; females: -4.1%; -3.1% in mid- and high-dose groups, respectively). The reduced food consumption was significant in males only, and was not consistently related to dose and was significant in high dose males only during days 3 to 5 and 12 to 15 and the mid dose males at day 12 only. No effects of skin irritation were observed in the 100 and 500 mg/kg/day dose groups (primary irritation index = 0 for both males and females). In the 1000 mg/kg/day group no irritation was observed in male animals (primary irritation index = 0). Very slight erythema was seen in some females from the second day of treatment onwards, and slight desquamation was observed during the last days of exposure (day 5-9) in one male and in 5 female animals. This effect however was completely resolved at day 12 (male) or day 18 (females) before the end of the recovery period.

A slight increase in relative liver weights of the high dose males (statistically different from control means, $p < 0.1$ for sacrifice males and $p < 0.05$ for recovery males) was not correlated with changes in liver enzyme activities or macroscopic changes. Marginal, but statistically significant body weight changes were observed in males at the mid- and high dose groups, but were not always dose-related and not consistent throughout the exposure period. These changes were therefore not considered biologically relevant.

The authors therefore concluded the NOAEL to be 1000 mg/kg/day.

Test condition:

TEST ORGANISMS

10 animals (CD, Sprague Dawley derived [Cr1: CD BR]) per dose and sex, with the control and high dose of 15 animals per dose per sex.

At the start of dosing the animals were 7 weeks (males) and 9 weeks (females) old. Body weights at start of study were: males: 228.3 (220-250) females: 207.3 (181-227) gram

TEST MATERIAL

Test material was administered as received (99.8% purity, clear slightly viscous liquid).

ADMINISTRATION

Test material was applied on the clipped skin of the back and sides and spread evenly over the clipped area (5x5 cm). A layer of gauze was placed over the site with a piece of impervious plastic on top and then secured with Elastoplast tape. Following 6 hours of application the wrappings were removed and the test site wiped free of any remaining test material. Control animals were similarly treated however without test material. Test material was applied once daily for 5 consecutive days, a treatment free weekend, followed by 4 consecutive days.

DOSES

Doses were calculated using the most recent body weights
Group II: 100 mg/kg/day
Group III: 500 mg/kg/day

Group IV: 1000 mg/kg/day

Dose volumes:

Group II: 0.1 mL/kg

Group III: 0.5 mL/kg

Group IV: 1.0 mL/kg

STATISTICAL ANALYSIS:

The following parameters were evaluated statistically: body weight, body weight change from week to week, food and water consumption, hematology, clinical chemistry, urine chemistry, urine pH, urine specific gravity, urine volume and organ weights.

Method of analysis used: Multiple Group Analysis, one way analysis of variance technique followed by a multiple comparison procedure if needed (Bartlett's test, ANOVA, Dunnett's test, Kruskal-Wallis test)

EXAMINATIONS

10 animals per dose and sex were sacrificed at the end of the exposure period and examined for hematology, clinical laboratory, urinalysis and necropsy and microscopic lesions.

5 animals per dose and sex of the high dose group and control animals were allowed a recovery period of 26 days, after which they were sacrificed. The recovery group was also examined for clinical chemistry, macroscopic and microscopic findings.

The following clinical chemistry parameters were measured:

AST, ALT, Alkaline Phosphatase, Lactate Dehydrogenase, Sorbitol Dehydrogenase, Blood Urea Nitrogen, Creatinine, Creatine Kinase, Total Protein, Albumin, Globulin (calculated), Total Bilirubin, Direct Bilirubin, Na, K, Cl, Phosphate, gamma-Glutamyl Transferase.

The following organ weights were recorded: adrenal glands, brain, kidneys, liver, ovaries and testes.

The following tissue were examined histopathologically: brain, kidneys, nerve, skin (treated and untreated), spinal cord, any tissues with macroscopic findings.

Physical observations (Irwin screen), body weight, food consumption, water consumption, neuro-behavioral observations

and skin irritation evaluations were performed on all animals pre-test and at selected intervals during the treatment and recovery periods.

Test substance: MDP from UCC; purity 99.8% as revealed by GC analysis; data contained in report, Appendix O

Conclusion: NOAEL: 1000 mg/kgxday

Reliability: (2) valid with restrictions
(2c) Valid study but deviating from standard test guidelines
(9 days exposure)

Flag: Critical study for SIDS endpoint

05-SEP-2003

(58)

Species: mouse **Sex:** male/female

Strain: Swiss Webster

Route of administration: inhalation

Exposure period: 5d

Frequency of treatment: 6 h/d

Post exposure period: none
Doses: 0, 5, 10, 25 ppm (main study; about 24, 48, 120 mg/m³);
50, 100, 500 ppm (probe study; about 240, 480, 960
mg/m³)
Control Group: yes
Method: other: Similar to OECD 474 using peripheral blood
Year: 1995
GLP: yes
Test substance: other TS: MDP from UCC

Remark: For a detailed study description see Section "Genotoxicity
in vivo (5.6)".

Result: NOTE: this study was designed as a micronucleus study with 5
day inhalation exposure, of which the results are described
in section 5.6.

Clinical observation:

In the probe study three and 4 male mice in the 100 and 500
ppm groups respectively, died during the study as did 1, 3
and 5 female mice in the 50, 100 and 500 ppm group
respectively. The remaining males of the 500 ppm group was
sacrificed on day 3 due to severity of the effects. Clinical
signs in the probe study at = 50 ppm (240 mg/m³) were spasms
of the lids and abdominal breathing. Clinical signs in the
main study, during exposure at concentrations = 10 ppm (48
mg/m³) were hypoactivity, and at = 25 ppm (120 mg/m³) lack
of startle reflex.

Body weights:

In the probe study, body weight gains decreased both in
males and females of the 50 and 100 ppm group, but these
effect could not be statistically evaluated due to the small
number of survivors. A decrease in body weight gain was also
observed in the 25 ppm males of the main study.

