Rhodia

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The Honorable Steve Johnson, Administrator
U.S. Environmental Protection Agency
P.O. Box 1473
Merrifield, VA. 22116

On behalf of the Trimethyl Phosphite HPV Consortium

December, 21st 2005

RE: Trimethyl Phosphite (CAS No. 121-45-9)- US EPA HPV Challenge Program.

Dear Mr. Johnson,

We would like to notify you of the formation of a consortium that is going to sponsor Trimethyl Phosphite in the US HPV challenge program. Our consortium is made up of three companies:

- Rhodia Inc., 8 Cedar Brook Drive, Cranbury, New Jersey, USA 08512
- United Phosphorus Inc., 423 Riverview Plaza, Trenton, New Jersey, USA 08611
- Sabero Organic Gujarat Ltd., A-302, Pheonix House, 462, S.B. Marg., Worli (East), Mumbai, 400 013, India

Attached to this letter are the robust summaries of existing studies and test plan documents for the listed chemical. We are aware that the likely deadline for submission of these documents is 31st December 2005 in order for them to be reviewed within the context of the HPV program.

Rhodia Inc. will serve as the lead company for the consortium and I will serve as the designated contact for the consortium, my contact details are given below:

Ian Bartlett
Rhodia Inc.
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Cranbury, New Jersey,
USA 08512-7500
e-mail: ian.bartlett@us.rhodia.com
tel : 609 860 3913/fax : 609 860 0076

If you have any questions relating to this letter or submission please feel free to contact me by e-mail or phone. We look forward to receiving EPA and public comments regarding our test plan.

Kind Regards,

Ian Bartlett Ph.D.
Product Stewardship Manager, Rhodia Inc.

On Behalf of Trimethyl Phosphite Consortium
e-mail: ian.bartlett@us.rhodia.com tel : 609 860 3913/fax : 609 860 0076

CC: Sunil Menon, United Phosphorus Inc., 423 Riverview Plaza, Trenton, New Jersey, USA 08611
Kailas Thakare, Sabero Organic Gujarat Ltd., A-302, Pheonix House, 462, S.B. Marg., Worli (East), Mumbai, 400 013, India

HIGH PRODUCTION VOLUME (HPV) CHEMICAL CHALLENGE PROGRAM

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TEST PLAN
For
Trimethyl phosphite
(TMP)
CAS No. 121-45-9

Submitted to the US EPA
By
Trimethyl Phosphite Consortium.

December 2005

1 INTRODUCTION

Under the U.S. Environmental Protection Agency (EPA) High Production Volume (HPV) Chemical Challenge Program, the Trimethyl Phosphite Consortium, voluntarily commits to compile basic screening data on:

- Phosphorus Acid, Trimethyl Ester
  CAS No. 121-45-9

This test plan follows up on the commitment. Specifically, this test plan sets forth how the Trimethyl Phosphite Consortium intends to address testing information for Trimethyl Phosphitwe.

In preparing the test plan the following steps were undertaken:

Step 1: A search was conducted for relevant published and unpublished literature on Trimethyl Phosphite.

Step 2:The compiled data was evaluated for adequacy in accordance with the EPA guidance documentation.

2 GENERAL SUBSTANCE INFORMATION

Chemical name: Trimethyl phosphite

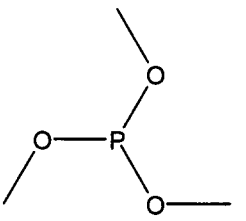
CAS No: 121-45-9

Synonyms: Phosphorous acid, trimethyl ester - Trimethoxyphosphine - TMP

Molecular formula: $C_3 H_9 O_3 P_1$

Molecular weight: 124.08

Structural diagram:



3 USE AND EXPOSURE INFORMATION

The subject chemical is used as a chemical intermediate in the manufacture of other phosphorus containing molecules. Trimethyl Phosphite is primarily manufactured overseas and imported into the USA for domestic market use. The downstream phosphorus-containing products produced from Trimethyl Phosphite may be used in a variety of applications including crop protection products, flame retardant chemicals and lubricant additives. Trimethyl Phosphite is typically fully reacted in the manufacture process with downstream products only containing trace residuals. As a chemical intermediate used in closed systems at chemical manufacturer sites, there will be limited potential for occupational exposure to the chemical at either manufacturer or user sites. Trimethyl Phosphite has a strong unpleasant odor with a reported odor threshold of 0.0001 parts per million. The additional engineering controls used to control odors further minimize occupational exposure.

4 REVIEW OF EXISTING DATA AND DEVELOPMENT OF TEST PLAN

The member companies have undertaken a comprehensive evaluation of all relevant data on the SIDS endpoints of concern for TMP.

The more significant and reliable data are gathered in table n° 6. The availability of the data on the specific SIDS endpoints is summarized in table n° 7.

4.1 Review of existing physicochemical data and proposed testing

Melting point, boiling point and vapor pressure values are available in standard data sources and are consistent with calculated values.

TMP hydrolyzes rapidly in water (see section 4.2). An octanol-water partition coefficient and a water solubility value cannot be generated experimentally. Estimations can be obtained with the KOWWIN and WSKOW programs.

No additional testing is proposed for the purposes of the HPV program.

4.2 Review of existing environmental fate data and proposed testing

– *Photodegradation*

A lifetime of 0.4 hour has been measured in dry air with OH radicals at an average 24-hour concentration of 10^6 molecules/cm^3. Trimethyl phosphate is the major degradation product.

An estimated half-life of 1.3 days is obtained with the AOP program considering an OH radical concentration of 1.5×10^6 molecules/cm^3 for 12 hours per day.

– *Stability in water*

Three hydrolysis studies of reliability (2) are available on TMP (cf. Table n° 1). These studies show that TMP is rapidly hydrolyzed to dimethyl phosphonate (DMHP) and methanol. Dimethyl phosphonate is further hydrolyzed to monomethyl phosphonate (MMHP) and methanol with a lower hydrolysis rate (cf. Table n° 1). Monomethyl phosphonate hydrolyzes slowly to phosphorous acid and methanol.

No further testing is proposed for this endpoint.

Table n° 1: Hydrolysis properties of TMP, DMHP and MMHP

Substance	Result	Method	Source
TMP CAS No 121-45-9	DT50 = 21 min at pH 10 and 25°C DT50 < 5 min at pH 6 and 0°C	In a two phase system (pentane/water), TMP initially introduced in the organic phase	Johnston, 1981 (Mobil Chemical Co.)
	100% hydrolysis after 0.5 h	In pure water, no control of pH (preliminary stability test prior to a fish acute toxicity test)	Bayer, 1992
	DT50= 8-9 min at 25 °C	In pure water	Arbuzov et al., 1957
DMHP CAS No 868-85-9	DT50 = 470 h (19.6 d) at pH 4 at 23°C DT50 = 3 h at pH 7 at 23°C DT50 < 0.3 h at pH 9 at 23°C	OECD 111	Bayer, 2002
	DT50 ca. 60h	In pure water, no control of pH (preliminary stability test prior to a fish acute toxicity test)	Bayer, 1992
	DT50 = 10.8 d at 25°C	In water, preliminary neutralized	Belskii et

			al.,1969
MMHP	Hydrolyzes slowly	In pure water, no control of pH (preliminary stability test prior to a fish acute toxicity test)	Bayer, 1992

– *Biodegradation*

Biodegradation data are not available on TMP. However TMP is rapidly hydrolyzed to DMHP (cf. hydrolysis studies above). A ready biodegradation study of reliability (1) is available on DMHP which shows that DMHP is not readily biodegradable (50 % biodegradation after 28 days in an OECD 301 E test, Bayer, 1992). Therefore TMP can be considered as not readily biodegradable and **no further testing is proposed for this endpoint**.

– *Transport and distribution*

As TMP is rapidly hydrolyzed to DMHP in presence of water, a level III fugacity modeling has been performed on DMHP with the EPIWIN program.

EPIWIN estimated physicochemical and fate data were used, except for the vapor pressure. A reliable experimental data of 1.35 hPa at 20°C (Bayer, 2001) has been used.

DMHP is shown to distribute mainly in water and soil when discharged equally in air, water and soil. When discharged solely in water or soil, DMHP remains mainly in the original receiving compartment with significant transfer to the soil or water compartment. When discharged in air, DMHP remains mainly in air with significant transfers to the soil and water compartments.

4.3 Review of existing ecotoxicity data and proposed testing

Toxicity studies on fish, algae and daphnia are not available on TMP. However TMP is rapidly hydrolyzed to DMHP and toxicity studies of reliability (1) on fish, algae and daphnia are available on DMHP (cf. Table n°2). **Therefore no further aquatic toxicity testing is proposed for purposes of the HPV program**.

Table n° 2: Most relevant ecotoxicity data on DMHP

Endpoint	Substance	Result	Method	Source
Acute toxicity to fish	DMHP	96h-LC0 ≥ 100 mg/l (nominal)	OECD 203	Bayer, 1992
Acute toxicity to daphnia	DMHP	48h-EC50 = 25 mg/l (nominal)	OECD 202	Bayer, 2003a
Toxicity to algae	DMHP	72h-EC0 ≥ 100 mg/l (nominal)	OECD 201	Bayer, 2003b

4.4 Review of existing toxicity data and proposed testing

– *Acute Toxicity*

A number of acute oral toxicity studies of reliability (2) in the rat are available on TMP (cf. Table n° 3), with consistent results. A conservative estimate of the rat oral LD50 is 1350 mg/kg bw. The mouse appears to be less sensitive, with an oral LD50 of 4280 mg/kg bw. The rabbit dermal LD50 is 934 mg/kg bw. The rat 1 hour inhalation LC50 is 182 mg/l, while inhalation for 4 hours was not lethal at 9000 ppm (45.7 mg/l). For both inhalation studies, stated concentrations were based on quantity of substance used, so may overestimate the actual exposure concentration. All the acute studies were conducted before the introduction of GLP guidelines, however the results are consistent, leading to the conclusion that TMP is of moderate acute toxicity. A study of cholinesterase inhibition following intravenous administration of TMP in rats, rabbits and dogs and in vitro studies of cholinesterase inhibition potential demonstrated that TMP does not have any significant specific cholinesterase inhibition potential. **Therefore no further acute toxicity testing is proposed for purposes of the HPV program**.

Table n° 3: Most relevant acute toxicity data on TMP

Endpoint	Substance	Species	Result	Method	Source
Acute oral toxicity	TMP	Rat	LD50 = 1350 mg/kg bw	Other	Ebbens, 1973
		"	LD50 = 1500 mg/kg bw	"	Terrell, 1976
		"	LD50 = 1595 mg/kg bw	"	Terrell, 1976
		"	LD50 = 1640 mg/kg bw	"	Terrell, 1976
		"	LD50 = 1970 mg/kg bw	"	Terrell, 1976
		"	LD50 = 2000 mg/kg bw	"	Terrell, 1976
		"	LD50 = 2000 mg/kg bw	"	Terrell, 1976
		"	LD50 = 2240 mg/kg bw	"	Terrell, 1976
		Mouse	LD50 = 4280 mg/kg bw	"	Terrell, 1976
Acute inhalation toxicity	TMP	Rat	1h LC50 = 182 mg/l (nominal)	Other	Zeigler, 1977
		"	4h LC50 > 45.7 mg/l (9000ppm) (nominal)	"	Gabriel, 1969
Acute dermal toxicity	TMP	Rabbit	LD50 = 934 mg/kg bw	Other	Ebbens, 1973
		"	LD50 = 7500 mg/kg bw	"	Becker, 1976
Acute dermal irritation	TMP	Rabbit	Slightly irritating	Other	Becker, 1976
Acute eye irritation	TMP	Rabbit	Slightly irritating	Other	Becker, 1976
Serum cholinesterase inhibition	TMP	Rat	No significant inhibition	Other	Munson, 1979
		Rabbit	"	"	"
		Dog	"	"	"
		In vitro (rat)	"	"	Dramlia, 1981
			"	"	Meeks, 1979

- *Repeat Dose Toxicity*

Effects of repeated exposure to TMP have been characterised in studies of reliability (2) for all relevant routes of exposure (cf. Table n° 4).

A 90-day oral gavage study in rats showed mortality and significant intermittent reduction in bodyweight gain at 160 mg/kg/day, with testicular hypoplasia and reduced spermatogenesis (spermatogonia and other spermatogenic cells reduced in size and number) at the same dose in males. However, the density of sperm in the epididymis was not greatly or uniformly reduced. No significant effects were observed at 80 mg/kg bw/day.

A dermal toxicity study in which rabbits were exposed for 6 hours per day for 21 days (both abraded and non-abraded sites) showed dose-related irritancy, with mortality and effects on lungs and liver, which may have been secondary to irritancy. The LOAEL for this study was 300 mg/kg bw/day.

A 28-day inhalation study in rats showed cataracts and effects on the lungs. Although they were both considered likely to be related to viral disease in the animals, two further studies were carried out to elucidate the effect. The conclusion from the three studies was that TMP was cataractogenic and a corneal irritant at concentrations from 50 ppm. There was some reversibility at this concentration and at 100 ppm, but cataracts seen at 600 ppm were irreversible. No lenticular or corneal damage was seen at 10 ppm. Inflammatory effects in the lungs at 600 ppm were likely to have resulted from exacerbation of pre-existing pneumonitis.

An early (1971) 8-week inhalation study in rats, at the single nominal concentration of 500 ppm, showed histopathological changes in the lungs (interstitial pneumonitis, increased number of mucus-producing goblet cells in bronchial mucosa, squamous metaplasia of alveoli plus tumorlets extending into, or filling, the alveolar spaces, pulmonary vascular sclerosis and emphysematous changes). These were considered to be likely to represent potential for serious irreversible lung damage, including pre-cancerous changes. Effects on the skin (hyperkeratosis; parakeratosis; acanthosis; focal folliculitis, infiltration of inflammatory cells) were considered less important and due to irritation. No histopathological effects on the testes were reported, and spermatogenesis was stated to be active.

