FOREWORD INTRODUCTION

DIMETHYL PHOSPHONATE

CAS N°: 868-85-9

SIDS Initial Assessment Report

For

SIAM 18

Paris, France, 20-23 April 2004

1.	**Chemical Name:**	Dimethyl phosphonate
2.	**CAS Number:**	868-85-9
3.	**Sponsor Country:**	Germany Contact Point: BMU (Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit) Contact person: Prof. Dr. Ulrich Schlottmann Postfach 12 06 29 D- 53048 Bonn
4.	**Shared Partnership with:**	Bayer AG, Germany; Rhodia Inc., USA
5.	**Roles/Responsibilities of the Partners:**	
•	Name of industry sponsor /consortium	Bayer AG, Germany Contact person: Dr. Burkhardt Stock D-51368 Leverkusen Gebäude 9115
•	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): 21 July 2003 (Ecotoxicology): databases CA, biosis; searchprofile CAS-No. and special search terms 19 September 2003 (Toxicology): databases medline, toxline; searchprofile 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:**	Deadline for circulation: 23 January 2004
10.	**Date of last Update:**	

11. Comments:

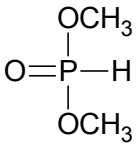
OECD/ICCA - THE BUA* PEER REVIEW PROCESS

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.	868-85-9
Chemical Name	Dimethyl phosphonate (DMP)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Dimethyl phosphonate (DMP) is rapidly absorbed via the oral and dermal routes. The main metabolic pathway in rodents is demethylation to monomethyl hydrogen phosphite (MMP) and further oxidation to CO_2. DMP was mainly eliminated via urine and expired air. Over the studied dose range between 10 and 200 mg/kg bw and 5 x 200 mg/kg bw, respectively, only little evidence of bioaccumulation or saturation of absorption and elimination was observed. The only difference in studied toxicokinetics between rats and mice was the more rapid metabolism and elimination in mice.

An inhalation LC_{50} value is not available, but an exposure of 7100 mg/m³ (concentration estimated based on air flow and net loss of material) over 6 hours was not lethal for rats, mice and guinea pigs. Clinical signs were observed in mice only, and included occasionally laboured respiration after approximately 2 hours of exposure and ptosis after 5 hours. The acute dermal LD_{50} was 681 mg/kg bw (rabbits). Signs of intoxication were depression, ptosis, labored respiration, ataxia and placidity. The acute oral LD_{50} values were: 3283 mg/kg bw for male rats, 3040 mg/kg bw for female rats, 2815 mg/kg bw for male mice, and between 2150 and 3160 mg/kg bw for female mice. Clinical signs were inactivity, weakness, prostration and shallow breathing at doses near to or exceeding the LD_{50} values. White opaque eyes were seen in male mice.

DMP is irritating to the skin and eyes of rabbits. After prolonged or repeated exposures moderate to severe irritation of skin and mucosa was observed in rats. No sensitisation studies are available.

In a repeat dose inhalation study on rats over 4 weeks, no NOAEL could be derived as increased kidney weights and keratitis were found in both sexes down to the lowest tested concentration (LOAEL: 49 mg/m³, corresponding to about 10 mg/kg bw/d). In the same study, DMP caused eye cataracts at concentrations equal to or greater 142 mg/m³, and an increase in mortality at concentrations equal to or greater 483 mg/m³.

In 13-week gavage studies on rats, decreased body weight gains were noted in females at 200 mg/kg bw/d, and for males at 400 mg/kg bw/d. At 400 mg/kg bw/d, eye changes (cataracts), and lung toxicity (inflammation, congestion, histiocytosis) occurred (NOAEL, male: 200 mg/kg bw, NOAEL, female: 100 mg/kg bw). At 375 mg/kg bw/d mortality was increased, and there were no surviving animals at 750 mg/kg bw/d. For mice the NOAEL (13 week, gavage), was 95 mg/kg bw/d, with histopathological changes in heart and liver appearing at 190 mg/kg bw/d.

In a 2-year gavage study on rats, lung effects were seen in both sexes at 100 mg/kg bw/d. At 200 mg/kg bw/d, males had cataracts and focal mineralization in the cerebellum (NOAEL, females: 50 mg/kg bw/d; LOAEL, males: 100 mg/kg bw/d, lowest tested dose in males). For female mice the NOAEL (2-yr, gavage) was 200 mg/kg bw/d (highest tested dose), whilst a NOAEL for male mice could not be derived as calcification of testis was still found at the lowest tested concentration of 100 mg/kg bw/d. An increased mortality was seen in male mice at 200 mg/kg bw/d.

In vitro data indicate that DMP has mutagenic and clastogenic potential. The available *in vivo* data are limited to the bone marrow and the results are conflicting with one study indicating clastogenicity. DMP should be regarded as having genotoxic potential *in vivo*.

DMP showed clear evidence of carcinogenicity in male F344 rats and equivocal evidence in female F344 rats. Target organs were lungs and forestomach. No evidence of carcinogenicity was observed in male and female B6C3F1 mice.

In a screening study on rats according to OECD TG 421 (gavage study), effects on fertility were seen in females at 270 mg/kg bw/d in the presence of severe general toxicity (decrease in number of females with corpora lutea and implantation sites) (NOAEL reproduction toxicity: 90 mg/kg bw/d; NOAEL general toxicity: 90 mg/kg bw/d). Focal testicular calcification was seen in mice treated orally with 100 mg/kg bw/d for 2-years, and hypospermatogenesis in rats after inhalation of 483 mg/m³ (corresponding to about 100 mg/kg bw/d) for 4 weeks. No developmental toxicity was found in rats at doses of 30 and 90 mg/kg bw/d (NOAEL developmental toxicity: 90 mg/kg bw/d).

Environment

DMP is a colourless liquid of mild odour with a melting point of < –60 °C, boiling point of 171.1 °C, density of 1.2 g/cm^3 and a vapour pressure of 1.35 hPa at 20 °C. The substance is very soluble in water with > 100 g/l at 19.5 °C. The log Kow of DMP was calculated to be –1.2.

DMP released into the atmosphere is rapidly degraded by OH-radicals with an estimated half-life of 2.9 hours. The main degradation process in water is hydrolysis. The degradation products are monomethyl phosphonate (MMP), phosphorous acid, and methanol. At pH 4 the experimentally determined half-life is about 470 h, at pH 7 it is about 3 h, and at pH 9 it is < 0.3 h.

DMP is not readily biodegradable (50 % after 28 d).

According to the Mackay Fugacity Model Level I, the main target compartments (environmental equilibrium distribution) for DMP are water (95 %) and air (5 %). The degradation product MMP will partition nearly exclusively to the water compartment based on a water solubility of 1000 mg/l, a vapor pressure of 25 Pa and a log Kow of –1.19. The calculated Henry's law constants of 0.33 Pa*m^3*mol^{-1} for DMP and of 0.002 Pa*m^3*mol^{-1} for MMP indicate a low to moderate potential for volatilization from surface waters. The calculated log Kow values (log Kow = -1.2 for DMP, log Kow = -1.19 for MMP) indicate no bioaccumulation potential. The calculated Koc values (Koc = 2.62 for DMP and 1.36 for MMP) suggest that both substances have a very low geoaccumulation potential.

Concerning the toxicity of DMP towards aquatic species, experimental results of short term tests with fish, *Daphnia*, and algae are available. During aquatic ecotoxicity tests DMP hydrolysed with half lives of several minutes to hours. Thus, during these tests, DMP itself and its degradation products MMP, methanol, and phosphorous acid were present. For testing the acute fish toxicity with *Danio rerio* a limit test with a concentration of (nominal) 100 mg/l was conducted and no effects were observed at this concentration level after 96 h. Another test with *Pimephales promelas* reported a 96 h-LC_{50} of (nominal) 225 mg/l. In a GLP study according to Directive 92/69/EEC, C.2, the EC_{50} (nominal) of *Daphnia magna* was 25 mg/l after 48 h. The geometric mean of the concentration of the hydrolysis product MMP over the exposure period was 8 mg/l. In a GLP study according to Directive 92/69/EEC, C.3, the 72 h EC_0 (nominal) of *Desmodesmus subspicatus* was >= 100 mg/l. The geometric mean of the concentration of the hydrolysis product MMP over the exposure period was 26 mg/l.

Data on long-term toxicity on aquatic organisms are not available. Valid tests on terrestrial species are not available as well.

Following the EU Technical Guidance Document, for the derivation of the $PNEC_{aqua}$ an assessment factor of 1000 is chosen since at least one short-term EC_{50} or LC_{50} value is available from each of the three trophic levels. Using the lowest determined concentration: *Daphnia magna* EC_{50} = 25 mg/l, a $PNEC_{aqua}$ of 25 µg/l is derived. This PNEC covers both the toxicity of DMPas well as the toxicity of its hydrolysis products.

Exposure

The global production capacity of DMP is estimated to be 3 000 – 15 000 t/a by about 10 producers. DMP is a basic chemical which is used industrially as an intermediate for the production of water treatment chemicals (about 50 %), pesticides and pharmaceuticals (about 20 %), flame retardants and other specialities (about 15 %),

textile finishing products (about 15 %).

Consumer exposure is not known to occur in the EU. Use as a reactive flame retardant in textile finishing is reported for the U.S.

From the Bayer Chemicals manufacturing and processing site no DMP was emitted into the environment in 2000. Workplace air sampling shows that there is no relevant exposure of workers at this site.

With respect to the use as an intermediate, the exposure of consumers is considered to be not relevant. Due to the low emissions and to the hydrolysis of DMP indirect exposure via the environment is not expected.

Methyl and ethyl esters of phosphorous acid can be converted by chemical synthesis to nerve gases. Therefore the production and export of DMP is stringently controlled under the International Chemical Weapons Convention.

RECOMMENDATION

The substance is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health:

DMP possesses properties indicating a hazard for human health (irritating, mutagenic and carcinogenic properties, repeated dose toxicity). In the Sponsor country, exposure is controlled in occupational settings and is negligible for consumers. Countries may desire to investigate any exposure scenarios (particularly use as a reactive flame retardant in textile finishing) that were not presented by the Sponsor country.

Environment:

The chemical possesses properties indicating a hazard for the environment. Based on data presented by the Sponsor country, exposure to the environment is anticipated to be low. Therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

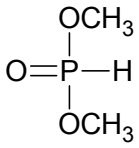
SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 868-85-9
IUPAC Name: Dimethyl phosphonate

Molecular Formula: $C_2H_7O_3P$
Structural Formula:



Molecular Weight: [click here to enter molecular weight]
Synonyms: Dimethyl hydrogen phosphite

Dimethylhydrogen phosphite

Dimethyl phosphite

DMHP

DMP

Phosphonic acid, dimethyl ester

Dimethyl phosphorous acid

Phosphorous acid dimethyl ester

Hydrogen dimethyl phosphite

Substance type: organic compound

Physical status: colourless liquid of mild odour

1.2 Purity/Impurities/Additives

Purity: 99.7 %

Impurities Methanol ca. 0.1 %, Monomethyl phosphonate (= Monomethyl hydrogen phosphonate, Monomethyl phosphite, MMP) ca. 0.1 %

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Value	Source
Physical state		
Melting point	< -60 °C	Bayer AG, 2003a
Boiling point at 1013.25 hPa	171.1 °C (Dir. 92/69/EEC, A.2)	Bayer AG, 2001a
Relative density at 20 °C	ca.1.200 g/cm³	Roempp, 1999
Vapour pressure at 20 °C	1.35 hPa (Dir. 92/69/EEC, A.4)	Bayer AG, 2001b
Water solubility Solubility in organic solvents	Not applicable due to hydrolysis ≥ 100 g/l at 19.5 °C soluble in alcohol and pyridine, pyrimidine at 20 °C: 0.82 % in hexan 0.64 % in dodecane 1.50 % in cyclohexane	Roempp, 1999 Chemfinder Internet Database, 2003 Roempp, 1999 Beilstein Databook, 2002
Partition coefficient n-octanol/water (log value)	-1.2 (calculated)	Bayer AG, 2003b
Henry's law constant		
Surface tension	37.6 mN/m at 20 °C	Bayer AG, 2003c
Flash point	ca. 70 °C (DIN 51758)	Bayer AG, 2003a
Auto flammability (ignition temperature)	237 °C (DIN 51794)	Bayer AG, 2003a
Explosive properties	Explosive limits: lower 5.8 % upper 38.1 %	Bayer AG, 2003a
Viscosity at 20°C	1.4 mPa s (dynamic)	Bayer AG, 2003a

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

Production

In Western Europe DMP is manufactured in an industrial scale only at the Bayer AG Leverkusen plant.

DMP is produced in a closed system by exothermic reaction of phosphorous trichloride with methanol according to

$PCl_3 + 3\ CH_3OH \rightarrow (CH_3O)_2P(O)H + CH_3Cl + 2\ HCl.$

The product is purified by distillation (Buechner et al. 1984). Alternatively, DMP is produced from PCl_3 using sodium methanolate (IARC, 1990).

The global production capacity of DMP is estimated to be 3000 - 15 000 t/a for about 10 producers in 2002. The regional distribution is described in table 2.

Table 2: Global Production Capacity

Manufacturing Capacity 2002	Capacity (estimated) t/a
Western Europe	1000 - 5000
USA	1000 - 5000
Rest of world	1000 - 5000

Processing and Use

DMP is a basic chemical which is used industrially as an intermediate. Because of its reactivity DMP participates in a large number of chemical reactions e.g.

- Addition to oxo compounds
- Addition to oxo compounds with subsequent condensation e.g. with amines
- Oxidation with oxygen or chlorine
- Addition to alkenes

Due to these properties DMP is used as an intermediate for the manufacturing of

- water treatment chemicals e.g. corrosion inhibitors for cooling-water circuits (about 50 %)
- pesticides and pharmaceuticals (about 20 %)
- flame retardants and other specialities (about 15 %)
- textile finishing products (about 15 %)

No direct use is known (Bayer Chemicals 2003).

Methyl and ethyl esters of phosphorous acid can be converted by chemical synthesis to nerve gases. Therefore the production and export of DMP is stringently controlled under the International Chemical Weapons Convention (1993, CWC Schedules 3B (high volume, dual-use precursor)).

Several sources report that DMP is used as a flame retardant on textiles and other materials.

- The IARC (1990) mentions that DMP is used as a flame retardant on Nylon 6 fibres and is used in combination with guanidine and formaldehyde to impart flame and crease resistance to cotton textiles. Other literature, which is later cited to support these claims, is secondary literature. However, the use of formaldehyde clearly indicates that DMP would not persist as a chemical entity (cf. the reactions mentioned above). This is presumably also true for the suspected application on polyamide fibres.
- According to NTP (2003) DMP "is used as a flame retardant". No reference for this statement is given.
- According to NTP Technical Report Number 287 (report created in 2001, NTP 2001), which was peer reviewed in 1984, DMP is an "INTERMEDIATE. ADDITIVE TO LUBRICANTS.

ADHESIVE. FIRE RETARDANT. (TDB)". Again, no reference for this is given. According to up to date information, DMP is an intermediate to manufacture flame retardants and other compounds.

- The Subcommittee on Flame-Retardant Chemicals reviews DMP in its book "Toxicological Risks of Selected Flame-Retardant Chemicals" (SFRC 2000). With reference to secondary sources DMP is described to be used in the manufacture of adhesives, pesticides and to impart flame resistance to textiles.

- IPCS (1997) reports that less than 1000 t/a of DMP production volume is used as a flame retardant to cotton textile (page 90 of IPCS 1997). The original reference cited by IPCS (1997) is IARC (1990) which clearly states that another reactant, e.g. formaldehyde (see above), is used in combination with DMP on cotton. Under these conditions, DMP forms a covalent reaction product. During this type of application, DMP looses its chemical identity and does not persist as a chemical entity on cotton textiles.

However, the following properties of DMP are not compatible with the use as flame retardant: DMP has a very low flash point and is a flammable liquid. Assumed that DMP does not react, it would evaporate from costumer textiles or from other open applications. If used on customer textiles, DMP would also hydrolyse in the presence of humidity within a short period of time compared to the typical periods of textile use. It will also be lost during washing. Although there are several reviews which report the use of DMP as flame retardant, it is assumed that this compound is not used as an additive flame retardant but - if it would be used in this application - it would be a reactive intermediate whose reaction products act as flame retardants. In these applications DMP would not persist as a chemical entity (see below).

The European Flame Retardants Association (EFRA) confirmed that, to the best of their knowledge, DMP is not used and has never been used as a flame retardant in Europe (EFRA, 2003).

The use of DMP as a reactive flame retardant in textile finishing is reported for the USA (SFRC, 2000; Yang et al., 2003). In contrast to an additive flame retardant which forms a mixture with the polymer to be protected (Sutker, 2000), reactive flame retardants are reactive components chemically built into a polymer molecule (IPCS, 1997; Roempp, 2004). This is consistent with the IARC (1990) report which reads that another reactant, e.g. formaldehyde, is used in combination with DMP on cotton. Under these conditions, DMP would form a covalent reaction product with the fibre. Also other types of fibres containing reactive nitrogen or oxygen could form phosphorus containing macromolecules from DMP. During this type of application, DMP looses its chemical identity and does not persist as a chemical entity. This process is also non-reversible in regard to DMP: Hydrolysis (if it occurs) would not lead to the release of DMP.

In the Swiss product register one industrially used product with 100 % DMP and five public products (herbicides) with 0.1 - 0.8 % DMP are listed. Since these herbicides contain the active ingredient Glyphosate which is synthesized from DMP, it is assumed that the DMP is not intentionally added to the products but stems from the synthesis (Swiss Product Register, 2003). In Denmark, Sweden, and Finland, DMP is not listed in a product register; for Norway information is confidential (SPIN Database, 2003; Swedish Product Register, 2003).

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

Releases of DMP into the environment may occur during manufacturing and processing.

Information on exposure from manufacturing and processing of the chemical is available for the Bayer production plant at Leverkusen, Germany.

The manufacturing, the processing and the filling of DMP are executed in closed, waterfree systems (e.g. transport via pipeline, sampling without dead volume, gas-shuttle pipe for filling processes). Cleaning of the reactors takes place only in the case of maintenance (Bayer Chemicals, 2003).

The exhaust from manufacturing and processing of DMP is connected to a thermal exhaust purification plant. Thus during normal operation no DMP or other organic byproducts are emitted into the atmosphere. There is no relevant emission of DMP into the atmosphere. In the official Emission Declaration of 2000 DMP was not listed since the emission rate was < 25 kg/a (Bayer Chemicals, 2003).

Waste from the manufacturing and processing of DMP is incinerated in a rotary kiln incinerator for hazardous wastes equipped with various exhaust air cleaning devices (Bayer Chemicals, 2003).

Due to the waterfree production process and since the product is kept separate from water (including humidity), significant releases of DMP and its hydrolysis products are not expected to occur in the wastewater from manufacturing. Due to precautions similar to these described for the manufacturing of DMP, it can also be assumed that no DMP is released into the wastewater during processing. During the wastewater treatment at neutral pH (hydraulic retention time about 3 d) a rapid hydrolysis (half-life about 3 h at pH 7, see below) and oxidation of DMP and its degradation products occurs. Therefore, DMP is not regularly monitored at the industrial wastewater treatment plant outlet of the manufacturing site (Bayer Chemicals, 2003).

Table 3: DMP Emissions from the Bayer Manufacturing and Processing Site in 2002

Loss into the air	<< 25 kg
Loss into the aquatic environment	ca. 0 kg

2.2.2 Biodegradation

Biodegradation was investigated in a ready test system according to the OECD 301E guideline. The initial test concentration was degraded to 50 % after 28 d by activated sludge from predominantly domestic origin. The degradation rate was fastest at the beginning of the test (ca. 45 % degradation at the first measurement after 7 d) (Bayer AG, 1992).

Based on the degradation results, DMP is classified as being not readily biodegradable. It has to be considered that under the conditions used in this test DMP hydrolyses to MMP and methanol. MMP hydrolyses further to phosphorous acid and methanol. Hydrolysis of DMP is faster than hydrolysis of MMP. The hydrolysis product methanol is readily biodegradable. Hydrolysis of DMP and MMP is the determining factor for the speed at which biodegradation of DMP occurs.

2.2.3 Bioaccumulation

A bioconcentration factor (BCF) cannot be measured due to hydrolysis. Experimental determination of the octanol-water partition coefficient for DMP is not appropriate for the same reason. The calculated log K_{ow} value (log K_{ow} = –1.2) indicates that there is no potential for bioaccumulation in aquatic organisms (Bayer AG 2003b). This statement is also valid for the degradation product MMP for which a calculated log K_{ow} of –1.19 is available (taken from EPIWIN)

2.2.4 Other Information on Environmental Fate

Stability and Abiotic Degradation

DMP entering into the atmosphere is expected to be photodegraded rapidly by OH-radicals. Based on the estimated degradation rate constant of 5.58 x 10^{-12} cm^3 (molecule x sec)$^{-1}$ the calculated half-life of DMP in air due to indirect photodegradation is $t_{½air}$ = 2.9 hours, considering a mean OH-radical concentration of 0.5 x 10^6 cm^{-3} during a 24 h day (Bayer AG, 2003b).

Knoevenagel and Himmelreich (1976) measured the degradation of the homologue diethyl phosphonate with aerobic water in the presence of UV-light. 50 % of this homologue were degraded within 29 h according to the released carbon dioxide. These results indicate that DMP is also degraded by photooxidation in water.

A guideline study to investigate the stability of DMP in water was conducted by the Bayer AG (2002a) and shows that DMP hydrolyses rapidly to moderately fast in water.

The study is in accordance with the principles of Good Laboratory Practice (GLP) and was conducted according to the directive 92/69/EEC, method C.7 using 31-Phosphorous-NMR for analysis. Incubations were performed in buffered water at 23 °C. The following results were obtained:

Table 4: Hydrolysis

PH	Test period	Residual DMP (%)	$T_{1/2}$ (h)	K (s^{-1})
4	7 d 18 d	79 51	470	4.09E-07
7	19 min 2 d	78 5	3.1	6.22E-05
9	19 min 4 h	2 0	<< 0.3	>> 6E-04

DMP hydrolysed faster in basic solution than at lower pH. The primary degradation products at every pH value were monomethyl phosphonate (MMP) and methanol (Bayer AG, 2002a).

In a study (Bayer AG 1992) on the stability of tri-, di-, and monomethyl phosphonate in unbuffered water without control of pH, the hydrolytic loss of DMP was monitored. Half-life of DMP was estimated to be 60 h. After 6 days 100 % of DMP was degraded. In the first phase of the incubation MMP was the only detected hydrolysis product, but starting after 74 h of incubation, phosphorous acid was also detected (Bayer AG, 1992).

The stability of MMP was further investigated by continuing the analysis of the DMP hydrolysis (paragraph above). After 6 days no DMP was detected, and 85 % of the initial DMP was recovered as monomethyl phosphonate, another 15 % was degraded supposably to phosphorous acid. After 10

days 68 % MMP were found and another 32 % were supposed to be degraded to phosphorous acid. It was concluded that MMP hydrolyses more slowly than DMP (Bayer AG, 1992).

Vilceanu and Schulz (1972) examined the hydrolysis of DMP with the aid of titration with sodium hydroxide. They deduced a S_{N2} mechanism for the DMP hydrolysis from titration curves with K = 1240 l s^{-1} Mol^{-1} at 20 °C.

For the environmental hazard assessment the guideline study performed by Bayer AG (2002a) with lower concentrations and under defined pH conditions is the relevant study and has to be considered.

Table 5: Abiotic Degradation of DMP

IUCLID	Parameter	Method	Result	Source
3.1.1	Indirect photodegradation in air	Calculation 24 h-day; 0.5 * 10^{-6} OH/cm³	$t_{½air}$ = 1.9 h	Bayer AG, 2003b
	Photodegradation in water	Illumination in photoreactor	$t_{½water}$ = 29 h	Knoevenagel and Himmelreich, 1976
3.1.2	Stability in water	OECD 111	$t_{1/2}$ at 23 °C, pH 4 = 470 h pH 7 = 3.1 h pH 9 < 0.3 h	Bayer AG, 2002a
		Screening test on stability of tri-, di- and monomethyl phosphonate	$t_{1/2}$ = 50 - 70 h	Bayer AG, 1992

Environmental Distribution

Calculated distributions of substances in air-water or in a “unit world” are only applicable as long as the test substance is stable enough to reach equilibrium. The following calculations of these distributions do not consider the hydrolysis of DMP.

According to the Mackay Fugacity Model Level I, the main target compartment for DMP in a “unit world” is water with 97 % (Bayer AG, 2003b).

Table 6: Mackay Fugacity Model Calculations

Input Parameters	Value
Melting point	< –60 °C
Temperature	20 °C
Vapour pressure	135 Pa
Water solubility	100 g/l
log K_{ow}	–1.2

Results (IUCLID 3.3.2) Compartment	Calculated distribution
Air	5.0 %
Water	95.0 %
Soil	< 0.01 %
Sediment	< 0.01 %
Susp. Sediment	< 0.01 %
Aerosol	< 0.01 %
Biota	< 0.01 %

As the water solubility of the degradation product MMP is about an order of magnitude higher and the vapor pressure an order of magnitude lower, it can be estimated that the exclusive target compartment according to a Mackay level 1 fugacity model for this substance is water.

The distribution of DMP between aqueous solutions and air was calculated from water solubility and vapour pressure. Using a solubility of 100 g/l and a vapour pressure of 135 Pa (20 °C), a Henry's law constant (HLC) of 0.15 $Pa*m^3$ mol^{-1} is calculated. Using the Bond Method a HLC of 0.33 $Pa*m^3$ mol^{-1} was estimated (Bayer AG, 2003b). Both results indicate that the compound has a moderate volatility according to the criteria of Thomas (1990). The volatility of the main degradation product MMP, is lower based on the Henry's law constant of about 0.002 $Pa*m^3/mol$ estimated based on a water solubility of 1000 g/l and a vapor pressure of 25 Pa (data taken from EPIWIN). With the bond estimation method a HLC of 0.001 $Pa*m^3$ mol^{-1} is calculated.

Geoaccumulation

There is no test result available on geoaccumulation. The distribution between the organic phase of soil or sediment solids and porewater can be calculated by using QSAR. A K_{oc} value of 2.62 was calculated (Bayer AG, 2003b), indicating a very low sorption potential of DMP to soil organic matter according to the criteria of Litz (1990). For MMP a K_{oc} of 1.36 was calculated indicating also a very low geoaccumulation potential for the degradation product.

Environmental Monitoring

There is no information on DMP concentrations in the environment.

IARC (1990) reports that DMP "is not known to occur as a natural product."

IARC (1990) also reports that DMP "is a degradation product of trichlorfon and malathion" (page 87 of IARC, 1990). Trichlorfon (dimethyl-p-(2,2,2-trichlor-1-hydroxyethyl)-phosphonate) contains a pentavalent phosphorous. Predicted from its chemical structure, the degradation of trichlorfon leads to inorganic phosphate. Malathion (O,O-dimethyl-S (1,2-dicarbethoxyethyl)-phosphorodithioate) is a phosphorodithionic acid derivative whose hydrolysis is thought to proceed to thiophosphates and (inorganic) phosphate (Munnecke et al. 1982). Intermediates of malathione hydrolysis are dimethyl phosphorothionic acid and dimethyl phosphorodithionic acid (Bender, 1969). Although it was stated by Wilson (1966) that DMP is a hydrolysis product of malathion, Bender (1969) made it clear that this was only a postulate.

2.3 Human Exposure

DMP is exclusively used as an intermediate for chemical synthesis (*cf* Chapter 2, Processing and use). No direct use is known.

2.3.1 Occupational Exposure

During manufacturing and processing of DMP workers may be exposed, with the dermal and inhalational routes being the primary routes of exposure.

At the Bayer manufacturing site, workplaces where DMP is manufactured or processed in continuously working closed systems (Bayer Chemicals, 2003), include

Manufacturing processes: Conversion of PCl_3 with methanol to DMP; purification.

Processing: on site in chemical synthesis.

For on-site processing at the Bayer Leverkusen plant, DMP is transported in pipelines in a liquid state.

To industrial customers DMP is transported in polyethylene drums, rolling channel drums with polyethylene inliner, and bulk volumes also in road tank cars or ISO-containers [20 feet containers] (Bayer Chemicals, 2003).

Investigations of the workplaces have been performed according to German Technical Guidance TRGS 402 (1997). This includes regular surveys in the working area for any possible exposure to a dangerous substance and appropriate control measures (Bayer Chemicals, 2003). Data on workplace measurements at down-stream user sites were not available.