Organ weight and necropsy findings (only performed in the
probe study):

Absolute and relative spleen weights were decreased and
absolute and relative lung weights were increased in the 50
and 100 ppm groups (240, 480 mg/m³). The epithelium of the
respiratory tract from the nasal cavity down to the
bronchi/bronchioles was necrotic with occasional ulceration
and inflammation resulting from the necrosis.

Test condition: NOTE: this study was designed as a micronucleus study with 5
day inhalation exposure, of which the results are described
in section 5.6.

TEST ORGANISMS

5 mice per sex and dose in both the probe and the main
study.

ADMINISTRATION

Groups of mice were exposed in a 900 l inhalation chamber
for 6 hrs each on 5 consecutive days. A 5-day probe study
was conducted using 5 mice per sex and dose at 0, 50, 100
and 500 ppm (BRRC report 93U1227 A). Test conditions were
close to those during the main study. MDP concentrations
were monitored hourly. Acrolein concentrations were below

the limit of detection (<3ppm) in each chamber. In the probe study, mortalities and severe toxicity was seen at 100 and 500 ppm. In the main study (93U1227B) therefore, mice (5/sex/group) were exposed for 6 hours/day for 5 consecutive day to 0, 5, 10 or 25 ppm of MDP vapor.

Vapor was generated by pumping liquid TS to an evaporator maintained at ca. 30-43°C. All the chamber air flowed through the evaporator in a countercurrent flow at 200 l/min.

Measurements during administration included chamber temperature, relative humidity, evaporator temperature, concentrations of MDP (twice each hour) and of acrolein. Negative controls received no MDP. Positive control animals received single ip injections of 15 mg/kg cyclophosphamide.

OBSERVATIONS AND MEASUREMENTS

NOTE: this study was designed as a micronucleus study with 5 day inhalation exposure, of which the results are described in section 5.6. Animals were observed for clinical signs. Body weight data were collected. All animals received an abbreviated necropsy, which included examination of the upper respiratory tract, thoracic cavity and spleen.

EVALUATION CRITERIA

NOTE: this study was designed as a micronucleus study with 5 day inhalation exposure, of which the results are described in section 5.6. Any significant clinical observations, body weight changes were noted and in the probe study also organ weight changes or necropsy findings were noted.

Test substance: MDP from UCC; purity 99.4% as revealed by GC analysis; data contained in report, Appendix 1. Acrolein 0.12%; acrolein dimer 0.32%

Reliability: (2) valid with restrictions
(2) reliable with restrictions; study performed to investigate in vivo mutagenicity; limited scope of tissues examined; small number of animals

Flag: Critical study for SIDS endpoint

08-SEP-2003

(59) (60)

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100, TA 1535, TA 1537
Concentration: 0, 0.02, 0.1, 0.5, 2.5, 5, 7.5 mg/plate
Cytotoxic Concentration: >7.5 mg/plate; no cytotoxicity observed
Metabolic activation: with and without
Result: positive

Method: OECD Guide-line 471
Year: 1983
GLP: no
Test substance: other TS

Remark: According to authors cytotoxicity was noted at concentrations >7500 µg/plate.

Result: Solubility of TS in DMSO was given. No bacteriotoxic effect was seen up to 7500 µg/plate.

No increase of revertants was seen without S9 in any of the tester strains.

With S9 mix a slight and apparently dose dependent increase was seen only in TA 100, i.e. by a factor of 1.8-2.7 in the range 500-2500 µg/plate, and 4.3-fold at 7500 µg/plate. No increase was noted at 5000 µg/plate.

Mean revertant increase by positive control substances 2-Aminoanthracene and MNNG in TA 100 was 14.5- and 9.5-fold, respectively.

Test condition: TEST SYSTEM
Base pair substitution (TA 1535, TA 100) and frameshift (TA 1537, TA 98) tester strains with and without metabolic activation.

ADMINISTRATION
Doses: 1st experiment: 0, 20, 100, 500, 2500, 5000 µg/plate tested with all tester strains. 2nd experiment: 0, 100, 500, 2500, 5000, 7500 µg/plate tested with TA 100. 3 plates per dose.

Positive controls: 10 µg 2-aminoanthracene (+S9, all strains); -S9: 5 µg MNNG (TA 100, TA 1535), 10 µg 4-nitrophenylenediamine (TA 98), 100 µg 9-aminoacridine chloride monohydrate (TA 1537). DMSO was used as solvent.

EVALUATION CRITERIA
Reaction to a substance is regarded as positive if the following is given

- doubling of spontaneous control mutation rate
- dose-response relationship
- reproducibility of results

Test substance: MDP; substance purity >99.9%

Conclusion: Mutagenic in the presence of S9 mix in TA 100, based on significantly increased numbers of revertants in independent experiments in the range 500-2500 µg and at 7500 µg per plate, but not at 5000 µg/plate.

Reliability: (1) valid without restriction
(1b) Comparable to guideline study.

Flag: Critical study for SIDS endpoint

19-AUG-2003 (61)

Type: HGPRT assay

System of testing: chinese hamster ovary cells (CHO-K1-BH4)

Concentration: 0.05, 0.1, 0.25, 0.5, 0.65, 0.75, 1.0, 2.0 mg/ml (+/- S9)

Cytotoxic Concentration: 0.250 mg/ml (-S9) and (+S9)

Metabolic activation: with and without

Result: ambiguous

Method: other

GLP: yes

Test substance: other TS

Method: Mammalian cell HGPRT forward mutation; according to Hsie et al. (1981)

Result: Cytotoxicity
(1) Range finding test: MDP produced excessive cytotoxicity at 1.0 mg/ml or more (-S9), and at 3.0 mg/ml or more (+S9).

No reduced relative survival was seen at 0.03 mg/ml (-S9) and 0.1 mg/ml (+S9) or less.

(2) Main test, 24 hr after MDP treatment: Without S9, cytotoxicity was seen at 0.25 and 0.5 mg/ml, with 0.75 mg/ml completely killing cell cultures. No cytotoxicity was seen at ≤ 0.1 mg/ml.