A later review of this study concluded that the interpretation of the lung effects was unreliable. Changes seen were considered likely to be related to chronic lung disease in the laboratory rats. Also, no precautions had been taken in the study to avoid hydrolysis of TMP to dimethyl hydrogen phosphite (DMHP), monomethyl phosphite and ultimately to phosphorous acid (see Stability in water, above) A carcinogenicity assay on DMHP in rats has concluded that there was clear evidence for carcinogenicity in male rats and equivocal evidence in female rats. The lung tumours seen in this DMHP study (dose-related squamous cell carcinomas, and alveolar/bronchiolar adenomas or carcinomas) are consistent with the changes seen in the 8-week "TMP" study. No significant lung changes were seen in the series of 28-day studies conducted on TMP protected from hydrolysis by a nitrogen blanket. If the effects in the 8-week study are substance-related, then it is considered that they relate to the hydrolysis product, not to TMP. No evidence of carcinogencity was seen in a carcinogenicity study on DMHP in the mouse.

Therefore no further repeated dose toxicity testing is proposed for purposes of the HPV program.

Table n° 4: Most relevant repeated dose toxicity data on TMP

Endpoint	Substance	Species	Result	Method	Source
21-day Oral	TMP	Rat	NOAEL: 32.8 mg/kg/d	Other	Rabold, 1977
90-day Oral	TMP	Rat	160 mg/kg/d: Testicular hypoplasia, reduced spermatogenesis. NOAEL: 80 mg/kg/d bw	Other	Klopp, 1977
21-day Dermal	TMP	Rabbit	300/600/1200 mg/kg/d: dose-related mortalities, irritation, effects on lungs and liver. LOAEL: 300 mg/kg/d bw	Other	Becker, 1977
28-day Inhalation	TMP	Rat	1) 581 ppm inflammatory changes in lung. 292/581 ppm: Cataracts NOAEL: 104 ppm	Other	Rusch, 1979
		Rat	2) 105 ppm Reversible lenticular opacities 600 ppm: Irreversible cataracts LOAEL: 105 ppm	"	Rusch, 1979
		Rat	3) 50/101 ppm Reversible lenticular opacities, irregular corneal surfaces. NOAEL: 10 ppm	"	Rusch, 1979

– *Genetic Toxicity in vitro and in vivo*

The genotoxicity of TMP has been examined in a battery of *in vitro* and *in vivo* assays of reliability (2) (cf. Table n° 5). Several of the *in vitro* studies for gene mutation indicate that TMP has mutagenic potential. However, no mammalian *in vivo* studies on his endpoint or on chromosomal aberration are available. The significance of the studies in Drosophila is uncertain. **Therefore it is proposed to conduct a micronucleus test, OECD 474, to satisfy this endpoint for purposes of the HPV program.**

Table n° 5: Most relevant genotoxicity data on TMP

Endpoint	Sub-stance	Test system	Activ-ation	Result	Method	Source
Bacterial mutagenicity in vitro	TMP	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	±	Negative	Other	Haworth, 1979
Bacterial mutagenicity in vitro	TMP	S. typhimurium TA1535, TA100, TA1537, TA1538, TA98 S. cerevisiae D4	±	Negative	Other	Brusick, 1979
Mammalian mutagenicity in vitro	TMP	L5178Y/TK+/- mouse lymphoma cells	±	Positive	Other	Kirby, 1979
Mammalian	TMP	L5178Y/TK+/- mouse lymphoma cells	±	Positive	Other	Kirby, 1979

mutagenicity in vitro						
Mammalian mutagenicity in vitro	TMP	L5178Y/TK+/- mouse lymphoma cells	±	Positive	Other	Kirby, 1979
DNA damage & repair assay in vitro	TMP	E coli WP2/WP100, S. typhimurium TA1978/TA1538	±	Positive	Other	Haworth, 1979
DNA damage & repair assay in vitro	TMP	E coli WP2/WP100, S. typhimurium TA1978/TA1538	±	Positive	Other	Haworth, 1979
DNA damage & repair assay in vitro	TMP	E coli WP2/WP100, S. typhimurium TA1978/TA1538	±	Negative	Other	Haworth, 1979
Call transformation assay in vitro	TMP	C3H/10T½ CL8 cells		Negative	Other	Thilagar, 1979
In vivo Drosophila mutagenicity assay	TMP	Point mutations: 1) Sex-linked Lethals 2) White-ivory Somatic Reversions. Chromosome aberrations and loss: 1) Dominant Lethal Mutations 2) Y Chromosome Loss 3) Bithorax Test of Lewis		 Negative " " " "	Other	Bowman, 1980
In vivo Drosophila mutagenicity assay	TMP	Point mutations: 1) Sex-linked Lethals 2) White-ivory Somatic Reversions. Chromosome aberrations and loss: 1) Dominant Lethal Mutations 2) Y Chromosome Loss 3) Bithorax Test of Lewis		 Positive Negative Positive Negative Positive	Other	Bowman, 1980
In vivo Drosophila mutagenicity assay	TMP	Point mutations: 1) Sex-linked Lethals 2) White-ivory Somatic Reversions. Chromosome aberrations and loss: 1) Dominant Lethal Mutations 2) Y Chromosome Loss 3) Bithorax Test of Lewis		 Positive Negative Positive Positive Positive	Other	Bowman, 1979

– *Carcinogenicity*

See discussion of effects in 8-week inhalation toxicity study, under repeat dose toxicity.

– *Toxicity to Reproduction*

Fertility
No dedicated study has been conducted on fertility. Testicular hypoplasia and reduced spermatogenesis were observed at 160 mg/kg/day in a 90-day oral gavage study in rats, but with little reduction in sperm density in the epididymis. Mortality and general toxicity (significant reduction in bodyweight gain) were also noted at this dose. No effects were seen at 80 mg/kg bw/day. Repeated dose studies by inhalation did not reveal any effects on the testes at up to 581 ppm (2.95 mg/l) for 28 days. No effects on male reproductive organs were seen in a 21-day dermal toxicity study at up to 600 mg/kg bw/day. No effects were seen on female reproductive organs in any of these studies. (see Repeat-dose toxicity, above). These findings are not considered to indicate a specific reproductive risk.

Development
A teratogenicity study by gavage in SD rats on days 6 through 15 of pregnancy showed teratologic effects at 164 mg/kg bw/day. Gross Abnormalities were exencephaly, spina bifida, scoliosis and cleft palate.

Skeletal abnormalities seen were primarily abnormalities of long bones. The incidence of abnormalities of sternebrae, rudimentary ribs and partial ossification of sternebrae and vertebrae was increased. Soft Tissue abnormalities seen at 164 mg/kg/day were a marked increased in dilated ventricles and in undescended testes. It was concluded that TMP was teratogenic during the period of major organogenesis at 164 mg/kg/day. Teratogenicity appears to be a direct result of exposure to TMP rather than secondary to maternal toxicity, which was seen only as a slight reduction in bodyweight gain. The maternal and foetal NOAEL in this study was 49 mg/kg/day.

Therefore no further reproductive toxicity testing is proposed for purposes of the HPV program.

– *Experiences with human Exposure (Work Place Exposure)*

Examination of the 180 employees at a TMP manufacturing plant, with varying degrees of exposure over a number of years showed no clinical cataracts in either the exposed (n=117) or non-exposed (n=63) employee groups. Numerous subclinical non-progressive congenital opacities and early progressive senile opacities were identified, with no association between TMP exposure and cataract formation. Analyses of workplace air indicated that average exposure in 1979 was between 0.3 and 4 ppm, with excursions to 15 ppm.

Female employees were questioned concerning pregnancy. Only one office worker had attempted conception, and had successfully conceived and delivered on three separate occasions. No male employees had been questioned. The sample was too small to draw any conclusions.

5 SUMMARY

In summary, the testing proposed in Table n° 7 will complete the data acquisition requirements for TMP under the U.S. Environmental Protection Agency High Production Volume (HPV) Chemical Challenge Program.

6 ROBUST STUDY SUMMARIES

An IUCLID Data Set for TMP is appended.

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Table n° 6: Significant Data on TMP

TMP CAS No 121-45-9		
Endpoint	**Result**	**Comment**
Physicochemical		
Melting point	-78 °C	Handbook data
Boiling point	111 °C at 1013 hPa	Handbook data
Density	1.046 at 20°C	Handbook data
Vapor pressure	32 hPa at 25°C	Handbook data
Log Pow	Hydrolyzes rapidly	Experimental data
	-0.73 at 25°C	Estimation
Water solubility	Hydrolyzes rapidly	Experimental data
	407 g/l at 25°C	Estimation
Environmental fate and pathway		
Photodegradation	Lifetime in air = 0.4 h	Experimental data
Stability in water	DT100 ≤ 0.5 h	Experimental data
Transport/distribution	Air = 5 % Water = 53 % Soil = 42% Sediment = 0.09%	Fugacity model level III performed on dimethyl phosphonate, the hydrolysis product of TMP, with discharge in air, water and soil
Biodegradation	Not readily biodegradable	Experimental data on dimethyl phosphonate, the hydrolysis product of TMP
Ecotoxicity		
Acute fish	LC0 ≥ 100 mg/l (nominal)	Experimental data on dimethyl phosphonate, the hydrolysis product of TMP
Acute daphnia	EC50 = 25 mg/l (nominal)	
Algae	LC0 ≥ 100 mg/l (nominal)	
Toxicology		
Acute toxicity	Oral LD50: 1350 mg/kg (Rat) Dermal LD50: 934 mg/kg (Rabbit) Inhalation LC50/1h: 182 mg/l (Rat)	Experimental data
Repeated dose toxicity	NOEL cateractogenicity: 10 ppm	Experimental data
Genetic toxicity *in vitro*		Experimental data
Gene mutation	Overall, positive	
Chromosomal aberration		
Genetic toxicity *In vivo*		
Toxicity to reproduction	Possible reduced male fertility, NOEL 80 mg/kg/d	Experimental data
Developmental tox/teratogenicity	Teratogenic NOEL 49 mg/kg/d	Experimental data
Human experience	No cataracts	Clinical data

Table n° 7 : Availability of data and proposed testing on TMP

TMP CAS No 121-45-9							
Endpoint	**Available**	**GLP**	**OECD study**	**Other study**	**Estim. method**	**Accept-able**	**SIDS testing required**
Physicochemical							
Melting point	Y	N	N	Y	N	Y	N
Boiling point	Y	N	N	Y	N	Y	N
Density	Y	N	N	Y	N	Y	N
Vapor pressure	Y	N	N	Y	N	Y	N
Oct:water partition coef	Y	N	N	N	Y	Y	N
Water solubility	Y	N	N	N	Y	Y	N
Environmental fate and pathway							
Photodegradation	Y	N	N	Y	N	Y	N
Stability in water	Y	N	N	Y	N	Y	N
Transport/distribution	Y	N	N	N	Y	Y	N
Biodegradation	Y	Y	Y	N	N	Y	N
Ecotoxicity							
Acute fish	Y	Y	Y	N	N	Y	N
Acute daphnia	Y	Y	Y	N	N	Y	N
Algae	Y	Y	Y	N	N	Y	N
Toxicology							
Acute toxicity	Y	N	N	Y	N	Y	N
Repeated dose toxicity	Y	N	N	Y	N	Y	N
Genetic toxicity:							
Gene mutation							
- Bacterial (Ames test)	Y	N	N	Y	N	Y	N
– Mammalian (L5178Y Mouse lymphoma test)	Y	N	N	Y	N	Y	N
Chromosome aberrat.	Y	N	N	Y	N	N	Y
Toxicity to reproduction	Y	N	N	Y	N	Y	N
Devel. tox/terat	Y	N	N	Y	N	Y	N
Human experience	Y	N	N	Y	N	Y	N

Y : yes
N : no

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IUCLID

Data Set

Existing Chemical	:	ID: 121-45-9
CAS No.	:	121-45-9
EINECS Name	:	trimethyl phosphite
EC No.	:	204-471-5
TSCA Name	:	Phosphorous acid, trimethyl ester
Molecular Formula	:	C3H9O3P

Producer related part

Company	:	Trimethyl Phosphite Consortium
Creation date	:	12.20.2005

Substance related part

Company	:	Trimethyl Phosphite Consortium
Creation date	:	12.20.2005
Status	:	
Memo	:	
Printing date	:	12.21.2005
Revision date	:	
Date of last update	:	12.21.2005
Number of pages	:	15
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	:	Importer/Manufacturer
Name	:	Rhodia Inc.
Contact person	:	Ian BARTLETT
Date	:	
Street	:	8 Cedar Brook Drive
Town	:	08512 Cranbury, NJ
Country	:	United States
Phone	:	609-860-3913
Telefax	:	609-860-0076
Telex	:	
Cedex	:	
Email	:	ian.bartlett@us.rhodia.com
Homepage	:	
Remark	:	All references in this document to Mobil Chemical are superseded by the transfer of ownership of the relevant businesses to Rhodia. The above company is a member of the trimethyl phosphite consortium.

Type	:	Manufacturer
Name	:	Sabero Organics Gujarat Ltd.
Contact person	:	Kailas THAKARE
Date	:	
Street	:	A-302 Pheonix House, 462 S.B. Marg
Town	:	Worli East, Mumbai
Country	:	India
Phone	:	+91 22-2496-0978
Telefax	:	+91 22-2495-3727
Telex	:	
Cedex	:	
Email	:	Kailas.thakare@sabero.com
Homepage	:	
Remark	:	The above company is a member of the trimethyl phosphite consortium.

Type	:	Manufacturer
Name	:	United Phosphorus Inc.
Contact person	:	Sunil MENON
Date	:	
Street	:	423 Riverview Plaza
Town	:	Trenton
Country	:	USA
Phone	:	905-791-2698
Telefax	:	240-282-8937
Telex	:	
Cedex	:	
Email	:	smenon@upi-usa.com
Homepage	:	
Remark	:	The above company is a member of the trimethyl phosphite consortium.

Type	:	Manufacturer
Name	:	United Phosphorus Ltd.
Contact person	:	
Date	:	
Street	:	Uniphos House, Madhu Park, 11th Road
Town	:	Khar (W), Mumbai
Country	:	India

Phone : 905-791-2698
Telefax : 240-282-8937
Telex :
Cedex :
Email : smenon@upi-usa.com
Homepage :

Remark : The above company is a member of the trimethyl phosphite consortium.