To protect workers several precautionary and protective measures are taken. These measures include technical equipment like suction devices at filling and sampling stations as well as appropriate personal protection equipment as prescribed in detail for different work situations e.g. during sampling, maintenance, and repair work. During sampling, for instance, gas filter masks, goggles, and gloves (material e.g. Baypren®) have to be worn. Depending on the work to be done during maintenance, gas filter masks (classification ABEK) or a respirator with independent air supply have to be used as well as full protective clothing (Bayer Chemicals, 2003).

Down stream users of DMP are informed by way of a material safety data sheet on the recommended safety measures (see above, Bayer Chemicals, 2003).

Workplace Monitoring

In accordance with the principles of Responsible Care and Sustainable Development, at Bayer Chemicals the exposure of workers is reduced to the lowest technically practicable level (Bayer Chemicals, 2003).

Although there is no workplace limit concentration laid down for DMP in Germany, workplace measurements were performed in the Bayer Chemicals DMP manufacturing unit. 10 total shift measurements and one short time measurement have been done in the relevant area between 1995 and 2001. 4 of these were above the detection limit (0.02 - 0.3 mg/m^3 depending on sampling conditions). The highest values (0.9 mg/m^3) were measured in 1996. Since 1999, the DMP concentration was always below the limit of detection. DMP was not detected in the other 7 samples. DMP was also measured in a Bayer processing unit. 3 total shift values and 2 short time values have been measured in 1988. All results were below the detection limit (see above, Bayer Chemicals, 2003).

2.3.2 Consumer Exposure

The only known use of DMP is that as an industrial intermediate (Bayer Chemicals, 2003). In all final products manufactured from DMP by Bayer, no DMP is detectable with a detection limit of

0.01 %.(Bayer Chemicals, 2003). With respect to the use as an intermediate, the exposure of consumers is considered to be not relevant.

No consumer products containing DMP were located in the Sponsor country (Bayer Chemicals 2003). In the Swiss product register, five herbicides with 0.1 - 0.8 % DMP are listed (Swiss Product Register, 2003). Since these herbicides contain the active ingredient Glyphosate which is synthesized from DMP, it is very likely that this DMP stems from the synthesis of Glyphosate. Glyphosate is commonly sold and applied in aqueous solution (US Department of Agriculture, 2003), and an exposure of the general public to DMP through the use of these herbicides can be excluded because of the rapid hydrolysis of DMP (see chapter 2.1). Even when the herbicide is sold as a dry formulation, exposure to DMP is very unlikely since several safety measures are prescribed for the preparation of the ready to use-solution. In general, herbicides are used in humid environments supporting plant growth, and as these herbicides are mostly used in the early phase of the plant growth, this DMP cannot persist to contaminate food products and no exposure of consumers occurs.

Due to the low emissions and due to the rapid hydrolysis of DMP, indirect exposure via the environment is not expected.

The production and export of DMP is stringently controlled under the International Chemical Weapons Convention.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

Based on the metabolic studies on rats and on mice it is supposed that DMP is oxidatively demethylated to monomethyl hydrogen phosphate (MMP) and the methanol formed is further oxidized via formaldehyde to CO2. Metabolism of DMP to formaldehyde was studied in in vitro investigations of various rat tissues. Formaldehyde was formed dose-dependently mainly in liver, lungs and kidneys, but also in forestomach and glandular stomach. Some formaldehyde may enter the one-carbon pool and lead to methylation of endogenous substances (many substances, which are metabolised via oxidative demethylation do, however, not methylate endogenous substances; this is often explained by a slow rate of generation of formaldehyde relative to formaldehyde oxidation). Fig. 1 also shows non-enzymatic hydrolysis of DMP to MMP, release of methanol and subsequent formation of formaldehyde.

The major difference seen between rats and mice was the more rapid metabolism and elimination of DMP equivalents by mice as compared to rats.

Metabolic Transformation

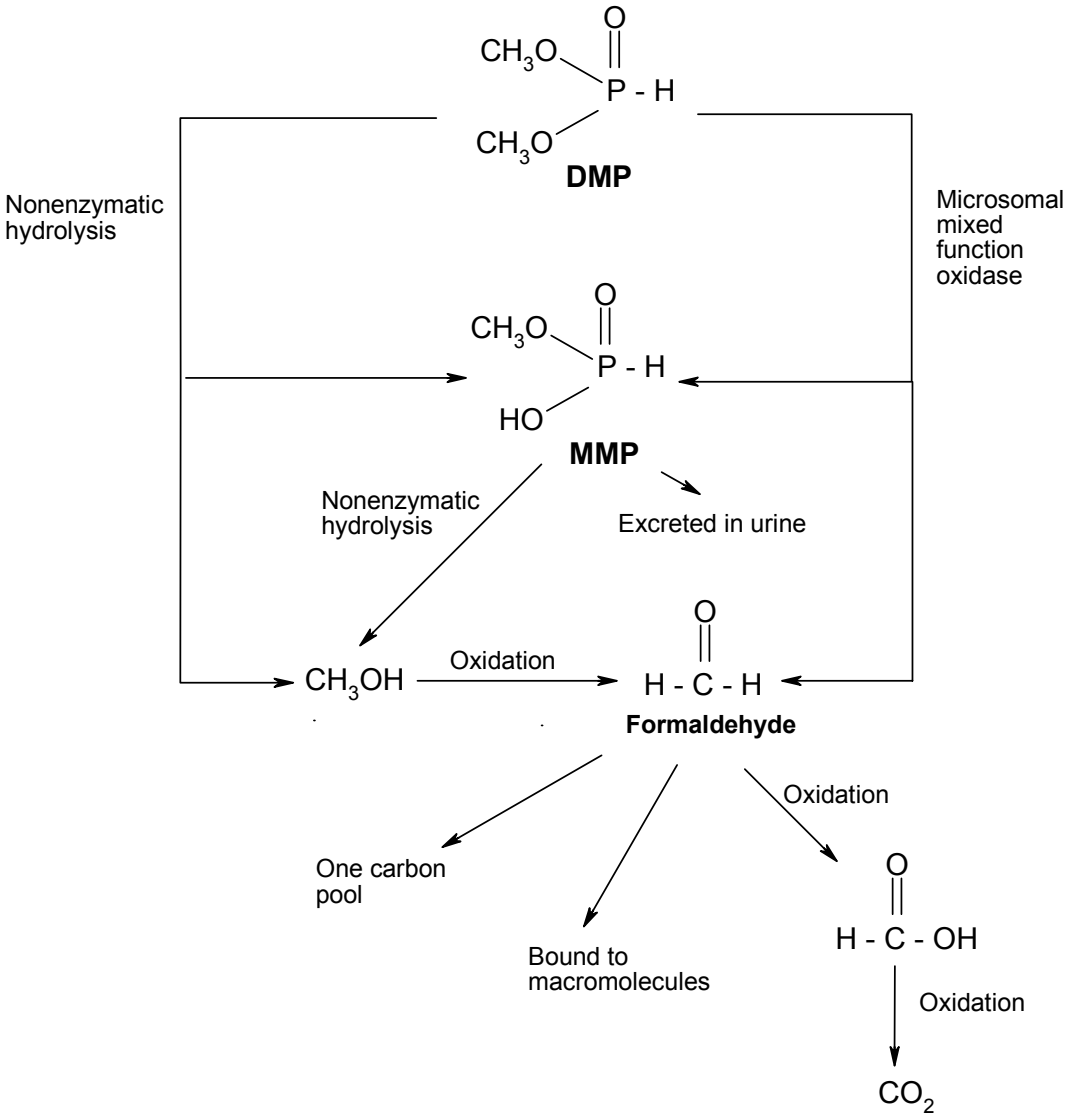


Fig. 1: Proposed metabolic pathways of DMP in rats and mice (Nomeir and Matthews, 1997)

Studies in Animals

Toxicokinetics

Information on toxicokinetics is available from one study where Fischer 344 rats and B6C3F1 mice were administered once orally 10 - 200 mg/kg 14C-labelled dimethyl phosphonate (DMP) by gavage. Further, rats were treated repeatedly for 5 days with an oral dose of 200 mg/kg bw 14C-labelled DMP (Nomeir and Matthews, 1997.

Absorption

From the studies on metabolism it can be concluded that DMP was readily and near completely absorbed from the gastrointestinal tracts of rats and mice. From the high acute dermal toxicity (see chapter 3.1.2) it can be concluded that also dermal absorption is high.

Distribution

DMP-derived radioactivity was widely distributed in tissues of rats and mice 24 h after dosing. The radioactivity in the tissues was approximately proportional to the dose. The highest concentrations

were observed in liver, kidney, spleen, lungs, and forestomach, and the lowest in brain, skeletal muscle, adipose tissue, and testes. Concentration of DMP derived radioactivity in all tissues increased as the number of daily doses increased. The pattern of tissue distribution in mice was similar to that observed in rats but the radioactivity measured in mice tissues after the administration of labeled DMP was lower.

Elimination

In rats 49 - 57 % of radioactivity was recovered as expired air (nearly complete after 12 hours), 28 - 38 % was found in urine (after 24 hours) and 2.5 % as organic volatiles. In mice approximately 44 % of radioactivity was eliminated via CO2 after 12 hours and appr. 49 % was found in urine after 24 hours. About 1 to 2 % of the radioactivity was found in the faeces in both species. The rate, extent and pattern of elimination of radioactivity were unaffected by dose over the range studied and by repeated administration.

Conclusion

Dimethyl phosphonate (DMP) is rapidly absorbed via the oral and dermal routes. The main metabolic pathway in rodents is demethylation to monomethyl hydrogen phosphite (MMP) and further oxidation to CO2. DMP was mainly eliminated via urine and expired air. Over the studied dose range between 10 and 200 mg/kg bw and 5 x 200 mg/kg bw respectively only little evidence of bioaccumulation or saturation of absorption or elimination was observed. The only difference in studied toxicokinetics between rats and mice was the more rapid metabolism and elimination in mice.

3.1.2 Acute Toxicity

Studies in Animals

Inhalation

Ten male rats, mice and guinea pigs per test group were exposed to 7100 mg/m^3 DMP (calculated exposure concentration from air flow and net loss of material) for 6 hours. If an absorption of 100 % was assumed the amount of inhaled DMP corresponded to about 1200 mg/kg bw in rats, about 2300 mg/kg bw in mice, and about 1000 mg/kg bw in guinea pigs in this investigation. No deaths occurred. Clinical signs like occasionally labored respiration after approximately 2 hours of exposure and ptosis after 5 hours were observed in mice only. At necropsy, congestion and hemorrhage in the lungs were observed in rats (Occidental Chemical Corporation, 1992b). It is noted, that this study is limited by the lack of analytical monitoring of the exposure concentrations, and the method used is likely to overestimate the concentration to which animals were exposed.

Dermal

The dermal LD_{50} in male and female rabbits was 681 mg/kg bw (Occidental Chemical Corporation, 1992a), which is lower than the oral LD_{50}s in rats and mice, and which may point to the fact that the rabbit may be a more sensitive species. Signs of intoxication and necropsy findings were similar as in the oral study. Signs of intoxication were depression, ptosis, labored respiration, ataxia and placidity at doses of ≥ 1000 mg/kg bw. At necropsy (concentrations of ≥ 1000 mg/kg bw) hemorrhagic lungs, red-tinged fluid in the pleural cavity, congestion of the thymus and kidneys, edema or thickening of the mucosa of the stomach, and inflammation of a portion of the intestines were observed (Occidental Chemical Corporation, 1992a).

Oral

The oral LD_{50} of DMP was 3040 mg/kg bw in female Fischer 344 rats and 3283 mg/kg bw in male rats (NTP 1985). In B6C3F1 mice the LD_{50} value was between 2150 and 3160 mg/kg bw for females, and 2815 mg/kg bw for males (NTP, 1985). Clinical signs of toxicity, that have been observed after oral administration of DMP, were inactivity, weakness, prostration and shallow breathing in rats and mice at dose groups of ≥ 3160 mg/kg bw and ≥ 2150 mg/kg bw, respectively (NTP, 1985). Additionally, labored respiration and tremors as clinical signs after DMP administration were shown (Occidental Chemical Corporation, 1992a). In male mice white opaque eyes were occasionally observed (NTP, 1985). Necropsy findings included gas in stomach and/or intestine (rats at dose groups ≥ 3160 mg/kg bw) (NTP, 1985). Further findings were gastrointestinal inflammation, hemorrhage of lungs and congested kidneys (Occidental Chemical Corporation, 1992a).

Conclusion

An inhalation LC_{50} value is not available, but an exposure of 7100 mg/m³ (concentration estimated based on air flow and net loss of material) over 6 hours was not lethal for rats, mice and guinea pigs. Clinical signs were observed in mice only, and included occasionally labored respiration after approximately 2 hours of exposure and ptosis after 5 hours.

The acute dermal LD_{50} was 681 mg/kg bw (rabbits). Signs of intoxication were depression, ptosis, labored respiration, ataxia and placidity. The acute oral LD_{50} values were: 3283 mg/kg bw for male rats, 3040 mg/kg bw for female rats, 2815 mg/kg bw for male mice, and between 2150 and 3160 mg/kg bw for female mice. Clinical signs were inactivity, weakness, prostration and shallow breathing at doses near to or exceeding the LD_{50} values. White opaque eyes were seen in male mice.

3.1.3 Irritation

Skin Irritation

Studies in Animals

Only studies with very limited information are available. When applied undiluted to the ears of rabbits for 1 - 4 hours, DMP was only slightly irritating. DMP was severely irritating to ear skin, when the exposure time was extended to 8 hours (Bayer AG, 1978). No signs of dermal irritation on the exposed skin area of any rabbit were reported in the acute dermal toxicity study with DMP (Occidental Chemical Corporation 1992a). In repeated dose toxicity studies skin irritation was observed in rats after inhalation administration of concentrations ≥ 142.1 mg/m^3. DMP caused massive skin necrosis at higher concentrations (further details see chapter 3.1.5).

Studies in Humans

No studies available.

Eye Irritation

Studies in Animals

When applied undiluted to the eyes of rabbits in accordance with a method comparable to the OECD guideline 405, DMP was moderately irritating to eyes (Occidental Chemical Corporation, 1992a). In an additional study 2 rabbits were treated with 100 µl/eye. The only effects were reddening of the conjunctivae in both animals. Full recovery was achieved within 5 days (Bayer AG 1978). Repeated dose toxicity studies showed moderate to severe changes in mucous membranes

and development of cataracts after oral and inhalation administration of DMP to rats (eye irritation at 12 ppm = 48.7 mg/m³) (further details see chapter 3.1.5).

Studies in Humans

No studies available.

Respiratory Tract Irritation

No studies available.

Conclusion

DMP is irritating to the skin and eyes of rabbits. After prolonged or repeated exposures moderate to severe irritation of skin and mucosa was observed in rats.

3.1.4 Sensitisation

There are no studies on skin or respiratory sensitization available.

3.1.5 Repeated Dose Toxicity

One inhalation as well as two sub-acute, two sub-chronic and two chronic oral investigations studying the repeated dose toxicity of DMP in rats and mice will be discussed below (see Table 7).

Studies in Animals

Inhalation

In a 4-week study, male and female Sprague-Dawley rats (20/sex per group) inhaled 48.7, 142.1, 483.1, and 803.9 mg/m^3 (12, 35, 119, and 198 ppm) DMP vapor for 6 hours/day on 5 days/week (Mobil Oil Corporation, 1982). At all concentrations increased kidney weights were observed in male and female rats. Irritation of superficial ocular structures, mucosal irritation and keratitis were shown in all dose groups and in both sexes. The eye changes progressed to cataracts in dose groups of ≥ 142.1 mg/m^3. At ≥ 142.1 mg/m^3 cutaneous irritation was observed, the skin effects progressed to dermatitis at 483.1 mg/m^3, and at 803.9 mg/m^3 necrosis and acute purulent inflammation of the skin were main causes of deaths. At 142.1 mg/m^3 inflammation of the anterior nares was visible in male and female rats. At 483.1 mg/m^3 the external nares were affected, and at 803.9 mg/m^3 red discoloration of the lungs and the nasal turbinates were observed in both sexes.

In male rats reduced body weight gains were observed at ≥ 142.1 mg/m^3. In the next higher dosage (483.1 mg/m^3) body weight losses and increased mortality was shown in male and female rats. Time to death varied between 7 and 26 days at 483.1 and 803.9 mg/m^3. Hypospermatogenesis was observed in male rats at lethal doses of ≥ 483.1 mg/m^3 (details see chapter 3.1.8). Hematopoiesis in the spleen occurred in 4/18 female rats at 803.9 mg/m^3 only and was not observed in the controls or the lower doses. No historical control data were provided.

The LOAEL derived for this study is 48.7 mg/m^3 (12 ppm; corresponds to about 10 mg/kg bw/d). No NOAEL was achieved in this study.

Dermal

No studies available.

Oral

Rats

In one sub-acute investigation male Fischer 344 rats were treated daily with 200 mg/kg bw for 4, 5, and 6 weeks respectively. The forestomach weights were elevated, and histopathological and biochemical changes were seen in all treated groups. Effects on forestomach weights were reversible. Slight biochemical changes in lungs were observed (Nomeir and Uraih, 1988).

In one sub-chronic investigation male and female Fischer 344 rats were administered 25, 50, 100, 200, 400 mg/kg bw/d DMP 5 days/week for 13 weeks via gavage (NTP, 1985). A decreased body weight gain was observed in female rats at 200 mg/kg bw/d and above and for male rats at 400 mg/kg bw/d. Mortality was increased at 400 mg/kg bw/d for both sexes. Eye changes (degeneration of the lens, acute diffuse inflammation of the cornea) and increased lung lesions (inflammation, congestion, histiocytosis) were found in male and female rats at 400 mg/kg bw/d. In male rats increased urinary bladder calculi were observed at 400 mg/kg bw/d.

The NOAEL is 100 mg/kg bw/d for female and 200 mg/kg bw/d for male rats.

In a chronic study male Fischer 344 rats were administered 100, 200 mg/kg bw/d DMP and female rats 50, 100 mg/kg bw, respectively, on 5 days/week for two years. At ≥ 100 mg/kg bw male rats showed dose-related lung effects (interstitial pneumonia, alveolar/bronchiolar adenoma or carcinoma) and at 200 mg/kg bw/d increased cataract formation, and squamous cell carcinoma. Focal mineralization in the cerebellum was observed in males at 200 mg/kg bw/d (NTP, 1985). Female rats showed forestomach hyperplasia and a statistically not significant, but dose-related increase in lung alveolar/bronchiolar carcinoma at ≥ 100 mg/kg bw/d (details on tumors see under chapter 3.1.7).

The LOAEL for male rats is 100 mg/kg bw/d and the NOAEL for female rats is 50 mg DMP/kg bw/d.

Mice

In a sub-acute study B6C3F1 mice were treated with 250, 500, 1000, 2000, or 3000 mg/kg bw/d for 14 days. A NOAEL could not be derived from this study due to stomach lesions down to the lowest test concentration (epithelial ulcerations, glandular stomach ulcerations, acute/chronic gastritis, squamous atrophy, hyperplastic gastropathy, hyperkeratosis, submucosal and intra-epithelial abscesses, massive necrosis (NTP, 1985).

In a sub-chronic investigation B6C3F1 mice were treated with 95, 190, 375, 750, 1500 mg DMP/kg bw/d. At 190 mg/kg bw/d and above cardiac mineralization was seen in male mice and hepatocellular vacuolization in female mice (NTP, 1985). At 375 mg/kg bw/d the liver changes were also seen in male mice. Lung congestions were observed with higher incidence at 375 mg/kg bw/d in both sexes, and mortality was increased at this dose. Testicular atrophy was observed at 375 mg/kg bw/d (details under chapter 3.1.7 and 3.1.8). 750 mg/kg bw/d were lethal for all animals within 4 weeks.

The NOAEL is therefore 95 mg/kg bw/d for male and female mice.

In a chronic investigation male B6C3F1 mice (males and females were administered 100, 200 mg/kg bw/d for two years) showed calcification of testis at concentrations of ≥ 100 mg/kg bw/d. At 200 mg/kg bw/d lower body weights and increased mortality was observed in males only (NTP, 1985).

The NOAEL for female mice is therefore 200 mg/kg bw/d and the LOAEL for male mice 100 mg/kg bw/d.

Table 7: Repeated dose toxicity of DMP

Appli-cation	Species Strain Sex	Duration	Doses	NOAEL	Effects/Target organs	References
Inhala-tion (vapor)	Rat Sprague-Dawley f/m	4 weeks (4 weeks recovery)	48.7; 142.1; 483.1; 803.9 mg/m^3	< 12 ppm; LOAEL = 12 ppm (48.7 mg/m^3)	≥ 48.7 mg/m^3, f + m: increased kidney weights ≥ 48.7 mg/m^3, f + m: eyes (keratitis, ≥ 142.1 mg/m^3, f + m: cataracts) ≥ 142.1 mg/m^3, m: reduced body weight gain ≥ 142.1 mg/m^3 f + m: skin irritation (≥ 483.1 mg/m^3: dermatitis, 803.9 mg/m^3: lethal skin necrosis) ≥ 142.1 mg/m^3 f + m: respiratory tract (inflammation of anterior nares; ≥ 483.1 mg/m^3: inflammation of the external nares, ≥ 803.9 mg/m^3: red discoloration of the lungs) ≥ 483.1 mg/m^3, m and f: body weight losses, increased mortality ≥ 483.1 mg/m^3, m: hypospermatogenesis	Mobil Oil Corporation, 1982
Oral, Gavage	Rat Fischer 344 m	4-6 weeks	200 mg/kg	Not derivable	Forestomach: increased weights, several lesions, biochemical changes Lung: biochemical changes	Nomeir and Uraih, 1988
	Rat Fischer 344 m/f	13 weeks	25, 50, 100, 200, 400 mg/kg bw	F: 100 mg/kg bw m: 200 mg/kg bw	≥ 200 mg/kg bw/d (f): decrease in body weight (at 200 mg/kg bw/d 13.5% decrease as compared to controls at study end) 400 mg/kg bw/d (m): decreased body weight gain 400 mg/kg bw/d, f + m: eyes (degeneration) 400 mg/kg bw/d, m: urinary bladder calculi 400 mg/kg bw/d, m + f: lung (inflammation, congestion, histiocytosis)	NTP, 1985
	Rat Fischer 344 m/f	103 weeks	m:100, 200, f: 50, 100 mg/kg bw/d	m: < 100 mg/kg bw/d f: 50 mg/kg bw/d	≥ 100 mg/kg bw/d, m: lung (interstitial pneumonia) 200 mg/kg bw/d, m: focal mineralization in cerebellum 200 mg/kg bw/d, m: eye (cataracts) 100 mg/kg bw/d, f: forestomach and lung changes (detail under chapter 3.1.10) Tumors: see chapter 3.1.7	NTP, 1985

Table 7 (cont)**:** Repeated dose toxicity of DMP

Appli-cation	Species Strain Sex	Duration	Doses	NOAEL	Effects/Target organs	References
	Mouse B6C3F1 m/f	13 weeks	95, 190, 375, 750, 1500 mg/kg bw/d	95 mg/kg bw/d	≥ 190 mg/kg bw/d, m: cardiac mineralization ≥ 190 mg/kg bw/d, f, ≥ 375 mg/kg bw/d, m: hepatocellular vacuolization ≥ 375 mg/kg bw/d: increased mortality ≥ 375 mg/kg bw/d, f + m: lung congestions ≥ 375 mg/kg bw/d, m: testicular atrophy (see 3.1.8 Toxicity to Reproduction) ≥ 750 mg/kg bw/d: lethal for all animals	NTP, 1985
	Mouse B6C3F1 m/f	103 weeks	100, 200 mg/kg bw/d	m: < 100 mg/kg bw/d f: 200 mg/kg bw/d	≥ 100 mg/kg bw/d: focal calcification in testis (see 3.1.8 toxicity to reproduction) ≥ 200 mg/kg bw/d, m: lower body weights, increased mortality	NTP, 1985

Conclusion

In a repeat dose inhalation study on rats over 4 weeks, no NOAEL could be derived as increased kidney weights and keratitis were found in both sexes down to the lowest tested concentration (LOAEL: 49 mg/m³, corresponding to about 10 mg/kg bw/d). In the same study, DMP caused eye cataracts at concentrations equal to or greater 142 mg/m³,and an increase in mortality at concentrations equal to or greater 483 mg/m³.

In 13-week gavage studies on rats, decreased body weight gains were noted in females at 200 mg/kg bw/d, and for males at 400 mg/kg bw/d. At 400 mg/kg bw/d, eye changes (cataracts), and lung toxicity (inflammation, congestion, histiocytosis) occurred (NOAEL, male: 200 mg/kg bw/d, NOAEL, female: 100 mg/kg bw/d). For mice the NOAEL (13 week, gavage), was 95 mg/kg bw/d, with histopathological changes in heart and liver appearing at 190 mg/kg bw/d. At 375 mg/kg bw/d mortality was increased, and there were no surviving animals at 750 mg/kg bw/d.

In a 2-year gavage study on rats, lung effects were seen in both sexes at 100 mg/kg bw/d. At 200 mg/kg bw/d, males had cataracts and focal mineralization in the cerebellum (NOAEL, females: 50 mg/kg bw/d; LOAEL, males: 100 mg/kg bw/d, lowest tested dose in males). For female mice the NOAEL (2-yr, gavage) was 200 mg/kg bw/d (highest tested dose), whilst a NOAEL for male mice could not be derived as calcification of testis was still found at the lowest tested concentration of 100 mg/kg bw/d. An increase in mortality was seen in male mice at 200 mg/kg bw/d.

3.1.6 Mutagenicity

Bacterial tests

Ames tests performed with DMP were primarily negative. In one NTP assay the results of the strains TA 98, 100, 1535, 1537 in concentrations up to 10 000 µg/plate were judged negative with and without metabolic activation. Cytotoxicity was reached at 10 000 µg DMP/plate (NTP, 1985). A further assay was judged negative: 775 to 12 400 µg DMP/plate were tested with the strains TA 98, 100, 1535 and 1537 in duplicates (Bayer AG, 1988). In the first experiment the mutant counts of TA 100 with S-9 mix were significantly increased. This result could not be reproduced in the replicate (Bayer AG, 1988). At 6200 µg/plate bacteriotoxic effects were observed but the test could be evaluated (Bayer AG, 1988).

Tests performed according to a NTP standard protocol gave positive results with strain TA 100 at a concentration of 10 000 µg/plate in the presence of S-9 mix. The other standard tester strains TA 98, 1535, 1537 were negative (Mortelmans et al., 1986; Zeiger, 1987; Tennant et al., 1987a). The data from the study by Tennant et al. (1987a) were re-evaluated by Prival and Dunkel (1989) using more stringent criteria for a positive result. The positive results with TA100 were made negative by disregarding the positive results at a dose of 10 000 µg/plate (Prival and Dunkel, 1989). It is noted that this concentration also exceeds the limit dose of 5000 µg/plate which is recommended in current guidelines.

Studies in Animals

In vitro Studies

In a cytogenetic assay, performed after NTP standard protocol, with L5178Y mouse lymphoma cells DMP showed positive results with metabolic activation at concentrations of ≥ 1700 µg/ml (Tennant et al., 1987a). A further mouse lymphoma assay showed also mutagenic activity of DMP in concentrations of ≥ 2100 µg/ml in the presence of S-9 mix (McGregor et al., 1988). 2600 µg DMP/ml were cytotoxic in this assay.

In chromosomal aberration tests with Chinese hamster ovary cells performed after NTP standard protocol DMP clearly induced chromosomal aberrations in the presence of S-9 mix and was weakly positive in the absence of S-9 mix at concentrations of ≥ 1600 µg/ml each (Tennant et al. 1987a; Gulati et al. 1989).

DMP was positive in a DNA damage and repair assay with primary rat hepatocytes pretreated with Aroclor-1254 (Aro) and 3-methylcholanthrene (3-MC). The netto nuclear grains (NNG) and the percentage of cells with three NNGs above the solvent control (% IR) respectively were evaluated. The % IR was clearly elevated in the rat hepatocytes pretreated with Aro (in concentrations of ≥ 0,01 µg/ml) and 3-MC (in concentrations of ≥ 0,025 µg/ml) representing unscheduled DNA synthesis and indicating DNA mutations of DMP (Shaddock et al., 1990). DMP was negative in untreated primary rat hepatocytes (Shaddock et al. 1990). A further negative result was obtained in an unscheduled DNA synthesis assay with primary rat hepatocytes and limited documentation (Tennant et al., 1987b).

In a sister chromatid exchange (SCE) assay with Chinese hamster ovary cells DMP caused increased total SCE numbers in cells and increased numbers of SCE/cell with and without metabolic activation at concentrations of ≥ 250 µg/ml. The concentration range tested was 5 - 1600 µg/ml without S-9 mix and 16 - 4000 µg/ml with S-9 mix and fifty second-division metaphase cells were scored per dose (Tennant et al., 1987a; Gulati et al., 1989).