With S9, cytotoxicity was observed at 0.25, 0.5, 0.75 mg/ml; excessive toxicity was seen at 2.0 mg/ml. No cytotoxicity was seen at ≤ 0.1 mg/ml.

Mutagenicity

The only statistically significant ($p < 0.05$) increases in mutation frequencies were seen at 0.5 mg/ml MDP (-S9) and at 0.25 mg/ml (+S9). These were reproducible between replicates, but not in independent tests.

Test quality parameters

Mutation frequencies of culture medium and vehicle controls, both (+ and - S9), were acceptable. Positive controls were mutagenic under the test conditions.

Test condition:

TEST SYSTEM

HGPRT gene mutation in CHO cells. With and without presence of rat metabolic activation enzymes, S9.

ADMINISTRATION

CHO cells were treated with positive control, vehicle control, and MDP both in the presence and absence of S9. Duplicate cultures were used except for positive controls (single culture). Two independent repetitions of the complete assay were performed.

Based on results of a range finding test, 5 concentrations of MDP were used ranging from 0.1-1.0 mg/ml (-S9) and from 0.1-2.0 mg/ml (+S9). In repeat test 5 concentrations ranged from 0.05-0.65 mg/ml (-S9) and 6 concentrations from 0.075-1.0 mg/ml (+S9). Vehicle was ethanol. Positive controls: EMS (ethyl methanesulfonate), DMN (dimethylnitrosamine); vehicle used was water.

EVALUATION CRITERIA

Mutation data analysis according to Irr&Snee (1979) after transformation according to Box&Cox (1964). data for positive controls were not compared if at least 5-fold of culture medium control value.

Criteria depend on both the level of significance with respect to the concurrent vehicle control and the evidence of a dose-response effect. Increases were positive if they met at least one of the criteria: statistically significant, concentration-related at 2 or more consecutive concentrations; or a significant, reproducible increase at 1 or more concentration levels. Increase of mutation frequency at least 2-fold with respect to vehicle. Also, spontaneous frequency between 0 and 20 per 10^6 viable cells, frequency of positive controls min. 2-fold of culture medium controls; viable fraction at least 80% for medium controls.

Test substance:

MDP; substance purity was 99.4% pretest and 99.5% posttest according to GC/MS and NMR. Average of triplicate analysis. Acrolein was 0.12% and acrolein dimer 0.32%. Further impurities were (percent) : trimethyl silanol & butanol

0.02; 114 mw pyran isomer 0.01; 130 mw pyran isomer 0.01;
114 and 130 mw 0.01 each; all other impurities 0.08.

Conclusion: MDP produced neither with nor without S9 consistent, statistically significant, dose-related increases in mutation frequencies in the CHO cell system. Therefore, MDP was not considered mutagenic.

Reliability: (1) valid without restriction
(1b) Comparable to guideline study.

Flag: Critical study for SIDS endpoint
19-AUG-2003 (62) (63)

Type: HGPRT assay
System of testing: V79 Chinese Hamster Cells
Concentration: 0, 0.050, 0.158, 0.5, 1.580, 2.810, 5.0 mg/ml
Cytotoxic Concentration: 2810 µg/ml (-S9)
Metabolic activation: with and without
Result: positive

Method: OECD Guide-line 476
Year: 1984
GLP: yes
Test substance: other TS

Method: In vitro mammalian cell (V79) gene mutation (HPRT)
Remark: (1) Range finding study: Cytotoxicity (relative cloning efficiency <0.75) was seen at 1580, 2810, and 5000 µg/ml (without S9) and at 500, 890, 1580, 2810, 5000 µg/ml with S9 (triplicate experiments).
(2) Main study: (1) reduced cells numbers and rel. cloning efficiencies with 2810 and 5000 µg/ml indicated cytotoxic effects. (2) 2810 µg/ml was only tested in 2nd series (3 incubations). (3) With 2810 µg/ml, increase of mutation frequency was only 2.07-fold that of controls.
(3) The authors point out that mutagenicity could be related to impurities of the TS. The rationale is that mutagenicity was only seen at very high concentrations which led to persistent visible precipitations. Addition of S9 inhibited mutagenic effects. The authors question whether S9 could metabolize such high amounts of TS. It should be mentioned that TS precipitations persisted in presence of S9, too.
(4) No statistical data analysis was performed.

Result: Range finding test:
The highest concentration should precipitate or exhibit toxicity (i.e. rel. cloning efficiency <0.75), or should be tested up to 5000 µg/ml. In the range finding, MDP precipitated at 890 µg/ml and dissolved during the test; precipitation persisted at 1580, 2810 and 5000 µg/ml. Clear cytotoxicity (reduced cloning efficiency) was seen according to authors at 2810, and 5000 µg/ml, both with and without S9.

Main study:
Toxic effects noted at 2810 and (reduced cell numbers) at 5000 µg/ml.

Mutation frequencies without S9:
Solvent controls: 4.76x10E-6 to 14.3x10E-6
MNNG: 1560x10E-6 to 2740x10E-6

MDP up to 1580 µg/ml: in the range of controls
MDP 2810 µg/ml: mean 25.1×10^{-6} (2nd series only)
MDP 5000 µg/ml: mean 43.5×10^{-6} (1st series) and 61.7×10^{-6}
(2nd series)

Mutation frequencies with S9:
Solvent controls: 1.01×10^{-6} to 7.66×10^{-6}
DMBA: 651×10^{-6} to 2210×10^{-6}
MDP up to 5000 µg/ml: in the range from 1.94×10^{-6} to
 25.0×10^{-6}

Test condition:

TEST SYSTEM
HPRT gene mutation in V79 cells. With and without presence
of rat metabolic activation enzymes, S9.