12.21.05

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 : Trimethyl phosphite
Smiles Code : COP(OC)OC
Molecular formula : C3 H9 O3 P
Molecular weight : 124.08
Petrol class :

03.01.2005

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type : typical for marketed substance
Substance type : organic
Physical status : liquid
Purity : > 96 % w/w
Colour : Clear, colourless, water-like
Odour : Characteristic

03.01.2005

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

Phosphorous acid, trimethyl ester

27.10.2004

TMP

27.10.2004

Trimethoxyphosphine

03.01.2005

1.3 IMPURITIES

Purity	:	typical for marketed substance
CAS-No	:	868-85-9
EC-No	:	212-783-8
EINECS-Name	:	dimethyl phosphonate
Molecular formula	:	C2 H7 O3 P1
Value	:	< 1 % w/w

03.01.2005

Purity	:	typical for marketed substance
CAS-No	:	109-66-0
EC-No	:	203-692-4
EINECS-Name	:	pentane
Molecular formula	:	C5 H12
Value	:	< .5 % w/w

03.01.2005

Purity	:	typical for marketed substance
CAS-No	:	67-56-1
EC-No	:	200-659-6
EINECS-Name	:	methanol
Molecular formula	:	C1 H4 O
Value	:	< .5 % w/w

03.01.2005

Purity	:	typical for marketed substance
CAS-No	:	512-56-1
EC-No	:	208-144-8
EINECS-Name	:	trimethyl phosphate
Molecular formula	:	C3 H9 O4 P1
Value	:	< .5 % w/w

03.01.2005

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

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 : 07.11.2003

Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
27.10.2004

Type of search : Internal and External
Chapters covered : 3, 4, 5

Date of search : 07.11.2003

Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
27.10.2004

1.13 REVIEWS

2.1 MELTING POINT

Value : = -78 °C
Sublimation :
Method :
Year :
GLP :
Test substance : no data

Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Reliability : (2) valid with restrictions
Cited in standard data source(s).
Flag : Critical study for SIDS endpoint
28.10.2004 (1) (2) (3) (4) (5)

Value : < -60 °C
Sublimation :
Method : other: pour point
Year :
GLP :
Test substance : no data

Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Reliability : (2) valid with restrictions
Cited in standard data source(s).
Flag : Critical study for SIDS endpoint
28.10.2004 (6)

Value : = -58 °C
Sublimation :
Method : other: calculated
Year :
GLP :
Test substance :

Method : Estimation by MPBPWIN programme, v1.41, US-EPA/Syracuse Research.
Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Reliability : (2) valid with restrictions
Accepted calculation method.
Flag : Critical study for SIDS endpoint
28.10.2004

2.2 BOILING POINT

Value : = 111 - 112 °C at 1013 hPa
Decomposition :
Method :
Year :
GLP :
Test substance : no data

Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Reliability : (2) valid with restrictions
Cited in standard data source(s).
Flag : Critical study for SIDS endpoint
28.10.2004 (7) (8) (4)

Value : = 111 °C at 1013 hPa
Decomposition :
Method :
Year :
GLP :
Test substance : no data

Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Reliability : (2) valid with restrictions
Cited in standard data source(s).
Flag : Critical study for SIDS endpoint
28.10.2004 (3) (5)

Value : = 108 - 108.5 °C at 1013 hPa
Decomposition :
Method :
Year :
GLP :
Test substance : no data

Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Reliability : (2) valid with restrictions
Cited in standard data source(s).
Flag : Critical study for SIDS endpoint
28.10.2004 (6)

Value : = 111 °C at 1013 hPa
Decomposition :
Method : other
Year : 1966
GLP :
Test substance : no data

Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Reliability : (2) valid with restrictions
Experimental result consistent with standard data source data.
Flag : Critical study for SIDS endpoint
30.11.2004 (9)

Value : = 111.2 °C at 1008 hPa
Decomposition :
Method : other
Year : 1970
GLP :
Test substance : no data

Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Reliability : (2) valid with restrictions
Experimental result consistent with standard data source data.
Flag : Critical study for SIDS endpoint
30.11.2004 (10)

Value : = 116 °C at 1013 hPa
Decomposition :
Method : other: calculated
Year :
GLP :
Test substance :

Method : Estimation by MPBPWIN programme, v1.41, US-EPA/Syracuse Research.
Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Reliability : (2) valid with restrictions

Accepted calculation method.
Flag : Critical study for SIDS endpoint
30.11.2004

Value : = 110 °C at 1013 hPa
Decomposition :
Method : other: calculated
Year :
GLP :
Test substance :

Method : Estimation by Advanced Chemistry Development (ACD) software Solaris, v4.67 ((C) 1994-2003 ACD).
Result : Boiling point = 110.2 +/- 8.0 °C.
Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Reliability : (2) valid with restrictions
Accepted calculation method.
Flag : Critical study for SIDS endpoint
30.11.2004

2.3 DENSITY

Type : relative density
Value : = 1.046 at 20 °C
Method :
Year :
GLP :
Test substance : no data

Method : Density at 20°C relative to water at 4°C.
Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Reliability : (2) valid with restrictions
Cited in standard data source(s).
28.10.2004 (4) (6) (5)

Type : relative density
Value : = 1.052 at 20 °C
Method :
Year :
GLP :
Test substance : no data

Method : Density at 20°C relative to water at 0°C.
Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Reliability : (2) valid with restrictions
Cited in standard data source(s).
28.10.2004 (8)

Type : relative density
Value : = 1.0512 at 20 °C
Method : other
Year : 1966
GLP :
Test substance : no data

Method : Density at 20°C relative to water at 4°C.
Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Reliability : (2) valid with restrictions
Experimental result consistent with standard data source data.
30.11.2004 (9)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : = 32 hPa at 25 °C
Decomposition :
Method :
Year :
GLP :
Test substance : no data

Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Reliability : (2) valid with restrictions
Cited in standard data source(s).
Flag : Critical study for SIDS endpoint
28.10.2004 (3)

Value : = 27 hPa at 25 °C
Decomposition :
Method : other (measured)
Year : 1982
GLP :
Test substance : other TS

Method : Measurements with an ebulliometer.
Pressures measured with a precision of 1 mm Hg.
Temperatures measured with a precision of 0.1 °C.
Temperature range : 29.2 °C to 70.3 °C.
Result : Vapor pressure values ranged from 30 mm Hg at 29.2°C to 200 mm Hg at 70.3°C.
Experimental figures fitted Antoine's equation:
log P = A - B/(t+C)
with:
A = 5.5434
B = 63.5817
C = 12.6886
t: temperature in °C
A Vapour pressure of 27 hPa at 25°C is obtained by extrapolation of these experimental data.
Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Test substance : Trimethyl phosphite supplied by Merck Co., Germany, and fractionnated in an 18-mm internal diameter and 1-m high column packed with Fenske helices at a reflux ratio of 1:20. The middle cuts showing a single peak on a gas-liquid chromatogram were used for the experiments.
Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles.
Flag : Critical study for SIDS endpoint
30.11.2004 (11)

Value : = 32 hPa at 25 °C
Decomposition :
Method : other (measured)
Year :
GLP :
Test substance : no data

Remark : Obtained graphically from:

VP = 10 mm Hg at 12°C
VP = 100 mm Hg at 55°C

Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Reliability : (2) valid with restrictions
Experimental result consistent with other data sources and calculated values.
Flag : Critical study for SIDS endpoint
30.11.2004 (2)

Value : = 34.4 hPa at 25 °C
Decomposition :
Method :
Year :
GLP :
Test substance : no data

Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Reliability : (2) valid with restrictions
Value consistent with standard data source data and calculated values.
Flag : Critical study for SIDS endpoint
02.12.2004 (12)

Value : = 152 hPa at 20 °C
Decomposition :
Method :
Year :
GLP :
Test substance : no data

Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Reliability : (4) not assignable
Cited in Rhodia SDS/MSDS.
30.11.2004

Value : = 30.4 hPa at 25 °C
Decomposition :
Method : other (calculated)
Year :
GLP :
Test substance :

Method : Estimation by MPBPWIN programme, v1.41, US-EPA/Syracuse Research.
Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Reliability : (2) valid with restrictions
Accepted calculation method.
Flag : Critical study for SIDS endpoint
30.11.2004

Value : = 37.5 hPa at 25 °C
Decomposition :
Method : other (calculated)
Year :
GLP :
Test substance :

Method : Estimation by Advanced Chemistry Development (ACD) software Solaris, v4.67 ((C) 1994-2003 ACD).
Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Reliability : (2) valid with restrictions
Accepted calculation method.
Flag : Critical study for SIDS endpoint
30.11.2004

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : at °C
pH value :

Remark : TMP hydrolyses rapidly in water (see section 3.1.2 Stability in water)
Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Flag : Critical study for SIDS endpoint
10.12.2004

Partition coefficient : octanol-water
Log pow : = -.73 at 25 °C
pH value :
Method : other (calculated)
Year :
GLP :
Test substance :

Method : Estimation by KOWWIN programme, v1.67, US-EPA/Syracuse Research.
Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Reliability : (2) valid with restrictions
Accepted calculation method.
Flag : Critical study for SIDS endpoint
10.12.2004

Partition coefficient : octanol-water
Log pow : = -.93 at 25 °C
pH value :
Method : other (calculated)
Year :
GLP :
Test substance :

Method : Estimation by Advanced Chemistry Development (ACD) software Solaris, v4.67 ((C) 1994-2003 ACD).
Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Reliability : (2) valid with restrictions
Accepted calculation method.
Flag : Critical study for SIDS endpoint
10.12.2004

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : at °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable : no

Remark : TMP hydrolyses rapidly in water (see section 3.1.2 Stability in water)
Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Flag : Critical study for SIDS endpoint

30.11.2004

Solubility in	:	Water
Value	:	= 407 g/l at 25 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	other: calculated
Year	:	
GLP	:	
Test substance	:	

Method	:	Estimation by WSKOW programme, v1.41, US-EPA/Syracuse Research.
Source	:	Rhodia Consumer Specialties LTD Oldbury, West Midlands
Reliability	:	(2) valid with restrictions Accepted calculation method.
Flag	:	Critical study for SIDS endpoint

30.11.2004

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value	:	= 15 °C
Type	:	closed cup
Method	:	other: Setaflash Closed Cup
Year	:	
GLP	:	
Test substance	:	no data

Source	:	Rhodia Consumer Specialties LTD Oldbury, West Midlands

30.11.2004 (13)

Value	:	= 54 °C
Type	:	open cup
Method	:	
Year	:	
GLP	:	
Test substance	:	no data

Source	:	Rhodia Consumer Specialties LTD Oldbury, West Midlands

30.11.2004 (2) (4)

Value	:	= 38 °C
Type	:	open cup
Method	:	
Year	:	
GLP	:	
Test substance	:	no data

Source	:	Rhodia Consumer Specialties LTD Oldbury, West Midlands

30.11.2004 (6)

Value : = 27 °C
Type :
Method :
Year :
GLP :
Test substance : no data

Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
30.11.2004 (5)

Value : = 27.8 °C
Type :
Method : other: calculated
Year :
GLP :
Test substance :

Method : Estimation by Advanced Chemistry Development (ACD) software Solaris, v4.67 ((C) 1994-2003 ACD).
Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
30.11.2004

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

Memo : Characteristic odour

Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
02.12.2004 (13)

Memo : Odour threshold 0.0001 ppm (0.0005 mg/m3)

Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
30.11.2004 (12) (2) (14)

Memo : Powerful sickly odour

Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
02.12.2004 (4)

Memo	:	Pyridine-like odour	
Source 02.12.2004	:	Rhodia Consumer Specialties LTD Oldbury, West Midlands	(14)
Memo	:	Vapour density = 4.3	
Source 02.12.2004	:	Rhodia Consumer Specialties LTD Oldbury, West Midlands	(4) (5)

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	Xenon lamp
Light spectrum	:	>= 300 nm
Relative intensity	:	based on intensity of sunlight
Conc. of substance	:	.0001 mmol/l at 25 °C
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	1000000 molecule/cm³
Rate constant	:	= .00000000071 cm³/(molecule*sec)
Degradation	:	= 100 % after .4 hour(s)
Deg. product	:	yes
Method	:	other (measured)
Year	:	2001
GLP	:	
Test substance	:	other TS
Deg. products	:	50-00-0 200-001-8 formaldehyde 512-56-1 208-144-8 trimethyl phosphate
Remark	:	A half-life of 0.27 hour can be calculated from: t1/2 = ln2/k[OH] with: k = 7.1 E-10 cm3/molecule/s [OH] = 1.0 E+06 molecule/cm3
Source	:	Rhodia Consumer Specialties LTD Oldbury, West Midlands
Test condition	:	- Rate constants were measured using a relative rate technique: the relative disappearance rates of TMP and a reference compound (cyclohexene), whose OH radical reaction rate constant is reliably known, were measured in presence of OH radicals. - Irradiation was provided by a 24 kW xenon arc lamp, with the light being passed through a Pyrex filter to remove wavelengths below 300 nm. - Hydroxyl radicals were generated by photolysis of methyl nitrite in air, with NO being added to the reactant mixture to suppress the formation of O3 and hence of NO3 radicals. - Rate constant determination were conducted in dry diluent air at 25°C and 1 atm. - Analysis was performed by in-situ Fourier transform infrared (FT-IR) spectroscopy. - Prior to irradiation, the dark decays of the test substance and the reference substance were monitored for periods of up to 40 mn. The irradiations were conducted for total periods ranging from 10 to 40 mn.
Test substance	:	Trimethyl phosphite, 99.999+% purity, from Aldrich.
Reliability	:	(2) valid with restrictions Study well documented, meets generally accepted scientific principles.
Flag	:	Critical study for SIDS endpoint

02.12.2004 (15)

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	1500000 molecule/cm³
Rate constant	:	= .0000000000084 cm³/(molecule*sec)
Degradation	:	= 50 % after 1.3 day(s)
Deg. product	:	
Method	:	other (calculated)

Year :
GLP :
Test substance :

Method : Estimation by AOP programme, v1.91, US-EPA/Syracuse Research.
Result : Half-life = 1.28 d (12-h per day, 1.5 E+06 OH/cm3)
Half-life = 15.35 h (24-h per day, 1.5 E+06 OH/cm3)
Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Reliability : (2) valid with restrictions
Accepted calculation method.
Flag : Critical study for SIDS endpoint
01.12.2004

3.1.2 STABILITY IN WATER

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : at °C
t1/2 pH9 : at °C
t1/2 pH 10 : = 21 minute(s) at 25 °C
Degradation : > 50 % after 5 minute(s) at pH 6 and 0 °C
Deg. product :
Method : other
Year : 1976
GLP :
Test substance : no data

Result : The following first order rate constants and half-lives were calculated for TMP hydrolysis in the aqueous phase:

Temperature (°C)	Rate constant (1/h)	Half-life (h)
0	0.14	5.1
10	0.40	1.7
25	2.0	0.35

Eliminating the ammonia dropped the pH to 6, resulting in rapid acid catalyzed hydrolysis even at 0°C with > 50% TMP loss in 5 minutes and no detectable residual TMP at 20 minutes.
Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Test condition : An organic solution (170 g) containing 77.4 wt% pentane, 16.4 wt% TMP, 4.3 wt% methanol and 1.9 wt% DMHP (dimethyl phosphonate) was mixed with an aqueous solution (161 g) containing 75 wt% water, 23 wt% NH4Cl and 2 wt% NH3 (pH = 10). The solutions were mixed for about 5 hours at 0, 10 and 25 °C in a rapidly stirred 1 liter flask. TMP levels were followed during the mixing by gas chromatography analysis of samples using an octane internal standard.
Reliability : (2) valid with restrictions
Basic data given.
Flag : Critical study for SIDS endpoint
10.12.2004 (16)

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : at °C
t1/2 pH9 : at °C
Degradation : = 100 % after 30 minute(s) at pH and °C
Deg. product : yes
Method : other
Year : 1992
GLP : no

Test substance : other TS
Deg. products : 13590-71-1 237-027-4 methyl hydrogenphosphonate
868-85-9 212-783-8 dimethyl phosphonate

Method : Preliminary test on stability of trimethyl phosphite, di- and monomethyl phosphonate in water (without buffer), as screening information for the fish toxicity test (see chapter 4.1, study on dimethyl phosphonate/Brachydanio rerio).