Table 8:Genotoxicity of DMP

Type of test		System/ Strain	Conc. tested	Result	Cytotoxicity	Reference
Ames Tests		TA 98, 100, 1535, 1537 (+ and – MA)	100, 333, 1000, 3333, 10 000 µg/plate	Negative (+ and – MA)	10 000 µg/plate	NTP, 1985
		TA 98, 100, 1535, 1537 (+ and – MA)	775, 1550, 3100, 6200, 12 400 µg/plate	Negative (+ and – MA)	≥ 6200 µg/plate (bacteriotoxic effects, could be evaluated)	Bayer AG, 1988
		TA 98, 100, 1535, 1537 or 97 (+ and – MA)	No data	Positive (TA 100, + MA)	No data	Mortelmanns et al., 1986; Zeiger, 1987
		TA 98, 100, 1535, 1537 or 97 (+ and – MA)	No data	Positive (strain TA 100, + MA at 10 000 µg/plate) Negative, if re-evaluation criteria are used	No data	Tennant et al., 1987 Prival and Dunkel, 1989
Mammalian cell culture tests	Mouse lymphoma test	L5178Y	No data	Positive (≥ 1700 µg/ml + MA)	No data	Tennant et al., 1987a
	Mouse lymphoma test	L5178Y	125 -2600 µg/ml (-MA), 1700 - 2500 (+ MA)	Positive (2100 µg/ml, + MA)	> 2500 µg/ml (with MA)	McGregor et al., 1988
	Chromosomal aberration	Chinese hamster ovary cells	50 - 1600 µg/ml (- MA), 16 - 5000 (+ MA)	Positive (≥ 1600 µg/ml, - MA); weak positive (without MA (≥ 1600 µg/ml, + MA)	5000 µg/ml	Tennant et al., 1987a ; Gulati et al., 1989
	DNA damage	Primary rat hepatocytes – Arochlor pretreated	0,01 - 5,0 µg/ml	Positive (≥ 0,01 µg/ml)	5,0 µg/ml	Shaddock et al., 1990
		Primary rat hepatocytes 3-methyl-cholanthrene pretreated	0,01-5,0 µg/ml	Positive (≥ 0,025 µg/ml)	≥ 1,0 µg/ml	Shaddock et al., 1990
		Primary rat hepatocytes untreated	0,01 - 5,0 µg/ml	Negative	≥ 2,5 µg/ml	Shaddock et al., 1990
		Primary rat hepatocytes	No data	Negative	No data	Tennant et al., 1987b
	Sister chromatid exchange	Chinese hamster ovary cells	5 - 1600 µg/ml (- MA), 16 -5000 µg/ml (+ MA)	Positive (≥ 250 µg/ml, + and – MA))	5000 µg/ml	Tennant et al., 1987a; Gulati et al., 1989

In vivo Studies

The *in vivo* mutagenicity of DMP was investigated in two *Drosophila* SLRL tests and in two mouse bone marrow micronucleus assays.

Canton-S males of *Drosophila* were administered DMP via feed in concentration of 650 ppm for 3 days and via one single injection into the abdomen in concentration of 1500 ppm. No genotoxicity for a total of 3 broods was observed (Woodruff et al, 1985).

In a micronucleus assay in bone marrow cells of B6C3F1 mice, which received daily i.p. injections of 250 and 500 mg/kg bw/d DMP for three days, the number of micro-nucleated polychromatic erythrocytes (PCEs) per 1000 PCEs scored was signifycantly elevated in the first trial at 500 mg/kg bw/d. This result could not be clearly reproduced in the second trial. The trend analysis of the repeat test gave P=0.078. The authors judged the data as "adequate evidence of an effect", though not conclusive: "... additional tests would be needed to provide conclusive evidence of MN-inducing ability" of DMP (Shelby et al., 1993).

In a separate micronucleus assay with NMRI mice, no clastogenic effect was observed according to the study authors after a single i.p. administration of 2000 mg/kg bw DMP (Bayer AG, 1994). The incidences of micro-nucleated polychromatic erythrocytes (PCEs) per 1000 PCEs scored were measured 16, 24 and 48 hours after i.p. injection of DMP. There was a statistically non-significant doubling of micro-nucleated PCEs after 48 hours (negative controls 1.3 ± 1.1, 16h 0.8 ± 1.1, 24h 1.8 ± 1.5, 48 h 2.7 ± 3.1). Although statistically significant, the values for the positive control group (cyclophosphamide, 20 mg/kg bw i.p.) were unusually low (7.3 ± 5.5 as compared to the laboratory`s historical positive control range of 10.2 – 25.1). It is therefore not certain, whether this test was sufficiently sensitive.

Table 9: Results of *in vivo* mutagenicity of DMP

Test system, species strain	Test conditions	Result	Reference
Drosophila SLRL	Feed, 3 days, 650 ppm, 3 broods	Negative	Woodruff et al., 1985
Drosophila SLRL	Injection, single administration, 1500 ppm, 3 broods	Negative	Woodruff et al., 1985
Micronucleus assay, B6C3F1, mouse bone marrow cells	3 daily i.p. injections (250, 500 mg/kg bw/d), cells taken 24 hours after last treatment	Positive (500 mg/kg bw/d) with the recommendation of further tests	Shelby et al., 1993
Micronucleus assay, NMRI , mouse bone marrow cells	2000 mg/kg bw, single i.p. administration, cells taken 16, 24, 48 hours after treatment	Negative	Bayer AG, 1994

Studies in Humans

No studies available.

Conclusion

In vitro data indicate that DMP has mutagenic and clastogenic potential. The available *in vivo* data are limited to the bone marrow and the results are conflicting with one study indicating clastogenicity. DMP should be regarded as having genotoxic potential *in vivo*.

3.1.7 Carcinogenicity

DMP was tested for carcinogenicity in doses of 100 and 200 mg/kg bw/d in male F344 rats and 50 and 100 mg/kg bw/d in female F344 rats respectively. The doses were administered orally via gavage on 5 days/week for 103 weeks. A clear evidence of carcinogenicity was found for male rats and an equivocal evidence for female rats. In gross pathology and histopathology statistically significant squamous cell carcinoma in lung and alveolar/bronchial cell adenoma or carcinoma in male rats were found to be treatment related. In female rats a marginally increase in alveolar/ bronchial cell adenoma or carcinoma was assessed as to be dose-related (0/50, 1/49, 3/50), but was not statistically significant (NTP, 1985).

Regarding the forestomach carcinogenicity, statistically significant hyperplasia, hyperkeratosis, and squamous cell carcinoma or adenoma were observed in male rats in the highest dose group. In the forestomach of female rats hyperplasia was found in the 100 mg/kg bw dose group. The incidence of forestomach neoplasms was only slightly, and not statistically significantly increased (NTP, 1985).

Statistically significant mononuclear cell leukemia was observed with higher incidences in male rats of the 100 mg/kg bw/d dose group. In the high dose group a slightly lower incidence was observed. The incidence was at the upper limit of the historical control and confined to male animals (NTP, 1985).

B6C3F1 mice were treated with 100 and 200 mg/kg bw/d in the same way as described above. Statistically significant increased numbers of hepatocellular adenomas were observed in the 100 mg/kg bw/d female group only. No evidence of carcinogenicity was concluded for B6C3F1 mice (NTP, 1985).

The International Agency for Research on Cancer concluded 1990 and 1999 that there is limited evidence for the carcinogenicity of DMP in experimental animals. DMP is not classifiable as to its carcinogenicity to humans (Group 3) (IARC, 1990; IARC, 1999).

Conclusion

DMP showed clear evidence of carcinogenicity in male F344 rats and equivocal evidence in female F344 rats. Target organs are lungs and forestomach. No evidence of carcinogenicity is observed in male and female B6C3F1 mice.

3.1.8 Toxicity for Reproduction

Studies in Animals

Effects of DMP on fertility and fetal development were assessed in a screening study according to OECD TG 421 (Bayer AG, 2002b). Groups of 12 male and female Wistar rats were dosed with 0, 30, 90 or 270 mg/kg bw/d by gavage. F0-Animals were treated from 2 weeks before mating to the end of gestation and up to 4 to 5 days of lactation. Males were killed after at least 28 days of treatment. Females and pups were killed on days 4 to 5 post partum. Ovaries, testes, epididymides and macroscopically altered tissues of F0 animals were examined histologically. Parameters of general toxicity and fertility, as well as pre- and post-natal development were recorded.

In the high dose group (270 mg/kg bw/d), animals of both sexes exhibited clear clinical signs of systemic toxicity (poor general state, apathy, high stepping gait, squatting position, bloody muzzle, piloerection, emaciation, tremor and/or desiccation of skin) and severe body weight loss. Two males of this group were found dead with discolored liver and/or lungs, and all females of this group had to be killed in moribund condition during mating or gestation. At 90 mg/kg bw/d soft feces and/or

diarrhea were noted in both sexes more frequently than in the control group. No substance related effects were found at 30 mg/kg bw/d.

The NOAEL for parental toxicity in rats (m, f) was set at 90 mg/kg bw/d by the study authors.

Effects on Fertility

At 270 mg/kg bw/d, the relative testis weight was increased and the absolute epididymidis weight decreased. No pathological changes were found at macroscopic and microscopic examinations in the testis and epididymides. The number of females with corpora lutea and implantation sites was decreased at 270 mg/kg bw/d, as well as the frequency and severity score of "large corpora lutea" and of granular luteal cells. All changes at 270 mg/kg bw/d were considered secondary to the toxic effects of DMP. Insemination and fertility indices were distinctly reduced at 270 mg/kg bw/d.

Reproductive parameters (insemination parameters, fertility index, gestation indices, gestation length, prenatal loss, number of implantation sites, macroscopically visible corpora lutea, life birth index, sex ratio, pup birth weight, litter size, pup weight development, viability and lactation of F1 rats) were not affected at 30 and 90 mg/kg bw/d.

It is noted that testicular atrophy was found in mice treated by gavage with ≥ 375 mg/kg bw/d for 13 weeks, probably secondary to general toxicity, as this dose level also induced mortality (NTP 1985). Focal calcification in the testis was seen in 9/47 mice dosed with 100 mg/kg bw/d and in 24/50 mice dosed with 200 mg/kg bw/d following chronic exposure (103 weeks). The shape and location of the deposits in the testis suggest mineralization of seminiferous tubules (NTP, 1985). Hypospermatogenesis was reported in rats after inhalation of 483.1 mg/m^3 (corresponding to about 100 mg/kg bw/d) for 4 weeks (Mobil Oil Corporation, 1982).

The NOAEL for reproduction toxicity in rats (m, f) was at 90 mg/kg bw/d.

Developmental Toxicity

In the afore described OECD Screening Study (Bayer AG 2002b), the sex ratio, mortality and weights of F1 pups were not affected by treatment up to and including 90 mg/kg bw/d, while evaluation was not possible at higher doses as there were no surviving pups. No externally malformed pups were observed.

The NOAEL for developmental toxicity in rats (m,f) was 90 mg/kg bw/d.

Conclusion

In a screening study on rats according to OECD TG 421 (gavage study), effects on fertility were seen in females at 270 mg/kg bw/d in the presence of severe general toxicity (decrease in number of females with corpora lutea and implantation sites) (NOAEL reproduction toxicity: 90 mg/kg bw/d; NOAEL general toxicity: 90 mg/kg bw/d). Focal testicular calcification was seen in mice treated orally with 100 mg/kg bw/d for 2-years, and hypospermatogenesis in rats after inhalation of 483.1 mg/m^3 (corresponding to about 100 mg/kg bw/d) for 4 weeks. No developmental toxicity was found in rats at doses of 30 and 90 mg/kg bw/d (NOAEL developmental toxicity: 90 mg/kg bw/d).

3.2 Initial Assessment for Human Health

Dimethyl phosphonate (DMP) is rapidly absorbed via the oral and dermal routes. The main metabolic pathway in rodents is demethylation to monomethyl hydrogen phosphite (MMP) and further oxidation to CO_2. DMP was mainly eliminated via urine and expired air. Over the studied dose range between 10 and 200 mg/kg bw and 5 x 200 mg/kg bw, respectively, only little evidence of bioaccumulation or saturation of absorption and elimination was observed. The only difference in

studied toxicokinetics between rats and mice was the more rapid metabolism and elimination in mice.

An inhalation LC_{50} value is not available, but an exposure of 7100 mg/m³ (concentration estimated based on air flow and net loss of material) over 6 hours was not lethal for rats, mice and guinea pigs. Clinical signs were observed in mice only, and included occasionally labored respiration after approximately 2 hours of exposure and ptosis after 5 hours.

The acute dermal LD_{50} was 681 mg/kg bw (rabbits). Signs of intoxication were depression, ptosis, labored respiration, ataxia and placidity. The acute oral LD_{50} values were: 3283 mg/kg bw for male rats, 3040 mg/kg bw for female rats, 2815 mg/kg bw for male mice, and between 2150 and 3160 mg/kg bw for female mice. Clinical signs were inactivity, weakness, prostration and shallow breathing at doses near to or exceeding the LD_{50} values. White opaque eyes were seen in male mice.

DMP is irritating to the skin and eyes of rabbits. After prolonged or repeated exposures moderate to severe irritation of skin and mucosa was observed in rats. No sensitization studies are available.

In a repeated dose inhalation study on rats over 4 weeks, no NOAEL could be derived as increased kidney weights and keratitis were found in both sexes down to the lowest tested concentration (LOAEL 49 mg/m^3, corresponding to about 10 mg/kg bw/d). In the same study, DMP caused eye cataracts at concentrations equal to or greater 142 mg/m^3, and an increase in mortality at concentrations equal to or greater 483 mg/m³.

In 13-week gavage studies on rats, decreased body weight gains were noted in females at 200 mg/kg bw/d, and for males at 400 mg/kg bw/d. At 400 mg/kg bw/d, eye changes (cataracts), and lung toxicity (inflammation, congestion, histiocytosis) occurred (NOAEL, male: 200 mg/kg bw, NOAEL, female: 100 mg/kg bw). For mice the NOAEL (13 week, gavage), was 95 mg/kg bw/d, with histopathological changes in heart and liver appearing at 190 mg/kg bw/d. At 375 mg/kg bw/d mortality was increased, and there were no surviving animals at 750 mg/kg bw/d.

In a 2-year gavage study on rats, lung effects were seen in both sexes at 100 mg/kg bw/d. At 200 mg/kg bw/d, males had cataracts and focal mineralization in the cerebellum (NOAEL, females: 50 mg/kg bw/d; LOAEL, males: 100 mg/kg bw/d, lowest tested dose in males). For female mice the NOAEL (2-yr, gavage) was 200 mg/kg bw/d (highest tested dose), whilst a NOAEL for male mice could not be derived as calcification of testis was still found at the lowest tested concentration of 100 mg/kg bw/d. An increased mortality was seen in male mice at 200 mg/kg bw/d.

In vitro data indicate that DMP has mutagenic and clastogenic potential. The available *in vivo* data are limited to the bone marrow and the results are conflicting with one study indicating clastogenicity. DMP should be regarded as having genotoxic potential *in vivo*.

DMP showed clear evidence of carcinogenicity in male F344 rats and equivocal evidence in female F344 rats. Target organs were lungs and forestomach. No evidence of carcinogenicity was observed in male and female B6C3F1 mice.

In a screening study on rats according to OECD TG 421 (gavage study), effects on fertility were seen in females at 270 mg/kg bw/d in the presence of severe general toxicity (decrease in number of females with corpora lutea and implantation sites) (NOAEL reproduction toxicity: 90 mg/kg bw/d; NOAEL general toxicity: 90 mg/kg bw/d). Focal testicular calcification was seen in mice treated orally with 100 mg/kg bw/d for 2-years, and hypospermatogenesis in rats after inhalation of 483 mg/m^3 (corresponding to about 100 mg/kg bw/d) for 4 weeks. No developmental toxicity was found in rats at doses of 30 and 90 mg/kg bw/d (NOAEL developmental toxicity: 90 mg/kg bw/d).

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Concerning the aquatic effects short term toxicity tests are available for each trophic level.

DMP hydrolyses to MMP and methanol, followed by hydrolysis to phosphorous acid. At pH 4 the experimentally determined half-life is about 470 h, at pH 7 it is about 3 h, and at pH 9 it is < 0.3 h. MMP hydrolysed slower (c/f Chapter 2.1). Depending on the duration of the test, ecotoxicological measurements will cover the effects of DMP and of its degradation products MMP, phosphorous acid, and methanol.

Acute toxicity to fish (*Danio rerio*) was tested in a static test system according to the method C.1 of the directive 67/548/EEC. The test substance was determined by GC-analysis. A limit test was conducted, testing toxicity at 100 mg/l (nominal concentration). During 96 h no effects were observed at the tested concentration level (Bayer AG, 1992).

Another acute toxicity test confirmed the low fish toxicity of the test compound. Although the test was not conducted according to any current guideline, the method can be accepted as valid. The LC_{50} was found to be 225 mg/l for *Pimephales promelas*. It must be assumed that this is a nominal concentration (Bender, 1969).

In a GLP study according to Directive 92/69/EEC, C.2, with analytical monitoring (DOC and HPLC), the EC_{50} of *Daphnia magna* was 25 mg/l (nominal) after 48 h (Bayer AG, 2003d). Due to rapid hydrolysis of DMP to MMP, and the slow hydrolysis of MMP to phosphorous acid (see above), there were significant concentrations of MMP at any DMP concentration (22 - 35 % w/w of initial DMP). At the nominal DMP concentration of 25 mg/l, the geometric mean of the measured MMP concentrations was 8.0 mg/l during this test. DOC measurements confirmed the presence of virtually all organic carbon of the initial carbon content of DMP.

Also for the performance of the growth inhibition test on algae, the results of the hydrolysis study (see above) were taken into account. In a GLP study according to Directive 92/69/EEC, C.3 with analytical monitoring, the 72 h EC_0 (nominal) of *Desmodesmus subspicatus* was ≥ 100 mg/l (Bayer AG, 2003e). Presumably due to pH and presence of catalytic ions, DMP hydrolysed completely to MMP within about 0.5 hours during the preparation of the test solutions. MMP remained stable during the algae test for 72 h, the geometric mean of the measured MMP concentrations being 26 mg/l. DOC measurements confirmed the presence of virtually all organic carbon of the initial carbon content of DMP.

Tests on long-term toxicity are not available.

The effect concentrations for DMP of the aquatic tests for fish, *Daphnia*, algae, and the results of the bacteria test are compiled in the following table:

Table 10: Acute aquatic toxicity of dimethyl phosphonate

Organisms	**Parameter**	**Concentration (mg/l)**
Fish (*Danio rerio*)	LC_0 (96 h)	100 mg/l (nominal)
Fish (*Pimephales promelas*)	EC_{50} (96 h)	225 (assumed to be nominal)
Invertebrates *(Daphnia magna)*	EC_{50} (48 h)	25 (nominal)
Algae (*Desmodesmus subspicatus*)	EC_0 (72 h)	≥ 100 mg/l (nominal)

Determination of $PNEC_{aqua}$

Since short-term tests for each of the three trophic levels are available, an assessment factor of 1000 was applied for the derivation of the $PNEC_{aqua}$ according to EU Technical Guidance Document. From the effect value of the most sensitive species, *Daphnia magna*, a

$PNEC_{aqua}$ of 25 µg/l

is calculated. This PNEC covers both the toxicity of DMP as well as the toxicity of its hydrolysis products.

Toxicity to Microorganisms

Regarding the toxicity to microorganisms, an oxygen consumption test in accordance with the ISO Norm 8192 with activated sludge during 3 h was performed with DMP and a nominal EC_{50} of > 10 000 mg/l was determined (Bayer AG, 1992).

4.2 Terrestrial Effects

No results from standard toxicity tests are available. There are some data from a study with seeds of rye, wheat and millet, which cannot be related to relevant environmental conditions (Smirnova et al., 1995).

4.3 Other Environmental Effects

No data available.

4.4 Initial Assessment for the Environment

DMP released into the atmosphere is rapidly degraded by OH-radicals with an estimated half-life of 2.9 hours. The main degradation process in water is hydrolysis. The degradation products are monomethyl phosphonate, phosphorous acid, and methanol. At pH 4 the experimentally determined half-life is about 470 h, at pH 7 it is about 3 h, and at pH 9 it is < 0.3 h.

DMP is not readily biodegradable (50 % after 28 d).

According to the Mackay Fugacity Model Level I, the main target compartments (environmental equilibrium distribution) for DMP are water (95 %) and air (5 %). The degradation product MMP will partition nearly exclusively to the water compartment. The calculated Henry's law constant of 0.33 $Pa*m^3*mol^{-1}$ for DMP and of 0.002 $Pa*m^3*mol^{-1}$ for MMP indicate a low potential for volatilization from surface waters. The calculated log Kow (log Kow = –1.2 for DMP, log Kow = –1.19 for MMP) indicates no bioaccumulation potential. The calculated Koc (Koc = 2.62 for DMP and 1.36 for MMP) suggests that both substances have a very low geoaccumulation potential.

Concerning the toxicity of DMP towards aquatic species, experimental results of short term tests with fish, *Daphnia*, and algae are available. During aquatic ecotoxicity tests DMP hydrolysed with half lives of several minutes to hours. Thus, during these tests, DMP itself and its degradation products MMP, methanol, and phosphorous acid were present. For testing the acute fish toxicity with *Danio rerio* a limit test with an effective concentration of (nominal) 100 mg/l was conducted and no effects were observed at this concentration level after 96 h. An effective LC_0 of ≥ 15.6 mg/l was determined for DMP. Another test with *Pimephales promelas* reported a 96 h-LC_{50} of (nominal) 225 mg/l. In a GLP study according to Directive 92/69/EEC, C.2, the EC_{50} (nominal) of *Daphnia magna* was 25 mg/l after 48 h. In a GLP study according to Directive 92/69/EEC, C.3, the 72 h EC_0 (nominal) of *Desmodesmus subspicatus* was ≥ 100 mg/l.

Data on long-term toxicity on aquatic organisms are not available. Valid tests on terrestrial species are not available as well.

Following the EU Technical Guidance Document, for the derivation of the $PNEC_{aqua}$ an assessment factor of 1,000 is chosen since at least one short-term EC_{50} or LC_{50} value is available from each of the three trophic levels. Using the lowest determined concentration: *Daphnia magna* EC_{50} = 25 mg/l, a **$PNEC_{aqua}$ = 25 µg/l** is derived.

5 RECOMMENDATIONS

Human Health:

The substance is currently of low priority for further work.

DMP possesses properties indicating a hazard for human health (irritating, mutagenic and carcinogenic properties, repeated dose toxicity). In the Sponsor country, exposure is controlled in occupational settings and is negligible for consumers. Countries may desire to investigate any exposure scenarios (particularly use as a reactive flame retardant in textile finishing) that were not presented by the Sponsor country.

Environment:

The substance is currently of low priority for further work.

The chemical possesses properties indicating a hazard for the environment. Based on data presented by the Sponsor country, exposure to the environment is anticipated to be low. Therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

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I U C L I D

D a t a S e t

Existing Chemical	ID: 868-85-9
CAS No.	868-85-9
EINECS Name	dimethyl phosphonate
EC No.	212-783-8
TSCA Name	Phosphonic acid, dimethyl ester
Molecular Formula	C2H7O3P

Producer Related Part	
Company:	Bayer AG
Creation date:	19-AUG-1993
Substance Related Part	
Company:	Bayer AG
Creation date:	19-AUG-1993
Memo:	OECD HPV Chemicals Programme, SIDS Dossier, approved at SIAM 18 (20-23 April 2004)

Printing date:	25-JAN-2006
Revision date:	02-JUN-1994
Date of last Update:	29-AUG-2005

Number of Pages:	111

Chapter (profile):	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile):	Reliability: without reliability, 1, 2, 3, 4
Flags (profile):	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 Applicant and Company Information

Type: lead organisation
Name: Bayer AG
Town: 51368 Leverkusen
Country: Germany

21-JAN-2004

Type: cooperating company
Name: Rhodia Inc.
Street: 259 Prospect Plains Road
Town: Cranbury, NJ 08512-7500
Country: United States

Remark: Rhodia Inc.
CN-7500
259 Prospect Plains Road
Cranbury, NJ 08512-7500
USA
21-JAN-2004

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

IUPAC Name: Phosphonic acid, dimethyl ester
Smiles Code: O=P(OC)OC
Mol. Formula: C2H7O3P
Mol. Weight: 110.05

Flag: Critical study for SIDS endpoint
30-MAY-2003

1.1.1 General Substance Information

Purity type: typical for marketed substance
Substance type: organic
Physical status: liquid
Purity: 99.7 - % w/w
Colour: colourless

Flag: Critical study for SIDS endpoint

30-MAY-2003

1.1.2 Spectra

1.2 Synonyms and Tradenames

DIMETHYL HYDROGEN PHOSPHITE

DIMETHYL PHOSPHITE

DIMETHYL PHOSPHONATE

DMHP

30-MAY-2003

PHOSPHONIC ACID, DIMETHYL ESTER

1.3 Impurities

Purity type:	typical for marketed substance
CAS-No:	67-56-1
EC-No:	200-659-6
EINECS-Name:	methanol
Mol. Formula:	CH4O
Contents:	ca. .1 - % w/w
Flag:	Critical study for SIDS endpoint

06-JUN-2003

Purity type:	typical for marketed substance
CAS-No:	13590-71-1
EC-No:	237-027-4
EINECS-Name:	methyl hydrogenphosphonate
Mol. Formula:	CH5O3P
Contents:	ca. .1 - % w/w
Flag:	Critical study for SIDS endpoint

06-JUN-2003

1.4 Additives

1.5 Total Quantity

Quantity:	3000 - 15000 tonnes produced in 2002
Remark:	Manufacturing Capacity 2002 (estimated) t/a Western Europe 1,000 - 5,000 USA 1,000 - 5,000 Rest of world 1,000 - 5,000 The global production capacity of DMP in 2002 is estimated to be 3,000 - 15,000 t/a for about 10 producers.
Flag:	Critical study for SIDS endpoint

13-NOV-2003

1.6.1 Labelling

Labelling: provisionally by manufacturer/importer
Symbols: (Xn) harmful
R-Phrases: (36/38) Irritating to eyes and skin
(40) Possible risks of irreversible effects
S-Phrases: (24/25) Avoid contact with skin and eyes
(26) In case of contact with eyes, rinse immediately with plenty of water and seek medical advice

Flag: Critical study for SIDS endpoint
06-JUN-2003

1.6.2 Classification

Classified: provisionally by manufacturer/importer
Class of danger: harmful
R-Phrases: (36/38) Irritating to eyes and skin
(40) Possible risks of irreversible effects

Flag: Critical study for SIDS endpoint
06-JUN-2003

1.6.3 Packaging

1.7 Use Pattern

Type: type
Category: Use in closed system

Type: industrial
Category: Chemical industry: used in synthesis

Type: use
Category: Intermediates

1.7.1 Detailed Use Pattern

1.7.2 Methods of Manufacture

Orig. of Subst.: Synthesis
Type: Production

30-MAY-2003

1.8 Regulatory Measures

1.8.1 Occupational Exposure Limit Values

Type of limit: MAK (DE)

Remark: Krebserzeugende Gruppe: III B

1.8.2 Acceptable Residues Levels

1.8.3 Water Pollution

Classified by: other: VwVwS
Class of danger: 1 (weakly water polluting)

Remark: Kenn-Nr. 1281
17-MAY-2000

1.8.4 Major Accident Hazards

Substance listed: no

1.8.5 Air Pollution

Classified by: other: Bayer AG
Labelled by: other: Bayer AG
Number: 3.1.7 (organic substances)
Class of danger: I

Remark: gem. Ziffer 3.1.7 Abs. 5

1.8.6 Listings e.g. Chemical Inventories

1.9.1 Degradation/Transformation Products

Type: degradation product in water
CAS-No: 13590-71-1
EC-No: 237-027-4
EINECS-Name: methyl hydrogenphosphonate
IUCLID Chapter: 3.1.2

Reliability: (1) valid without restriction
14-NOV-2003 (16)

Type: degradation product in water
CAS-No: 67-56-1
EC-No: 200-659-6
EINECS-Name: methanol
IUCLID Chapter: 3.1.2

Reliability: (2) valid with restrictions
14-NOV-2003 (78)

Type: degradation product in water
CAS-No: 10294-56-1

EC-No: 233-663-1
EINECS-Name: phosphorous acid
IUCLID Chapter: 3.1.2

Reliability: (2) valid with restrictions
14-NOV-2003 (78)

1.9.2 Components

1.10 Source of Exposure

1.11 Additional Remarks

1.12 Last Literature Search

Type of Search: Internal and External
Chapters covered: 2
Date of Search: 06-MAR-2003