ADMINISTRATION

Doses were based on results of a range finding test: 50,
158, 500, 1580, 5000 µg/ml with S9 and first series without
S9; second series without S9: 1580, 2810, 5000 µg/ml
dissolved in DMSO. 2 parallel cultures per concentration and
positive controls, 3 cultures for negative (solvent)
controls. Usual negative controls: solvent; water, or DMSO
(used in this study; max. 1 %), or acetone or ethanol (max.
0.1%). Positive controls: 1 µg/ml MNNG (-S9), 20 µg/ml 7,12
DMBA (+S9)

EVALUATION CRITERIA

Negative controls: spontaneous mutation frequency should be
< 20×10^{-6}

Positive controls: at the selected concentrations MNNG and
DMBA should cause 10-fold increase in mean mutation
frequencies.

"No increase": mean mutat. frequency < 20×10^{-6} , OR mean
frequency of 2 parallel incubations less than 2.0-fold above
the mean of the negative controls.

"Clear increase": 5.0-fold above the mean of neg. controls,
AND the mean mutat. frequ. > 40×10^{-6}

"weak increase": all other results

"non-mutagenic": if no effect in two independent
experiments, or no effect in one and weak effect in the
second experiment

"mutagenic": a clear effect occurs at similar
concentrations, or a clear effect in one series and a weak
effect in the other series, or weak effects occur
dose-dependently (over at least 2 concentrations) and
reproducibly at identical concentrations in the 2 series.

Test substance:

Conclusion:

MDP, purity >99.9%, traces of water and dimeric acrolein.
Slight increases in mutation frequencies were obtained only
at very high concentrations of 2810 and 5000 µg/ml which
caused cytotoxicity and led to precipitations. The authors
did not exclude that the observed weak mutagenicity seen
under these conditions was due to impurities of the test
substance.

Reliability:

The positive effect was only borderline at 2810 µg/ml in the
absence of S9-mix (2.07-fold increase). No increase in
mutation frequency was seen in the presence of S9-mix.
(2) valid with restrictions
(2b) Guideline study with acceptable restrictions.

Conflicting interpretation of data by the authors. Outlined under Remarks.

Flag: Critical study for SIDS endpoint (64)
05-SEP-2003

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Concentration: 0.03, 0.1, 0.3, 1.0, 3.0 mg/plate
Cytotoxic Concentration: 3 mg/plate (TA 100)
Metabolic activation: with and without
Result: positive

Method: other
GLP: yes
Test substance: other TS: MDP

Method: Similar to OECD guideline 471
Remark: Dose-relation given in TA 100, -S9, in the range 0.03-1.0 mg MDP/plate.

No dose-relation in TA 98, -S9: numbers of revertants close to vehicle control in the range 0.03-0.3 mg MDP/plate; 2- to 3-fold increase at 1.0 and 3.0 mg MDP/plate.

Result: Cytotoxicity Study:
Cytotoxicity was tested in the range 0.001-10 mg/plate. In the absence of S9, MDP was nontoxic at 1 mg/plate and below, but complete absence of background lawn was seen at 3 mg/plate.

MDP was nontoxic to TA 100 at 1.0 mg/plate or less in presence or absence of S9. Extreme toxicity (absence of background lawn) was seen at 3 mg/plate and more, both with or without S9.

Main Study:
All 5 strains showed mutagenic responses to the positive control substances, and mean numbers of spontaneous revertants were acceptable.

Absence of S9:
No effects in TA 98, TA 1535, nor in TA 1538.
With TA 100 increases of approx. 2- to 3-fold, apparently increasing with dose in the range 0.3-1.0 mg MDP/plate.
In TA 1537 approx. 2-fold increase at 1 mg MDP/plate; reproducible effect, but no evidence of a dose response.

Presence of S9:
TA 98: apparently dose-related revertant increase; max. average 3.36-fold (test 1, 3 mg/plate) and 2-fold (test 2, at 1 mg MDP/plate).
TA 100: apparently dose-related increase; max. average 3.5-fold (test 1, 1 mg/plate) and 4.08-fold (test 2, 1 mg MDP/plate).
TA 1535: no clear dose response; max. average of 1.50- (test 1, 1 mg/plate) and 2.50-fold (test 2, 3 mg/plate).
TA 1537: no clear dose-response; max. average 2.4-fold increase at 1 mg MDP/plate.
Approx. 2-fold increases in TA 1535 and TA 1537 did not appear to be dose-related and were not reproducible.
TA 1538: no effect

Test condition: TEST SYSTEM

Base pair substitution (TA 1535, TA 100) and frameshift (TA 1537, TA 1538, TA 98) tester strains with and without metabolic activation.

ADMINISTRATION

Doses: 0, 30, 100, 300, 1000, 3000 µg/plate tested with all tester strains, both in presence and absence of metabolic activation (S9, + or -). Triplicate experiments. Positive controls were included. Two independent repetitions of the complete assay were performed. DMSO was used as solvent. Doses were based on results of a preliminary cytotoxicity study with TA 100 in the range 0.001 to 10 mg/plate with and without S9.

EVALUATION CRITERIA

In the preliminary study, cytotoxicity was evaluated in TA 100 by determining the growth of background lawn (confluent, sparse, absent) and revertant colonies (1 plate). Cytotoxicity was also monitored during the main study. Plate was excluded if background lawn was absent, or, if sparse, toxicity was assumed if number of spontaneous revertant colonies was less than 50% of mean for vehicle control.

Test substance: MDP; substance purity was 99.4% pretest and 99.5% posttest according to GC/MS and NMR. Average of triplicate analysis.

Acrolein was 0.12% and acrolein dimer 0.32%. Further impurities were (percent) : trimethyl silanol & butanol 0.02; 114 mw pyran isomer 0.01; 130 mw pyran isomer 0.01; 114 and 130 mw 0.01 each; all other impurities 0.08.

Conclusion: Small increases in mutation frequencies were seen with TA 98 in the presence of S9, and with TA 100 in both absence and presence of S9.