Result : Trimethyl phosphite

Test concentration (%) : 1
Hydrolysis (%) : 100
Time (h) : 0.5
Product of hydrolysis : Dimethyl phosphonate
After 30 h the recovery of trimethyl phosphite 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 dimethyl phosphonate, 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 phosphonate remained and 85 % of the expected monomethyl phosphonate 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 monomethyl phosphonate 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.

Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Test condition : Test was conducted with the test substance in pure water, no control of pH. Analysis with phosphorus nuclear magnetic resonance.
Test substance : Trimethyl phosphite, 99.2% purity.
Conclusion : In water being neutral at the beginning of the hydrolysis:
- trimethyl phosphite (concentration 1 %) hydrolyses completely in less than 30 mn,
- dimethyl phosphonate (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
10.12.2004 (17)

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : at °C

t1/2 pH9 : at °C
t1/2 pH : = 8 - 9 minute(s) at 25 °C
Degradation : = 100 % after 61 minute(s) at pH and 25 °C
Deg. product :
Method : other
Year : 1957
GLP :
Test substance : no data

Result : Kinetics of hydrolysis of trimethyl phosphite:
25 % after 8 minutes
50 % after 8-9 minutes
75 % after 10 minutes
100 % after 61 minutes
Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Test condition : In pure water, at 25°C, with equimolar ratios of trimethyl phosphite and water.
Reliability : (2) valid with restrictions
Experimental result consistent with other data sources.
Flag : Critical study for SIDS endpoint
10.12.2004 (18)

Type : abiotic
t1/2 pH4 : = 470 hour(s) at 23 °C
t1/2 pH7 : = 3.1 hour(s) at 23 °C
t1/2 pH9 : at °C
Degradation : = 95.2 % after 2 day(s) at pH 7 and 23 °C
Deg. product : yes
Method : Directive 92/69/EEC, C.7
Year : 2002
GLP : yes
Test substance : other TS
Deg. products : 13590-71-1 237-027-4 methyl hydrogenphosphonate

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.
Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Test condition : - Buffered solution at pH = 4, 7, 9,
- Temperature 23°C,
- Duration up to 432 h (18 d),
- Concentrations tested: 0.10 %.
Analytical method: 31-Phosphorus NMR spectroscopy.
Test substance : Dimethyl phosphonate, CAS 868-85-9, 99.8 % purity.
Reliability : (1) valid without restriction
Guideline study.
Flag : Critical study for SIDS endpoint
10.12.2004 (19)

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : at °C
t1/2 pH9 : at °C
Deg. product :
Method : other
Year : 1969
GLP :
Test substance : other TS

Result : The hydrolysis rate constant of dimethyl phosphonate in water was found to be 1.33 E-05 /s at 50°C.
The values of the rate constants at various temperatures satisfied the Arrhenius's equation [k = A exp(-E/RT)], and the following values were obtained:
E = 22.1 kcal/mol
log A = 10.10
From these experimental results, dimethyl phosphonate hydrolytic half-life at 25°C is calculated to be 10.8 days.
The rate of hydrolysis of the first alkyl group was higher than the rate of hydrolysis of the second alkyl group (demonstrated on diethyl phosphonate).
Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Test condition : Hydrolysis tests were carried out in water at various temperatures, ranging from 50°C to 98°C, and at an initial concentration of substrate of approximately 0.01 mol/l.
Dialkyl phosphonates ranging from dimethyl to dibutyl, linear and branched, were tested.
Dialkyl phosphonates were directly determined in preliminary neutralised samples.
Test substance : Dimethyl phosphonate, CAS 868-85-9, no data.
Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles, basic data given.
Flag : Critical study for SIDS endpoint
10.12.2004 (20)

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : at °C
t1/2 pH9 : at °C
Deg. product :
Method : other
Year : 1972
GLP :
Test substance : other TS

Result : For dimethyl phosphonate, a SN2 reaction kinetics was observed. An hydrolysis rate constant of 1240 l/mol/s at 20°C was obtained.
The rates of hydrolysis decreased when the alkyl chains grow and branch.
Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Test condition : Hydrolysis tests were carried out with a range of dialkyl phosphonates (dimethyl, diethyl, dipropyl, dibutyl, dipentyl, di-i-propyl, di-i-butyl and di-t-butyl). Samples containing 10-20 mg of substrate in 40 ml of water were automatically titrated at constant temperature (ranging from 20°C to 50 °C), under intensive agitation, with 0.1-0.25 N NaOH, in presence of a glass electrode.
Test substance : Dimethyl phosphonate, CAS 868-85-9, no data.
Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles, basic data given.
Flag : Critical study for SIDS endpoint
10.12.2004 (21)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : fugacity model level III
Media :
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: calculation according MacKay, Level III
Year :

Method : Calculation with EPIWIN programme, v3.11, US-EPA/Syracuse Research.
Remark : Trimethyl phosphite hydrolyses rapidly to dimethyl phosphonate in presence of water (see section 3.2.1). Therefore the Level III fugacity modeling is performed on dimethyl phosphonate.
Result : INPUT:
Chem Name : Phosphonic acid, dimethyl ester
Molecular Wt: 110.05
Henry's LC : 3.28e-006 atm-m3/mole (Henrywin program)
Vapor Press : 1 mm Hg (user-entered)
Log Kow : -1.13 (Kowwin program)
Soil Koc : 0.0304 (calc by model)

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
Air: 46.03
Water: 360
Soil: 360
Sediment: 1440
Biowin estimate: 2.956 (weeks)

Advection Times (hr):
Air: 100
Water: 1000
Sediment: 5e+004

EMISSION IN AIR, WATER AND SOIL:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	4.94	46	1000
Water	53.2	360	1000
Soil	41.7	360	1000
Sediment	0.0887	1.44e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	9.15e-011	620	412	20.7	13.7
Water	6.61e-011	854	444	28.5	14.8

Soil	1.92e-009	670	0	22.3	0
Sediment	5.51e-011	0.356	0.0148	0.0119	0.000493

Persistence Time: 278 hr
Reaction Time: 389 hr
Advection Time: 974 hr
Percent Reacted: 71.5
Percent Advected: 28.5

EMISSION IN AIR:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	65.9	46	1000
Water	17.3	360	0
Soil	16.8	360	0
Sediment	0.0289	1.44e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	8.44e-011	572	380	57.2	38
Water	1.49e-012	19.3	10	1.93	1
Soil	5.32e-011	18.6	0	1.86	0
Sediment	1.24e-012	0.00803	0.000334	0.000803	3.34e-005

Persistence Time: 57.7 hr
Reaction Time: 94.6 hr
Advection Time: 148 hr
Percent Reacted: 61
Percent Advected: 39

EMISSION IN WATER:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.125	46	0
Water	99.7	360	1000
Soil	0.0319	360	0
Sediment	0.166	1.44e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	9.44e-013	6.4	4.25	0.64	0.425
Water	5.04e-011	651	338	65.1	33.8
Soil	5.96e-013	0.208	0	0.0208	0
Sediment	4.2e-011	0.271	0.0113	0.0271	0.00113

Persistence Time: 339 hr
Reaction Time: 516 hr
Advection Time: 991 hr
Percent Reacted: 65.8
Percent Advected: 34.2

EMISSION IN SOIL:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.635	46	0
Water	21.9	360	0

Soil	77.4	360	1000
Sediment	0.0365	1.44e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	6.16e-012	41.8	27.7	4.18	2.77
Water	1.42e-011	184	95.5	18.4	9.55
Soil	1.86e-009	651	0	65.1	0
Sediment	1.19e-011	0.0766	0.00319	0.00766	0.000319

Persistence Time: 437 hr
Reaction Time: 498 hr
Advection Time: 3.54e+003 hr
Percent Reacted: 87.7
Percent Advected: 12.3

Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Reliability : (2) valid with restrictions
Accepted calculation method.
Flag : Critical study for SIDS endpoint
02.12.2004

3.3.2 DISTRIBUTION

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)
related to
Contact time : 28 day(s)
Degradation : = 50 (±) % after 28 day(s)
Result : other: not readily biodegradable
Kinetic of testsubst. : 7 day(s) = 44 %
14 day(s) = 50 %
21 day(s) = 50 %
28 day(s) = 50 %
%
Deg. product :
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

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 monomethyl 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.
Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands
Test substance : Dimethyl phosphonate, CAS 868-85-9, 99.2 % purity.
Reliability : (1) valid without restriction

Guideline study.

Flag : Critical study for SIDS endpoint
01.12.2004 (17)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Brachydanio rerio (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC0	:	>= 15.6
Limit test	:	yes
Analytical monitoring	:	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
Remark	:	A preliminary test showed that the test substance dimethyl phosphonate in unbuffered water has a half-life between 50 and 70 hours (See section 3.1.2, study performed with trimethyl phosphite). 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. Expressed as nominal concentration: 96h-LC0 >= 100 mg/l.
Source	:	Rhodia Consumer Specialties LTD Oldbury, West Midlands
Test condition	:	- 3-month old fish 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).
Test substance	:	Dimethyl phosphonate, CAS 868-85-9, 99.2 % purity.
Reliability	:	(1) valid without restriction Guideline study.
Flag	:	Critical study for SIDS endpoint

01.12.2004 (17)

Type	:	static
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 225
Limit test	:	
Analytical monitoring	:	no data
Method	:	other: as described in the "Standard Methods for the examination of Water and Waste Water" (1960)
Year	:	1969
GLP	:	no
Test substance	:	other TS
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.

Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands

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

Test substance : Dimethyl phosphonate, CAS 868-85-9, no data.

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

Flag : Critical study for SIDS endpoint

01.12.2004 (22) (23)

Type : other: not specified
Species : Pimephales promelas (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : = 225
Limit test :
Analytical monitoring : no data
Method : other
Year : 1966
GLP : no
Test substance : other TS

Result : In the report the result is a TLm-value (medium tolerance limit), which is the same as a LC50.

Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands

Test substance : Dimethyl phosphonate, CAS 868-85-9, no data.

Reliability : (4) not assignable
Documentation insufficient for assessment.

01.12.2004 (24)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
EC0 : = 12.5
EC50 : = 24.8
EC100 : = 100
Limit Test : no
Analytical monitoring : yes
Method : Directive 92/69/EEC, C.2
Year : 2003
GLP : yes
Test substance : other TS

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 dimethyl phosphonate (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

Time	DMP 0 d	DMP 2 d	MMP 0 d	MMP 2 d	pH 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

Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands

Test condition : . Test vessel: 50 ml glass beaker holding 10 neonates in 20 ml of test medium
. Experimental design: 5 test concentrations 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 and 48h.

Test substance : Dimethyl phosphonate, CAS 868-85-9, 99.8 % purity.

Reliability : (1) valid without restriction
Guideline study.

Flag : Critical study for SIDS endpoint
01.12.2004

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
EC0	:	>= 100
Limit test	:	yes
Analytical monitoring	:	yes
Method	:	Directive 92/69/EEC, C.3
Year	:	2003
GLP	:	yes
Test substance	:	other TS

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 E+04 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 magnetic 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 dimethyl phosphonate (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.

Source : Rhodia Consumer Specialties LTD Oldbury, West Midlands

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

Test substance : Dimethyl phosphonate, CAS 868-85-9, 99.8 % purity.
Reliability : (1) valid without restriction
Guideline study.
Flag : Critical study for SIDS endpoint
01.12.2004

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type : LD50
Value : = 1350 mg/kg bw
Species : rat
Strain : Sprague-Dawley
Sex : male/female
Number of animals : 16
Vehicle : other: undiluted
Doses : 900, 1350, 2025, 3038 mg/kg
Method : other: screening toxicity study
Year : 1973
GLP : no data
Test substance : other TS

Remark : No information on whether the sample was protected from hydrolysis
Result : Mortality:
900: 0/4
1350: 2/4
2025: 4/4
3038: 4/4
Signs of toxicity:
Hypoactivity, piloerection, laboured breathing, muscular weakness, diarrhea, death. Normal body activity returned within 6 days in surviving animals. Necropsy of animals that died during the study revealed hemorrhages in the gastrointestinal tracts and chemical burns. No gross pathological alterations were noted in survivors.
LD50 was calculated as 1350 mg/kg bw
Test condition : Male and female rats, 2 per sex per group were administered the test material into the stomach using a syringe equipped with a ball-tipped intubating needle. Animals were observed for the following 14 days. Initial and final body weights, mortalities and reactions were recorded. A necropsy was carried out on all animals.
Test substance : Trimethyl phosphite Lot #0411338, purity not stated
Reliability : (2) valid with restrictions
Screening study with acceptable level of documentation.