06-JUN-2003

Type of Search: Internal and External
Chapters covered: 3, 4
Date of Search: 06-FEB-2003

06-JUN-2003

Type of Search: Internal and External
Chapters covered: 5
Date of Search: 01-APR-2002

06-JUN-2003

1.13 Reviews

2.1 Melting Point

Value: < -60 degree C
Decomposition: at = degree C

Method: other: not given
Year: 2003
GLP: no data
Test substance: no data

Reliability: (2) valid with restrictions
Verification system for MSDS in operation
Flag: Critical study for SIDS endpoint
30-MAY-2003 (19)

2.2 Boiling Point

Value: 171.1 degree C at 1013.25 hPa

Method: Directive 92/69/EEC, A.2
Year: 2001
GLP: yes
Test substance: other TS: 99.8% purity

Method: Capillary method (Photocell detection)
Reliability: (1) valid without restriction
GLP guideline study
Flag: Critical study for SIDS endpoint
30-MAY-2003 (13)

Value: 169.2 degree C at 1013.25 hPa

Method: other: not given
Year: 2003
GLP: no data
Test substance: no data

Reliability: (2) valid with restrictions
Data from handbook or collection of data
30-MAY-2003 (20)

Value: 170 - 171 degree C at 1013 hPa

Method: other:not specified
Year: 1999
GLP: no data
Test substance: no data

Reliability: (2) valid with restrictions
Data from handbook or collection of data
30-MAY-2003 (94)

Value: 170.6 degree C at 1013.25 hPa

Method: other
Year: 1958
GLP: no

Test substance: other TS: supplied by Messrs. Albright and Wilson; purity is not given

Reliability: (2) valid with restrictions
Data consistent with Bayer data and handbook data
30-MAY-2003 (85)

Value: 72 - 73 degree C at 33.3 hPa

Method: other: not specified
Year: 1987
Test substance: no data

Reliability: (2) valid with restrictions
Data from handbook or collection of data
30-MAY-2003 (43)

Value: 63 degree C at 20 hPa

Method: other: not given
Year: 2003
GLP: no data
Test substance: no data

Reliability: (2) valid with restrictions
Verification process for MSDS in operation
30-MAY-2003 (19)

Value: 44 - 60 degree C

Method: other: no data
Year: 2002
GLP: no data
Test substance: no data

Result: Beilstein's reported boiling point values are in the range of 44-60°C (at 3.33-21.30 hPa)
Reliability: (2) valid with restrictions
Data from handbook or collection of data
30-MAY-2003 (23)

Value: 220 degree C at 1015 hPa
Decomposition: yes

Method: other: not given
Year: 1987
GLP: no data
Test substance: no data

Source: The new SDS of 2003 does not contain this value.
Reliability: (4) not assignable
Information not consistent with data from handbook or data collection
30-MAY-2003 (8)

2.3 Density

Type: density

Method: other: not given
Year: 1999
GLP: no data
Test substance: no data

Result: 1.200 g/cm³ at 20 °C
Reliability: (2) valid with restrictions
Data from handbook or collection of data
Flag: Critical study for SIDS endpoint
13-NOV-2003 (94)

Type: density
Value: 1.2 g/cm³ at 20 degree C

Method: other: not given
Year: 1987
GLP: no data
Test substance: no data

Remark: HSDB cites Sax NI, Lewis RJ (1987) Hawley's Condensed Chemical Dictionary 11 ed., 417
Reliability: (2) valid with restrictions
Data from handbook or collection of data
30-MAY-2003 (43)

Type: density

Method: other: not given
Year: 2003
GLP: no data
Test substance: no data

Result: 1218.2 kg/m3 at 0°C
1199.7 kg/m3 at 20°C (MSDS-Value)
1178.3 kg/m3 at 40°C
1156.6 kg/m3 at 60°C
1128.4 kg/m3 at 85°C
Reliability: (2) valid with restrictions
Data from handbook or collection of data
14-NOV-2003 (20)

Type: density
Value: at 20 degree C

Year: 2002

Result: Beilstein's reported density values are all ca.1.200 g/cm3 (at 20°C).
Reliability: (2) valid with restrictions
Data from handbook or collection of data
14-NOV-2003 (23)

2.3.1 Granulometry

2.4 Vapour Pressure

Value: 1.35 hPa at 20 degree C

Method: Directive 92/69/EEC, A.4
Year: 2001
GLP: yes
Test substance: other TS: 99.8% purity

Method: Dynamic method
Result: Results of regression calculation:
1.90 hPa at 25 °C
8.99 hPa at 50 °C
1.89 hPa at 24.88 °C
1050.81 hPa at 170.51°C
Reliability: (1) valid without restriction
GLP guideline study
Flag: Critical study for SIDS endpoint
30-MAY-2003 (14)

Value: 1.5 hPa at 20 degree C

Method: other (measured): description of the method is not given
Year: 2003
GLP: no data
Test substance: no data

Reliability: (2) valid with restrictions
Data similar to data from GLP guideline study
30-MAY-2003 (19)

Method: other (measured): description of the method is not given
Year: 2003
GLP: no data
Test substance: no data

Result: Results were taken from secondary literature. Secondary literature is not given.
First data source:
533.3 Pa at 40 °C
1326.9 Pa at 55 °C
101325.0 Pa at 169.19 °C
127669.0 Pa at 178 °C
Second data source:
5197.1 Pa at 73 °C
32876.9 Pa at 128 °C
133299.2 Pa at 183 °C
Reliability: (2) valid with restrictions
Data from handbook or collection of data
30-MAY-2003 (20)

Method: other (measured): see below
Year: 1958
GLP: no
Test substance: other TS: supplied by private source, redistilled but still

traces of alcohol containing

Result: Results can be represented by the equation:
log10 P = A-B/T
P= vapour pressure in mm Hg
A= 7.439
B= 2.0226
Test condition: The manometer and bulb after being sealed off on vacuum line, were completely immersed in a paraffin-oil bath. The pressures observed were corrected for expansion of mercury.
Reliability: (3) invalid
Vapour pressure equation not consistent with data in Fig. 1 of this publication
30-MAY-2003 (85)

Value: 6.03 hPa at 25 degree C

Method: other (measured)
Year: 1984
GLP: no data
Test substance: no data

Reliability: (4) not assignable
Literature not available
30-MAY-2003 (32)

2.5 Partition Coefficient

Partition Coeff.: octanol-water
log Pow: -1.2

Method: other (calculated): with KOWWIN, v.1.66
Year: 2003

Remark: The estimate is not reliable because rapid hydrolysis occurs. Experimental determination of the octanol-water partition coefficient for DMP is not appropriate for the same reason.
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
13-NOV-2003 (21)

Partition Coeff.: octanol-water

Method: other (measured):Shake-flask experiments with reversed phase HPLC
Year: 1987
GLP: no data

Result: The log Kow of dimethyl methyl phosphonate -0.61 and log Kow of dimethyl ethyl phosphonate 0.66 suggest that the log Kow for dimethyl phosphonate is very low.
Reliability: (2) valid with restrictions
Study meets generally accepted scientific methods
30-MAY-2003 (51)
Partition Coeff.: octanol-water

log Pow: -.89

Method: other (calculated): see method
Year: 1990
GLP: no data

Method: The partition coefficient was calculated using an equation as suggested by Klopman et al. in 1985 [Klopman G, Namboodiri K, Schochet M (1985) Simple method of computing the partition coefficient, J Comput Chem 6: 28 - 38]
Reliability: (2) valid with restrictions
Accepted calculation method
07-SEP-2004 (61)

2.6.1 Solubility in different media

Solubility in: Water
Value: 100 g/l at 25 degree C

Method: other: calculated with WSKOW, v.1.40
Year: 2003

Remark: The estimate is not reliable because rapid hydrolysis occurs.
Reliability: (2) valid with restrictions
Accepted caculation method
Flag: Critical study for SIDS endpoint
17-NOV-2003 (21)

Solubility in: Water

Year: 1999

Remark: The estimate is not reliable because rapid hydrolysis occurs.
Reliability: (2) valid with restrictions
Data from handbook or collection of data
Flag: Critical study for SIDS endpoint
17-NOV-2003 (94)

Solubility in: Water
Value: >= 100 g/l at 19.5 degree C

Method: other: not specified
Year: 2003
GLP: no data
Test substance: no data

Reliability: (4) not assignable
Documentation insufficient for assessment
Flag: Critical study for SIDS endpoint
17-NOV-2003 (33)

Solubility in: Water

Year: 2003
Result: DMP will not volatilise from water.

Reliability: (2) valid with restrictions
Data from handbook or collection of data
17-NOV-2003 (44)

Solubility in: Organic Solvents

Year: 1999

Remark: Dimethyl phosphonate is soluble in alcohol and pyridine
Reliability: (2) valid with restrictions
Data from handbook or collection of data
Flag: Critical study for SIDS endpoint
17-NOV-2003 (94)

Solubility in: Organic Solvents

Year: 2002

Remark: 0.82 % (w/w) in hexan at 20 °C
0.64 % (w/w) in dodecane at 20 °C
1.50 % (w/w) in cyclohexane at 20 °C
Reliability: (2) valid with restrictions
Data from handbook or collection of data
Flag: Critical study for SIDS endpoint
17-NOV-2003 (23)

Solubility in: other: water, organic solvents

Year: 1987

Remark: Soluble in water, miscible with most organic solvents
Source: HSDB (2003) Hazardous Substances Data Bank, data sheet for dimethyl phosphonate
Reliability: (2) valid with restrictions
Data from handbook or collection of data
17-NOV-2003

Solubility in: other: pyrimidine

Year: 1992

Remark: Soluble in pyrimidine
Reliability: (2) valid with restrictions
Data from handbook or collection of data
Flag: Critical study for SIDS endpoint
17-NOV-2003 (55)

2.6.2 Surface Tension

Test type: other: not given
Value: 37.6 mN/m at 20 degree C

Method: other: not specified
Year: 2003
GLP: no data
Test substance: no data

Result: Surface tension at 85°C is 29.9 mN/m.

Reliability: (4) not assignable
Manufacturers data without proof
Flag: Critical study for SIDS endpoint
14-NOV-2003 (20)

2.7 Flash Point

Value: ca. 70 degree C
Type: closed cup

Method: other: DIN 51758
Year: 2003
GLP: no data
Test substance: no data

Reliability: (4) not assignable
Manufacturers data without proof
Flag: Critical study for SIDS endpoint
14-NOV-2003 (19)

Value: 29 degree C

Method: other: not specified
Year: 1993
GLP: no data
Test substance: no data

Source: Bayer AG data of 1993.
Reliability: (4) not assignable
Manufacturers data without proof
14-NOV-2003 (20)

2.8 Auto Flammability

Value: 237 degree C

Method: other: DIN 51794
Year: 1993
GLP: no data
Test substance: no data

Source: Bayer AG data of 1993. Report not available.
Reliability: (2) valid with restrictions
Manufacturers data without proof
Flag: Critical study for SIDS endpoint
30-MAY-2003 (19) (20)

2.9 Flammability

2.10 Explosive Properties

Method: other: not specified
Year: 1993
GLP: no data
Test substance: no data

Result: Lower explosion limit: 5.8%
Upper explosion limit: 38.1%
Reliability: (4) not assignable
Manufacturers data without proof
Flag: Critical study for SIDS endpoint
14-NOV-2003 (19) (20)

2.11 Oxidizing Properties

2.12 Dissociation Constant

2.13 Viscosity

Value: 1.4 mPa s (dynamic) at 20 degree C

Method: other: not specified
Year: 2003
GLP: no data
Test substance: no data

Reliability: (4) not assignable
Manufacturers data without proof
Flag: Critical study for SIDS endpoint
14-NOV-2003 (19)

2.14 Additional Remarks

3.1.1 Photodegradation

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 500000 molecule/cm³
Rate constant: .00000000000558 cm³/(molecule * sec)
Degradation: 50 % after 2.9 day(s)

Method: other (calculated): with AOPWIN v.1.90 by U.S-EPA (2000)
Year: 2003

Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
04-JUN-2003 (21)

Type: water
Light source: other: high pressure mercury-vapor lamp

Method: other (measured): according to the method of Knoevenagel and Himmelreich (1973)
Year: 1976
GLP: no
Test substance: other TS: diethyl phosphonate

Method: Water is circulated from a 2 l reservoir bottle into a 20 l four-necked round-bottom flask (equipped with an UV-lamp) as a fine spray and recycled to the reservoir bottle. In a second circulation system, air is pumped into a 1 l flask containing a sample of diethyl phosphite. Satured vapor is forced through 20 l four-necked round-bottom flask and, after passing two gas washing bottles filled with aqueous Ba(OH)2, recycled to the 1 l flask.
Result: 50 % of the theoretical CO2 expected to form from diethyl phosphonate was achieved after 28.8 hours.
The results of the ethyl homologue of dimethyl phosphonate indicate that dimethyl phosphonate may also be degraded by the impact of UV-light, oxygen and water.
Test condition: The conversion of diethyl phosphonate to carbon dioxide was measured.
The conversion was influenced by light, oxygen, and water.
Reliability: (2) valid with restrictions
Study well documented, meets generally accepted scientific principles
Flag: Critical study for SIDS endpoint
14-NOV-2003 (50)

Type: other: 2.5 mg TiO2 (mainly anatase) suspended in water
Light source: other: Philips HPK 125 W UV
Light spect.: > 340 nm
INDIRECT PHOTOLYSIS
Sensitizer: water with additives
Conc. of sens.: 2.5 mg/l
Degradation: > 70 % after 150 minute(s)
Deg. products: yes

Method: other (measured): GC-MS

Year:	1996
GLP:	no data
Test substance:	other TS: Fenitrothion, 99.3 % purity
Method:	Fenitrothion in was irradiated in an aqueous suspension of 2.5 mg TiO2 (mainly anatase, 50 m2/g) with UV-light > 340 nm. For comparison, Fenitrothion in was also irradiated in water without TiO2. After 0-300 min of irradiation, the suspension was filtered, acidified with HCl, and extracted with dichloromethane. The intermediates of the mineralization of Fenitrothion were analyzed after concentration of the dichloromethane solution to 10-50 µl by GC/MS. DMP was identified by "interpretation" of a mass spectrum (no spectrum for comparison used).
Remark:	Significant methodological deficiencies: - No literature mass spectrum used to verify the hypothetical identification of DMP - No peak intensities reported - No controls performed to eliminate the possibility that DMP was a thermal degradation product, e.g. of fenitrothion during heating in the injector bloc of the GC-MS - Impurities of the fenitrothion used in the experiments not taken into account - Although oxygen is essential for mineralization, no attempt made to supply any information on oxygen, e.g. on initial oxygen content of test solution
Result:	Fenitrothion was completely degraded within 50 minutes. For the degradation of DMP, no specific compound was measured. However, the formation of phosphate was observed, and the intermediate occurrance of formate. The mass spectrum of DMP is not depicted as was done with other spectra in the publication. It is (incompletely) reported to have peaks (m/z) at 79, 80, 47, 29, 95, 66, 109, and 110. Intensities were not reported. It was stated that DMP occured as an intermediate of complete fenitrothion mineralization.
Reliability:	(3) invalid Significant methodological deficiencies

20-NOV-2003 (49)

3.1.2 Stability in Water

Type:	abiotic
t1/2 pH4:	470 hour(s) at 23 degree C
t1/2 pH7:	3.1 hour(s) at 23 degree C
Degradation:	95.2 % after 2 day(s) at pH 7 and 23 degree C
Deg. products:	yes 13590-71-1 237-027-4 methyl hydrogenphosphonate
Method:	Directive 92/69/EEC, C.7
Year:	2002
GLP:	yes
Test substance:	other TS: 99.8 % purity
Result:	Degradation product at all pH-conditions was detected to be monomethyl phosphonate.

The following degradation rates were obtained at 23°C

	Dimethyl phosphonate	Monomethyl phosphonate	
pH 4	79.3 %	20.7 %	after 7 d
	50.5 %	49.5 %	after 18 d
pH 7	77.6 %	22.4 %	after 19 min
	4.8 %	95.2 %	after 2 d
pH 9	2.2 %	99.8 %	after 19 min
	0.0 %	100.0 %	after 4 h

Estimated half life and the rate constants
pH 4 t1/2 = 470 h and k = 4.09E-07 1/s.
pH 7 t1/2 = 3.1 h and k = 6.22E-05 1/s
pH 9 t1/2 could not be estimated, very rapid reaction
At 50 °C (only measured at pH 4) the following results were obtained:
pH 4 t1/2 = 17.3 h and k = 1.11E-05 1/s.

Test condition: The test was performed
- Buffered solution at pH = 4, 7, 9
- Temperature 23°C,
- Duration up to 432 h (18 d)
- Concentrations tested: 0.10 %
Analytical method: 31-Phosphor NMR spectroscopy

Reliability: (1) valid without restriction
Guideline study

Flag: Critical study for SIDS endpoint

14-NOV-2003 (16)

Type: abiotic
Degradation: 100 % after 6 day(s)
Deg. products: yes
13590-71-1 237-027-4 methyl hydrogenphosphonate

Method: other: Test on stability in water with phosphor nuclear magnetic resonance
Year: 1992
GLP: no
Test substance: other TS: Trimethyl phosphite 99.2 % purity

Remark: Preliminary test on stability of tri-, di- and monoethyl phosphite in water (without buffer), as screening information for the fish toxicity test (see chapter 4.1)

Result: Trimethyl phosphonate

Test concentration (%) : 1
Hydrolysis (%) : 100
Time (h) : 0.5
Product of hydrolysis : Dimethyl phosphonate
After 30 h the recovery of trimethyl phosphonate was 0 % and in its place dimethyl phosphonate (92.5 %) and monomethyl phosphonate (7.5 %) had been formed as hydrolysis products.

Dimethyl phosphonate

Test concentration (%) : 1
Hydrolysis (%) : 11
Time (h) : 31
Product of hydrolysis : Monomethyl phosphonate
Half-life ca. 60 h

After 144 h, 100 % hydrolysis was achieved.

Monomethyl phosphonate

Test concentration (%) : 0.87
Product of hydrolysis : Phosphorous acid
Instead of testing monomethyl phosphonate, hydrolysis of the parent substance dimethyl phosphonate (see above) was measured. When complete hydrolysis of dimethyl phosphonate (1 % in water) occurs, 0.87 % monomethyl phosphonate is expected to be formed. 25.5 h after the beginning of the hydrolysis test with DMP, monomethyl phosphonate was detected for the first time. After 74 h phosphorous acid was detected the first time. After 144 h monomethyl phosphonate reached its maximum concentration with 0.741 %. At that time no dimethyl phosphite remained and 85 % of the expected monoethyl phosphite was found. Recovery rates during the test were 68 - 70.3 % of the theoretical concentration. The test ended after 238 h with 68 % of expected monoethyl phosphite being found and another 32 % hydrolysed to P-containing acids. Since the recovery rate did not vary significantly, it can be concluded that monomethyl phosphonate hydrolyses slowly.

Test condition: Test was conducted with the test substance in pure water, no control of pH.

Conclusion: In water being neutral at the beginning of the hydrolysis, dimethyl phosphite (concentration 1 %) hydrolyses completely within 144 h. The half life is about 60 h.

Reliability: (2) valid with restrictions
Basic data given

Flag: Critical study for SIDS endpoint

14-NOV-2003 (11)

Type: abiotic
Deg. products: yes
10294-56-1 233-663-1 phosphorous acid
13590-71-1 237-027-4 methyl hydrogenphosphonate
67-56-1 200-659-6 methanol

Method: other: see below
Year: 1988
GLP: no data
Test substance: other TS: > 99 % purity

Remark: The measured drop of pH of the 10 % solution (= 0.9 mol/l) in deionizied water during 6 h is equivalent to 0.2 mol/l of protons being liberated from DMP during decomposition. The decomposition could not be detected analytically with the analytical method used. Therefore the analytical method was inadequate.

Result: 10 % concentration, deionized water:
At 22 °C the substance was stable up to 8 h, after this period the half-life was calculated to be 8 h
At 8 °C the substance was stable up to 24 h, after this period the half-life was calculated to be 22 h
At -8 °C the substance was stable up to 72 h, after this period the half-life was calculated to be 187 h

5 % concentration, at 37 °C:
At pH 2: stability period of 2 h, half-life decomposition of 1.7 h
At pH 8: stability period of 8 h, no half-life measured
10% concentration, at 37 °C:
At pH 2: stability period of 1 h, half-life decomposition of 1.1 h
At pH 7.4: stability period of 3.6 h, half-life decomposition of 2.4 h
At pH 8: stability period of 4 h, half-life decomposition of 2.6 h

In all conditions DMHP gave rise to the same pattern: monomethyl hydrogen phosphite and methanol and further phophorous acid and methanol.

pH change was followed with 5% (5) and 10% (10) solution in deionized water (A), aquatic HCl pH 2 (B), and 0.1 M phosphate buffer pH 7 (C) and pH 8 (D)

hours	5A	10A	5B	10B	5C	10C	5D	10D
0	2.6	2.1	1.9	1.8	6.8	6.6	7.0	6.8
2	2.1	1.4	1.6	1.2	6.0	5.1	6.1	5.3
4	1.9	1.1	1.3	0.8	5.4	4.0	5.6	4.1
6	1.6	0.7	1.0	0.5	4.7	3.5	5.0	3.6
24	0.4	0.2	0.4	0.2	2.8	1.8	2.9	1.9

In spite of the drop of pH there was no significant change in DMP concentration in water for up to 8 h according to GC-analysis.

Test condition: The stability of dimethyl phosphonate (DMP) in water was investigated at different temperatures (-8, 8, 22 and 37 °C) and different pH-values (2, 7.4, 8).
The decomposition products of DMP were identified by HPLC and proton nuclear magnetic resonance spectroscopy.
GC was used to analyze DMP.
Solutions were made at 2, 5 or 10 % (w/v) concentrations in water.
The sample was measured after 1, 5, 15, 30 min and 1, 2, 4, 6, 8, 10, 24, 48 h, then daily for 1 week and after that weekly.
A methanol solution of equal concentration was used as a reference standard for all test systems.

Reliability: (3) invalid
Significant methodological deficiencies

14-NOV-2003 (78)

Type: abiotic

Method: other: according to the method of Bernhart and Rattenbury (1956)
Year: 1969
GLP: no
Test substance: no data

Method: Direct determination of preliminary neutralized samples analogously to the work of Bernhart and Rattenbury (1956)
Remark: The temperature dependence satisfied an Arrhenius equation. ($k = a \exp(-E/RT)$ with $\lg A = 10.10$ and $E = 22.1$ kcal/mol).

Hydrolysis follows a first order reaction rate which is evidence that the acids formed do not catalyse the hydrolysis of DMP.
Degradation product was quantitatively determined.
Result: Rate constant (pH unspecified):
at 98 °K = 116*10E5 1/sec
at 90 °K = 61.5*10E5 1/sec
at 80 °K = 25.1*10E5 1/sec
at 70 °K = 11.1*10E5 1/sec
at 60 °K = 3.96*10E5 1/sec
at 50 °K = 1.33*10E5 1/sec
In the HSDB Database the half-lives at 20 °C and 25 °C were extrapolated from the measured data at higher temperatures: 19 days (20 °C) and 10 days (25 °C).
Reliability: (2) valid with restrictions
Study meets generally accepted scientific principles, basic data given

26-MAY-2004 (24)

Type: abiotic
Deg. products: not measured

Method: other: Titration with alkali hydroxide at constant titration velocity, potentiometric pH measurement.
Year: 1971
GLP: no
Test substance: other TS: purity checked by GC

Result: Biomolecular kinetic (SN2) with K = 1240 l s-1 Mol-1 at 20 °C
Test condition: 10-20 mg/l test substance in 40 ml water
Test at constant temperature
Titration with a 0.1 - 0.25 mol/l solution of sodium hydroxide
Reliability: (2) valid with restrictions
Study meets generally accepted scientific principles, basic data given
14-NOV-2003 (106) (107)

3.1.3 Stability in Soil

3.2.1 Monitoring Data (Environment)

Type of measurement: background concentration
Medium: soil

Remark: Malathion (O,O-dimethyl-S (1,2-dicarbethoxyethyl)-phosphorodithioate) is a phosphorodithionic acid derivative whose hydrolysis is thought to proceed to thiophosphates and (inorganic) phosphate, but not to DMP.
Reliability: (2) valid with restrictions
Data from handbook or collection of data
Flag: Critical study for SIDS endpoint

21-NOV-2003 (69)

3.2.2 Field Studies

3.3.1 Transport between Environmental Compartments

Type: volatility
Media: water - air
Method: other: Bond-Method. Calculated with HENRYWIN, v.1.90
Year: 2003

Result: Henry's Law Constant: 0.33 Pa m-3 mol-1 at 25 °C
Reliability: (2) valid with restrictions
Acceptable calculation method
Flag: Critical study for SIDS endpoint
14-NOV-2003 (21)

Type: adsorption
Media: water - soil
Method: other: Calculated with PCKOCWIN, v.1.66
Year: 2003

Result: A Koc value of 2.62 was calculated (Bayer AG 2003b), indicating a very low sorption potential of DMP to soil organic matter according to the criteria of Litz (1990). For monomethyl phosphonate a Koc of 1.36 was calculated indicating also a very low geoaccumulation potential for this degradation product.
Flag: Critical study for SIDS endpoint
07-SEP-2004 (21) (57)

3.3.2 Distribution

Media: air - biota - sediment(s) - soil - water
Method: other (calculation): Calculation according Mackay-model, Level I (1991)
Year: 2003

Result: Calculated distribution between environmental compartments:

water:	95.0 %
air:	5.0 %
sediment:	<0.01 %
soil:	<0.01 %
aerosol:	<0.01 %
suspended sediment:	<0.01 %
biota:	<0.01 %

Test condition: Data used in the calculation:

temperature (°C):	20
molar mass (g/mol):	110.05
vapor pressure (Pa):	135
water solubility (g/l):	100
log Kow:	-1.20
melting point (°C):	-60

Unit world Modelling Data*

	Volumes (m3)	Organic C (g/g)	Density (kg/m³)

air:	6.0E+9		1.185
water:	7.0E+6		1000
soil:	4.5E+4	0.02	1500
sediment:	2.1E+4	0.05	1300
susp. sediment:	3.5E+1	0.167	1500
biota (fish):	7.0E+0		1000
aerosol	1.2E-1		1500

*Compartment properties were based on the parameters from the first publication of Mackay (1991), modified by the Federal Environmental Agency (UBA, Germany).

Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
14-NOV-2003 (21)

3.4 Mode of Degradation in Actual Use

3.5 Biodegradation

Type: aerobic
Inoculum: predominantly domestic sewage
Concentration: 20 mg/l related to DOC (Dissolved Organic Carbon)
Degradation: 50 % after 28 day(s)
Result: other: not readily biodegradable
Kinetic:

0 day(s)	0 %
7 day(s)	44 %
14 day(s)	50 %
21 day(s)	50 %
28 day(s)	50 %

Method: other: Directive 79/831/EEC, Annex V, C.4.B (actualised version of July 1990): Modified OECD Screening Test
Year: 1992
GLP: yes
Test substance: other TS: 99.2 %

Remark: Dimethyl phosphonate hydrolyses to monomethyl phosphonate and methanol. Monomethyl phosphonate hydrolyses further to phosphorous acid and methanol. Hydrolysis of dimethyl phosphonate is faster than hydrolysis of monoethyl phosphonate.
The hydrolysis product methanol is readily biodegradable. Hydrolysis of di- and monomethyl phosphonate is the determining factor for the speed at which biodegradation of dimethyl phosphonate occurs.
Reliability: (1) valid without restriction
Guideline study
Flag: Critical study for SIDS endpoint
14-NOV-2003 (11)

Type: aerobic
Inoculum: other: Hyphomicrobium sp.
Result: other: Dimethylphosphite is degraded
Method: other: see test condition
Year: 1983

GLP: no data
Test substance: no data

Result: Dimethyl phosphonate can be degraded by various Hyphomicrobium cultures isolated from an industrial wastewater treatment plant or a waste dump
Test condition: In the patent isolation, gowth and characterization of the microorganisms is described in detail. However, there is only a general remark on the effectiveness of these cultures on wastewater containing dimethyl phosphite but no other data are given
Reliability: (3) invalid
Study not appropriate for hazard assessment
04-JUN-2003 (37)

3.6 BOD5, COD or BOD5/COD Ratio

3.7 Bioaccumulation

Method: other: estimate from Kow
Year: 2003

Remark: A bioconcentration factor (BCF) cannot be measured due to hydrolysis.
The calculated log Kow of -1.2 indicates that there is no potential for bioaccumulation in aquatic organisms. This statement is also valid for the degradation product monomethylphosphonate for which a calculated log Kow of -1.19 is available (taken from EPIWIN)
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
26-MAY-2004 (21)

3.8 Additional Remarks

Memo: Geoaccumulation

Remark: There is no test result available on geoaccumulation. The results for DMP and monomethylphosphonate indicate a very low sorption to soil organic matter according to the criteria of Litz (1990).
Result: The distribution between the organic phase of soil or sediment solids and porewater was calculated by using QSAR. For DMP a Koc value of 2.62 was calculated. For monomethylphosphonate a Koc of 1.36 was calculated
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
26-MAY-2004 (21) (56)

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type:	static
Species:	Brachydanio rerio (Fish, fresh water)
Exposure period:	96 hour(s)
Unit:	mg/l Analytical monitoring: yes
LC0:	>= 15.6 -
Limit Test:	yes
Method:	other: "Acute Toxicity for Fish" (C.1) of the directive 67/548/EEC, Annex V (Draft 1992)
Year:	1992
GLP:	yes
Test substance:	other TS: 99.2 %
Method:	Accepted new scientific name for Brachydanio rerio: Danio rerio
Remark:	A preliminary test (see chapter 3.1.2) showed that the test substance dimethyl phosphonate in unbuffered water has a half-life between 50 and 70 hours. Analytical monitoring: GC.
Result:	LCO is the arithmetic mean of the analytically determined values for dimethyl phosphonate over the test period between 24-96 hours. The 0-hour value of the accompanying analysis was ignored when calculating the arithmetic mean of the measured values as hydrolysis of the test substance from dimethyl phosphonate to monomethyl phosphonate was not completed at this point in time.
Test condition:	- 3-months-old fishes were used. Length: 2.5 to 3.5 cm - Tank: 300 x 135 x 200 mm; 5l test medium, synthetic origin, prepared according to ISO; no replicates, one control - Only one concentration tested (100 mg/l). This was analytically checked every 24 h with GC. - Temperature during the test: no significant variation (21.1 to 21.8 °C) - 0xygen concentration: no significant variation (98.1-117.6% of the saturation level was reported during the test). - pH: at the start of the test the pH was 7.5, in the middle of the test was reported to be 5.4 remaining in this pH-range till the end of the test (pH=5.0).
Reliability:	(1) valid without restriction Guideline study
Flag:	Critical study for SIDS endpoint

19-MAY-2003 (11)

Type:	static
Species:	Pimephales promelas (Fish, fresh water)
Exposure period:	96 hour(s)
Unit:	mg/l Analytical monitoring: no data
LC50:	225 -

Method: other: as described in the "Standard Methods for the examination of Water and Waste Water" (1960)
Year: 1969
GLP: no
Test substance: no data

Method: Method description published by Am Publ Health Ass New York; 11th Ed., pp 626
Result: In the report the result is a TLm-value (medium tolerance limit), which is the same as a LC50
Test condition: -Fish were collected in the field, were acclimated to laboratory conditions for at least one week and they were fed frozen brine shrimp.
-Temperature of the test system: 17 °C
-10 fish were used for the test in 5 l tap water.
-The stock solution was prepared with acetone.
-Oxygen: 7 - 8 mg/l
-pH: 7.0 - 7.3
-Alkalinity 50 - 70 mg/l, dissolved solids 60 - 100 mg/l; iron < 0.1 mg/l
Reliability: (2) valid with restrictions
Study well documented meets generally accepted scientific principles
Flag: Critical study for SIDS endpoint
11-NOV-2003 (25) (48)

Type: other: not specified
Species: Pimephales promelas (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no data
LC50: 225 -

Method: other:
Year: 1966
GLP: no
Test substance: no data

Result: In the report the result is a TLm-value (medium tolerance limit), which is the same as a LC50
Reliability: (4) not assignable
Documentation insufficient for assessment
11-NOV-2003 (108)

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: = 12.5 -
EC50: = 24.8 -
EC100: 100 -
Limit Test: no

Method: Directive 92/69/EEC, C.2
Year: 2003
GLP: yes

Test substance: other TS: Dimethyl phosphonate, purity 99.8 %

Method: . Test species: Daphnia magna Straus, parthenogenetic females, strain of Bundesgesundheitsamt Berlin
. Maintenance: A population of parthenogenetic females of synchronized age structure is maintained since more than 15 years in the test facility under constant temperature conditions (20 +/- 1 °C) at a 16 : 8 light-dark photoperiod (illumination < 1000 lux). The culture water (so-called 'M4 medium') is partly renewed once a week. The daphnia are exclusively fed with unicellular green algae (Desmodesmus subspicatus) 'ad libitum'. Mortalities of parent daphnia during the culture period are recorded daily in a semi-quantitaive way. The neonates are separated from their parent daphnia by filtration prior the acute test.
. Hardness of dilution water: 14.8 °dH (= 264.2 mg/l CaCO3)
. Analysis: HPLC-MS

Remark: EC50 = 24.8 mg/l (nominal)
95 % confidence limits: 20.8 - 29.6 mg/l (nominal)
At 25 mg/l DMP concentration, the effective monomethyl phosphonate (MMP) concentration was 8.0 mg/l (geometric mean of 8.18 mg/l at start of incubation and 7.89 mg/l after 2 d of incubation).
After the start of incubation (short hydrolysis period) as well as after 2 d of incubation the concentration of MMP was about 1/3 of the initial DMP concentration, accounting for about 40 % of the DMP. It is assumed that MMP is rapidly formed during the preparation of the stock and test solutions. Its hydrolysis is less rapid. During the incubation the MMP concentration might even increase due to formation from DMP, but levels out due to concomittant hydrolysis to phosphorous acid.

Result: Concentrations (mg/l) and pH of Daphnia tests

	DMP	DMP	MMP	MMP	pH	%*	%*
Time	0 d	2 d	0 d	2 d	2 d	0 d	2 d
control		0**	0	0	0	7.9	
6.25***		0	0	2.20	1.83	7.9	35 29
12.5	1.64	0	4.32	3.90	7.9	35	31
25	5.10	0	8.18	7.89	7.9	33	32
50	10.25	0	15.27	14.49	7.7	31	29
100	48.11	0	22.22	26.22	7.2	22	26

*MMP content in % w/w of DMP initially added to the medium
**0 = below the detection limit of 0.375 mg/l
***Initial DMP concentration
Cumulative immobilisation (number of immobilised Daphnias from 20 initially tested)

Time	0 d	1 d	2 d
control	0	0	0
6.25	0	0	0
12.5	0	0	0
25	0	7	13
50	0	12	18
100	0	17	20

Test condition: . Test vessel: 50 ml glass beaker holding 10 neonates in 20 ml of test medium
. Experimental design: 5 test concentration plus 1 control; 10 neonates per vessel, 2 replicates per

concentration/control; no feeding during the exposure period
. Photoperiod: 16 h light,8 h dark
. Temperature: 21.1 °C +/- 1 °C
. Nominal test concentrations: 6.25, 12.5, 25, 50, 100 mg/l
. Criteria of effects: The criterion of adverse effects used was alteration of the normal mobility behaviour and the loss of locomotory actions of the neonates, observed at 24 h
Reliability: (1) valid without restriction
GLP guideline study
Flag: Critical study for SIDS endpoint
26-MAY-2004 (17)

Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: yes
EC0: = 12.5 -
EC50: = 41.7 -
EC100: > 100 -
Limit Test: no

Method: Directive 92/69/EEC, C.2
Year: 2003
GLP: yes
Test substance: other TS: Dimethyl phosphonate, purity 99.8 %

Method: . Test species: Daphnia magna Straus, parthenogenetic females, strain of Bundesgesundheitsamt Berlin
. Maintenance: A population of parthenogenetic females of synchronized age structure is maintained since more than 15 years in the test facility under constant temperature conditions (20 +/- 1 °C) at a 16 : 8 light-dark photoperiod (illumination < 1000 lux). The culture water (so-called 'M4 medium') is partly renewed once a week. The daphnia are exclusively fed with unicellular green algae (Desmodesmus subspicatus) 'ad libitum'. Mortalities of parent daphnia during the culture period are recorded daily in a semi-quantitaive way. The neonates are separated from their parent daphnia by filtration prior the acute test.
. Hardness of dilution water: 14.8 °dH (= 264.2 mg/l CaCO3)
. Analysis: HPLC-MS
Remark: EC50 = 41.7 mg/l (nominal)
95 % confidence limits: 32.7-53.0 mg/l (nominal)
Test condition: . Test vessel: 50 ml glass beaker holding 10 neonates in 20 ml of test medium
. Experimental design: 5 test concentration plus 1 control; 10 neonates per vessel, 2 replicates per concentration/control; no feeding during the exposure period
. Photoperiod: 16 h light, 8 h dark
. Temperature: 21.1 °C +/- 1 °C
. Nominal test concentrations: 6.25, 12.5, 25, 50, 100 mg/l
. Criteria of effects: The criterion of adverse effects used was the alteration of the normal mobility behaviour and the loss of locomotory actions of the neonates, observed at 24 h
Reliability: (1) valid without restriction
GLP guideline study
12-NOV-2003 (17)

Type: other: not specified
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no data
TT : 125 -

Method: other: not specified
Year: 1968
GLP: no
Test substance: other TS: no purity given

Remark: TT = Toxicity threshold
Source: Personal communication of G. Bringmann, Berlin-Dahlem, Institute for Water, Soil, Air (WaBoLu)
Reliability: (4) not assignable
Secondary literature
06-OCT-2003 (64)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: other algae: Desmodesmus subspicatus
Endpoint: growth rate
Exposure period: 72 hour(s)
Unit: mg/l Analytical monitoring: yes
EC0: >= 100 -
Limit Test: yes

Method: Directive 92/69/EEC, C.3
Year: 2003
GLP: yes
Test substance: other TS: Dimethyl phosphonate, purity 99.8 %

Method: . Test species: Desmodesmus subspicatus, non-axenic strain of the test species obtained from 'The Collection of Algal Cultures' of the Institute of Plant Physiology at the University of Göttingen (Germany)
. Maintenance of stock cultures: Exponentially-growing stock cultures are maintained in the test facility under constant temperature conditions (23 +/- 2°C) at a light intensity in the range 60 - 120 µE. x m-2 x s-1 (measured in the range 400 to 700 nm using a spherical quantum flux meter). The nutrient medium (according to BRINGMANN & KÜHN (1977) is renewed once a week. Cell density measurements are made using a microcell counter
. Preparation of pre-cultures: Pre-cultures are set up three days before the start of a test. They are grown under identical exposure conditions as the stock cultures, except from the use of a different nutrient medium
. Test cultures: The algal inocula for a test are taken from an exponentially-growing pre-culture and are mixed with the nutrient medium to make up to a final cell density of about 104 cells per millilitre in the test medium.
. Pretreatment of the test item: To produce the only test concentration 125.1 mg of the test item were added to 1 litre of dilution water and treated for 30 minutes on a magntic stirrer
. Nutrient medium:

Nutrient	Concentration	
NH4Cl	15	mg/l
MgCl2 x 6 H2O	12	mg/l
CaCl2 x 2 H2O	18	mg/l
MgSO4 x 7 H2O	15	mg/l
KH2PO4	1.6	mg/l
FeCl3 x 6 H2O	80	µg/l
Na2EDTA x 2 H2O	100	µg/l
H3BO3	185	µg/l
MnCl2 x 4 H2O	415	µg/l
ZnCl2	3	µg/l
CoCl2 x 6 H2O	1.5	µg/l
CuCl2 x 2 H2O	0.01	µg/l
Na2MoO4 x 2 H2O	7	µg/l

Solid NaHCO3 is added to the nutrient media to make up a final concentration of 50 mg/l in the solutions of the pre-cultures and test cultures.

Remark: At the nominal concentration of 100 mg/l DMP the monomethyl phosphonate concentration was about 25 mg/l during the incubation period.

Result: Growth rate control = 1.17, growth rate 100 mg/l (nominal) = 1.26

Test condition: . Test vessels: 300 ml Erlenmeyer flasks with stoppers
. Culturing apparatus: Light chamber in which a temperature in the range 21°C to 25°C can be maintained at +/- 2°C, and continuous uniform illumination is provided in the spectral range 400 to 700 nm.
. Light intensity: At the average of the test solutions, a light intensity in the range 60 to 120 µE m-2 s-1, or an equivalent range of 4000 to 8000 lx, is recommended for use.
. Cell density measurements: Cell densities are measured in a microcell counter or, alternatively, are determined by means of a microscopic counting chamber.
. Experimental design: 1 test concentration plus 1 control, 3 replicates per concentration, 6 replicates per control, initial cell density in the test cultures approximately 10000 cells per millilitre
. Nominal test concentration: 100 mg/l
. Method of administration: direct weighing
. Criteria of effects: The criteria of adverse effects were the inhibition of growth and growth rate, respectively, of the algal population
. pH-values at 0 h and 72 h
controls: 8.2 and 10.5
100 mg/l: 8.1 and 10.6

Reliability: (1) valid without restriction
GLP guideline study

Flag: Critical study for SIDS endpoint

26-MAY-2004 (18)

Species: Scenedesmus sp. (Algae)
Endpoint: other: not specified
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no data
TT : 12.5 -

Method: other: not specified
Year: 1968

GLP: no
Test substance: other TS: no purity given

Remark: TT = Toxicity threshold
Source: Personal Communication of G.Bringmann, Berlin-Dahlem, WaBoLu
Test condition: No test conditions reported
Reliability: (4) not assignable
Secondary literature
14-JAN-2004 (64)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: aquatic
Species: activated sludge
Exposure period: 3 hour(s)
Unit: mg/l Analytical monitoring: no
EC50: > 10000 -

Method: other: "Test for Inhibition of Oxygen Consumption by Activated Sludge" ISO 8192 (1986)
Year: 1992
GLP: yes
Test substance: other TS: 99.2 %

Remark: Reported concentrations are nominal.
Concentrations tested: 100, 1000, 10000 mg/l.
Reference-substance: 3,5-Dichlorophenol.
Reliability: (1) valid without restriction
Guideline study
Flag: Critical study for SIDS endpoint
19-MAY-2003 (11)

Type: other: in vitro
Species: other fungi: nine Phytophthora species
Exposure period: 4 day(s)
Unit: mmol/l Analytical monitoring: no data
EC50: .09 - 57.47

Method: other: see below
Year: 1989
GLP: no data
Test substance: other TS: 99% purity

Remark: The study demonstrates the effectiveness of dimethyl phosphonate as fungicide.
Test condition: Inhibition is based on comparison to unamended medium.
Mycelial growth was measured after 4 days in the dark at 24°C.
Tested Phytophthora species were: cactorum, capsici, cinnamoni, citricola, citrophthora, cryptogea, megasperma, palmivora, parasitica
Reliability: (2) valid with restrictions
Basic data given
04-JUN-2003 (84)

Type: aquatic
Species: other protozoa: Colpoda sp.

Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no data
TT : 500 -

Method: other: not specified
Year: 1968
GLP: no
Test substance: other TS: no purity given

Remark: TT = Toxicity threshold
Source: Personal communication of G. Bringmann, Berlin-Dahlem, Institute for Water, Soil, Air (WaBoLu)
Reliability: (2) valid with restrictions
Data from handbook or collection of data
06-JUN-2003 (64)

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

Species: other terrestrial plant: rye, wheat, millet
Endpoint: other: development of pollen

Method: other: see below
Year: 1995
GLP: no
Test substance: no data

Result: Results are given as % seed formation which is the ratio of seed number in treated to untreated plants without free pollination and % male sterilization is the ratio of seed number in treated to untreated plants without free pollination; the data for each crop were averaged for all cultivars and experiments.

% seed formation/% male sterilization
Rye: 85/97
Wheat: 71/96 (winter)
82/100 (spring)
Millet 43/22

Source: PCT-Gazette (Geneva-Switzerland) SU/88/00058
Test condition: - Data was taken from field experiments over a decade (19870-1980). The measurements on pollen sterilization and seed formation were done after open pollination.
- The concentrations with which it was investigated are in the range of 1 - 3% and 2 - 6-fold molar.
- Corp used in the tests: Secale cereale L (rye), Triticum aestivumj L (wheat), Panicum miliaceum moench (millet).
Reliability: (4) not assignable
Secondary literature, insufficient data for hazard assessment
19-MAY-2003 (100)

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

5.0 Toxicokinetics, Metabolism and Distribution

In Vitro/in vivo:	In vivo
Type:	Excretion
Species:	rat
No. of animals, males:	3
Doses, males:	10, 20, 200 mg/kg bw (single administration) and 200 mg/kg bw for 5 d (repeated administration)
Route of administration:	gavage

Method:	other
Year:	1997
GLP:	no data
Test substance:	other TS: purity of unlabeled DMP> 99 %; radiochemical purity (14C labeled): 97%
Result:	single administration: Expired air (14CO2): 49-57 % (nearly complete 12 h after dosing) Urine: 28-38 % (almost linear fashion up to 24 h after dosing, nearly complete 24 h after dosing) Feces: 1-2 % repeat administration: No effect on studied metabolism to CO2 or elimination in urine
Test condition:	Animals: F344/N, 180-220 g (8-10 wk-old) No. of Animals: at least 3 per time point Housing: individual metabolism cages - separate collection of urine, feces, exhaled radioactivity
Reliability:	(2) valid with restrictions Study well documented, meets generally accepted scientific principles, acceptable for assessment.
Flag:	Critical study for SIDS endpoint

06-SEP-2002 (79)

In Vitro/in vivo:	In vivo
Type:	Excretion
Species:	mouse
No. of animals, males:	3
Doses, males:	10, 20, 200 mg/kg bw (single administration)
Route of administration:	gavage

Method:	other
Year:	1997
GLP:	no data
Test substance:	other TS: purity of unlabeled DMP> 99 %; radiochemical purity (14C labeled): 97%
Result:	Expired air (14CO2): appr. 44 % (nearly complete 12 h after dosing) Urine: appr. 49 % (almost linear fashion up to 24 h after dosing, nearly complete 24 h after dosing) Volatile Organics: appr. 2.5 %

More rapid metabolism and elimination of DMHP in mice compared to rats.
Test condition: Animals: B6C3F1, 20-25 g (6-8 wk-old)
No. of Animals: at least 3 per time point
Housing: individual metabolism cages - separate collection of urine, feces, exhaled radioactivity
Reliability: (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment.
Flag: Critical study for SIDS endpoint
06-SEP-2002 (79)

In Vitro/in vivo:	In vivo
Type:	Distribution
Species:	rat
No. of animals, males:	3
Doses, males:	10, 100, 200 mg/kg bw (single administration), 200 mg/kg bw (1, 2, 5 daily doses - repeated administration)
Route of administration:	gavage

Method: other
Year: 1997
GLP: no data
Test substance: other TS: purity of unlabeled DMP> 99 %; radiochemical purity (14C labeled): 97%

Result: 1. High to low concentration of radioactivity: Liver, kidney, forestomach, spleen, lung, brain, adipose tissue, muscle, and testes. Concentrations were nearly proportional to the dose.
2. Similar distribution with marked decrease in the clearance rate
3. Increased radioactivity
4.
Dose / Urine/CO2/Feces/Organic volatiles / Tissue / Total
10 mg/kg bw / 39 / 49 / 1.2 / 0.9 / 17 / 107
100 mg/kg bw / 29 / 57 / 0.9 / 1.1 / 13 / 100
200 mg/kg bw / 30 / 53 / 1.8 / 1.7 / 17 / 103
5 x 200 mg/kg bw / 43 / 41 / 2.1 / 2.2 / 9.0 / 97

Conclusion: Little evidence of bioaccumulation or saturation of absorption or elimination
Test condition: Animals: F344/N, 180-220 g (8-10 wk-old)
No. of Animals: at least 3 per time point
Housing: individual metabolism cages - separate collection of urine, feces, exhaled radioactivity
Examinations:
1. Radioactivity measurements in tissues 24 h after single administration of 10, 100, 200 mg/kg bw
2. Radioactivity measurements in tissues 1, 2, 5, 10 days after a single dose of 200 mg/kg bw
3. Radioactivity measurements in tissues 24 h after last dose of 1, 2, 5 daily doses of 200 mg/kg bw
4. Total recovery was studied
Reliability: (2) valid with restrictions
Study well documented, meets generally accepted scientific

principles, acceptable for assessment.
Flag: Critical study for SIDS endpoint
06-SEP-2002 (79)

In Vitro/in vivo: In vivo
Type: Distribution
Species: mouse
No. of animals, males: 3
Doses, males: 200 mg/kg bw
Route of administration: gavage

Method: other
Year: 1997
GLP: no data
Test substance: other TS: purity of unlabeled DMP> 99 %; radiochemical purity (14C labeled): 97%

Result: 1. High to low concentration of radioactivity: Liver, kidney, forestomach, spleen, lung, brain, adipose tissue, muscle, and testes.
2.
Dose /Urine/CO2/Feces/Organic volatiles/Tissue/Total (%)
200 mg/kg / 50 / 44 / 1.6 / 2.0 / 6.0 / 104

Conclusions: Similar distribution pattern as in rats with lower concentrations.
Little evidence of bioaccumulation or saturation of absorption or elimination.
Test condition: Animals: B6C3F1, 20-25 g (6-8 wk-old)
No. of Animals: at least 3 per time point
Housing: individual metabolism cages - separate collection of urine, feces, exhaled radioactivity
Examinations:
1. Radioactivity measurements in tissues 1, 2, 5 days after a single dose of 200 mg/kg bw
2. Total recovery was studied
Reliability: (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment.
Flag: Critical study for SIDS endpoint
06-SEP-2002 (79)

In Vitro/in vivo: In vivo
Type: Metabolism
Species: rat
Doses, males: 10, 100, 200 mg/kg bw (single administration), 200 mg/kg bw for 5 d (repeated administration)
Route of administration: gavage

Method: other
Year: 1997
GLP: no data
Test substance: other TS: purity of unlabeled DMP> 99 %; radiochemical purity (14C labeled): 97%

Result: In HPLC measurements of urine only one peak was detected; the retention time corresponds to monomethyl hydrogen phosphite (MMP).

The percent dose recovery of radioactivity in CO2 varied between 41 and 57 % and was not dose-dependant.

It is supposed, that DMP is demethylated to MMP. The Methylgroup is subsequently oxidized to CO2 via formaldehyde and expired.

Test condition: Animals: F344/N, 180-220 g (8-10 wk-old)
No. of Animals: at least 3 per time point
Housing: individual metabolism cages - separate collection of urine, feces, exhaled radioactivity
Examinations:
Retention time of dimethyl hydrogen phosphite (DMP) and monomethyl hydrogen phosphite (MMP) was determined using three different HPLC systems (standard retention times).
Urinary radioactivity was measured and compared with the standard retention times.
Radioactive CO2 concentration is measured.

Reliability: (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment.

Flag: Critical study for SIDS endpoint

06-SEP-2002 (79)

In Vitro/in vivo: In vitro
Type: Metabolism
Species: rat

Method: other
Year: 1997
GLP: no data

Test substance: other TS: purity of unlabeled DMP> 99 %; radiochemical purity (14C labeled): 97%

Result: Tissue / Formaldehyde formed (nmol/mg protein/2h)
Liver*1 / 46 (2 mM), 142 (20 mM), 176 (200 mM)
Lung*2 / 34 (2 mM), 104 (20 mM)
Kidney*2 / 30 (2 mM), 90 (20 mM)
Forestomach*3 / 8 (2 mM), 24 (20 mM)
Glandular stomach*2 / 4 (2 mM), 19 (20 mM)

*1 data from three rats
*2 data from three pools, each pool from three rats
*3 data from two pools, each pool from five rats

Conclusion: Formaldehyde was formed dose-dependently mainly in liver and lungs, but also in kidneys, forestomach and glandular stomach.

Test condition: Microsomal fraction of liver, lungs, kidneys, glandular stomach and forestomach (5 animals) were prepared from male rats.

Reliability: (2) valid with restrictions
Study well documented, meets generally accepted scientific

principles, acceptable for assessment.
06-SEP-2002 (79)

In Vitro/in vivo: In vitro

Year: 1988
GLP: no
Test substance: other TS: >99% pure; radioactive material: >97%

Result: Stability period:

10% DMHP in water:

22 C	8 h
8 C	24 h
-8 C	72 h
-80 C	>2160 h

5% in water/puffer at 37-38 C:

pH	hours
2	2
8	8

10% in water/puffer at 37-38 C:

pH	hours
2	1
7.4	3.6
8	4

After a period of stability DMHP degrades according to first order kinetics. Stability increases at lower temperature and higher pH.
The pattern of degradation products was identical under all conditions: orthophosphorous acid; monomethyl hydrogen phosphite, methanol

Test condition: Concentration range:
2, 5 or 10% (W/V)
Temperature range:
37, 22, 8, -8, -80 C
Solvent:
methanol,
THF
0,9% NaCl in water
0.1 M sodium phosphate puffer at pH=7, 7.4, 8
HCl in water pH=2
Storage duration:
1-5-15-30 min;
1-2-4-6-8-10-24-48 h;
1-2-3-4-5-6-7 days; then weekly
Analysis:
Gaschromatography, flame ionisation detector;
HPLC with radiactivity detector; 4 different systems

Reliability: (2) valid with restrictions
artificial system; relevance in vivo not examined

Flag: Critical study for SIDS endpoint
01-OCT-2003 (78)

Type: Metabolism

Result: No induction of cytochrome P 450 enzymes and glutathiontransferase after administration of 200 mg/kg/day DMP for 6 weeks to Fischer rats. Details under 5.4 Repeated dose toxicity
Test condition: Details under 5.4 Repeated dose toxicity.
Reliability: (2) valid with restrictions
Study well documented, meets generally accepted scientific standard, acceptable for assessment.
02-OCT-2003 (77)

Result: Based on Computer modelling, dimethyl hydrogen phosphite is a possible substrate for CYP2E, not for CYP1 enzymes.
Reliability: (4) not assignable
Non-valid test system
02-OCT-2003 (54)

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Strain: Fischer 344
Sex: male/female
No. of Animals: 5
Vehicle: other: corn oil
Doses: 1470, 2150, 3160, 4640, 6810 mg/kg bw
Value: 3040 - 3283 mg/kg bw

Method: other: comparable to OECD-guideline 401
Year: 1985
GLP: no data
Test substance: other TS: 96 % purity

Result: MORTALITY:
- Time of death: 1 day after application
- Number of deaths at each dose:
dose (mg/kg bw)/number of deaths:
male rats (LD50: 3283 mg/kg bw)
1470: 0/5
2150: 0/5
3160: 2/5
4640: 5/5
6810: 5/5

female rats (LD50: 3040 mg/kg bw)
1470: 0/5
2150: 0/5
3160: 3/5
4640: 5/5
6810: 5/5

```
                  CLINICAL SIGNS: >= 3160 mg/kg bw: inactivity, weakness,
                  shallow breathing
                  NECROPSY FINDINGS: >= 3160 mg/kg bw: gas in the stomach
                  and/or intestine
Test condition:   Number of animals per dose group and sex: 5
                  Observation period: 14 days
Reliability:      (1)  valid without restriction
                  Comparable to guideline study.
Flag:             Critical study for SIDS endpoint
01-APR-2003                                                          (74)

Type:             LD50
Species:          mouse
Strain:           B6C3F1
Sex:              male/female
No. of Animals:   5
Vehicle:          other: corn oil
Doses:            1470, 2150, 3160, 4640, 6810 mg/kg bw
Value:            > 2150 - 2815 mg/kg bw

Method:           other: comparable to OECD guideline 401
  Year:           1985
   GLP:           no data
Test substance:   other TS: 96 % purity

Remark:           LD50 value of female mice could not be determined due to
                  steep survival curve.
Result:           MORTALITY:
                  - Time of death: 1-2 days after application
                  - Number of deaths at each dose:
                  dose (mg/kg bw)/number of deaths:
                  male mice (2815 mg/kg bw)
                  1470: 0/5
                  2150: 0/5
                  3160: 4/5
                  4640: 5/5
                  6810: 5/5

                  female mice (>2150 mg/kg bw)
                  1470: 0/5
                  2150: 0/5
                  3160: 5/5
                  4640: 5/5
                  6810: 5/5

                  CLINICAL SIGNS: >= 2150 mg/kg bw: inactivity, prostration,
                  shallow breathing
                  NECROPSY FINDINGS: 2/10 mice, m: white opaque eyes
Test condition:   Number of animals per dose group and sex: 5
                  Observation period: 14 days
Reliability:      (1)  valid without restriction
                  Comparable to guideline study.
Flag:             Critical study for SIDS endpoint
01-APR-2003                                                          (74)

Type:             other: estimated median lethal dose (range-finding study)
Species:          rat
Strain:           other: albino
```

Sex: no data
No. of Animals: 2
Vehicle: other: 0,5% aqueous methyl cellulose solution
Doses: 10.0, 31.6, 100, 316, 1000, 3160 mg/kg bw
Value: 3160 mg/kg bw

Method: other
Year: 1961
GLP: no
Test substance: other TS: colourless, liquid, not further specified

Result: MORTALITY:
- Time of death: 3160 mg/kg bw - 1/2 after 4 hours; no deaths at other dosages
CLINICAL SIGNS: Prostration, labored respiration, and tremors only in animal that died
NECROPSY FINDINGS: Hemorrhage of lungs, congested kidneys, and gastrointestinal inflammation
Test condition: - Observation period: 48 h
EXAMINATIONS: mortality, toxic effects, autopsy
Reliability: (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment. Restrictions: Only 2 animals/dose group were used (dose-range finding study).
Flag: Critical study for SIDS endpoint
01-APR-2003 (82)

Type: LD50
Species: rat
Strain: no data
Sex: no data
Vehicle: no data
Value: 3050 mg/kg bw

Method: other
Year: 1977
GLP: no
Test substance: other TS: not further specified

Reliability: (4) not assignable
Secondary literature
28-FEB-2002 (2) (66)

Type: LD50
Species: rat
Strain: no data
Sex: no data
Vehicle: no data
Value: 3800 mg/kg bw

Method: other
Year: 1973
GLP: no
Test substance: other TS: not further specified

Reliability: (4) not assignable
Secondary literature
01-MAR-2002 (53)

Type: LD50
Species: rat
Strain: no data
Sex: no data
Vehicle: no data
Value: 4250 mg/kg bw

Method: other
Year: 1972
GLP: no
Test substance: other TS: not further specified

Reliability: (4) not assignable
Secondary literature
01-MAR-2002 (58) (72) (76)

Type: LD50
Species: rat
Value: >= 178 - 7100 mg/kg bw

Result: The LD50 values of 16 phosphites - among them dimethyl hydrogen phosphite - ranged from 178 mg/kg bw to 7100 mg/kg bw. The toxicity of the phosphites appeared to be related to their lipophilic and electronic properties. The most toxic compounds had electronegative substituents and unsaturated alkyl chains.