In the authors' opinion, MDP produced consistent, dose-related mutagenic effects in TA 100 in both absence and presence of S9, and in TA 98 in the presence of S9. MDP was not mutagenic to TA 98, TA 1535 or TA 1538 in the absence of S9, or TA 1538 in the presence of S9. All other results from tester strains with or without S9 were equivocal since increase, if any, was small or not dose-related or not reproducible.

Reliability: MDP was considered mutagenic.
(1) valid without restriction
(1b) Comparable to guideline study.

Flag: Critical study for SIDS endpoint

09-FEB-2003

(65) (66)

Type: Sister chromatid exchange assay
System of testing: Cultured CHO cells
Concentration: 0.05-0.5 mg/ml (-S9), 0.05-1.0 mg/ml (+S9)
Cytotoxic Concentration: not reported
Metabolic activation: with and without
Result: ambiguous

Method: other

GLP: yes

Test substance: other TS: MDP from UCC

Method: Similar to Directive 88/302, B19
Result: Technical problems arose throughout the study as evidenced by reduced number of cell divisions in medium control and vehicle control cells. Less than 60% of these cells had completed 2 cell division cycles. Since the untreated and vehicle control cultures did not exhibit appropriate staining characteristics, evaluation of the MDP-treated slides was not valid.

The reason for the technical problems remained unclear due to time restrictions because of the shut-down of the facility. Therefore no evaluation of the MDP-treated cells was possible, and no detailed results for MDP-treatment were reported.

Test condition: TEST SYSTEM
CHO cells with and without metabolic activation (+S9 or -S9)

ADMINISTRATION
5 concentrations of MDP were tested both with and without S9, ranging from 0.05-0.5 mg/ml in the absence of S9 and from 0.05-1.0 mg/ml in the presence of S9. Ethylmethane sulfonate (EMS) and dimethylnitrosamine (DMN) served as positive control substances. Vehicle control substance was ethanol. Cells were treated for a period of 4 hrs (DMN: 2-3 hrs), then washed and incubated with Bromodesoxyuridine for 24-28 hrs. Colchicine was added 2-3 hrs prior to cell harvest and staining.

Test substance: MDP from UCC; purity 99.4% as revealed by GC analysis; data contained in report, Appendix 1. Acrolein 0.12%; acrolein dimer 0.32%

Reliability: (3) invalid
(3a) Significant methodological deficiencies. Technical problems.

21-JAN-2003

(67)

5.6 Genetic Toxicity 'in Vivo'

Type: Micronucleus assay
Species: mouse **Sex:** male/female
Strain: NMRI
Route of admin.: gavage
Exposure period: single dose
Doses: 250, 500, 1000 mg/kg
Result: negative

Method: OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"
Year: 1983
GLP: yes
Test substance: other TS

Result: Range finding study: at 1210 mg/kg deaths had been observed whereas 1000 mg/kg were survived. Signs of toxicity included irregular breathing, piloerection, squatting posture, gasping, closed eyelids.

Main study:
Analytical examination of olive oil samples revealed concentrations of 27, 54.7, and 109.2 g/l. Clinical signs:

none after vehicle only nor after positive control substances. TS at 250 mg/kg: irregular respiration, piloerection 15-60 min after dosing; at 500 mg/kg additionally staggering, squatting posture after 15-60 min; at 1000 mg/kg: additionally gasping, abdominal position after 0.5 -4 hr .

Micronuclei counts at 24 hr after dosing, expressed as 0/00 in poly- (=pe) and normochromatic (=ne) erythrocytes:

Solvent control:	pe= 1.5	ne= 0.74
cyclophosphamide:	pe= 12.4	ne= 1.33
vincristine:	pe= 139.0	ne= 3.09
MDP, 250 mg/kg:	pe= 2.2	ne= 1.17
MDP, 500 mg/kg:	pe= 1.9	ne= 1.80
MDP, 1000 mg/kg:	pe= 2.3	ne= 1.58

Test condition:

TEST ORGANISM

70 NMRI mice, male and female, mean bw 26 g. 5 animals per dose and sex were used for TS and negative control, and 5 animals for each of the positive control substances.

ADMINISTRATION

MDP administered by gavage in olive oil at 10ml/kg. Concentrations were 25, 50, and 100 g/l oil. Negative controls received vehicle only. Positive controls received the clastogen cyclophosphamide (20mg/kg, in water, gavage at 10 ml/kg) or the spindle poison vincristine (0.15 mg/kg, in water, i.p. at 10 ml/kg). Femoral bone marrow was prepared 24 hr post dosing, and at 16 hr and 48 hr after 1000 mg/kg MDP.

EVALUATION CRITERIA

Generally, 1000 polychromatic erythrocytes per animal are evaluated for the parameters: (1) no. of polychromatic erythrocytes with/without micronuclei and calculation of clastogenic index, no. of normochromatic erythrocytes with/without micronuclei, calculation of ratio polychromatic/normochromatic erythrocytes, no. of small ($d < 1/4$) and large ($d > 1/4$) micronuclei.

No statistical data analysis performed.

Test substance:

MDP, grade 99.9%

Conclusion:

MDP was not clastogenic nor was impairment of spindle apparatus seen at any dose or time (16, 24, 48 hr tested), as evidenced by numbers of micronuclei (small or large) in the range of vehicle controls.

Erythropoiesis was not affected by any dose of MDP as evidenced by the unaffected ration of polychromatic/normochromatic erythrocytes.

MDP was tested in doses up to just below oral LDlow (24 hr) in mice.

Reliability:

(1) valid without restriction
(1a) GLP guideline study

Flag:

20-FEB-2002

Critical study for SIDS endpoint

(68)

Type:

Micronucleus assay

Species:

mouse

Sex: male/female

Strain:

Swiss Webster

Route of admin.:

inhalation

Exposure period:

5 consecutive days, 6 hrs/d

Doses:

0, 5, 10, 25 ppm (approx. 23, 47, 118 mg/m³; calculated using

[ppm=(molvolume/molweight)(mg/m³)]

Result: negative

Method: other

GLP: yes

Test substance: other TS: MDP from UCC

Method: Similar to OECD 474 using peripheral blood

Remark: Additional observations were also made during 2 range finding studies. Effects related to the ratio of PCE/NCE (polychromatophilic and normochromatophilic erythrocytes, resp.) and micronucleated PCE are outlined below.