29.12.2004 (25)

Type : LD50
Value : = 1500 mg/kg bw
Species : rat
Strain : Wistar
Sex : male/female
Number of animals : 50
Vehicle : no data
Doses : 1000, 1300, 1500, 1800, 2000
Method : other
Year : 1979
GLP : no data
Test substance : other TS

Result : Mortality:
1000: 0/10
1300: 1/10
1500: 6/10

1800: 8/10
2000: 10/10
Signs of toxicity:
Decreased locomotor activity, ptosis, piloerection, respiratory depression, death. Normal body activity returned within 7 days in all survivors. Autopsies revealed ulceration of the stomach and adhesion of the stomach, spleen, liver, small intestine and transverse abdomen.
LD50 was calculated as 1500 +/- 58.1 mg/kg bw

Test condition : Male and female rats, 5 per sex per group, weighing 200-300g, were fasted for 24 hours prior to administration of the test material. Administration was oral by intubation. Animals were observed for mortality and signs of toxicity at 1, 3, 6, 24 and 72 hours, then daily to 14 days. All animals were autopsied and observed for gross pathological organ changes. The LD50 value was determined.

Test substance : Trimethyl phosphite 99% containing 2500 ppm nitrogen. Batch analysis not available.

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

29.12.2004 (26)

Type : LD50
Value : = 1595 mg/kg bw
Species : rat
Strain : Wistar
Sex : male/female
Number of animals : 50
Vehicle : no data
Doses : 500, 1000, 1500, 2000, 2500 mg/kg
Method : other
Year : 1976
GLP : no data
Test substance : other TS

Result : Mortality:
500: 0/10
1000: 1/10
1500: 4/10
2000: 8/10
2500: 10/10
Signs of toxicity:
Decreased locomotor activity, ptosis, piloerection, respiratory depression, ataxia, loss of righting reflex, death. Normal body activity returned within 6 days in surviving animals.
LD50 was calculated as 1595.0 +/- 143.4 mg/kg bw

Test condition : Male and female rats, 5 per sex per group, weighing 200-300g, were fasted for 24 hours prior to administration of the test material. Administration was oral by intubation. Animals were observed for mortality and signs of toxicity at 1, 3, 6, 24, 48 and 72 hours, then daily to 14 days.

Test substance : Trimethyl phosphite (TMP-S) 99%. Batch analysis not available.

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

Flag : Critical study for SIDS endpoint

29.12.2004 (27)

Type : LD50
Value : = 1640 mg/kg bw
Species : rat
Strain : Wistar
Sex : male/female
Number of animals : 50

Vehicle : no data
Doses : 1000, 1250, 1500, 1750, 2000 mg/kg
Method : other: no data
Year : 1976
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Result : Mortality:
1000: 0/10
1250: 0/10
1500: 2/10
1750: 7/10
2000: 10/10
Signs of toxicity:
Decreased locomotor activity, ptosis, piloerection, respiratory depression, ataxia, death. Normal body activity returned within 6 days in surviving animals.
LD50 was calculated as 1640.0 +/- 60.1 mg/kg bw

Test condition : Male and female rats, 5 per sex per group, weighing 200-300g, were fasted for 24 hours prior to administration of the test material. Administration was oral by intubation. Animals were observed for mortality and signs of toxicity at 1, 3, 6, 24, 48 and 72 hours, then daily to 14 days. All animals were autopsied and observed for gross pathological organ changes.

Test substance : Trimethyl phosphite Lot# VT-14: 98.5% protected from hydrolysis with N2
Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment.
Flag : Critical study for SIDS endpoint
29.12.2004 (28)

Type : LD50
Value : = 1970 mg/kg bw
Species : rat
Strain : Wistar
Sex : male/female
Number of animals : 50
Vehicle : no data
Doses : 1000, 1600, 2000, 2500, 3000 mg/kg bw
Method : other
Year : 1976
GLP : no data
Test substance : other TS

Remark : Study well documented, meets generally accepted scientific principles, acceptable for assessment.
Result : Mortality:
1000: 0/10
1600: 1/10
2000: 6/10
2500: 9/10
3000: 10/10
Signs of toxicity:
Decreased locomotor activity, ptosis, piloerection, respiratory depression, death. Normal body activity returned within 6 days in all survivors. Autopsies revealed ulceration of the stomach and adhesion of the stomach, spleen, liver, small intestine and transverse abdomen.
LD50 was calculated as 1970 +/- 86.8 mg/kg bw

Test condition : Male and female rats, 5 per sex per group, weighing 200-300g, were fasted for 24 hours prior to administration of the test material. Administration was oral by intubation. Animals were observed for mortality and signs of toxicity at 1, 3, 6, 24 and 72 hours, then daily to 14 days. All animals were autopsied and observed for gross pathological organ changes.

Test substance : Trimethyl phosphite 99% containing 576 ppm nitrogen. Batch analysis not available.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
29.12.2004 (29)

Type : LD50
Value : = 2000 mg/kg bw
Species : rat
Strain : Wistar
Sex : male/female
Number of animals : 50
Vehicle : no data
Doses : 1000, 1500, 1800, 2300, 2800 mg/kg bw
Method : other
Year : 1976
GLP : no data
Test substance : other TS

Result : Mortality:
1000: 0/10
1500: 1/10
1800: 6/10
2300: 8/10
2800: 10/10
Signs of Toxicity:
Decreased locomotor activity, ptosis, piloerection, respiratory depression, death. Normal body activity returned within 5 days in surviving animals. Autopsies revealed ulceration of the stomach and adhesion of the stomach, spleen, liver, small intestine and transverse abdomen.
Test condition : Male and female rats, 5 per sex per group, weighing 200-300g, were fasted for 24 hours prior to administration of the test material. Administration was oral by intubation. Animals were observed for mortality and signs of toxicity at 1, 3, 6, 24 and 72 hours, then daily to 14 days. All animals were autopsied and observed for gross pathological organ changes.
Test substance : Trimethyl phosphite 99%. batch analysis not available.
Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment.
Flag : Critical study for SIDS endpoint
29.12.2004 (30)

Type : LD50
Value : = 2000 mg/kg bw
Species : rat
Strain : Wistar
Sex : male/female
Number of animals : 50
Vehicle : no data
Doses : 1000, 1500, 2000, 2500, 3000 mg/kg bw
Method : other
Year : 1976
GLP : no data
Test substance : other TS

Result : Mortality:
1000: 0/10
1500: 2/10
2000: 6/10
2500: 6/10
3000: 10/10
Signs of toxicity:

Decreased locomotor activity, ptosis, piloerection, respiratory depression, death. Normal body activity returned within 6 days in all survivors. Autopsies revealed ulceration of the stomach and adhesion of the stomach, spleen, liver, small intestine and transverse abdomen.
LD50 was calculated as 2000 +/- 178.5 mg/kg bw

Test condition : Male and female rats, 5 per sex per group, weighing 200-300g, were fasted for 24 hours prior to administration of the test material. Administration was oral by intubation. Animals were observed for mortality and signs of toxicity at 1, 3, 6, 24 and 72 hours, then daily to 14 days. All animals were autopsied and observed for gross pathological organ changes.

Test substance : Trimethyl phosphite 99% containing 1579 ppm nitrogen. Batch analysis not available.

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

Flag : Critical study for SIDS endpoint

29.12.2004 (31)

Type : LD50
Value : = 2240 mg/kg bw
Species : rat
Strain : Wistar
Sex : male/female
Number of animals : 50
Vehicle : no data
Doses : 1000, 1500, 2000, 2500, 3000 mg/kg
Method : other
Year : 1976
GLP : no data
Test substance : other TS

Result : Mortality:
1000: 0/10
1500: 0/10
2000: 2/10
2500: 7/10
3000: 10/10
Signs of toxicity:
Decreased locomotor activity, ptosis, piloerection, respiratory depression, ataxia, loss of righting reflex, death. Normal body activity returned within 8 days in surviving animals.
LD50 was calculated as 2240 +/- 110.8 mg/kg bw

Test condition : Male and female rats, 5 per sex per group, weighing 200-300g, were fasted for 24 hours prior to administration of the test material. Administration was oral by intubation. Animals were observed for mortality and signs of toxicity at 1, 3, 6, 24, 48 and 72 hours, then daily to 14 days.

Test substance : Trimethyl phosphite 99%. Batch analysis not available.

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

Flag : Critical study for SIDS endpoint

29.12.2004 (32)

Type : LD50
Value : = 4280 mg/kg bw
Species : mouse
Strain : ICR
Sex : male/female
Number of animals : 50
Vehicle : no data
Doses : 3000, 3500, 4000, 4500, 5000 mg/kg
Method : other

Year : 1977
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Result : Mortality:
3000: 2/10
3500: 2/10
4000: 3/10
4500: 7/10
5000: 8/10
Signs of toxicity:
Decreased locomotor activity, ptosis, piloerection, respiratory depression, lacrimation, ataxia, convulsions, death. Normal body activity returned within 5 days in surviving animals. Autopsies revealed no outstanding gross pathological organ changes.
LD50 was calculated as 4280.0 +/- 137 mg/kg bw

Test condition : Male and female mice, 5 per sex per group, weighing 18-25 g, were fasted for 24 hours prior to administration of the test material. Administration was oral by intubation. Animals were observed for mortality and signs of toxicity at 1, 3, 6, 24, 48 and 72 hours, then daily to 14 days. All animals were autopsied and observed for gross pathological organ changes.

Test substance : Trimethyl phosphite Lot# VT-14: 98.5% protected from hydrolysis with N2

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

Flag : Critical study for SIDS endpoint

29.12.2004 (33)

5.1.2 ACUTE INHALATION TOXICITY

Type : LC50
Value : = 182 mg/l
Species : rat
Strain : no data
Sex : male
Number of animals : 40
Vehicle : other: air
Doses : 151.38, 162.54, 177.52, 203.21 mg/l
Exposure time : 1 hour(s)
Method : other
Year : 1977
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Result : Mortality:
151.38: 1/10
162.54: 2/10
177.52: 4/10
203.21: 10/10

Observations during exposure were inactivity, incoordination and pallor at all concentrations, with unresponsiveness to sound and laboured respiration at 162.54 mg/l and above.

All surviving animals lost weight for the first 7 days, and made moderate weight gain thereafter.

The one-hour LC50 was calculated to be 182.0 mg/l nominal concentration.

Test condition : The test material was metered, using a syringe infusion pump, via a spraying system driven by houseline air into a 40 litre exposure chamber. 10 male

rats, per group, weighing 200-300g, were exposed to the test material by whole body exposure for 1 hour. Survivors were observed daily and weighed periodically for 14 days post-exposure.
Nominal concentrations (mg/l) were calculated from:
Delivery rate (ml/min) x Density (mg/ml) / Air Flow (l/min).

Test substance : Trimethyl phosphite Lot# VT-14: 98.5% protected from hydrolysis with N2

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

Flag : Critical study for SIDS endpoint

29.12.2004 (34)

Type : LC50
Value : > 9000 ppm
Species : rat
Strain : no data
Sex : male
Number of animals : 30
Vehicle : other: air
Doses : Saturated vapour (9000-14000 ppm)
Exposure time : 4 hour(s)
Method : other
Year : 1969
GLP : no data
Test substance : other TS

Result : Chamber concentrations were:
Initial:
8 h: 9000 ppm
Repeat:
1 h: 14000 ppm
2 h: 9000 ppm
4 h: 9000 ppm
8 h: 10000 ppm
Mortality:
Initial:
8 h: 10/10
Repeat:
1 h: 0/5
2 h: 0/5
4 h: 0/5
8 h: 5/5
Signs of Toxicity:
Observations during the initial exposure were hyperactivity followed by listlessness, eye irritation, respiratory distress and death after 5 or 7 hours. The rats exposed for 4 hours showed hyperactivity, then listlessness and eye irritation but recovered quickly after exposure. The rats exposed for 1 or 2 hours showed minimal signs of irritation and were relatively normal when removed from the chamber. Of the rats exposed for 8 hours, 3 were dead by 7 hours. The remaining 2 died immediately after removal from the chamber. They showed signs of irritation. On necropsy, their lungs showed signs of haemorrhage and exudate.
A 5-6 hour exposure was considered as an approximate time likely for 50% survival to a saturated atmosphere. LC50/5 h was considered to be approximately 10000 ppm.
From this study, LC50/4h > 9000 ppm (45.7 mg/l).

Test condition : Initially, 10 male rats were to be exposed to a saturated atmosphere of the test material by whole body exposure for 8 hours. Following mortalities during the exposure period, further tests exposed 5 male rats per group to a saturated atmosphere for 1, 2, 4 and 8 hours.
Nominal concentrations were calculated from the amount of material used and the total air volume.

Test substance : Trimethyl phosphite, purity unstated. No precautions were taken to prevent hydrolysis to dimethyl hydrogen phosphite.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
29.12.2004 (35)

Type : LC50
Value : < 203.21 mg/l
Species : rat
Strain : no data
Sex : male
Number of animals : 10
Vehicle : other: air
Doses : 203.21 mg/l
Exposure time : 1 hour(s)
Method : other
Year : 1976
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Result : Mortality:
203.21: 10/10
Observations during exposure were incoordination, pallor, unresponsiveness to sound and laboured respiration. All animals were found dead at 18 hours.
The test material was lethal to male rats exposed to 302.21 mg/l nominal concentration for one hour.
Test condition : The test material was metered, using a syringe infusion pump, via a spraying system driven by houseline air into a 40 litre exposure chamber. 10 male rats, average weight 239g, were exposed to the test material by whole body exposure for 1 hour. Survivors were observed daily and weighed periodically for 14 days post-exposure.
Nominal concentration was calculated from the amount of material used and the total air volume.
Test substance : Trimethyl phosphite Lot# VT-14: 98.5% protected from hydrolysis with N2
Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment. Single concentration only tested.
Flag : Critical study for SIDS endpoint
29.12.2004 (36)

Type : LC50
Value : > 19.7 mg/l
Species : rat
Strain : Sprague-Dawley
Sex : male/female
Number of animals : 10
Vehicle : other: none
Doses : 19.7 mg/l
Exposure time : 1 hour(s)
Method : other: range-finding study for 4-week inhalation study
Year : 1978
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Remark : The single concentration tested in this range-finding study was not high enough to assist in determining an acute LC50 value.
Result : During the exposure period, a total of 35.4 g of test material was delivered, yielding a nominal concentration of 19.7 mg/l.
There were no mortalities during or after exposure.
No abnormalities were observed during the exposure period. At termination of the exposure some animals exhibited excessive lacrimation. Upon

removal from the exposure chamber, signs observed in some of the animals were yellow staining of the ano-genital fur, excessive salivation, excessive lacrimation and mucoid discharge. Mucoid nasal discharge, dry rales and yellow staining of the ano-genital area were noted sporadically in the 4-hour post-exposure period. Signs observed in the 14-day in-life period were mucoid nasal discharge, red nasal discharge, dry rales, laboured breathing, hair loss and poor general condition. All animals lost weight immediately after the exposure. Two males and one female continued to lose weight up to day 7. The only necropsy observations considered to be related to exposure to the test substance were a high incidence of lung discolouration. The one-hour LC50 is greater than 19.7 mg/l nominal concentration.