No further detail on DMP given
Reliability: (4) not assignable
documentation insufficient
08-OCT-2003 (93)

Type: LD50
Species: mouse
Strain: no data
Sex: no data
Vehicle: no data
Value: 1831 mg/kg bw

Method: other
Year: 1992
GLP: no data
Test substance: other TS: not further specified

Reliability: (4) not assignable
Secondary literature
28-FEB-2002 (71)

Type: LD50
Species: guinea pig
Strain: no data
Sex: no data
Vehicle: no data
Value: 900 mg/kg bw

Method: other

```
  Year:           1992
   GLP:           no data
Test substance:   other TS: not further specified

Reliability:      (4)  not assignable
                  Secondary literature
28-FEB-2002                                                    (71)
```

5.1.2 Acute Inhalation Toxicity

```
Type:             other: LT (Time to death)
Species:          rat
Strain:           Wistar
Sex:              male
No. of Animals:   10
Vehicle:          other: no
Doses:            7.1 g/m3
Exposure time:    6 hour(s)

Method:           other
  Year:           1992
   GLP:           no data
Test substance:   other TS: technical product; assumed purity: 100 %

Result:           MORTALITY: no deaths
                  CLINICAL SIGNS: no
                  NECROPSY FINDINGS: congestion and hemorrhage in the lungs
Test condition:   Exposure concentration is calculated from air flow and net
                  loss of material; "near saturated vapor" at room temperature
                  Post Exposure Period: 7 d
                  Examinations: Mortality, toxic effects, autopsy
Reliability:      (2)  valid with restrictions
                  Test procedure in accordance with generally accepted
                  scientific standards and described in sufficient detail.
                  Restriction: No detailed information on purity of test
                  compound.
Flag:             Critical study for SIDS endpoint
14-APR-2003                                                    (83)

Type:             other: LT (Time to death)
Species:          mouse
Strain:           Swiss
Sex:              male
No. of Animals:   10
Vehicle:          other: no
Doses:            7.1 g/m3
Exposure time:    6 hour(s)

Method:           other
  Year:           1992
   GLP:           no data
Test substance:   other TS: technical product; assumed purity: 100 %

Result:           MORTALITY:no deaths
                  CLINICAL SIGNS: labored respiration after 1 h 50 min (2
                  mice); ptosis after 5 hours (10 mice)
                  NECROPSY FINDINGS: no findings
```

Test condition: Exposure concentration is calculated from air flow and net loss of material; "near saturated vapor" at room temperature
Post Exposure Period: 7 d
Examinations: Mortality, toxic effects, autopsy
Reliability: (2) valid with restrictions
Test procedure in accordance with generally accepted scientific standards and described in sufficient detail.
Restriction: No detailed information on purity of test compound.
Flag: Critical study for SIDS endpoint
14-APR-2003 (73) (83)

Type: other: LT (Time to death)
Species: guinea pig
Strain: Shorthair
Sex: male
No. of Animals: 10
Vehicle: other: no
Doses: 7.1 g/m3
Exposure time: 6 hour(s)

Method: other
Year: 1992
GLP: no data
Test substance: other TS: technical product; assumed purity: 100 %

Result: +no deaths
CLINICAL SIGNS: no
NECROPSY FINDINGS: small hemorrhagic areas on the lungs (2 guinea pigs)
Test condition: Exposure concentration is calculated from air flow and net loss of material; "near saturated vapor" at room temperature
Post Exposure Period: 7 d
Examinations: Mortality, toxic effects, autopsy
Reliability: (2) valid with restrictions
Test procedure in accordance with generally accepted scientific standards and described in sufficient detail.
Restriction: No detailed information on purity of test compound.
Flag: Critical study for SIDS endpoint
03-AUG-2005 (73) (83)

Type: LC50
Species: rat
Strain: no data
Sex: no data
Vehicle: no data
Exposure time: unspecified
Value: > 20000 mg/m³

Method: other
Year: 1984
GLP: no data
Test substance: other TS: not further specified

Reliability: (4) not assignable
Data from handbook or collection of data
12-NOV-2003 (2)

5.1.3 Acute Dermal Toxicity

Type:	LD50
Species:	rabbit
Strain:	other: albino
Sex:	male/female
No. of Animals:	4
Vehicle:	other: no
Doses:	100, 316, 1000, 3160 mg/kg
Value:	= 681 mg/kg bw
Method:	other
Year:	1961
GLP:	no data
Test substance:	other TS: colourless, liquid, not further specified
Result:	MORTALITY: Deaths occurred in dose groups 1000 (4/4) and 3160 (3/4) mg/kg bw 2 and 3 days after application. CLINICAL SIGNS: 48 h after application >= 1000 mg/kg bw: depression, ptosis, labored respiration, ataxia, placidity NECROPSY FINDINGS: hemorrhagic lungs, red-tinged fluid in the pleural cavity, congestion of the thymus and kidneys, edema or thickening of the mucosa of the stomach, inflammation of a portion of the intestines (1000 and 3160 mg/kg bw). Dermal effects: no signs of irritation
Test condition:	Application: under a dental damming binder placed around the trunk of the animals. Exposure time: 24 h, skin was washed Observation period: immediately, 1 h, 24 h, once daily for a total of 7 days Examinations: mortality, toxic effects, autopsy, animals at lowest and highest dosage were observed for signs of dermal irritation
Reliability:	(2) valid with restrictions Study well documented, meets generally accepted scientific principles, acceptable for assessment. Restrictions: only 2 males and 2 females are used per dose group; the dental damming binder placed under the trunk may be ingested.
Flag:	Critical study for SIDS endpoint

10-SEP-2004 (73) (82)

Type:	LD50
Species:	rabbit
Strain:	no data
Sex:	no data
Vehicle:	no data
Value:	= 2400 mg/kg bw
Method:	other
Year:	1990
GLP:	no data
Test substance:	other TS: not further specified
Reliability:	(4) not assignable Secondary literature

06-SEP-2002 (2)

5.1.4 Acute Toxicity, other Routes

Type: LD50
Species: rat
Strain: no data
Sex: no data
Vehicle: no data
Route of admin.: s.c.
Exposure time: unspecified
Value: = 2970 mg/kg bw

Method: other
Year: 1992
GLP: no data
Test substance: other TS: not further specified

Reliability: (4) not assignable
Secondary literature
06-SEP-2002 (71)

Type: LD50
Species: rat
Strain: Wistar
Sex: female
Vehicle: peanut oil
Doses: no data
Route of admin.: s.c.
Value: = 2300 mg/kg bw

Method: other
Year: 1975
GLP: no data
Test substance: other TS: not further specified

Result: Time of death: 1-4 days after application
Necropsy findings: massive hemorrhages in the lung and necrosis at the injection site
Reliability: (4) not assignable
Internal report.
06-SEP-2002 (7) (10)

Type: LD50
Species: mouse
Strain: no data
Sex: no data
Vehicle: no data
Route of admin.: s.c.
Exposure time: unspecified
Value: = 2610 mg/kg bw

Method: other
Year: 1992
GLP: no data
Test substance: other TS: not further specified

Reliability: (4) not assignable
Secondary literature

06-SEP-2002 (71)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Concentration: undiluted
Exposure: no data
Exposure Time: 4 hour(s)
No. of Animals: 2
Result: slightly irritating

Method: other
Year: 1978
GLP: no
Test substance: other TS: not further specified

Test condition: Animals: New Zealand white (3-4 kg), male/female
Dosage: 0.5 ml
Exposure time: 1-4 hours
Application: via plaster tapes (no further information)
Application region: ear
Observation period: 7 days
Reliability: (2) valid with restrictions
Test procedure in accordance with german standard methods with acceptable restrictions: No data on exact time of exposure and on effects.
Flag: Critical study for SIDS endpoint
14-APR-2003 (10) (22)

Species: rabbit
Concentration: undiluted
Exposure: no data
Exposure Time: 8 hour(s)
No. of Animals: 2
Result: corrosive

Method: other
Year: 1978
GLP: no
Test substance: other TS: not further specified

Test condition: Animals: New Zeeland white (3-4 kg), male/female
Dosage: 0.5 ml
Application: via plaster tapes (no further information)
Application region: ear
Observation period: 7 days
Reliability: (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions: No data on type of exposure and on effects.
Flag: Critical study for SIDS endpoint
14-APR-2003 (22)

Species: rabbit
Concentration: other: 100, 3160 mg/kg bw

Exposure: Semiocclusive
Exposure Time: 24 hour(s)
No. of Animals: 4
Vehicle: other: no
Result: not irritating

Method: other
Year: 1961
GLP: no
Test substance: other TS: colourless, liquid, not further specified

Result: At removal abdomens and binders were dry. No signs of dermal irritation on the exposed skin area of any animal are shown.

3/4 animals in the 3160 mg/kg bw group died at day 2 after removal of substance.
Test condition: Application: under a dental damming binder placed around the trunk of the animals.
Exposure time: 24 h, skin was washed
Observation times: after 24 h, thereafter once daily for a total of 7 days
Reliability: (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment. Restrictions: Study was conducted to investigate acute dermal toxicity. Animals of the high dosage group died during study. No data on effects, binders may be ingested.
Flag: Critical study for SIDS endpoint
01-APR-2003 (82)

Species: rabbit
Concentration: 500 mg
Exposure Time: 24 hour(s)
Vehicle: no data
Result: slightly irritating

Method: other: no data
Year: 1986
GLP: no data
Test substance: other TS: not further specified

Remark: In a further handbook (p 1167) the result of the skin irritation assay was classified as moderately irritating.
Reliability: (4) not assignable
Data from handbook or collection of data
12-NOV-2003 (59) (96)

5.2.2 Eye Irritation

Species: rabbit
Concentration: undiluted
Dose: .05 ml
Comment: not rinsed
No. of Animals: 3
Vehicle: none
Result: moderately irritating

Method: other: comparable to OECD guideline 405
Year: 1961
GLP: no
Test substance: other TS: colourless, liquid, not further specified

Remark: No Signs of systemic toxicity from mucous membrane absorption were observed after autopsy.
Result: Observation results:
immediately: moderate edema, nictitating membrane, vascularisation of sclera (3/3), lacrimation (1/3)
1 and 4 h: mild to moderate edema, nictitating membrane, lacrimation (3/3); mild iritis at 4 h (1/3)
Signs of eye irritation decreased.
3 days: mild erythema (3/3)
4 days: mild erythema (1/3)
5-7 days: no effect
Test condition: Administration: left eye was treated (held closed 30 s)
Control: right eye
Observation times: immediately, 1 h, 4 h, 24 h, daily for a total of 7 days
Reliability: (1) valid without restriction
Comparable to guideline study.
Flag: Critical study for SIDS endpoint
01-APR-2003 (82)

Species: rabbit
Concentration: undiluted
Dose: .1 ml
No. of Animals: 2
Result: slightly irritating

Method: other
Year: 1978
GLP: no data
Test substance: other TS: not further specified

Result: Reddening of the conjunctiva (grade 2) 1h after treatment; no other effects
Effects reversible in 5 days
Test condition: observation period: 7 days
100 µl/animal
Reliability: (2) valid with restrictions
Test procedure in accordance with german standard methods with acceptable restrictions
Flag: Critical study for SIDS endpoint

07-MAY-2003 (22)

Species: rabbit
Concentration: 20 mg
Exposure Time: 24 hour(s)
Vehicle: no data
Result: moderately irritating

Method: other: no data
Year: 1986
GLP: no data

Test substance: other TS: not further specified

Remark: In a further handbook the results of the eye irritation assay are classified as severely irritating.
Reliability: (4) not assignable
Secondary literature
14-APR-2003 (58) (59) (96)

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: 4 weeks
Frequency of treatment: 6 hours/day, 5 days/week
Post exposure period: 4 weeks
Doses: target concentration: 10(40.6), 30(121.8), 100(406), 300(1218) ppm(mg/m³) (effective inhaled concentration: 12(48,7), 35(142.1), 119(483.14), 198(803.88) ppm(mg/m³))
Control Group: yes, concurrent vehicle
NOAEL: < 12 ppm
LOAEL: 12 ppm

Method: other: comparable to guideline 407
Year: 1981
GLP: no data
Test substance: other TS: colourless, liquid, not further specified

Result: LOAEL is 12 ppm (= 48.7 mg/m³; eye effects and kidney weights)
TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
- Mortality and time to death:
119 ppm (number of deaths in week 1-4): 0, 0, 1, 2
198 ppm (number of deaths in week 1-5): 0, 8, 5, 11, 3
(Causes of deaths may have been necrosis and acute purulent inflammation of the skin)
Time to death varied between 7 and 26 days at 483.1 and 803.9 mg/m3.

>= 12 ppm (= 48.7 mg/m³; m and f):
Eyes:
- irritation of superficial ocular structures (associated with inflammatory changes of
intraocular structures in many rats)
- mucosal irritation
- keratitis
Kidney:
- increased absolute and relative kidney weights

>= 35 ppm
Body weight m:
- reduced body weight gain

Eyes m and f:
- lenticular opacities, progressed to cataracts
Skin m and f:
- cutaneous and mucosal irritation (increased lacrimal, nasal or buccal secretions and/or erythema, edema, loss of elasticity, fissuring, necrosis or eschar formation of the skin); nasal and ocular responses disappeared within one week; cutaneous changes were not fully reversible during the observation period
Respiratory tract m and f:
- Inflammation of the anterior nares (control: 4/39, 12 ppm: 4/38, 35 ppm: 6/39, 119 ppm: 7/39, 198 ppm: 9/36) - seems to be an extension of the effect on the skin

>= 119 ppm
Mortality, m and f:
- increased mortality;
Time of death
- 119 ppm: on days 14(1,f) and 23(1,m)
- 198 ppm: on days 7 to 26 incl. (13,m + 14,f)
Body weight m and f:
- body weight losses
Clinical signs, m and f:
- neurological impairment (lack of coordination, lack of grip)
Skin m and f:
- Dermatitis (control, 12, 35 ppm: 0/40, 119 ppm: 7/39, 198 ppm: 27/36)
Respiratory tract m and f:
- irritation of the respiratory tract (dry or moist rales labored or irregular breathing); changes were reversible within one to two weeks
- Inflammation of the external nares (control, 12 and 35 ppm: 0/40, 119 ppm: 5/39, 198 ppm: 22/36)
Haematology:
- m: hematocrit and hemoglobin reduced
- m and f: neutrophils increased, increased total leukocyte numbers
Clinical chemistry:
- m: increased SGPT
- m and f: decreased glucose concentration
Fertility m:
- hypospermatogenesis (control, 12, 35 ppm: 0/20, 119 ppm: 3/20, 198 ppm: 4/19). In each case the content of sperm in the epididymis was below normal.

198 ppm m and f:
Respiratory tract:
- red discoloration of lungs and nasal turbinates; 9 rats (4 m and 5 f) had no discernible thymus tissue
Haematology:
- hemoglobin reduced
Clinical chemistry:
- increased SGPT, alkaline phophatase and urea levels
Spleen:
- hematopoiesis in the spleen (control, 12, 35, 119 ppm: each 0/40, 198 ppm: 4/18)
Prostate m:

- acute prostatitis 4/18 (low incidence of prostatitis was seen in general)

Further findings:
enlarged costochondral junction (control: 1/40, 12 and 35 ppm: 0/40, 119 ppm: 6/40, 198 ppm: 2/36) - treatment relation was not studied

OTHER EXAMINATIONS: Cataract formation and cessation was studied in animals of the 119 ppm group. Cataract formation had stopped after two weeks post-exposure and at four weeks post-exposure the formation of normal lens fibers had recommenced.

Test condition: TEST ORGANISMS
- Age: 28 days
- Weight at study initiation: m: 349-437 g (mean 397 g), f: 187-278 g (mean 239 g)
- Number of animals: 200 (20/sex/group)
ADMINISTRATION / EXPOSURE
- Interim sacrifices: Five male and five female rats from each group were sacrificed 2, 4 and 6 week after commencement of exposure (exceptions: In the 119 ppm group only 8 animals were necropsied after 6 weeks; in the 198 ppm group no animals were necropsied after 4 and after 6 weeks each)
- Determination of chamber concentration:
A calibration curve relating concentration to the absorption at this wavelength was prepared (Calibration was carried out with dry air). One to two samples were taken daily from each exposure chamber. The exposure concentration was calculated by comparing the infrared absorption of the sample to the standard curve.
- Vehicle: nitrogen
CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs: observed daily; full recorded physical assessment was performed weekly
- Mortality: observed daily
- Body weight: weekly during exposure and post-exposure period
- Organ weight: brain, gonads (ovary or testicle paired), heart, kidneys (right and left separately), liver, lungs, pituitary, spleen
- Food consumption: no
- Water consumption: no
- Ophthalmoscopic examination: every two weeks (in a pre-exposure ophthalmoscopic examination those animals were discarded from study who showed ocular abnomalities)
- Haematology: once in week 4; parameter evaluated: hemoglobin, hematocrit, erythrocyte count, leukocyte count (total and differential), clotting time
- Biochemistry: once in week 4; parameter evaluated: blood urea nitrogen, serum glutamic pyruvic transaminase, serum alkaline phosphatase, glucose
- Urinalysis: once in week 4; parameter evaluated: appearance, specific gravity, occult blood, pH, protein, bilirubin, ketones, glucose
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
- macroscopic: yes; all animals died during study or killed

in extremis and at scheduled sacrifice respectively
- microscopic: tissues fixed and exposed to histopathology according to OECD guideline 407
OTHER EXAMINATION: The reversibility of cataract formation was studied in detail
STATISTICAL METHODS: Body weights, hematology, clinical chemistry paramethers, organ weights, and organ/body weight ratios were statistically evaluated; References: Snedecor, G.W. and Cochran, W.G., Statistical Methods, 6th Edition, Iowa State Univ. Press (1967), Hollander and Wolfe, Nonparametric Statistical Methods, John Wiley and Sons, New York (1973); Dunnett, C.W. J. Am. Sta. Assn., Vol. 50 (1955), Biometrics, Vol. 20 (1964)

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

Flag: Critical study for SIDS endpoint

10-SEP-2004 (67)

Type: Sub-acute
Species: rat Sex: male/female
Strain: other: F344/N
Route of administration: gavage
Exposure period: 15 days
Frequency of treatment: daily
Post exposure period: no
Doses: 250, 500, 1000, 2000, 3000 mg/kg bw/day
Control Group: yes, concurrent vehicle
NOAEL: = 250 mg/kg bw

Method: other: dose-range finding for 13 week study
Year: 1978
GLP: no
Test substance: other TS: purity ca. 96%

Result: NOAEL is 250 mg/kg bw (mortality and clinical signs).
TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
- Mortality:
m: 500 mg/kg bw: 4/5 (day 8-11), >= 1000 mg/kg bw: 5/5(day 2-6, dose-related)
f: 500 mg/kg bw: 2/5 (day 13), >= 1000 mg/kg bw: 5/5 (day 1-7, dose-related)

>= 500 mg/kg bw, m and f
Mortality:
- increased mortality
Clinical signs
- inactive after dosing

Test condition: TEST ORGANISMS
- Age: 43 days
- Weight at study initiation: m: 115-130 g, f: 91-95 g
- Number of animals/dose group: 5
ADMINISTRATION / EXPOSURE
- Vehicle: corn oil; 3000 mg/kg bw was applied undiluted
- Total volume applied: 2.5 ml/kg bw
CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs: yes (limited)
- Mortality: yes (observed twice per day)
- Body weight: no (only initial weight)

- Organ weight: no
- Food consumption: no
- Water consumption: no
- Ophthalmoscopic examination: no
- Haematology: no
- Biochemistry: no
- Urinalysis: no

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC): Necropsies performed on all animals. No histopathologic examinations were performed on rats.

Reliability: (2) valid with restrictions
Study well documented, meets generally accepted scientific standard, acceptable for assessment. Restrictions: No histopathological examination, no organ weight determination.

14-APR-2003 (74)

Type: Sub-acute
Species: rat Sex: male
Strain: other: F344/N
Route of administration: gavage
Exposure period: 4-6 weeks
Frequency of treatment: 5 days/week
Post exposure period: up to 2 weeks
Doses: 200 mg/kg bw
Control Group: yes, concurrent vehicle

Method: other
Year: 1988
GLP: no data
Test substance: other TS: no further specified

Remark: Study was performed after NTP-study (1985) in order to investigate the biochemical systems in target and non-target organs (target organs: forestomach and lung).

Result: NOAEL (NOEL), LOAEL (LOEL): not derivable
TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
Forestomach:
- significant increase in forestomach weight in treated rats (after 1 week recovery organ weights were comparable to controls)
- thickening of mucosa, epithelial hyperplasia, hyperkeratosis, subepithelial inflammation and edema (4/5 treated rats)
- significant increase in the level of nonprotein sulfhydryls in treated rats
- significantly reduced carboxylesterase activity in treated rats

Lung
- significantly reduced carboxylesterase activity in treated rats
- angiotensin converting enzyme: significant increase in the activity of the enzyme (after 1 or 2 week recovery: activity level returned to near control values)

No treatment related effect on the microsomal p-nitroanisole

demethylase, soluble glutathione-S-transferase, soluble superoxide dismutase and cytochrome P450 levels

Conclusion: Signs of forestomach toxicity could be detected. Biochemical changes in lung were observed.

Test condition: TEST ORGANISMS
- Weight at study initiation: 200-220 g
- Number of animals: 18
ADMINISTRATION / EXPOSURE
- Vehicle: corn oil
CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs: no
- Mortality: no
- Body weight: yes (recorded weekly)
- Organ weight: yes (liver, lungs, kidneys, glandular stomach, forestomach)
- Food consumption: no
- Water consumption: no
- Ophthalmoscopic examination: no
- Haematology: yes
- Biochemistry: yes (angiotensin converting enzyme measurements- as a possible biomarker for lung injury, determination of nonprotein soluble sulfhydryls, microsomal p-nitroanisomle demethylase, carboxylesterase, soluble glutathione-S-transferase and soluble superoxide-dismutase in liver, lung, kidney, forestomach, glandular stomach; microsomal cytochrome P450 in liver and kidney)
- Urinalysis: no
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
Pathology examination of livers, lungs, kidneys, forestomach and glandular stomach
OTHER EXAMINATION:
In a second experiment 4 groups of rats (each 5 animals) were treated mit DMP for 4 and 5 weeks respectively and for 4 weeks with a 1 and 2 week respecitively recovery period.

Reliability: (2) valid with restrictions
Study well documented, meets generally accepted scientific standard, acceptable for assessment. Restriction: Pathology and organ weight determination of only selected organs.

Flag: Critical study for SIDS endpoint

02-APR-2003 (77) (80)

Type: Sub-chronic
Species: rat Sex: male/female
Strain: other: F344/N
Route of administration: gavage
Exposure period: 13 weeks
Frequency of treatment: 5 days/week
Post exposure period: 2-3 days
Doses: 25, 50, 100, 200, 400 mg/kg bw/day
Control Group: yes, concurrent vehicle
NOAEL: = 200 mg/kg bw
NOAEL female rat (reduced body weight gain) :
= 100 mg/kg bw

Method: other
Year: 1979
GLP: no

Test substance: other TS: purity ca. 96%

Result: NOAEL is 200 mg/kg bw m and 100 mg/kg bw f (body weight gain)

TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
- Mortality:
100 mg/kg bw, f: 2/10*
200 mg/kg bw, m: 1/10*; f: 2/10*
400 mg/kg bw, m: 9/10; f: 8/10

* 3/5 deaths may be due to gavage accidents

200 mg/kg bw f:
Body weight:
- decreased body weight gain (13.5% at study end)

400 mg/kg bw:
Mortality, m and f:
- increased mortality
Body weight m and f:
- decreased body weight gain
Eyes m and f:
- m and f: degeneration of the lens
- f: acute diffused inflammation of the cornea
Lung:
- m and f: chronic inflammation diffuse: m: 3/10, 0/10, 0/10, 5/10; f: 2/10, 0/10, 1/10, 6/10
- m: congestion 0/10, 0/10, 1/10, 4/10
- m: histiocytosis 0/10, 0/10, 0/10, 5/10
Urinary bladder, m:
- urinary bladder calculi
Effects are possibly due to infection (viral infections found in control animals)

Test condition: TEST ORGANISMS
- Age: 6-7 weeks
- Weight at study initiation: m: 184-194 g, f: 135-138 g
- Number of animals/dose group: 10
ADMINISTRATION / EXPOSURE
- Vehicle: corn oil
- Total volume applied: 3.33 ml/kg
CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs: yes (observed twice per day)
- Mortality: yes (observed twice per day)
- Body weight: yes (initial and final)
- Organ weight: no
- Food consumption: no
- Water consumption: no
- Haematology: no
- Biochemistry: no
- Urinalysis: no
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
Necropsy performed on all animals; microscopic examination in control and in 400 mg/kg bw group (Organs see OECD guideline 408). Eyes of control and of 200 mg/kg bw groups examined

Reliability: (2) valid with restrictions
Study well documented, meets generally accepted scientific

standard, acceptable for assessment. Restrictions: No organ weight determination, no haematological/biochemical examinations, no data on statistics.
Flag: Critical study for SIDS endpoint
03-AUG-2005 (74)

Type: Chronic
Species: rat Sex: male/female
Strain: Fischer 344
Route of administration: gavage
Exposure period: 2 years
Frequency of treatment: 5 days/week
Post exposure period: 10-13 days
Doses: 100, 200 mg/kg bw/day male rats; 50, 100 mg/kg bw/day female rat
Control Group: yes, concurrent vehicle
NOAEL: < 100 mg/kg bw
NOAEL (female rats) : = 50 mg/kg bw

Method: other: comparable to OECD guideline 451
Year: 1982
GLP: no data
Test substance: other TS: purity ca. 98%

Result: NOAEL is 50 mg/kg bw for female rat (forestomach changes) and < 100 mg/kg bw for male rats (respiratory tract)
TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
>= 100 mg/kg bw m (control, low dose, high dose):
Body weight:
- marginal decreased body weight gain (4-5% lower than controls)
Hematopoietic System
- Mononuclear cell leukemia (9/50, 15/50*, 13/50)
Respiratory tract:
- Interstitial pneumonia in animals that died early (0/10, 4/19, 18/24)

>= 200 mg/kg bw m:
Body weight:
- decreased body weight gain
Eye:
- Cataracts (25/50, 19/50, 36/50)
Cerebellum:
- focal mineralization in the granular layer of the cerebellum (0/50, 0/50, 12/49)
Lung:
- Squamous cell carcinoma: 0/50, 0/50, 5/50*
- Alveolar/bronchiolar adenoma or carcinoma: 0/50, 1/50, 24/50* (dose-related)
Forestomach:
- Hyperkeratosis: 0/50, 1/50, 8/50*
- Hyperplasia: 8/50, 16/50, 32/50*
- Squamous cell carcinoma or papilloma: 0/50, 1/50, 6/50* (dose-related)

>= 100 mg/kg bw f:
Body weight:
- marginal decreased body weight gain (4-5% lower than

controls)
Lung:
- Alveolar/bronchiolar carcinoma: 0/50, 1/49, 3/50 (dose-related)
Forestomach:
- Hyperplasia: 4/50, 2/50, 14/50
- Squamous cell carcinoma or papilloma: 0/50, 0/50, 2/48

* statistically significant
Conclusions: Equivocal evidence of carcinogenicity in female rats was concluded (details see chapter 5.7).