(1) A 9-day rat inhalation toxicity study (BRRC report 92U1013) was conducted with MDP at 100, 1000, and 5000 ppm. Adverse effects were seen in all treated groups.

(2) A 5-day probe study was conducted using 5 mice per sex and dose at 0, 50, 100 and 500 ppm (BRRC report 93U1227 A). Test conditions were close to those during the main study. MDP concentrations were monitored hourly. Acrolein concentrations were below the limit of detection (<3ppm) in each chamber. Mortalities and severe toxicity was seen at 100 and 500 ppm. Therefore, only control animals and those at 50 ppm were evaluated for PCE/NCE ratio. This ratio was 0.024 and 0.02 in male and female control animals, and 0.004 and 0.002 in males and females at 50 ppm MDP, respectively. Values below 0.01 were considered to indicate cytotoxicity. On this basis it was decided to use lower concentrations during the main study.

Result: Main Study results

(1) PCE/NCE ratio (see also attached document)

In females of all MDP treated groups significant decreases in polychromatophilic (PCE) to normochromatophilic (NCE) erythrocytes were seen. Values reached 20.8, 22.8 and 14.% of controls at 24 hrs for animals at 5, 10, and 25 ppm, respectively (respective values at 48 hrs: 26.5, 29.2, 21% of controls). Unexpectedly high PCE counts were noted in female control animals which contributed to unusually high mean control PCE/NCE ratio value.

In males this effect was not significantly different from controls despite its magnitude: at 24 hrs values reached 44, 37.4 and 35% of controls in animals receiving 5, 10, and 25 ppm, resp. (respective values at 48 hrs: 27.4, 34.6, 47.5% of controls). According to the authors unexpectedly high PCE count in 1 control male led to a large standard deviation which obscured potentially significant differences. The authors discussed that the phenomenon could be due to bleeding during determination of reticulocyte counts.

(2) Micronucleated PCE (see also attached document)

No significant increase was seen at 5, 10 and 25 ppm MDP in either sex at either sampling time. The test was valid since cyclophosphamide produced the expected significant increase, and since numbers of micronuclei in negative control animal were in a low and acceptable range.

Test condition: TEST ORGANISMS

5 mice per sex and dose

ADMINISTRATION

Groups of mice were exposed in a 900 l inhalation chamber for 6 hrs each on 5 consecutive days. Doses were based on results of previous studies using mice (BRRC 93U1227 A) or rats (BRRC 92U1013). Vapor was generated by pumping liquid TS to an evaporator maintained at ca. 30-43°C. All the chamber air flowed through the evaporator in a countercurrent flow at 200 l/min.

Measurements during administration included chamber temperature, relative humidity, evaporator temperature, concentrations of MDP (twice each hour) and of acrolein. Negative controls received no MDP. Positive control animals received single ip injections of 15 mg/kg cyclophosphamide.

OBSERVATIONS AND MEASUREMENTS

Animals were observed for clinical signs. Body weight data were collected. Reticulocytes were counted in blood taken from control and high dose animals on days -2, 2, and 4. For micronucleus evaluation blood samples were taken at 24 and 48 hrs after the final exposure and 2 blood smears/animal were stained with Giemsa. 2000 PCE/animal were evaluated. Blood smears of positive control animals were prepared only 48 hrs after treatment. The PCE/NCE ratio was calculated for 1000 total cells to provide an estimate for cytotoxicity.

EVALUATION CRITERIA

Excessive cytotoxicity was assumed by a PCE/NCE ratio of 0.01 or less. Micronuclei were evaluated according to OECD 474.

Micronucleus data were statistically evaluated using the Mann-Whitney-U-test. Probability values of p<0.05 were used as level of significance.

Test substance: MDP from UCC; purity 99.4% as revealed by GC analysis; data contained in report, Appendix 1. Acrolein 0.12%; acrolein dimer 0.32%

Attached doc.: Table: Summary of Micronucleated PCE

Dose	Sex	N	MN-PCE/ 2000 PCE	Total MN-PCE	Mean 2000	MN-PCE/ PCE (S.D.)	Mean % MN-PCE
24 HOUR SAMPLE							
0 ppm	M	5	8,1,4,2,5	20	4.0	(2.74)	0.20
	F	5	5,5,6,8,9	33	6.6	(1.82)	0.33
5 ppm	M	5	4,5,4,5,3	21	4.2	(0.84)	0.21
	F	5	6,2,3,6,7	14	4.8	(2.17)	0.24
10 ppm	M	5	7,5,0,7,1	20	4.0	(3.32)	0.20
	F	5	2,3,2,7,2	16	3.2	(2.17)	0.16
25 ppm	M	5	5,8,2,7,3	25	5.0	(2.55)	0.25
	F	4	1,0,2,0	3	0.8	(0.96)	0.04
48 HOUR SAMPLE							
0 ppm	M	5	5,2,5,2,5	19	3.8	(1.64)	0.19
	F	5	4,3,2,3,5	17	3.4	(1.14)	0.17
5 ppm	M	5	2,5,2,2,3	14	2.8	(1.30)	0.14
	F	5	3,0,1,1,2	7	1.4	(1.14)	0.07
10 ppm	M	5	4,1,4,5,2	16	3.2	(1.64)	0.16

	F	5	1,0,3,2,1	7	1.4	(1.14)	0.07
25 ppm	M	5	3,7,3,2,3	18	3.6	(1.95)	0.18
	F	4	5,1,2,2	10	2.5	(1.73)	0.13
Pos. Control Cyclophosphamide (15 mg/kg)	M	5	16,15,16,18,12	77	15.4	(2.19)	0.77 **
	F	5	13,15,15,19,18	80	16.0	(2.45)	0.80 **