Test condition : An aerosol was generated by passing a stream of nitrogen through a nebuliser fitted to a flask containing TMP. The aerosol was diluted with dry air.
Male and female rats, 5 per sex per group, weighing 216-295g, were exposed to the test material by whole body exposure in a 26.5 litre inhalation chamber for 1 hour. The flask containing the test material was weighed before and after the exposure period to determine the nominal exposure concentration. Animals were observed for abnormal signs continuously during exposure, upon removal from the exposure chamber, hourly post-exposure for four hours, then daily for 14 days. All animals were autopsied and observed for gross pathological organ changes.

Test substance : Trimethyl phosphite, Distilled Lot# 0110815100 (containing 3 ppm N): 99.67% TMP, kept under nitrogen.

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

29.12.2004 (37)

5.1.3 ACUTE DERMAL TOXICITY

Type : LD50
Value : = 933.8 mg/kg bw
Species : rabbit
Strain : New Zealand white
Sex : male/female
Number of animals : 64
Vehicle : other: none
Doses : 266.7, 400, 600, 900, 1350, 2025, 3000, 4556 mg/kg
Method : other
Year : 1973
GLP : no data
Test substance : other TS

Result : Mortality (Run #1):
900: 4/4 (day 3)
1350: 3/4 (day 3-5)
2025: 2/4 (day 3)
3000: 3/4 (day 3-12)
4556: 4/4 (day 2-3)
Mortality (Run #2):
400: 2/4 (day 3)
600: 0/4
Mortality (Run #3):
266.7: 0/8
400: 0/4
600: 1/4 (day 4)
900: 2/4 (day 4)
1350: 2/4 (day 2-4)
2025: 2/4 (day 2-4)

3000: 4/4 (day 2-4)
4556: 4/4 (day 2-3)

Signs of toxicity:
Hypoactivity, muscular weakness and laboured breathing were noted prior to death. No behavioural reactions were noted in survivors. Local skin reactions were characterised by mild erythema after 24 hours, followed by slight desquamation by 7 days. Autopsies of animals which died during the study revealed haemorrhaged lungs and enlarged gall bladders. No gross pathological alterations were noted in surviving animals.
LD50 was calculated as 933.8 mg/kg bw (95% Confidence Limits 578.0-1508.8) based on 8 animals per dose level.

Test condition : 24 hours prior to the dermal applications, the backs of the rabbits were shaved free of hair over about 20% of the total body surface. Initially, two male and two female rabbits were tested at each dose level (one per sex abraded skin, one per sex non-abraded), with more animals being used in later runs to better define the LD50. The test site was covered by wrapping the trunk of the animal with impervious plastic sheeting securely taped in place. At the end of the 24 hour period all residual test material was removed. Animals were observed for mortality, local skin reactions and behavioural abnormalities for a total of 14 days. A necropsy was carried out on all animals.

Test substance : Trimethyl phosphite Lot #0411338. Batch analysis not available.

Reliability : (2) valid with restrictions
Study well reported, meets generally accepted scientific principles.

Flag : Critical study for SIDS endpoint

30.12.2004 (25)

Type : LD50
Value : = 7500 mg/kg bw
Species : rabbit
Strain : New Zealand white
Sex : male
Number of animals : 12
Vehicle : other: none
Doses : 6.0, 7.5, 9.2 g/kg bw
Method : other
Year : 1977
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Result : Mortality:
6000: 0/4
7500: 2/4
9200: 4/4

Signs of toxicity:
Hypoactivity were noted prior to death at 9200 mg/kg. No other reactions were noted at any dose level.
No dermal reactions were reported.

LD50 was calculated as 7500 ± 390 mg/kg bw.

Test condition : 12 male New Zealand white rabbits, 4 per group, weight 2.3 to 3.0 kg were used.
The animals were immobilised and their backs were clipped free of hair over about 10% of the total body surface. Animals were observed for mortality at 1, 3, 6, 24, 48 and 72 hours then daily for a total of 14 days. The dermal LD50 was calculated.

Test substance : Trimethyl phosphite Lot# VT-14: 98.5% protected from hydrolysis with N2

Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles, acceptable for assessment. Restrictions: no information on whether sites were abraded or

on occlusion status. Limited observations, no necropsy reported.

29.12.2004 (38)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Occlusive
Exposure time	:	24 hour(s)
Number of animals	:	6
Vehicle	:	no data
PDII	:	0
Result	:	not irritating
Classification	:	not irritating
Method	:	other: in accordance with Section 1500.41 of the Federal Hazardous Substance Labelling Act
Year	:	1976
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	In accordance with Section 1500.41 of the Federal Hazardous Substance Labelling Act
Result	:	Mean Score Intact skin: Erythema 24 h: 0 72 h: 0 Oedema: 24 h: 0 72h: 0 Subtotal: 0 Abraded skin: Erythema 24 h: 0 72 h: 0 Oedema: 24 h: 0 72h: 0 Subtotal: 0 PDII: 0
Test condition	:	Prior to the dermal applications, the hair was clipped from the back and sides of 6 New Zealand albino rabbits. A one inch square was abraded to the left of the spinal column while a one inch square on the right was left intact. 0.5 ml of undiluted test material (0.5 g moistened with a minimal amount of water) was applied to each of the test sites. The test sites were occluded with gauze patches secured by tape. The rabbits were wrapped with rubber damming. At the end od 24 hours, the wrappings, patches and residual test material were removed. The test sites were examined and scored for erythema, oedema and eschar formation. The sites were examined again after 72 hours and the primary dermal irritation index was calculated.
Test substance	:	Trimethyl phosphite Lot# VT-14: 98.5% protected from hydrolysis with N2
Reliability	:	(2) valid with restrictions Short report on test comparable to guideline study.
Flag	:	Critical study for SIDS endpoint

29.12.2004 (39)

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Occlusive
Exposure time	:	24 hour(s)
Number of animals	:	6
Vehicle	:	water
PDII	:	1.3
Result	:	slightly irritating
Classification	:	not irritating
Method	:	Draize Test
Year	:	1973
GLP	:	no data
Test substance	:	other TS

Result : Mean Score:

Intact skin:
Erythema
24 h: 1.3
72 h: 0.5
Oedema:
24 h: 0.7
72h: 0.0
Subtotal: 2.5

Abraded skin:
Erythema
24 h: 1.2
72 h: 0.5
Oedema:
24 h: 0.8
72h: 0.0
Subtotal: 2.6

PDII: 1.3

Test condition : Prior to the dermal applications, the hair was clipped from the back and flanks of 6 New Zealand albino rabbits. Two test sites were selected; one was abraded the other remained intact. 0.5 ml of undiluted test material (0.5 g moistened with a minimal amount of water) was applied to each of the test sites. The test sites were occluded with gauze patches secured by masking tape. The trunk of each animal was wrapped with impervious plastic sheeting. At the end of the 24 hour period all residual test material was removed. The test sites were examined and scored for erythema and oedema. The sites were examined again after 72 hours and the primary dermal irritation index was calculated.

Test substance : Trimethyl phosphite Lot #0411338, purity not stated

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

Flag : Critical study for SIDS endpoint

17.12.2004 (25)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.1 ml
Exposure time	:	168 hour(s)
Comment	:	not rinsed
Number of animals	:	6
Vehicle	:	none

Result : not irritating
Classification : not irritating
Method : other: In accordance with Section 1500.42 of the Federal Hazardous Substance Labelling Act
Year : 1976
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Result :

Mean Scores	1	24	48	72	7d	
Cornea:		0	0	0	0	0
Iris:	0	0	0	0	0	
Conjunctiva:	0	0	0	0	0	
Total:	0	0	0	0	0	

Test condition : 6 New Zealand albino rabbits were used in the study. 0.1 ml of undiluted test material was instilled into the conjunctival sac of one eye of each rabbit. The treated eyes remained unwashed. Ocular reactions were graded at each scoring period of 1, 24, 48 and 72 hours, 4 and 7 days.
Test substance : Trimethyl phosphite Lot# VT-14: 98.5% protected from hydrolysis with N2
Reliability : (2) valid with restrictions
Short report of test comparable to guideline study
Flag : Critical study for SIDS endpoint
29.12.2004 (40)

Species : rabbit
Concentration : undiluted
Dose : .1 ml
Exposure time : 168 hour(s)
Comment : not rinsed
Number of animals : 6
Vehicle : none
Result : slightly irritating
Classification : not irritating
Method : Draize Test
Year : 1973
GLP : no data
Test substance : other TS

Result :

Mean Scores	1h	24h	48h	72h	7d	
Cornea:		0.0	0.0	0.0	0.0	0.0
Iris:	5.0	0.0	0.0	0.0	0.0	
Conjunctiva:	6.0	1.3	0.0	0.0	0.0	
Total:	11.0	1.3	0.0	0.0	0.0	

Test condition : 6 New Zealand albino rabbits were used in the study. 0.1 ml of undiluted test material was instilled into the conjunctival sac of the right eye of each rabbit. At each scoring period of 1, 24, 48 and 72 hours, and 7 days, the cornea, iris and conjunctiva were examined and graded.
Test substance : Trimethyl phosphite Lot #0411338, purity not stated
Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles.
Flag : Critical study for SIDS endpoint
17.12.2004 (25)

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Type : Sub-acute
Species : rat

Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	21 days
Frequency of treatm.	:	Consecutive days
Post exposure period	:	None
Doses	:	32.8, 164, 328 mg/kg
Control group	:	yes, concurrent no treatment
NOAEL	:	= 32.8 mg/kg
Method	:	other
Year	:	1977
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Remark : The purpose of the study was to define the maximum tolerable intake and to establish dose levels for a 90-day study.

Result : Mortality:
0 1/10 (m)
32.8 0/10
164 1/10 (m)
328 8/10 (4m, 4f)
Clinical observations:
328 mg/kg: Decreased locomotor activity, abnormal gait, rough coat in all animals
164 mg/kg: Decreased locomotor activity in 5 animals
Bodyweight:
Females at 164 and 328 mg/kg showed significantly lower bodyweight gain in weeks 2 & 3.
Food consumption:
Females at 328 mg/kg: sig. lower in weeks 2 & 3
Females at 164 mg/kg: sig. lower in week 3
Food utilisation:
Males at 328 mg/kg: inferior week 2
Females at 164 & 328 mg/kg: inferior weeks 2 & 3
Haematology, Clinical chemistry, Urinalysis: No significant differences
Gross pathology:
328 mg/kg: All animals congestion of stomach. 2 animals loss of mucosal surface of stomach plus minor effects in lungs, kidneys, liver.
Controls, 32.8 & 164 mg/kg: minor changes in lungs kidneys & stomach

NOAEL: 32.8 mg/kg
Effects demonstrated dose-response

Test condition : TEST ANIMALS
Age: 28 days
Weight at study initiation: m: 82-185 g, f: 97-154 g
Number of animals: 40 (5/sex/group)

ADMINISTRATION / EXPOSURE
The test substance was kept refrigerated and under nitrogen during the study. TMP was administered orally by gavage for 21 consecutive days.

CLINICAL OBSERVATIONS AND FREQUENCY:
Clinical signs: observed daily for neurological deficits and changes in gross external appearance.
Mortality: observed daily
Body weight: weekly
Food consumption/ food utilisation efficiency: weekly
Haematology parameters:
Hemoglobin, hematocrit, WBC (total and differential)
Clinical chemistry: Alkaline phosphatase, BUN, SGOT, SGPT, Bilirubin, FBS
Urinalysis:
Specific gravity, pH, protein, ketones, sediment

POST-MORTEM STUDIES:
Macroscopic: All major organs

Test substance : Trimethyl phosphite Lot# VT-14: 98.5% protected from hydrolysis with N2
Reliability : (2) valid with restrictions
29.12.2004 (41)

Type : Sub-chronic
Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : 90 days
Frequency of treatm. : Consecutive, daily
Post exposure period : None
Doses : 40.0, 80.0, 160.0 mg/kg
Control group : yes
NOAEL : = 80 mg/kg
Method : other
Year : 1977
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Result : Mortality:

0	0/30
40	0/30
80	0/30
160	7/30 (4m, 3f)

Clinical observations:
160 mg/kg: Tremors in weeks 11 in two animals
Bodyweight:
Males at 160 mg/kg showed significantly lower bodyweight gain in weeks 6-9 and 11-13
Females at 160 mg/kg showed significantly lower bodyweight gain in weeks 11 and 12.
Food consumption:
Males at 160 mg/kg: significantly lower than controls in all weeks except 9 & 10
Females at 160 mg/kg: significantly lower in weeks 11 & 12
Food utilisation:
No consistent pattern was seen
Haematology, Clinical chemistry, Urinalysis: No significant differences
Organ weight & organ to bodyweight ratio:
160 mg/kg/d: significantly higher adrenal, brain, kidney weight. Females also showed significantly higher relative heart & spleen weights.
Gross pathology:
Chronic pulmonary disease in 1 or 2 animals from all groups.
160 mg/kg/d: 1 animal with irregular thickening of the stomach, 2 animals with decrease in size of spleen.
40.0, 80.0 mg/kg/d: no significant effects.
Histopathology:
160 mg/kg/d:
Liver: Minor fatty changes in 2/12 females and 10/12 males. 3 males also showed occasional hepatocytes containing an eosinophilic substance, probably representing a change in cytoplasmic proteins.
Gonads: Hypoplasia in 11/12 males. Spermatogenesis was reduced, with spermatogonia and other spermatogenic cells reduced in size and number. However, the density of sperm in the epididymis was not greatly or uniformly reduced.
40.0, 80.0 mg/kg/d: no significant effects.