Test condition: TEST ORGANISMS
- Age: 7 week
- Weight at study initiation: m: 139g, f: 111g
- Number of animals/dose group: 50 m, 50 f
ADMINISTRATION / EXPOSURE
- Vehicle: corn oil
- Total volume applied: 4.0 ml/kg
CLINICAL OBSERVATIONS AND FREQUENCY
- Body weight: yes (once per week)
- Food consumption: no
- Water consumption: no
- Clinical signs: yes
- Organ weight: no
- Mortality: yes (observed twice per day)
- Macroscopic examination: yes (see below)
- Haematology: no
- Clinical chemistry: no
- Urinalysis: no
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
Organs examined and necropsied according OECD guideline 451

Reliability: (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment. Carcinogenicity study: no clinical chemistry examinations.

Flag: Critical study for SIDS endpoint

14-APR-2003 (74)

Type: Sub-acute
Species: mouse Sex: male/female
Strain: B6C3F1
Route of administration: gavage
Exposure period: 15 days
Frequency of treatment: daily
Post exposure period: no
Doses: 250, 500, 1000, 2000, 3000 mg/kg bw/day
Control Group: yes, concurrent vehicle
NOAEL: < 250 mg/kg bw
LOAEL: = 250 mg/kg bw

Method: other: dose-range finding for 13 week study
Year: 1978
GLP: no
Test substance: other TS: purity ca. 96%

Result: NOAEL is < 250 mg/kg bw (stomach lesions).
TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
- Mortality and time to death:

m: >= 2000 mg/kg bw: 5/5 (day 1-7, dose-related)
f: 250 mg/kg bw, f: 1/5 death (day 7; not considered compound related by the authors), >= 2000 mg/kg bw, f: 5/5 deaths (day 2-9, dose-related)

>= 250 mg/kg bw m and f:
Stomach:
- several lesions (epithelial ulcerations, glandular stomach ulcerations, acute/chronic gastritis, squamous atrophy, hyperplastic gastropathy, hyperkeratosis, submucosal and intra-epithelial abscesses, massive necrosis, information taken from table)

>= 500 mg/kg bw m and f:
Body weight:
- body weight losses
Stomach:
- Slight irregular to irregular thickening or irregular nodules in the squamous
portion of the stomach (500, 1000 mg/kg bw: 3/10, 9/10)

>= 1000 mg/kg bw m and f:
Clinical signs:
- Inactivity

>= 2000 mg/kg bw m and f:
Mortality:
- Increased mortality

Test condition: TEST ORGANISMS
- Age: 6 weeks
- Weight at study initiation: m: 27 g, f: 21 g
- Number of animals/dose group: 5
ADMINISTRATION / EXPOSURE
- Vehicle: corn oil; 3000 mg/kg bw was applied undiluted
- Total volume applied: 10 ml/kg bw
CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs: yes (limited)
- Mortality: yes (observed twice per day)
- Body weight: yes (initial and final)
- Organ weight: no
- Food consumption: no
- Water consumption: no
- Ophthalmoscopic examination: no
- Haematology: no
- Biochemistry: no
- Urinalysis: no
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
Necropsies performed on all animals. Stomach lesions examined
microscopically. No further histopathological examinations.

Reliability: (2) valid with restrictions
Study well documented, meets generally accepted scientific standard, acceptable for assessment. Restriction: No organ weight determination, no histopathological examinations.

Flag: Critical study for SIDS endpoint
14-APR-2003 (74)

```
Type:                    Sub-chronic
Species:                 mouse                              Sex: male/female
Strain:                  B6C3F1
Route of administration: gavage
Exposure period:         13 weeks
Frequency of treatment:  5 days/week
Post exposure period:    3-4 days
Doses:                   95, 190, 375, 750, 1500 mg/kg/day
Control Group:           yes, concurrent vehicle
NOAEL:                   = 95 mg/kg bw

Method:           other
  Year:           1979
   GLP:           no
Test substance:   other TS: purity ca. 96%

Result:           NOAEL is 95 mg/kg bw (heart and liver changes).
                  TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
                  - Mortality and time to death:
                  m: 375 mg/kg bw: 2/10 (week 11, 12),
                     >= 750 mg/kg bw: 10/10 (week 1-4)
                  f: 375 mg/kg bw: 5/10 (week 5-12, dose-related),
                     >= 750 mg/kg bw: 10/10 (week 1-4)

                  >= 190 mg/kg bw:
                  Heart m:
                  - cardiac mineralization (minimal severity)
                  Liver f:
                  - hepatocellular vacuolization

                  >= 375 mg/kg bw:
                  Mortality, m and f:
                  - increased mortality
                  Clinical signs m and f:
                  - tremors and decreased activity
                  Liver m:
                  - hepatocellular vacuolization
                  Lung m and f:
                  - lung congestion
                  Testes m:
                  - testicular atrophy
Test condition:   TEST ORGANISMS
                  - Age: 6-8 weeks
                  - Weight at study initiation: m: 23-25 g, f: 18-19 g
                  - Number of animals/dose group: 10
                  ADMINISTRATION / EXPOSURE
                  - Vehicle: corn oil
                  - Total volume applied: 3.33 ml/kg
                  CLINICAL OBSERVATIONS AND FREQUENCY:
                  - Clinical signs: yes (observed 2xd)
                  - Mortality: yes (observed 2xd)
                  - Body weight: yes (initial and final)
                  - Organ weight: no
                  - Food consumption: no
                  - Water consumption: no
                  - Haematology: no
                  - Biochemistry: no
                  - Urinalysis: no
```

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC): Necropsy performed on all animals; microscopic examination of all but the 95 mg/kg w group (Organs see OECD guideline 408). Only heart, liver, and kidney examined for the 95 mg/kg bw group.

Reliability: (2) valid with restrictions
Study well documented, meets generally accepted scientific standard, acceptable for assessment. Restrictions: No organ weight determination, no haematological/biochemical examinations, no data on statistics.

Flag: Critical study for SIDS endpoint

25-MAR-2004 (74)

Type: Chronic
Species: mouse Sex: male/female
Strain: B6C3F1
Route of administration: gavage
Exposure period: 103 weeks
Frequency of treatment: 5 days/week
Post exposure period: 10-13 days
Doses: 100, 200 mg/kg bw
Control Group: yes, concurrent vehicle
NOAEL: < 100 mg/kg bw
NOAEL (female mice) : = 200 mg/kg bw

Method: other: comparable to OECD guideline 451
Year: 1982
GLP: no data
Test substance: other TS

Result: NOAEL is < 100 mg/kg bw for male mice (testis changes) and 200 mg/kg bw for females.
TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
>= 100 mg/kg bw m:
Testis
- Focal calcification (2/50, 9/47, 24/50)

>= 200 mg/kg bw, m:
Mortality:
- increased mortality
Body weight:
- lower body weights after week 28 (5-10% lower than controls)

100, 200 mg/kg bw f:
Liver
- fatty metamorphoses (0/50, 1/49, 4/50)
- Hepatocellular adenoma (0/50, 6/49*, 3/50)
- Hepatocellular adenoma or carcinoma (2/50, 6/49, 3/50)

*: statistically significant
No evidence of carcinogenicity was concluded.

Test condition: TEST ORGANISMS
- Age: 6-8 week
- Weight at study initiation: m: 23g, f: 19g
- Number of animals/dose group: 50 m, 50 f
ADMINISTRATION / EXPOSURE
- Vehicle: corn oil

- Total volume applied: 4.0 ml/kg
CLINICAL OBSERVATIONS AND FREQUENCY
- Body weight: yes (once per week)
- Food consumption: no
- Water consumption: no
- Clinical signs: yes
- Organ weight: no
- Mortality: yes (observed twice per day)
- Macroscopic examination: yes (see below)
- Haematology: no
- Clinical chemistry: no
- Urinalysis: no
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
Organs examined and necropsied according OECD guideline 451

Reliability: (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment. Carcinogenicity study: no clinical chemistry examinations.

Flag: Critical study for SIDS endpoint

14-APR-2003 (74)

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test
System of testing: S. typhimurium TA 98, 100, 1535, 1537 or TA 97
Concentration: no data
Cytotoxic Concentration: no data
Metabolic activation: with and without
Result: positive

Method: other: NTP standard protocol (according Ames et al 1975)
Year: 1986
GLP: no data
Test substance: other TS: purity: 97.8 %

Result: The mutagenicity of DMP was tested in two laboratories. In one lab (Case Western University) it was judged equivocal, in the other lab (EG&G Mason Research Institute, later Microbiological Associates) it was tested with a positive result in strain TA 100.

Zeiger (1987) define DMP as a mutagenic substance in Ames test based on the tests results published by Mortelmanns K. et al (1986) (positive Ames assay with TA 100)

Conclusion: Positive with TA 100, negative with TA 98, 1535, 1537 or 97

Test condition: Solvent: distilled water or DMSO
S-9 mix: Aroclor 1254-induced male Sprague Dawley rats
Positive controls: sodium azide (TA 1535 and TA 100), 4-nitro-o-phenylenediamine (TA 98), 9-aminoacridine (TA 97 and TA 1537), 2-aminoanthracene (all strains)

Reliability: (1) valid without restriction
Test procedure in accordance with national standard methods.

Flag: Critical study for SIDS endpoint

30-MAR-2004 (68) (110)

```
Type:                    Ames test
System of testing:       S. typhimurium TA 98, 100, 1535, 1537
Concentration:           100, 333, 1000, 3333, 10000 µg/plate
Cytotoxic Concentration: 10000 µg/plate
Metabolic activation:    with and without
Result:                  negative

Method:           other: according Ames et al. 1975
  Year:           1985
   GLP:           no data
Test substance:   other TS: purity: 96-98 %

Result:           The results of the Ames test with the strain TA 100 (with
                  metabolic activation, rat and without metabolic activation)
                  in detail:
                  with MA
                  Dose (µg/plate)/Revertants per plate
                  0/197
                  100/170
                  333/186
                  1000/189
                  3333/199
                  10000/224

                  without MA
                  Dose (µg/plate)/Revertants per plate
                  0/149
                  100/152
                  333/156
                  1000/151
                  3333/179
                  10000/168

                  Tests with all other strains with or without metabolic
                  activation were clearly negative.
Test condition:   S-9 mix: Aroclor 1254-induced Sprague-Dawley rat or Syrian
                  hamster liver.
Reliability:      (1)  valid without restriction
                  Test procedure in accordance with national standard methods.
Flag:             Critical study for SIDS endpoint
02-APR-2003                                                              (74)


Type:                    Ames test
System of testing:       S. typhimurium TA 98, 100, 1535, 1537 or TA 97
Concentration:           no data
Cytotoxic Concentration: no data
Metabolic activation:    with and without
Result:                  positive

Method:           other: NTP standard protocol (according Ames et al)
  Year:           1987
   GLP:           no data
Test substance:   other TS: not further specified

Result:           Positive results were only obtained in strain TA 100 (10000
                  µg/plate) with metabolic activation.
Test condition:   S-9 mix: Aroclor 1254-induced male Sprague Dawley rats
```

Reliability: (1) valid without restriction
Test procedure in accordance with national standard methods.
Flag: Critical study for SIDS endpoint
02-APR-2003 (26) (27) (29) (31) (101)

Type: Ames test
System of testing: S. typhimurium TA 98, 100, 1535, 1537
Concentration: orientating: 20, 100, 500, 2500, 12500 µg/plate 775, 1550, 3100, 6200, 12400 µg/plate
Cytotoxic Concentration: >= 6200 µg/plate weak strain-specific bacteriotoxic effect, but could be evaluated
Metabolic activation: with and without
Result: negative

Method: other: according Ames et al (1973) Proc.nat.Acad.Sci. 70, 2281-2285
Year: 1988
GLP: yes
Test substance: other TS: purity: 99.8%

Result: Tests with TA 100 and S-9 mix gave equivocal results. In a first assay the mutant counts were significantly increased. As in a second test the results could not be reproduced, they were regarded as a random result.

DMP caused no biologically relevant (parameters: dose effect, doubling) variation from the respective negative control.

Conclusion: No indications of mutagenic effects of DMP could be found.
Test condition: Positive controls: sodium azide (TA1535), nitrofurantoin (TA100), 4-nitro-1,2-phenylene diamine (TA 1537, TA98), 2-aminoanthracene (all strains with S-9 mix)
Reliability: (1) valid without restriction
Test procedure in accordance with national standard methods.
Flag: Critical study for SIDS endpoint
02-APR-2003 (9)

Type: Bacterial reverse mutation assay
System of testing: one strain of Photobacterium phosphoricum
Concentration: no data
Cytotoxic Concentration: no data
Metabolic activation: no data
Result: negative

Method: other
Year: 1990
GLP: no data
Test substance: other TS: purity: 97.8 %

Remark: 52 NTP Carcinogens were studied.
The sensitivity of the bioluminescence assay was 38.2% and the specificity was 38.9 %.
Test condition: SYSTEM OF TESTING
- Deficiences/Proficiences: presumably luminescence operon
- Metabolic activation system: rat liver microsomes induced by a poly-chlorinated diphenyl preparation (Chlophen-A50)

```
Reliability:      (4)  not assignable
                  No original data available.
14-APR-2003                                                    (35) (104) (105)

Type:                     Mouse lymphoma assay
System of testing:        L5178Y mouse lymphoma cells
Concentration:            no data
Cytotoxic Concentration: no data
Metabolic activation:     with and without
Result:                   positive

Method:            other: NTP standard protocol
  Year:            1987
   GLP:            no data
Test substance:    other TS: purity: 97.8 %

Result:            Mouse lymphoma assay was positive with metabolic activation
                   for concentration >= 1700 µg/ml.
Test condition:    S9-mix: Liver of Aroclor-1254 induced and noninduced Fischer
                   344 male rats
                   Criteria for positivity: significant response for at least 1
                   of the 3 highest dose sets and a significant trend;
                   replicate experiments are positive or questionable
                   experiments are reproducible.
Reliability:       (1)  valid without restriction
                   Test procedure in accordance with national standard methods.
Flag:              Critical study for SIDS endpoint
02-APR-2003                                    (26) (27) (29) (31) (70) (101)

Type:                     Mouse lymphoma assay
System of testing:        L5178Y mouse lymphoma cells
Concentration:            125, 250, 500, 1000, 2000 µg/ml (first trial without
                          S-9 mix), 600, 1000, 1400, 1800, 2200, 2600 µg/ml
                          (second trial, without S-9 mix); 1700, 1900, 2100,
                          2300, 2500 µg/ml (first and second trial with S-9 mix)
Cytotoxic Concentration: > 2200 µg/ml (without S-9 mix), > 2500 µg/ml (with S-9
                          mix)
Metabolic activation:     with and without
Result:                   positive

Method:            other: according Clive and Spector 1975 and Clive et al. 1979
  Year:            1988
   GLP:            no data
Test substance:    other TS: purity: 97.8 %

Result:            With S-9 mix:
                   pH decreasing: >= 1700 µg/ml.
                   Without S-9 mix:
                   pH decreasing: >= 500 µg/ml

                   Positive results were obtained only in the presence of S-9
                   mix at concentrations >= 2100 µg/ml
Test condition:    Solvent: culture medium without serum
                   Metabolic activation: Aroclor 1254 induced male Fischer 344
                   rat liver homogenates
                   Positive controls: methylmethanesulfonate (without S-9 mix)
                   3-methylcholanthrene (with S-9 mix)
                   Negative controls: Solvent
```

```
                Criteria for positive test result:
                - RTG values not smaller than 10 % (Cytotoxicity)
                - Mutant frequency more than two-fold compared to negative
                control
Reliability:    (1)  valid without restriction
                Test procedure in accordance with national standard methods.
Flag:           Critical study for SIDS endpoint
02-APR-2003                                                    (62) (63) (75)

Type:                   Chromosomal aberration test
System of testing:      Chinese hamster ovary cells
Concentration:          without S-9 mix: 50, 160, 500, 1600 µg/ml (second
                        trial: 500, 1000, 1600 µg/ml); with S-9 mix: 16, 50,
                        160, 500, 1600 µg/ml (second trial: 1600, 3000, 4000,
                        5000 µg/ml)
Cytotoxic Concentration: >= 5000 µg/ml
Metabolic activation:   with and without
Result:                 positive

Method:         other: NTP standard protocol (Galloway S.M. et al, 1985)
  Year:         1987
   GLP:         no data
Test substance: other TS: purity 97.8 %

Result:         DMP induced chromosomal aberration in CHO cells in
                concentrations >= 1600 µg/ml with and without metabolic
                activation.
                The result was positive without metabolic activation system
                and weak positive with S9-mix.
Test condition: Solvent: serum-free culture medium
                S-9 mix: Aroclor 1254-induced male Sprague Dawley rats
                Analysis: 100 or 200 cells were scored for each dose (cells
                with chromosome number lower than 19 or higher than 23 were
                excluded)
Reliability:    (1)  valid without restriction
                Test procedure in accordance with national standard methods.
Flag:           Critical study for SIDS endpoint
02-APR-2003                              (26) (27) (29) (31) (36) (39) (101)

Type:                   Chromosomal aberration test
System of testing:      chinese hamster ovary cells
Metabolic activation:   no data
Result:                 ambiguous

Method:         other
  Year:         1984
   GLP:         no data
Test substance: no data

Reliability:    (4)  not assignable
                No original data available.
16-AUG-2002                                                          (75)

Type:                   Unscheduled DNA synthesis
System of testing:      primary rat hepatocytes, Arochlor 1254-pretreated
Concentration:          0.010, 0.025, 0.050, 0.100, 0.250, 0.500, 1.000, 2.500,
                        5.000 µg/ml
Cytotoxic Concentration: 5.0 µg/ml
```

```
Metabolic activation:    without
Result:                  positive

Method:           Guidelines for screening mutagenicity testing of chemicals,
                  JAPAN
  Year:           1990
   GLP:           no data
Test substance:   other TS: not further specified

Result:           concentration (µg/ml) / NNG (netto-nuclear grain) (% IR)
                  0.01 / 1.60* (61)
                  0.025 / 1.64* (62)
                  0.05 / 3.16* (67)
                  0.1 / 4.22* (74)
                  0.25 / 3.21* (66)
                  0.5 / 5.14* (74)
                  1.0 / 5.29* (75)
                  2.5 / 5.98* (77)

                  DMSO / -3.60 (8)
                  2-AAF 19.69 (100)

                  IR (in repair): percentage of cells with three NNGs above
                  the solvent control
                  * evaluated as positive
Test condition:   Induction: i.p., 500 mg/kg bw (1 day prior to sacrifice)
                  Positive control: 2-AAF
                  Negative control: Solvent (DMSO)
                  Evaluation criteria: 50 viable cells/slide; response is
                  evaluated positive, if the NNG (Netto Nuclear Grains) count
                  is three NNGs higher than the solvent control for the same
                  animal.
Reliability:      (2)  valid with restrictions
                  Test procedure in accordance with national standard methods.
                  Limited documentation.
Flag:             Critical study for SIDS endpoint
14-APR-2003                                                              (97)

Type:                    Unscheduled DNA synthesis
System of testing:       primary rat hepatocytes, 3-methylcholanthrene
                         pretreated
Concentration:           0.010, 0.025, 0.050, 0.100, 0.250, 0.500, 1.000, 2.500,
                         5.000 µg/ml
Cytotoxic Concentration: >= 1.0 µg/ml
Metabolic activation:    without
Result:                  positive

Method:           Guidelines for screening mutagenicity testing of chemicals,
                  JAPAN
  Year:           1990
   GLP:           no data
Test substance:   other TS: not further specified

Result:           concentration (µg/ml) / NNG (% IR)
                  0.01 / 1.35 (20)
                  0.025 / 3.21* (66)
                  0.05 / 3.42* (68)
                  0.1 / 3.88* (67)
```

0.25 / 3.24* (59)
0.5 / 0.99 (13)

DMSO / -1.24 (4)
2-AAF / 9.70 (100)

IR (in repair): percentage of cells with three NNGs above the solvent control
* evaluated as positive

Test condition: Induction: i.p., 80 mg/kg bw (1 day prior to sacrifice)
Positive control: 2-AAF
Negative control: Solvent (DMSO)
Evaluation criteria: 50 viable cells/slide; response is evaluated positive, if the NNG (Netto Nuclear Grains) count is three NNGs higher than the solvent control for the same animal.

Reliability: (2) valid with restrictions
Test procedure in accordance with national standard methods. Limited documentation.

Flag: Critical study for SIDS endpoint

03-APR-2003 (97)

Type: Unscheduled DNA synthesis
System of testing: primary rat hepatocytes, untreated
Concentration: 0.010, 0.025, 0.050, 0.100, 0.250, 0.500, 1.000, 2.500, 5.000 µg/ml
Cytotoxic Concentration: >= 2.5 µg/ml
Metabolic activation: without
Result: negative

Method: Guidelines for screening mutagenicity testing of chemicals, JAPAN
Year: 1990
GLP: no data
Test substance: other TS: not further specified

Result: concentration (µg/ml) / NNG (% IR)
0.01 / -1.62 (22)
0.025 / -1.18 (11)
0.05 / -1.76 (15)
0.1 / -1.41 (14)
0.25 / -0.82 (21)
0.5 / -2.71 (3)
1.0 / -2.16 (3)

DMSO / -2.01 (4)
2-AAF / 9.75 (100)

IR (in repair): percentage of cells with three NNGs above the solvent control

Test condition: Positive control: 2-AAF
Negative control: Solvent (DMSO)
Evaluation criteria: 50 viable cells/slide; response is evaluated positive, if the NNG (Netto Nuclear Grains) count is three NNGs higher than the solvent control for the same animal.

Reliability: (2) valid with restrictions

```
                Test procedure in accordance with national standard methods.
                Limited documentation.
Flag:           Critical study for SIDS endpoint
03-APR-2003                                                          (97)

Type:                   Unscheduled DNA synthesis
System of testing:      primary rat hepatocytes
Concentration:          no data
Cytotoxic Concentration: no data
Metabolic activation:   without
Result:                 negative

Method:         other
  Year:         1987
   GLP:         no data
Test substance: other TS: no further specified

Result:         DMP was tested among 13 other rodent carcinogens. 13 of them
                induced liver tumours, but only three of the carcinogens
                were positive in in vitro UDS assay.
Reliability:    (2)  valid with restrictions
                Test procedure in accordance with national standards.
                Limited documentation.
Flag:           Critical study for SIDS endpoint
29-AUG-2005                                                  (65) (102)

Type:                   Sister chromatid exchange assay
System of testing:      chinese hamster ovary cells
Concentration:          without S-9 mix: 5, 16, 50, 160, 500 µg/ml (second
                        trial: 250, 500, 1000, 1600 µg/ml) with S-9 mix: 16,
                        50, 160, 500, 1600 µg/ml (second trial: 250, 500, 1000,
                        1600, 3000, 4000 µg/ml)
Cytotoxic Concentration: >= 5000 µg/ml (taken from CAB assay)
Metabolic activation:   with and without
Result:                 positive

Method:         other: NTP standard protocol (Galloway S.M. et al., 1985)
  Year:         1987
   GLP:         no data
Test substance: other TS: purity 97.8 %

Result:         DMP caused increased total SCE numbers in cells as well as
                an increase in number SCE/cell with and without metabolic
                activation in concentrations >= 250 µg/ml.
Test condition: Solvent: serum-free culture medium
                S-9 mix: Aroclor 1254-induced male Sprague Dawley rats
                Analysis: Fifty second-division metaphase cells were
                scored/dose (cells with chromosome number lower than 19 or
                higher than 23 were excluded)
Reliability:    (1)  valid without restriction
                Test procedure in accordance with national standard methods.
Flag:           Critical study for SIDS endpoint
02-APR-2003                          (26) (27) (29) (31) (36) (39) (75) (101)

Type:                   other: re-evaluation of  false positive Ames tests

  Year:         1989
Test substance: no data
```

Remark: New criteria were chosen to prevent the high proportion of false positive findings in the AMES-Test as compared to carcinogenicity bioassays.
Doses higher tahn 500 µg/plate were excluded because such high doses could well lead to positive results due to impurities in the test substance that would prove ineffective in the bioassay.
Result: Under the criteria of this test dimethyl hydrogen phosphite is non-mutagenic in S. typhimurium assay.
Test condition: Criteria used in reevaluation of S.typhimurium mutagenicity data published by Tennant et al, Science 1987:
- a response of >= 3x over the spontaneous count at any dose of <= 500 µg/plate is a positive response if the increase is >= 20 colonies per plate.
- a response of >= 2x over the spontaneous count at any dose of <= 100 µg/plate is a positive response if the increase is >= 20 colonies per plate
- Any responses seen at doses of > 500 µg are disregarded in this reevaluation
- Conflicting results from different experiments, different laboratories, or different studies are evaluated overall as positive if at least half of the experiments, laboratories, or studies had a positive response.
Reliability: (2) valid with restrictions
Study well documented, meets generally accepted scientific standard, acceptable for assessment.
30-MAR-2004 (88)

5.6 Genetic Toxicity 'in Vivo'

Type: Drosophila SLRL test
Species: Drosophila melanogaster Sex: male
Route of admin.: oral feed
Exposure period: 3 days
Doses: 650 ppm
Result: negative

Method: other: according Abrahamson and Lewis (1971) cited in Hollaender, A. ed: Chemical Mutagens: Principles and Methods for Their Detection, Vol. 2, New York, Plenum Press, 461-487
Year: 1985
GLP: no data
Test substance: other TS: purity: 97.8 %

Test condition: vehicle: 5 % sucrose in water
Age of males: 1 day
Age of males at mating: 4 days (immediately after feeding)
Mating procedure: males were mated to 3 Basc females for 3 d and given fresh females at 2-d intervals - 3 broods are produced.
Reliability: (1) valid without restriction
Test procedure in accordance with national standard methods.
Flag: Critical study for SIDS endpoint
02-APR-2003 (74) (109)

Type: Drosophila SLRL test

Species: Drosophila melanogaster Sex: male
Route of admin.: other: injection to the abdomen
Exposure period: single injection
Doses: 1500 ppm
Result: negative

Method: other: according Abrahamson and Lewis (1971) cited in Hollaender, A. ed: Chemical Mutagens: Principles and Methods for Their Detection, Vol. 2, New York, Plenum Press, 461-487
Year: 1985
GLP: no data
Test substance: other TS: purity: 97.8 %

Test condition: vehicle: 0.7 % sodium chloride
Age of males: 72 hours
Age of males at mating: 96 hours (24 hours recovering after injection)
Mating procedure: males were mated to 3 Basc females for 3 d and given fresh females at 2-d intervals - 3 broods are produced.
Reliability: (1) valid without restriction
Test procedure in accordance with national standard methods.
Flag: Critical study for SIDS endpoint
02-APR-2003 (74) (109)

Type: Micronucleus assay
Species: mouse Sex: male/female
Strain: NMRI
Route of admin.: i.p.
Exposure period: 16, 24 and 48 hours after single administration
Doses: 2000 mg/kg bw
Result: negative

Method: OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"
Year: 1994
GLP: yes
Test substance: other TS: purity: 99.2 %

Remark: According to the study author, there was no biologically relevant or statistically significant variation between negative controls and DMP treated groups.
There was, however, a statistically non-significant doubling of micro-nucleated PCEs after 48 hours (negative controls 1.3 ± 1.1, 16h 0.8 ± 1.1, 24h 1.8 ± 1.5, 48 h 2.7 ± 3.1). Although statistically significant, the values for the positive control group (cyclophosphamide, 20 mg/kg bw i.p.) were unusually low (7.3 ± 5.5 as compared to the laboratory`s historical positive control range of 10.2 - 25.1). It is therefore not certain, whether this test was sufficiently sensitive
Result: Compound-related symptoms: apathy, roughened fur, staggering gait, difficulty in breathing (all symptoms were noted until sacrifice); all animals survived until the end of the study. No symptoms were recorded in the control group

Cytotoxicity:
ratio of polychromatic to normochromatic erythrocytes

negative control: 1000/842 / 54 %
DMP, 16 h: 1000/1066 / 48 %
DMP, 24 h: 1000/1250 / 44 %
DMP, 48 h: 1000/1559 / 39 %
positive control: 1000/963 / 51 % (cyclophosphamide)

Time-dependent alteration caused by DMP; Cyclophosphamide had no effect on the ratio of polychromatic to normochromatic erythrocytes

Micronucleated PCEs per 1000 PCE scored:
negative control: 1.3 +/-1.1
DMP, 16 h: 0.8 +/-1.1
DMP, 24 h: 1.8 +/-1.5
DMP, 48 h: 2.7 +/-3.1
positive control: 7.3 +/-5.5 (cyclophosphamide; stat. significant to <0.01)
Range of historical laboratory controls for micronucleated PCE per 1000 PCE scored:
Physiologic saline: 1.3 to 2.6
Positive controls : 10.2 to 25.1 (cyclophosphamide, 20 mg/kg bw, i.p.)