** = p<0.01

Abbreviations: PCE - Polychromatophilic erythrocyte;
MN-PCE - Micronucleated polychromatophilic erythrocyte
S.D. - Standard deviation; M - Male; F - Female

Table : Summary PCE/NCE ratios

24 Hour Sample						48 Hour Sample		
PCE/1000 NCE						PCE/1000 NCE		
Dose ppm	Sex	N	Mean	(S.D.)	% of Control	Mean	(S.D.)	% of Control
0	M	5	51.4	(45.73)	---	52.6	(41.42)	---
	F	5	82.6	(49.63)	---	59.6	(16.85)	---
			----- 67.0	----- (22.06)		----- --	----- -	
5	M	5	22.6	(5.50)	44.0	14.4	(1.67)	27.4
	F	5	17.2	(2.59)	20.8*	15.8	(3.42)	26.5**
			----- 19.9	----- (3.82)		----- --	----- -	
10	M	5	19.2	(3.27)	37.4	18.2	(3.96)	34.6
	F	5	18.8	(3.90)	22.8*	17.4	(6.80)	29.2**
			----- 19.0	----- (0.28)		----- --	----- -	
25	M	5	18.0	(5.57)	35.0	25.0	(14.28)	47.5
	F	4	11.8	(2.36)	14.2*	12.5	(3.00)	21.0**
			----- 14.9	----- (4.42)		----- --	----- -	
	M	5	Positive Control			7.8	(2.77)	14.8
	F	5	Cyclophosphamide (15mg/kg)			21.4	(8.47)	35.9
			NOT EVALUATED			----- -	----- -	
						14.6	(9.62)	

* = p<0.05; ** = p<0.01. Statistical evaluation of positive control was not performed.

Abbreviations: PCE - Polychromatophilic erythrocytes;
NCE - Normochromatophilic erythrocytes
S.D. - Standard deviation; M - Male; F - Female

Conclusion: MDP did not produce significant and dose-related increases in micronucleated PCE in peripheral blood of mice at 24 or 48 hrs after the final of total 5 exposures against 5, 10 or 25 ppm.

Reliability: (1) valid without restriction
(1a) GLP guideline study

Flag: Critical study for SIDS endpoint

08-SEP-2003

(59) (60)

5.7 Carcinogenicity

5.8.1 Toxicity to Fertility

5.8.2 Developmental Toxicity/Teratogenicity

5.8.3 Toxicity to Reproduction, Other Studies

5.9 Specific Investigations

5.10 Exposure Experience

Type of experience: other: air monitoring data

Method: Occupational air monitoring. Air sampling and personal air sampling followed by certified analytical method.

Result: MDP was present in the worker's respiration zone at a concentration of 36 mg/m³ (8 ppm). At a distance of 0.5 m the concentration of MDP in air was 12 mg/m³ (2 ppm). Directly above the drum opening the concentration of MDP exceeded 770 mg/m³.

Test condition: Air monitoring was conducted during filling of MDP into the reaction vessel using personal air sampling. Additionally stationary sampling was performed at a distance of 0.5 m apart from the work place, and immediately at the drum opening. Air samples were collected for 30 minutes. MDP was adsorbed to a test tube during sampling and desorped prior to analysis. Temperature of ambient air was 32°C.

Sampling was not conducted during routine work procedure because this type of work, i.e. manual drum emptying, is only occasionally performed. Therefore, the work situation was imitated. However, work conditions during sampling differed in this study from routine work conditions in that the worker placed himself at the drum for the full 30 min sampling period, whereas in the normal work situation the worker remains only few minutes next to the drum when having started the pump for emptying the drum. The workers exposure periods may largely vary. Estimates range from 10 minutes to 5 hours on some days. Exposure periods per year are estimated to range between 2 and 120 hours per year.

During the sampling the employee used the same standard of respiratory protection as it is used under normal work conditions.

Test substance: MDP

Conclusion: Manual emptying of drums using pumps is occasionally performed at some of the producer's sites. This exposure situation was mimicked in order to perform air monitoring. Sampling was performed at an elevated ambient air

temperature of 32°C. Therefore it is concluded that the measured concentrations represent worst-case conditions.

The concentration of MDP in the breathing zone was 8 ppm.

The annual workers exposure period may largely vary between 2 and 120 hours per year for those workers who are emptying drums containing MDP. The exposure is however low because standard personal protective equipment to be used does include respiratory protection.

Reliability:

(1) valid without restriction
Meets national standard methods (TRGS 402) and is described in sufficient detail

Flag:

05-SEP-2003

Critical study for SIDS endpoint

(69)

5.11 Additional Remarks

Type:

other: acrolein inhalation toxicity

Method:

Similar to OECD guideline 403. Whole body inhalation chamber exposure at 1000 ppm and at near vapor saturation.

Remark:

Inhalation experiments with impure acrolein-containing MDP described by Dodd et al. are also described in this publication.

Result:

LC50 values (with 95% confidence intervals) for pure Acrolein to rat, combined male and female: :
26 (24-27) ppm (1 hr exposure time; corresponds to 65 (60-68) mg/m³), and 8.3 (7.0-9.9) ppm (4 hr exposure time, corresponds to 20.8 (17.5-24.8) mg/m³).

Test condition:

TEST ORGANISMS
90 male/female Sprague-Dawley rats, 5 animals per dose and sex, were used. Body weight between 200 - 300 g.
ADMINISTRATION
Whole body inhalation chamber. Pure acrolein atmosphere was dynamically generated. Concentrations were 5, 7, 9 and 12 ppm (1 hr exposure) and 15, 20, 25, 30, and 80 ppm (4 hrs exposure time).
EXAMINATIONS
Observation for signs of toxicity for 14 d. Necropsy of animals that died or that were sacrificed at the end of the observation period.

Test substance:

Acrolein

Conclusion:

Acrolein led to severe signs of irritancy, and death was due to lung injury.
LC50 to rats was found to be 26 ppm after 1 hr and 8.3 ppm after 4 hr exposure time.