NOAEL: 80 mg/kg/day

Test condition : TEST ANIMALS
Age: approximately 5 weeks
Weight at study initiation: 100-150 g
Number of animals: 120 (15/sex/group)
ADMINISTRATION / EXPOSURE
The test substance was administered orally by gavage as a 10% solution in corn oil for 90 consecutive days. Before dosing, a steady stream of nitrogen was continuously passed over the sample to prevent the accumulation of moisture. The study report does not specify whether control animals were administered vehicle only or were untreated.
CLINICAL OBSERVATIONS AND FREQUENCY:
Clinical signs: observed at least 3 times daily for pharmacologic and/or toxic effects.
Body weight: weekly
Food consumption/ food utilisation efficiency: weekly
Haematology parameters (15 m & 5 f per group):
Hemoglobin, Erythrocyte, haemoglobin, reticulocyte, red cell induced MCV, MCH, MCHC, WBC (total and differential), platelet count, haematocrit
Clinical chemistry: Serum alkaline phosphatase, BUN, SGOT, SGPT, Bilirubin, total lipid & uric acid, total cholesterol, glucose, lactic acid hydrogenase, total protein.
Urinalysis:
Volume, specific gravity, pH, colour, protein, glucose, ketones, sediment, bile
POST-MORTEM STUDIES:
Macroscopic: All major organs for animals dying during study and at termination.
Histopathology;
26 organs examined in corntrol & high dose.
STATISTICAL ANALYSIS:
Conducted on bodyweight, food consumption, feed efficiency, organ weight and organ to bodyweight ratio.

Test substance : Trimethyl phosphite Lot# VT-14: 98.5% protected from hydrolysis with N2

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

Flag : Critical study for SIDS endpoint

29.12.2004 (42)

Type : Sub-acute
Species : rabbit
Sex : male/female
Strain : New Zealand white
Route of admin. : dermal
Exposure period : 21 days
Frequency of treatm. : 6 hours per day, 21 consecutive days
Post exposure period : none
Doses : 300, 600, 1200 mg/kg
Control group : yes, concurrent vehicle
LOAEL : = 300 mg/kg bw
Method : other
Year : 1977
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Result : Mortality:

0	0/12
300	1/12 (female, abraded, day 17)
600	2/12 (2 females, abraded, days 8 & 17)
1200	11/12 (5 males, days 8-12 + 6 females, days 3-16)

Clinical observations:

600, 1200 mg/kg: Vocalisation after application, decreased locomotor activity, loss of righting reflex
300 mg/kg: Vocalisation after application, decreased locomotor activity

Irritation:
Treated animals showed dermal irritation (erythema and oedema) which was dose-related, more severe in animals with abraded skin, and increasing in severity over time.

Bodyweight:
Males at 1200 mg/kg showed significantly lower bodyweight gain.

Food consumption: No consistent effect
Clinical chemistry: significant decrease in cholinesterase in all groups, including controls

Haematology, Urinalysis: No significant differences
Gross pathology:
Dose-related incidence of light coloured spots on lungs.

Histopathology:
1200 mg/kg: Tissues not examined due to autolysis
600 mg/kg: Lung: congestion & oedema. Liver: advanced parenchymatious degeneration with chronic round cell infiltration
300 mg/kg: Lung: congestion and oedema of same degree as for 600 mg/kg. Liver: changes less marked than for 600 mg/kg
The effects in the lungs and liver were considered to be drug-related and of quantitative significance.

Test condition : TEST ANIMALS:
Weight at study initiation: 2-3.5 kg
Number of animals: 48 (6/sex/group)
Trunks of all animals were clipped free of hair. The skin of half of the animals was further prepared by making epidermal abrasions longitudinally 2 and 3 cm apart. Test substance applied undiluted to 10-15% total body surface. Test material remained in contact with the skin for 6 hours per day after which it was removed by gentle washing with watrm water and wiping with a soft cloth. The procedure was repeated for a total of 21 days.
CLINICAL OBSERVATIONS AND FREQUENCY
Mortality & behavioural reactions, erythema, edema: daily
Body weight, food consumption: weekly
Haematology: Haematocrit, RBC, total & differential leukocytes, haemoglobin, initially & terminally.
Clinical chemistry: SGPT, fasting blood sugar, serum albumin, SGOT, cholinesterase, initially & terminally.
Urinalysis: pH, glucose, protein, specific gravity, albumin, bilirubin, initially & terminally
Gross pathology:
Heart, lung, pancreas, spleen, skin, liver, kidney, adrenals, gonads, brain, muscle, thyroid.
Organ weights:
Lung, kidney, liver, brain, spleen, adrenal.
Histopathology:
13 major organs

Test substance : Trimethyl phosphite Lot# VT-14: 98.5% protected from hydrolysis with N2

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

Flag : Critical study for SIDS endpoint

30.12.2004 (43)

Type : Sub-acute

Species : rat

Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	inhalation
Exposure period	:	4 weeks
Frequency of treatm.	:	6 hours per day, 5 days per week
Post exposure period	:	none
Doses	:	target concentration: 100(0.51), 300(1.52), 600(3.04) ppm (mg/l) effective inhaled concentration: 104(0.53), 292(1.48), 581(2.95) ppm(mg/l)
Control group	:	yes, concurrent vehicle
NOAEL	:	= 104 ppm
LOAEL	:	= 292 ppm
Method	:	other: comparable to guideline 407
Year	:	1979
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	NOAEL: 104 ppm (= 0.51 mg/l)

TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:

Mortality and time to death:
292 ppm (number of deaths in each of weeks 1-4): 1, 0, 0, 0
581 ppm (number of deaths in each of weeks 1-4): 0, 0, 2, 5
Deaths were considered to be treatment-related

Clinical observations considered related to treatment (number of animals affected):
104 ppm:
Yellow staining of ano-genital fur (2)
292 ppm:
Yellow staining of ano-genital fur (10)
Laboured breathing (6)
Excessive lacrimation (9)
Chromodacryorrhea (6)
581 ppm:
Yellow staining of ano-genital fur (11)
Laboured breathing (18)
Reduced activity (18)
Coldness of body (3)
Poor general condition (4)
Excessive lacrimation (16)
Chromodacryorrhea (18)
Closed eyes (2)

Bodyweight gain:
581 ppm:
Mean body weights and weight gains lower throughout duration of the study

Haematology:
581 ppm:
Elevated red blood cell count (males)

Clinical chemistry, Urinalysis:
No significant treatment-related findings

Ophthalmic examination:
The following effects on eyes observed clinically (number of animals) were considered to be secondary to infectious disease and/or debilitation.
104 ppm:
Corneal opacity (1)
292 ppm:
Corneal opacity (4)

Cloudy eyes (3)
581 ppm:
Corneal opacity (2)
Cloudy eyes (11)
Film covering one or both eyes (5)

Organ weights, Organ/Body weight ratios, Organ/Brain weight ratios:
292 ppm:
Increased kidney weight, kidney/bw, kidney/brain weight (f)
581 ppm:
Terminal body weight depression
Decreased brain weights, increased brain/bw ratio
Decreased kidney weight, increased kidney/bw ratio, increased kidney/brain weight (f)
Other significant increases in organ/bw ratio were considered to reflect depressed terminal bodyweight
Decreased liver/brain weight (m)

Gross pathology:
Scattered lung abnormalities in all groups
581 ppm:
Increased lung discoloration
Stomach abnormalities

Histopathology:
292 ppm:
Cataracts
581 ppm:
Acute bronchiolitis, granulomatous foci, oedema, focal acute inflammatory cell infiltrate. These changes were considered to be effects of exacerbations of pneumonitis, which was already present in animals in all test groups, including controls.
Cataracts

Test condition : TEST ANIMALS
Age on receipt: 5 weeks
Equilibration period: 2 weeks
Weight at study initiation: m: 247-316 g (mean 283 g), f: 157-189 g (mean 174 g)
Number of animals: 80 (10/sex/group)

ADMINISTRATION / EXPOSURE
Determination of chamber concentration:
A calibration curve relating concentration to the absorption at this wavelength was prepared. Three 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 was used to volatilise the TMP.

CLINICAL OBSERVATIONS AND FREQUENCY:
Clinical signs: observed daily; full recorded physical assessment was performed weekly.
Mortality: observed daily
Body weight: weekly.
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: at termination (added to protocol by amendment due to in-life observations)
Haematology: 5/sex/group once in week 4; parameter evaluated: Hemoglobin, hematocrit, erythrocyte count, leukocyte count, (total and differential), clotting time

Clinical chemistry: 5/sex/group once in week 4; parameter evaluated: Blood urea nitrogen, serum glutamic pyruvic transaminase, serum alkaline phosphatase, glucose
Urinalysis: 5/sex/group 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: 27 tissues fixed and exposed to histopathology
STATISTICAL METHODS: Body weights, hematology, clinical chemistry paramethers, organ weights, and organ/body weight ratios were statistically evaluated; References: Dunnett, C.W. J. Am. Sta. Assn., Vol. 50 (1955), Biometrics, Vol. 20 (1964)

Test substance : Trimethyl phosphite, Distilled Lot# 0110815100 (containing 3 ppm N): 99.67% TMP, kept under nitrogen.

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

Flag : Critical study for SIDS endpoint

30.12.2004 (44) (45)

Type : Sub-acute
Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : inhalation
Exposure period : 28 days
Frequency of treatm. : 6 hours/day, 5 days/week
Post exposure period : 8 weeks
Doses : target concentration: 100(0.51), 600(3.04) ppm (mg/l)
effective inhaled concentration: 105(0.53), 600(3.04) ppm(mg/l)
Control group : yes, concurrent vehicle
LOAEL : = 105 ppm
Method : other
Year : 1979
GLP : no data
Test substance : other TS

Remark : Following the observation of lenticular opacities in a 28-day inhalation study, a repeat study was carried out. This study was designed to confirm or deny, by in vivo examination and by histopathology, that lenticular cataracts are produced in rats by inhalation of the test substance at high concentration (600 ppm) and that no cataracts are produced by inhalation of a lower concentration (100 ppm). In addition, to establish whether cataracts, if produced, are reversible.

Result : LOAEL: 105 ppm (= 0.51 mg/l)

TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:

Mortality:
Control: 1 (f)
600 ppm: 31 (m), 20 (f) (exposure week 3-4)

Clinical Signs:
No relevant non-ocular clinical observations were recorded

Ophthalmoscopy:
105 ppm:
Reversible striate opacities (7/30)
600 ppm:

Irreversible cataracts in almost all animals

Bodyweight gain:
600 ppm:
Mean body weights and weight gains lower throughout weeks 1-5.
Bodyweight gain for survivors had become comparable to controls by the end of the 8 week recovery period.

Organ weights:
600 ppm
Increase in absolute and relative lung weights.

Gross pathology:
105 ppm:
No significant findings
600 ppm:
High incidence of lung abnormalities

Histopathology:
600 ppm:
Mortality from acute bronchopneumonia was high (23/31 m, 14/20 f)
Pulmonary granulomatous foci (22/31 m, 10/20 f)
Irreversible cataracts.

Focal pneumonitis was noted in all groups, including controls. This was more reversible in females than males. Evidence of pulmonary complications was first evident from the second week of exposure.

Test condition : TEST ORGANISMS
Age on receipt: 4 weeks
Equilibration period: 6 weeks
Weight at study initiation: m: 247-316 g (mean 283 g), f: 157-189 g (mean 174 g)
Number of animals: 152 (20/sex/group for control & 100 ppm, 36/sex at 600 ppm to compensate for anticipated mortalities)
ADMINISTRATION / EXPOSURE
Determination of chamber concentration:
A calibration curve relating concentration to the absorption at this wavelength was prepared. Four 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. In addition, three samples per day were taken and analysed by gas chromatography.
Vehicle: nitrogen
CLINICAL OBSERVATIONS AND FREQUENCY:
Clinical signs: observed daily; full recorded physical assessment was performed weekly.
Mortality: observed twice daily
Body weight: weekly during exposure and post-exposure period
Organ weight: lungs only
Food consumption: no
Water consumption: no
Ophthalmoscopic examination:lids, lacrimal apparatus and conjunctiva were examined grossly; cornea, anterior chamber, lens, vitreous humour, retina and optic disc were examined by split lamp and ophthalmoscope.
Examinations were made pre-test, at 2 and 4 weeks of exposure and at 2 and 4 weeks post-exposure.
Haematology: no
Clinical chemistry: no
Urinalysis: no
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
Macroscopic: yes; all animals dying during study or killed in extremis and at

scheduled sacrifice respectively
Microscopic: lungs with main stem bronchi, eyes (both) and gross lesions

Test substance : Trimethyl phosphite, Distilled Lot# 01159150, purity not stated
Reliability : (2) valid with restrictions
Comparable to guideline study, but examining limited endpoints. Full report not available for assessment
Flag : Critical study for SIDS endpoint
29.12.2004 (46) (47)

Type : Sub-acute
Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : inhalation
Exposure period : 4 weeks
Frequency of treatm. : 6 hours/day, 5 days/week
Post exposure period : 8 weeks
Doses : Target concentration: 10 (0.051), 50 (0.25), 100(0.51), ppm (mg/l)
Effective inhaled concentration: 10 (0.051), 51 (0.26), 101(0.51) ppm (mg/l)
Control group : yes, concurrent vehicle
NOAEL : = 10 ppm
Method : other
Year : 1979
GLP : no data
Test substance : other TS

Result : NOAEL: 10 ppm (0.051 mg/l)

TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
Mortality:
Control: 1m & 1f died spontaneously on day 12 during ophthaloscopic examination.
There were no deaths in test groups.

No non-ocular clinical observations were considered to be treatment-related.