Test condition: ANIMALS: 5 male, 5 female animals per dose group;
CELL TYPE: femur bone-marrow cells; smears were prepared according to Schmid's method and were stained with an Ames Hema-Tek Slide Stainer. At least one intact femur was prepared from each sacrificed animal (not pretreated with a spindle inhibitor)

EVALUATION: 1000 polychromatic erythrocytes were counted per animal and the number of normochromatic erythrocytes per 1000 polychromatic erythrocytes was noted. In addition the number of polychromatic cells with micronuclei and the number of normochromatic erythrocytes with micronuclei was determined.

ADMINISTRATION:
- No. of dosed groups and time of sacrifice: 4 dosed groups; sacrifice after 16, 24, 48 hours, replacement group
- Positive and negative control groups and treatment:
negative control vehicle (physiologic saline): i.p.; sacrifice after 24 h
positive control cyclophosphamide: 20 mg/kg bw, i.p.; sacrifice after 24h

CRITERIA FOR EVALUATING RESULTS: A test is judged positive if a biological relevant and significant increase in the number of polychromatic erythrocytes showing micronuclei is observed. A test was also considered negative if there was a significant increase in that rate which, according to the laboratories experience, was within the range of negative controls.

STATISTICS:
Significance was determined by Wilcoxon's non parametric rank sum test. Variation was considered significant at an error probaility of <5%

Reliability: (2) valid with restrictions

positive controls outside laboratory historical control range;
Flag: Critical study for SIDS endpoint
01-DEC-2003 (12)

Type: Micronucleus assay
Species: mouse Sex: male
Strain: B6C3F1
Route of admin.: i.p.
Exposure period: three consecutive days (one injection/day)
Doses: 250, 500 mg/kg bw/d
Result: ambiguous

Method: other
Year: 1993
GLP: no data
Test substance: other TS: purity: 97.8 %

Remark: Only 5 of the 25 NTP rodent carcinogens are tested positive in the micronucleus assay by Shelby et al.. The positive reactions were weak and at relatively high dose levels.
Result: Micronucleated PCEs* per 1000 PCEs scored /first trial /snd trial
0 mg/kg / 2.10 / 2.70
250 mg/kg / 1.10 / 2.20
500 mg/kg / 6.10* / 4.17
Positive Control DMBA / mean mn PCE: 6.93 +/- 2.59
Positive Control MMC / mean mn PCE: 6.82 +/- 1.24
Solvent Control / 2.10

Cytotoxicity
% of PCEs (No. of PCE/No. of PCE + No. of NCE) / first trial / snd trial
0 mg/kg / 29.5 / 50.3
250 mg/kg / 42.8 / 41.7
500 mg/kg / 30.6 / 19.7

*: statistically significant
PCE - polychromatic erythrocytes

The trend analysis of the repeat test gave P=0.078. Chemical was judged positive by the authors of the study, although the results were not fully reproducible.
Test condition: Time of death: 48 hours after last treatment
Solvent: PBS
Negative Control: Solvent
Positive Control: 7,12-dimethylbenzanthracene - DMBA (12,5 mg/kg), mitomycin C - MMC (0,2 mg/kg)
Time of deaths: 24 hours after last injection
Evaluating criteria: Statistical significant increase in micronucleated PCEs.
Reliability: (2) valid with restrictions
Test procedure in accordance with national standard methods.
Restrictions: variations in the dose groups; missing reproducibility
Flag: Critical study for SIDS endpoint
08-OCT-2003 (98) (103)

5.7 Carcinogenicity

Species: rat Sex: male/female
Strain: other: F344/N
Route of administration: gavage
Exposure period: 103 weeks
Frequency of treatment: 5 days/week
Post exposure period: 10-13 days
Doses: 100, 200 mg/kg bw/day male rats; 50, 100 mg/kg bw/day female rat
Result: positive
Control Group: yes

Method: other: comparable to OECD guideline 451
Year: 1982
GLP: no data
Test substance: other TS: purity ca. 98%

Result: MORTALITY AND TIME TO DEATH: 200 mg/kg bw, m: significantly lower survival
BODY WEIGHT GAIN: 200 mg/kg bw, m: decreased body weight gain
GROSS PATHOLOGY and HISTOPATHOLOGY:
>= 100 mg/kg bw m (control, low dose, high dose):
Hematopoietic System
- Mononuclear cell leukemia (9/50, 15/50*, 13/50)

>= 200 mg/kg bw m:
Body weight:
- decreased body weight gain
Lung:
- Squamous cell carcinoma: 0/50, 0/50, 5/50*
- Alveolar/bronchiolar adenoma or carcinoma: 0/50, 1/50, 24/50* (dose-related)
Forestomach:
- Hyperkeratosis: 0/50, 1/50, 8/50*
- Hyperplasia: 8/50, 16/50, 32/50*
- Squamous cell carcinoma or papilloma: 0/50, 1/50, 6/50* (dose-related)

>= 100 mg/kg bw f:
Lung:
- Alveolar/bronchiolar carcinoma: 0/50, 1/49, 3/50 (dose-related)
Forestomach:
- Hyperplasia: 4/50, 2/50, 14/50
- Squamous cell carcinoma or papilloma: 0/50, 0/50, 2/48
>= 200 mg/kg bw m

OTHER:
TIME TO TUMOURS: 200 mg/kg bw, m: 10/24, that died early had lung tumors.
*: statistically significant
CONCLUSION: Clear evidence of carcinogenicity in male rats and equivocal evidence of carcinogenicity in female rats.
Test condition: TEST ORGANISMS
- Age: 7 week

- Weight at study initiation: m: 139g, f: 111g
- Number of animals/dose group: 50 m, 50 f
ADMINISTRATION / EXPOSURE
- Vehicle: corn oil
- Total volume applied: 4.0 ml/kg
CLINICAL OBSERVATIONS AND FREQUENCY
- Body weight: yes (once per week)
- Food consumption: no
- Water consumption: no
- Clinical signs: yes
- Organ weight: no
- Mortality: yes (observed 2xd)
- Haematology: no
- Clinical chemistry: no
- Urinalysis: no
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
Organs examined and necropsied according OECD guideline 451

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

Flag: Critical study for SIDS endpoint

14-APR-2003 (34) (40) (42) (45) (74) (81)

Species: mouse Sex: male/female
Strain: B6C3F1
Route of administration: gavage
Exposure period: 103 weeks
Frequency of treatment: 5 days/week
Post exposure period: no
Doses: 100, 200 mg/kg bw/day
Result: negative
Control Group: yes

Method: other: comparable to OECD guideline 451
Year: 1982
GLP: no data
Test substance: other TS: purity ca. 98%

Result: MORTALITY AND TIME TO DEATH (control, 100, 200 mg/kg bw):
significantly lower survival: m: 7/50, 8/50, 18/50; f: 11/50, 8/50, 15/50
>= 200 mg/kg bw m
Body weight:
- lower body weight after week 28

100, 200 mg/kg bw f:
Liver
- Hepatocellular adenoma (0/50, 6/49*, 3/50)
- Hepatocellular adenoma or carcinoma (2/50, 6/49, 3/50)

*: statistically significant
CONCLUSION: No evidence of carcinogenicity was concluded.

Test condition: TEST ORGANISMS
- Age: 6-8 week
- Weight at study initiation: m: 23g, f: 19g
- Number of animals/dose group: 50 m, 50 f
ADMINISTRATION / EXPOSURE
- Vehicle: corn oil

- Total volume applied: 4.0 ml/kg
CLINICAL OBSERVATIONS AND FREQUENCY
- Body weight: yes (once per week)
- Food consumption: no
- Water consumption: no
- Clinical signs: yes
- Organ weight: no
- Mortality: yes (observed 2xd)
- Haematology: no
- Clinical chemistry: no
- Urinalysis: no
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
Organs examined and necropsied according OECD guideline 451

Reliability: (1) valid without restriction
Comparable to guideline study.
Flag: Critical study for SIDS endpoint
02-APR-2003 (34) (40) (42) (45) (74) (81)

Species: rat Sex: male/female
Strain: Wistar
Route of administration: s.c.
Exposure period: 728 d
Frequency of treatment: up to once per week
Post exposure period: yes, until natural death
Doses: 100 to 150 mg/kg bw/dose, total dose 7550 mg/kg bw
Result: negative
Control Group: yes

Method: other: orientating carcinogenesis study
Year: 1975
GLP: no
Test substance: other TS: purity ca. 98%

Result: MORTALITY AND TIME TO DEATH (days): exposed m: 867, control m: 762, exposed f: 785, control f: 787
Body weight: no changes
HISTOPATHOLOGY:
no. of animals with malign tumors (control, exposed):
m: 7/25, 3/25 (subcutanous, injection site, lung)
f: 7/25, 4/25 (leucemia, uterus, intraperitoneal)
Hypophyse tumors (control, exposed):
m: 2/25, 2/25
f: 6/25, 10/25
Other: no focal necroses
Conclusions: No substance-related change in mortality; no increased malign tumor incidence; number of benign tumors and of hypophyse tumors (questionable nature) is higher in exposed rats compared to control. No signs of carcinogenicity
Test condition: TEST ORGANISMS
- Age: 100 days
- Weight at study initiation: no data
- Number of animals: 25 m, 25 f
- Controls: 25 m, 25 f treated with peanut oil (total dosis: 60 ml/kg bw)
APPLICATION
Area of injection: middle of the back
Numbers of injections:

chronological order: 24 injections with 100 mg/kg bw, 12 injections with 150 mg/kg bw, 1 injection with 100 mg/kg bw, 2 injection with 150 mg/kg bw, 19 injections with 100 mg/kg bw and 6 injections with 150 mg/kg bw.
FOR Subcutanous STUDIES:
- Vehicle: peanut oil
- Total volume applied: 1 ml/kg bw
CLINICAL OBSERVATIONS AND FREQUENCY
- Body weight: yes (no detailed data)
- Food consumption: no
- Water consumption: no
- Clinical signs: no
- Organ weights: no
- Mortality: yes
- Ophthalmoscopic examination: no
- Haematology: no
- Clinical chemistry: no
- Urinalysis: no
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
All animals were accurately dissected. The tumors and the tissues suspected to have tumors were histopathologically examined.

Reliability: (3) invalid
Study was conducted as an orientating investigation.
Restrictions: Dosages are not reproducible, no macroscopic and no fully histopathological examinations.

09-SEP-2002 (7)

Species: other: Cell-transformation in vitro Sex:
Strain: other: Balb /c3t3

Result: DMP is classified as a non-cytotoxic chemical.
Significant transformation response was detected at treatment doses that exceeded the upper dose limit of the assay.
Therefore DMP was classified as a false-positive by the authors.

Test condition: A malign transformation assay with BALB/c-3T3 cells was performed.

Upper-dose-limit of the assay:
100 milli osmolar

Technical problems:
stock solutions of DMP had to be neutralized with NaOH due to high acidity of substance - substance may have been altered during testing period.

Reliability: (3) invalid
Invalid test system. The treatment doses exceeded the upper dose limit of the assay, after addition of NaOH to DMP, substance may have been degraded.

08-OCT-2003 (60)

5.8.1 Toxicity to Fertility

5.8.2 Developmental Toxicity/Teratogenicity

Species: other: Studies are described under chapter 5.8.3 Sex:

14-APR-2003

5.8.3 Toxicity to Reproduction, Other Studies

Type: other: Reproduction/Developmental Toxicity Screening Test
In Vitro/in vivo: In vivo
Species: rat
Strain: Wistar Sex: male/female
Route of administration: gavage
Exposure period: Females: 2 weeks before mating, during mating, gestation and lactation period (d 4 or 5 p.p.), males: during mating
Frequency of treatment: daily
Duration of test: Females: about 8 weeks; males: at least 28 days
Doses: 30, 90, 270 mg/kg bw/d
Control Group: yes, concurrent vehicle
Result: 270 mg/kg bw: increased mortality, increased relative testis and absolute epididymides weights, reduced frequency and severity score of "large corpora lutea" and granular luteal cells.

Method: other: OECD guideline 421 (1995)
Year: 2002
GLP: yes
Test substance: other TS: 99.8% purity

Method: Exception from guideline: food intake was recorded only during the premating period.
Result: NOAEL is 90 mg/kg bw (general maternal toxicity)
ACTUAL DOSE RECEIVED BY DOSE LEVEL BY SEX:
TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
Parental data (F0 generation):
- Mortality:
270 mg/kg bw, : increased mortality* (m: 2/12; f: all)
- Body weight:
270 mg/kg bw m: no body weight gain (week 2)*, severe body weight loss (week 3-5; 8.6 to 15 g/week)*
270 mg/kg bw f (data of females without implantation or without litters are not included): body weight loss (week 2; 3 g/week)*
- Food consumption (during premating period): no effect
- Clinical signs:
90 mg/kg bw m,f: soft feces, diarrhoea
270 mg/kg bw m,f: poor condition, apathy, piloerection, emaciation, tremor
- Time to insemination: no effect
- Insemination index:
270 mg/kg bw f: decreased index (41.7 % of those paired), secondary to the severe maternal toxicity

- Fertility index:
270 mg/kg bw f: decreased index (40.0 % of those paired), secondary to the severe maternal toxicity
- Duration of gestation:
270 mg/kg bw: no data, no effect up to 90 mg/kg bw
- Gestation index:
270 mg/kg bw f: decreased index (0 %, no viable pups), all females were sacrificed moribund (end of mating or early gestation)
- Course of birth:
270 mg/kg bw: no data, no effect (actual process could rarely be observed)
- Lactation behaviour:
270 mg/kg bw: no data, no effect up to 90 mg/kg bw
- Gross pathology:
270 mg/kg bw m: thickened urinary bladder wall
- Number of implantation sites/litter:
270 mg/kg bw: no quantification possible; no effect up to 90 mg/kg bw
- Number of corpora lutea (all females):
270 mg/kg bw: no quantification possible; no effect up to 90 mg/kg bw
- Number of corpora lutea (pregnant females):
270 mg/kg bw: no quantification possible; no effect up to 90 mg/kg bw
- Frequency and severity score of the finding "large corpora lutea" and granular luteal cells:
270 mg/kg bw: reduced (these animals were necropsied before term)
- Organ weights:
270 mg/kg bw m: increased relative testis weight(~10 % of control)*, decreased absolute epididymides weights (~22%)*

Toxicity F1:
- Litter size and weights:
270 mg/kg bw: no data; no effect up to 90 mg/kg bw
- Sex and sex ratios:
270 mg/kg bw: no data; no effect up to 90 mg/kg bw
- Live Birth Index:
270 mg/kg bw: no data; no effect up to 90 mg/kg bw
- Viability index:
270 mg/kg bw: no data; no effect up to 90 mg/kg bw
- Necropsy/Malformations:
no effects reported

Toxicity Pups:
No findings

STATISTICAL RESULTS: * results were statistically significant

Test condition: ADMINISTRATION / EXPOSURE
- Vehicle: polyethylene glycol 400
- Concentration in vehicle:
30 mg/kg bw: 6.0 mg/ml
90 mg/kg bw: 18.0 mg/ml
270 mg/kg bw: 54 mg/ml
- Total volume applied: 5 ml/kg bw
MATING PROCEDURES: One F0 female was mated with one F0 male

overnight, until positive sperm detection (2-week mating period). F0 females found sperm-positive after the first mating day, without being pregnant were remated over one week with the same male without checking insemination or measuring body weight.
DEATHS OF P GENERATION:
Males: day 37
Females and pups: day 4 to 6 p.p.

PARAMETERS ASSESSED DURING STUDY P:
m,f:
Clinical signs: twice daily
detailed clinical observations: once a week
Body weights: weekly
Food consumption: weekly (during premating period)
Gross pathology: all animales on scheduled or unscheduled deaths

Necropsy:
Organs fixed: Testes, epididymides, prostate, seminal vesicles (coagulation glands, uterus with cervix, vagina, ovaries with oviducts, stomach, esphagus, mamma with skin and gross lesions
Organ weights: Testis, epididymes
Histopathology: Testes epididymides, ovaries

Other examinations:
- insemination day
- Insemination index (%): No of females inseminated x 100/No. of females paired
- Fertility index (%): No of females with implantation sites x 100/No of females inseminated
- Gestation index (%): No of females with viable pups x 100/No of females with implantation sites
- Duration of gestation
- Course of birth (if observed)
- Lactation behaviour (milk ingestion in pups at necropsy)
- No of corpora lutea in right or left ovary
- No of implantation sites (ammoniumsulfide staining)

PARAMETERS ASSESSED DURING STUDY F1:
Clinical signs: twice daily
detailed clinical observations: day of birth and day 4 p.p.
Necropsy: no detailed data given
- Others:
- Livebirth index (%): No of viable pups at birth x 100/No of pups born
- Sex ratio
- pup weights (day of birth and day 4 p.p.)

STATISTICAL METHODS:
- Variance analysis and Dunnett´s test (organ weights, time to insemination, duration of gestation, nuber of implantation sites per females, prenatal loss per female, live birth and viability index, number of pups delivered, stillborn, died, missing and/or cannibalized, number of live pups per female at the individual weighing times, sex ratio of pups, pup weights and pup weight changes)

- N CHI2 test, Fisher´s exact test (insemination, fertility and gestation index, number of females with live pups, stillborn pups, all pups stillborn, number of females with total postnatal litter loss up to day 4 p.p.
- F-test, t-test, Welch t-Test (number of implantation sites per female
- Dunnett-Test (body weights of parent animals)

Reliability: (1) valid without restriction
Guideline study
Flag: Critical study for SIDS endpoint
03-AUG-2005 (15)

Type:	other: sub-acute
In Vitro/in vivo:	In vivo
Species:	rat
Strain:	Sprague-Dawley Sex: male/female
Route of administration:	inhalation
Exposure period:	4 weeks
Frequency of treatment:	6 days/week 6 hours/day
Duration of test:	8 weeks
Doses:	target concentration: 10, 30, 100, 300 ppm (effective inhaled concentration: 12, 35, 119, 198 ppm)
Control Group:	yes, concurrent vehicle
Result:	>= 119 ppm, m: hypospermatogenesis

Method:	other
Year:	1981
GLP:	no data
Test substance:	other TS: colourless, liquid, not further specified

Remark: Details of the study see under 5.4 Repeated dose toxicity
Result: >= 119 ppm m: hypospermatogenesis (control, 12+35 ppm: 0/20, 119 ppm: 3/20, 198 ppm: 4/19). In each case the content of sperm in the epididymis was below normal.
No changes in organ weights were reported.
No further pathological findings were reported.
Test condition: Organ weights: Gonads (Ovary and testicle paired)
Histopathology: Gonads, uterus, prostate, adrenals, testes (among other organs)
Reliability: (2) valid with restrictions
Study well documented, meets generally accepted scientific standard, acceptable for assessment. Restriction: Study was not conducted in order to investigate reproduction toxicity.
Flag: Critical study for SIDS endpoint
03-AUG-2005 (67)

Type:	other: sub-chronic
In Vitro/in vivo:	In vivo
Species:	rat
Strain:	Fischer 344 Sex: male/female
Route of administration:	gavage
Exposure period:	13 weeks
Frequency of treatment:	5 days/week
Duration of test:	94 days
Doses:	25, 50, 100, 200, 400 mg/kg bw/day
Control Group:	yes, concurrent vehicle
Result:	No pathological findings were reported.

Method: other
Year: 1985
GLP: no data
Test substance: other TS: purity ca. 97 %

Remark: Details of the study see under 5.4 Repeated dose toxicity.
Test condition: Ovaries/Uterus and testes and mammary gland were microscopically examined. No organ weight determination performed. Further details of the study see under 5.4. Repeated dose toxicity
Reliability: (2) valid with restrictions
Study well documented, meets generally accepted scientific standard, acceptable for assessment. Restriction: Study was not conducted in order to investigate reproduction toxicity.
Flag: Critical study for SIDS endpoint
02-APR-2003 (74)

Type: other: chronic
In Vitro/in vivo: In vivo
Species: rat
Strain: Fischer 344 Sex: male/female
Route of administration: gavage
Exposure period: 2 years (103 weeks)
Frequency of treatment: 5 days/week
Duration of test: 105 weeks
Doses: 100, 200 mg/kg bw/day male rat; 50, 100 mg/kg bw/day female rat
Control Group: yes, concurrent vehicle
Result: No pathological findings were reported.

Method: other
Year: 1985
GLP: no data
Test substance: other TS: purity ca. 97 %

Remark: Details of the study see under 5.4 Repeated dose toxicity and 5.7 Carcinogenicity.
Test condition: Seminal vesicles/prostate/testes or ovaries/uterus and the mammary gland were examined microscopically.
Further details of the study see under 5.4 Repeated dose toxicity and 5.7 Carcinogenicity.
Reliability: (2) valid with restrictions
Study well documented, meets generally accepted scientific standard, acceptable for assessment. Restriction: Study was not conducted in order to investigate reproduction toxicity.
Flag: Critical study for SIDS endpoint
03-AUG-2005 (74)

Type: other: sub-chronic
In Vitro/in vivo: In vivo
Species: mouse
Strain: B6C3F1 Sex: male/female
Route of administration: gavage
Exposure period: 13 weeks
Frequency of treatment: 5 days/week
Duration of test: 94 days
Doses: 95, 190, 375, 750, 1500 mg/kg/day

Control Group: yes, concurrent vehicle
Result: >= 375 mg/kg bw, m: testicular atrophy

Method: other
Year: 1985
GLP: no data
Test substance: other TS: purity ca. 97 %

Remark: Details of the study see under 5.4 Repeated dose toxicity.
Test condition: Ovaries/Uterus and prostate/testes and mammary gland were microscopically examined with the exception of the 95 mg/kg bw/day group. No organ weight determination were performed. Further details of the study see under 5.4. Repeated dose toxicity
Reliability: (2) valid with restrictions
Study well documented, meets generally accepted scientific standard, acceptable for assessment. Restriction: Study was not conducted in order to investigate reproduction toxicity.
Flag: Critical study for SIDS endpoint
02-APR-2003 (74)

Type: other: chronic
In Vitro/in vivo: In vivo
Species: mouse
Strain: B6C3F1 Sex: male/female
Route of administration: gavage
Exposure period: 2 years (103 weeks)
Frequency of treatment: 5 days/week
Duration of test: 105 weeks
Doses: 100, 200 mg/kg bw/day
Control Group: yes, concurrent vehicle
Result: >= 100 mg/kg bw/day: focal calcification in testis

Method: other
Year: 1985
GLP: no data
Test substance: other TS: purity ca. 97 %

Remark: Details of the study see under 5.4 Repeated dose toxicity and 5.7 Carcinogenicity.
Result: >= 100 mg/kg bw/day: focal calcification in testis (control: 2/50, 100 mg/kg bw: 9/47, 200 mg/kg bw: 24/50). The shape and location of the deposits in testis suggest mineralization of seminiferous tubules.
Test condition: Seminal vesicles/prostate/testes or ovaries/uterus and the mammary gland were examined microscopically. Further details of the study see under 5.4 Repeated dose toxicity and 5.7 Carcinogenicity.
Reliability: (2) valid with restrictions
Study well documented, meets generally accepted scientific standard, acceptable for assessment. Restriction: Study was not conducted in order to investigate reproduction toxicity.
Flag: Critical study for SIDS endpoint
02-APR-2003 (74)

5.9 Specific Investigations

02-APR-2003

5.10 Exposure Experience

Type of experience: Human - Epidemiology

Result: Acute toxicity: moderately toxic
Substance is characterized by marked cumulative properties, absorption from skin and local irritative action.
Acute and chronic poisoning induces disorders of the nervous
system
MAC (in the air): 0.5 mg/m3 (established by Ministry of Health - Russia in 1987)
Reliability: (4) not assignable

Only abstract in english available (Kuziminov). Information taken out of MAK-values table (Sidoror).
04-SEP-2002 (52) (99)

5.11 Additional Remarks

Type: other: IARC reports 1990 and 1999

Remark: IARC (International Agency for the Research on Cancer) has classified DMP in "Group 3"; i.e.: DMP is not classifieable as to its carcinogenicity to humans

01-OCT-2003 (46) (47)

Type: other: Historical controls of micronucleus frequencies (NMRI and B6C3F1)

Remark: The study shows that a value of 2.7 mnPCE/1000 PCE - as found in the study by Bayer AG/Herbold - is within the historical control range
Result: NMRI mice:
Number of determination: 202 (1026)
Range of means (mnPCE/1000 PCE): 0.4-7.0
Weighted mean mnPCE/1000 PCE: 2.06
The mean bone marrow micronucleus negative control frequencies (mnPCE/1000 PCE) decreased from 1973 until 1993 from about 3 to 2.06 (mean); range:0.4 -3.5, extremes up to 7)

B6C3F1 mice (No. of animals):
Number of determination: 266 (1832)
Range of means (mnPCE/1000 PCE): 0.0-5.4
Weighted mean mnPCE/1000 PCE: 1.66
The mean bone marrow micronucleus negative control frequencies (mnPCE/1000 PCE) increased from 1973 until 1993 from about 0.5 to 1.7 (mean).
Test condition: The published negative control data from 581 papers on micronucleated bone marrow polychromatic erythrocytes (mnPCE) were examined.

Reliability: (2) valid with restrictions
well documented, meets generally accepted scientific standard; metanalysis of negative control incidences

02-OCT-2003 (95)

Type: other: Correlation of structure, mutagenicity and carcinogenicity

Result: NTP/NCI Carcinogens were clustered.
DMP was put in Cluster 2 with clear evidence to induce lung and stomach cancer in male rats. The Ames test result of DMP is positive (50% of Cluster 2 Carcinogens had a positive Ames test result and 50 % a negative result).

DMP is classified as a mutagenic substance.

DMP is put in Group B: Agents found to be carcinogenic to only a single species but to be active at 2 or more sites in that species.

The structure-activity prediction forcarcinogenicity of DMP was positive (i.e.: carcinogenic) based on its alkyl phosphate ester structure (natural electrophile).

Test condition: The correlation between the chemical structure, the Salmonella mutagenicity and the extent of carcinogenicity as indicators of genotoxic carcinogenesis among 222 and 301 chemicals respectively (among them dimethyl hydrogen phosphite = DMP) tested in rodents by the U.S. NCI/NTP are evaluated.

Reliability: (2) valid with restrictions
non-validated test system

27-SEP-2002 (3) (4) (5) (6) (28) (38)

Type: other: Correlation of short term tests, mutagenicity and carcinogenicity

Result: The correlation of the results of genotoxicity short term tests (STT) with the results of carcinogenicity testing is evaluated.

DMP was positive in all 4 STT (Salmonella typhimurium assay, strain TA 100, Chromosomal aberration assay with CHO, Sister Chromatid Exchange assay with CHO, Mouse lymphoma assay with L5178Y) and tested positive as carcinogen in male rats with equivocal results in female rats.

Reliability: (4) not assignable
secondary references

02-OCT-2003 (30) (111)

Type: other: Toxicity prediction (CASE)

Result: Toxicity
The toxicity prediction expressed in terms of maximum tolerated dose for dimethyl hydrogen phosphite is negative

for rats and marginal positive for mice.
Genotoxicity
The structural predictivity of genotoxicity for dimethyl hydrogen phosphite is marginal to positive; substance is set in category B with a 57-66 % chance of being active due to substructure.

Reliability: (4) not assignable
secondary literature, SAR-study

08-OCT-2003 (90) (91) (92)

Type: other: Review on Carcinogenicity and Genotoxicity studies

Result: Dimethyl hydrogen phosphite - tested in NTP bioassays - was positive in mutagenicity assays (Ames Salmonella) and in chromosomal aberration and sister chromatid exchange assays. The substance among others is classified by the authors as a potential warfare agent (Albert RE, 1997) and the Tumor score is set on 2 (number of different organs that showed tumor induction in mice and rats of both sexes)
A Contact Sensitization caused by DMP is not reported.
The log P value (octanol/water partition coefficient) of DMP is low, as mainly observed for the mutagenic carcinogens.

Test condition: Various reviews with different intentions based on the NTP carcinogenicity and genotoxicity databases (including DMP) have been undertaken. A brief summary of the DMP relevant results is given under Results.

Reliability: (4) not assignable
reviews

02-OCT-2003 (1) (41) (42) (61) (86) (87) (89)

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