0.037% acrolein impurity in MDP caused acrolein concentration of 240 ppm inside the inhalation chamber when a statical atmosphere of 8044 ppm MDP was generated. Under these conditions mortality was 100%. Acrolein concentration was almost 10-fold the LC50 for acrolein. In the absence of acrolein mortality was 0% when animals were exposed to atmospheres with MDP concentrations of 8613, 7748 and 1095 ppm.

Acrolein, contained as trace contaminant in MDP, was

identified to cause deaths of rats exposed to impure MDP under conditions which allow acrolein to accumulate.

Reliability: (1) valid without restriction
(1b) Comparable to guideline study.

Flag: Critical study for SIDS endpoint

20-FEB-2002 (49)

Type: other: review article MDP

Remark: Publication provides summary of physico-chemical and toxicological data, the latter pertaining to acute and subacute toxicity, skin and eye irritation, and genetic toxicity. The studies cited in the review are also contained in the respective chapters of this IUCLID document.

No permissible exposure level (PEL) is given in the review article.

Reliability: (4) not assignable
(4b) Secondary literature

14-DEC-2001 (70)

6.1 Analytical Methods

6.2 Detection and Identification

7.1 Function

7.2 Effects on Organisms to be Controlled

7.3 Organisms to be Protected

7.4 User

7.5 Resistance

8.1 Methods Handling and Storing

Safe Handling: Ensure thorough ventilation of stores and work areas.
Fire/Exp. Prot.: Take precautionary measures against static discharges.
Storage Req.: Containers should be stored tightly sealed in a dry place.

Remark: PERSONAL PROTECTIVE EQUIPMENT

Respiratory protection:
 Gas filter EN141 Type A for gases/vapours of organic compounds
 (boiling point >65 °C).

Hand protection:
 Chemical resistant protective gloves (EN 374)
 Suitable materials also with prolonged, direct contact
 (Recommended: Protective index 6, corresponding > 480 minutes
 of permeation time according to EN 374)
 nitrile rubber (NBR) - 0.4 mm coating thickness

Eye protection:
 Safety glasses with side-shields (frame goggles) (EN 166)

General safety and hygiene measures:
 Handle in accordance with good industrial hygiene and safety
 practice. Wearing of closed work clothing is required
 additionally to the stated personal protection equipment.

TRANSPORT INFORMATION

Land transport

ADR : Class 3
 Packaging group II
 Substance no. 1993
 Designation of goods FLAMMABLE LIQUID, N.O.S.
 (Contains: 2-METHOXY-2.3-DIHYDRO-4H-PYRAN)
 RID : Class 3
 Packaging group II
 Substance no. 1993
 Designation of goods FLAMMABLE LIQUID, N.O.S.
 (Contains: 2-METHOXY-2.3-DIHYDRO-4H-PYRAN)

Inland waterway transport

ADNR : Class 3
 Item/Letter 3b)
 Packaging group II
 Substance no. 1993
 Designation of goods FLAMMABLE LIQUID, N.O.S.
 (Contains: 2-METHOXY-2.3-DIHYDRO-4H-PYRAN)

Sea transport

IMDG/GGVSee : Class 3
 Packaging group II
 UN-number 1993
 Marine pollutant NO
 Exact technical name FLAMMABLE LIQUID, N.O.S.

(contains 2-METHOXY-2.3-DIHYDRO-4H-PYRAN)

Air transport

ICAO/IATA : Class 3
 Packaging group II
 UN-number 1993
 Exact technical name FLAMMABLE LIQUID, N.O.S.

(contains 2-METHOXY-2.3-DIHYDRO-4H-PYRAN)

Flag: non confidential, Critical study for SIDS endpoint (5)
 13-FEB-2003

8.2 Fire Guidance

Prot. Equipment: Wear self-contained breathing apparatus and chemical-protective clothing.
Ext. Medium: water, dry extinguishing media, foam, carbon dioxide
Add. Information: Collect separately contaminated extinguishing water, do not allow to reach sewage or effluent systems.

Flag: non confidential, Critical study for SIDS endpoint (5)
 13-FEB-2003

8.3 Emergency Measures

Type: other: General advice

Remark: Remove contaminated clothing. If danger of loss of consciousness, place patient in recovery position and transport accordingly. Apply artificial respiration if necessary.

Flag: non confidential, Critical study for SIDS endpoint (5)
 14-JAN-2003

Type: injury to persons (inhalation)

Remark: Keep patient calm, remove to fresh air, summon medical attention.

Flag: non confidential, Critical study for SIDS endpoint (5)
 12-NOV-2001

Type: injury to persons (skin)

Remark: Wash thoroughly with soap and water.

Flag: non confidential, Critical study for SIDS endpoint (5)
 12-NOV-2001

Type: injury to persons (eye)

Remark: Immediately wash affected eyes for at least 15 minutes under running water with eyelids held open, consult an eye specialist.

Flag: non confidential, Critical study for SIDS endpoint (5)
 12-NOV-2001

Type: injury to persons (oral)

Remark: Immediately rinse mouth and then drink plenty of water, seek medical attention.
Flag: non confidential, Critical study for SIDS endpoint
12-NOV-2001 (5)

Type: accidental spillage

Remark: Personal precautions:
Avoid inhalation. Take appropriate protective measures.

Environmental precautions:
Do not empty into drains.

Methods for cleaning up or taking up:
Pump off large amounts. Pick up residues with suitable absorbent material (e.g. sand, sawdust, general-purpose binder, kieselguhr). Dispose of absorbed material in accordance with the regulations.

Flag: non confidential, Critical study for SIDS endpoint
14-JAN-2003 (5)

8.4 Possib. of Rendering Subst. Harmless

8.5 Waste Management

Memo: other: Must be dumped or incinerated in accordance with local regulations.

Flag: non confidential, Critical study for SIDS endpoint
13-FEB-2003 (5)

8.6 Side-effects Detection

8.7 Substance Registered as Dangerous for Ground Water

8.8 Reactivity Towards Container Material

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