Ophthalmoscopy:
Abnormalities were first observed at the week 4 examination:
50 ppm:
Irregularities of the corneal surface (3/15 m, 7/17 f)
101 ppm:
Irregularities of the corneal surface (5/15 m, 7/17 f)
Week 2 post-exposure:
50 ppm
Lenticular opacities (2/10f)
101 ppm
Lenticular opacities (6/10f)
Both effects were considered to be dose-related, but rats corneal irregularities did not necessarily progress to opacity, nor were opacities necessarily preceded by irregularities.
Week 4 post-exposure:
101 ppm
Lenticular opacities (3/5f, in one case opacity reduced to unilateral)
Week 8 post-exposure:
Lenticular opacities (2/5f)
Test material was concluded to be cataractogenic and a corneal irritant at 50 and 100 ppm.

Bodyweight gain:
Bodyweigh gain was comparable to controls throughout the study.

Organ weights, organ/bodyweight ratios:

No statistical differences from controls.

Gross pathology:
Lung discoloration was seen in a number animals from all groups including controls. Neither this nor any other abnormality was considered to be test substance-related.

Histopathology:
50 and 101 ppm:
Mild inflammatory changes in corneas of approximately 60% of males and females sacrificed after 4 weeks exposure. This was not observed at the 10 ppm level, or in any animal sacrificed after the 2 or 8 week recovery period.

Test condition : TEST ORGANISMS
Age: 28 days
Weight at study initiation: m: 319-411), f: 171-242 g
Number of animals: 220 (20/sex/group)
ADMINISTRATION / EXPOSURE
Determination of chamber concentration:
A calibration curve relating concentration to the absorption at this wavelength was prepared. Four 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. In addition, three samples per day were taken and analysed by gas chromatography.
Vehicle: nitrogen
CLINICAL OBSERVATIONS AND FREQUENCY:
Clinical signs: observed daily; full recorded physical assessment was performed weekly.
Mortality: observed twice daily
Body weight: weekly during exposure and post-exposure period
Organ weight: lungs only
Food consumption: no
Water consumption: no
Ophthalmoscopic examination:lids, lacrimal apparatus and conjunctiva were examined grossly; cornea, anterior chamber, lens, vitreous humour, retina and optic disc were examined by split lamp and ophthalmoscope.
Examinations were made pre-test, at 2 and 4 weeks of exposure and at 2 and 4 weeks post-exposure.
Haematology: no
Clinical chemistry: no
Urinalysis: no
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
Macroscopic: yes; all animals dying during study or killed in extremis and at scheduled sacrifice respectively
Microscopic: lungs with main stem bronchi, eyes (both) and gross lesions

Test substance : Trimethyl phosphite, purity not stated.

Reliability : (2) valid with restrictions
Comparable to guideline study, but examining limited endpoints.

Flag : Critical study for SIDS endpoint

29.12.2004 (48) (49)

Type : Sub-chronic
Species : rat
Sex : male
Strain : no data
Route of admin. : inhalation
Exposure period : 8 weeks
Frequency of treatm. : 7.5 hours/day, 5 days/week
Post exposure period : none
Doses : Target concentration 500 ppm (2.54 mg/l) +/- 15%
Control group : yes, concurrent vehicle

LOAEL : = 500 ppm
Method : other
Year : 1971
GLP : no data
Test substance : other TS

Remark : Photomicrographs of the lung and skin lesions were re-examined by Mobil toxicologists. The conclusions of the study were considered to be unreliable for several reasons:

1. In 1971, when the study was conducted, chronic respiratory disease was extremely common in laboratory rats. It was accepted that TMP exposure contributed to the inflammatory responses, but the lung lesions (squamous metaplasia, local proliferative responses and severe inflammation) were considered to be characteristic of "chronic murine pneumonia with bronchiectasis".

2. Accurate systems for measuring chamber concentration were not available at the time of the study. Results of later inhalation studies of 4 weeks duration indicate that a concentration of 500 ppm for 8 weeks should have led to a high mortality and marked incidence of cataracts. Since neither was seen, the stated nominal concentration was considered to be unreliable.

3. At the time of the study, the susceptibility of TMP to hydrolysis was not appreciated. TMP hydrolyses rapidly to dimethyl hydrogen phosphite and methanol. DMHP itself hydrolyses more slowly to monomethyl phosphite and ultimately to phosphorous acid (See 3.1.2). Since no precautions were taken to pevent hydrolysis, it is probable that considerable degradation of TMP may have taken place during the study.

Result : LOAEL: 500 ppm (= 2.54 mg/l)

TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:

Mortality: no animals died during the study
No data are available on clinical signs observable during the study.

Bodyweight gain:
The test animals gained weight at nearly the same rate as controls up to week 4. Controls continued to gain weight, while the test animals lost weight from week 5 to the end of the study.

Haematology:
No notable differences.

Organ weights:
No significant differences were reported.

Gross pathology:
Severe effects on lung and skin. Skin showed severe eczematoid changes including peeling, redness, oozing, crusting, with hair loss and fissuring.

Histopathology:
Lungs:
Interstitial pneumonitis (4/5)
Increased number of mucus-producing goblet cells in bronchial mucosa (5/5, marked in 4/5)
Squamous metaplasia of the alveolar lining cells with tumourlets extending into, or filling, the alveolar spaces (3/5)
Pulmonary vascular sclerosis (thickening of wall sof medium sized branches of pulmonary arteries & veins) (3/5)
Emphysematous changes resulting from the breakdown of alveolar walls

(5/5, focal in 4, widespread in 1).
Skin: hyperkeratosis; parakeratosis; acanthosis; focal folliculitis; crust and scab formation; loss of flexibility; focal infiltration of chronic inflammatory cells beneath the epidermis.

The conclusion drawn by the pathologist was that the pathological changes found in the lungs were of greater importance than those in the skin:
1. The squamous metaplasia and appearance of tumourlets were considered likely to represent pre-malignant changes similar to those seen in heavy cigarette smokers.
2. The pulmonary vascular sclerosis was considered to suggest pulmonary hypertension in the treated animals.
3. The increased number of mucus-producing cells in the bronchial mucosa was considered to be comparable to those found in human chronic bronchitis.
4. The emphysematous changes were considered to be comparable to those seen in human chronic obstructive pulmonary emphysema and likely to be largely irreversible.

The pathologic changes in the skin were considered to be similar to those seen in contact dermatitis, and were thought likely to revert to normal following cessation of exposure.

Test condition : TEST ANIMALS
Age on receipt: not stated
Equilibration period: 2 weeks
Weight at study initiation: 198-281 g (mean control 230.0 g, mean test group 260.8 g)
Number of animals: 10 (5 males in test group, 4 males + 1 female in control group
ADMINISTRATION / EXPOSURE
Animals were exposed to air at 15 cubic feet per hour this air flow plus test substance in a 2.25 cubic feet chamber. No details are given of the method of generation of vapour/aerosol of measurement of chamber concentration.
Vehicle: air
PARAMETERS STUDIED:
Body weight: weekly
Organ weights at termination:
Haematology: weekly: Hemoglobin, hematocrit, RBC, WBC, (total and differential)
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
Macroscopic: all animals dying during study or killed in extremis and at scheduled sacrifice
Microscopic: tissue from heart, lungs, liver, testes, brain, muscle, spleen, kidneys and skin were fixed and exposed to histopathology

Test substance : Trimethyl phosphite, purity not stated. No precautions taken against hydrolysis to dimethyl hydrogen phosphite.

Reliability : (4) not assignable
Short report with limited experimental detail. Limited parameters studied for a single concentration only. No precautions were taken to prevent hydrolysis, so it cannot be determined whether effects were due to TMP or a degradation product.

29.12.2004 (50) (51)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Ames test
System of testing : S. typhimurium TA98, TA100, TA1535, TA1537, TA1538
Test concentration : 0.5 to 50.0 µl per plate
Cycotoxic concentr. : Without activation: 50.0 µl per plate. With activation: 30.0 µl per plate.

Metabolic activation : with and without
Result : negative
Method : other: Bacterial Reverse Mutation Test (Ames Test)
Year : 1979
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Result : Dose-related increases in TA98 and TA100 revertants per plate were observed. However, in neither case did the increase reach a doubling of the number observed in the solvent control plates.

The test substance was markedly more toxic to the tester strains in the presence of rat liver microsomes than in their absence.

Test condition : The test compound was examined for mutagenic activity in the presence and absence of liver microsomal enzyme preparations from Aroclor-induced rats. Dimethylsulphoxide was used as a solvent. Concentrations evaluated were 0.5, 3.0. 15.0, 30.0 and 50.0 ul/plate. Positive controls were used to confirm the validity of the test.
Test substance : Trimethyl phosphite, Commercial Lot# 060194800, 98.95%
Reliability : (1) valid without restriction
Comparable to guideline study.
Flag : Critical study for SIDS endpoint
29.12.2004 (52)

Type : Ames test
System of testing : S. typhimurium TA1535, TA100, TA1537, TA1538, TA98
S. cerevisiae D4
Test concentration : 0.001 to 5.0 µl per plate
Cycotoxic concentr. : Not cytotoxic at any tested concentration
Metabolic activation : with and without
Result : negative
Method : other: Bacterial Reverse Mutation Test (Ames Test)
Year : 1976
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Result : The results of the test in the absence of metabolic activation were all negative. In the first test, a higher incidence of revertants was observed with strain TA1357. However the result of the second replicate in this strain and the test in all other strains with metabolic activation was negative.
Test condition : The test compound was examined for mutagenic activity in the presence and absence of liver microsomal enzyme preparations from Aroclor-induced rats. Dimethylsulphoxide was used as a solvent. Concentrations evaluated were 0.001, 0.01. 0.1, 1.0 and 5.0 ul/plate. One replicate only was conducted, except for strain TA1537 with metabolic activation, where a second replicate was carried out. Positive controls were used to confirm the validity of the test.
Test substance : Trimethyl phosphite Lot# VT-14: 98.5% protected from hydrolysis with N2
Reliability : (2) valid with restrictions
Comparable to guideline study except that only one replicate was used in five out of the six tested strains.
Flag : Critical study for SIDS endpoint
29.12.2004 (53)

Type : Mouse lymphoma assay
System of testing : L5178Y/TK+/- mouse lymphoma cells
Test concentration : 0.18 to 2.7 µl/ml without metabolic activation and 0.24 to 3.2 µl/ml with S9 activation
Cycotoxic concentr. : 1.0 µl/ml
Metabolic activation : with and without
Result : positive
Method : other

Year	:	1979
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	The two highest test concentrations cloned for the non-activated cultures exhibited a mutant frequency significantly greater than solvent controls. All S-9 activated cultures which were cloned exhibited mutant frequencies which were significantly greater than the solvent controls and all concentrations showed a clear dose-response ranging from twice to eight times controls. Although MCTR-98-79 has some direct mutagenic activity, mutagenicity results primarily from active metabolites.
Test condition	:	The test compound was examined directly and in the presence of liver microsomal enzyme preparations from Aroclor-induced rats. Dimethylsulphoxide was used as a solvent. Concentrations evaluated were 0.13, 0.18, 0.24, 0.32, 0.42, 0.56, 0.75, 1.0, 1.3 and 1.8 ul/ml for non-activated cultures and 0.24, 0.32, 0.42, 0.56, 0.75, 1.0, 1.3, 1.8, 2.4 and 3.2 ul/ml for activated cultures. Positive controls were used to confirm the validity of the test.
Test substance	:	Trimethyl phosphite, Commercial Lot# 060194800, 98.95%
Reliability	:	(1) valid without restriction Comparable to guideline study
Flag	:	Critical study for SIDS endpoint

29.12.2004 (54)

Type	:	Mouse lymphoma assay
System of testing	:	L5178Y/TK+/- mouse lymphoma cells
Test concentration	:	0.13 to 1.8 µl/ml without metabolic activation and 0.24 to 3.2 µl/ml with S9 activation
Cycotoxic concentr.	:	10.0 µl/ml
Metabolic activation	:	with and without
Result	:	positive
Method	:	other: Mouse Lymphoma Assay
Year	:	1979
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	The highest test concentration cloned for the non-activated cultures exhibited a mutant frequency approximately 2.8 times greater than the average mutant frequency of the solvent control cultures. The three highest of the S-9 activated cultures which were cloned exhibited mutant frequencies which were significantly greater than the solvent controls and all concentrations showed a clear dose-response.
Test condition	:	The test compound was examined directly and in the presence of liver microsomal enzyme preparations from Aroclor-induced rats. Dimethylsulphoxide was used as a solvent. Concentrations evaluated were 0.13, 0.18, 0.24, 0.32, 0.42, 0.56, 0.75, 1.0, 1.3 and 1.8 ul/ml for non-activated cultures and 0.24, 0.32, 0.42, 0.56, 0.75, 1.0, 1.3, 1.8, 2.4 and 3.2 ul/ml for activated cultures. Positive controls were used to confirm the validity of the test.
Test substance	:	Trimethyl phosphite, Distilled Lot# 060991500, 99.51%
Reliability	:	(1) valid without restriction Comparable to guideline study.
Flag	:	Critical study for SIDS endpoint

29.12.2004 (55)

Type	:	Mouse lymphoma assay
System of testing	:	L5178Y/TK+/- mouse lymphoma cells
Test concentration	:	0.18 to 2.7 µl/ml without metabolic activation and 0.24 to 3.2 µl/ml with S9 activation
Cycotoxic concentr.	:	10.0 µl/ml
Metabolic activation	:	with and without
Result	:	positive

Method : other
Year : 1979
GLP : no data
Test substance : other TS

Result : The two highest test concentration cloned for the non-activated cultures exhibited a mutant frequency 4.8 and 2.8 times greater than solvent control cultures. Two of the S-9 activated cultures which were cloned exhibited mutant frequencies which were 4.6 nd 4.1 times greater than the solvent controls.
Test condition : The test compound was examined directly and in the presence of liver microsomal enzyme preparations from Aroclor-induced rats. Dimethylsulphoxide was used as a solvent. Concentrations evaluated were 0.42, 0.56, 0.75, 1.0, 1.3, 1.78, 2.37 and 3.16 ul/ml for both activated and non-activated cultures. Positive controls were used to confirm the validity of the test.
Test substance : Trimethyl phosphite Lot# 091884800, purity not stated.
Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment.
Flag : Critical study for SIDS endpoint
29.12.2004 (56)

Type : DNA damage and repair assay
System of testing : E coli WP2/WP100, S. typhimurium TA1978/TA1538
Test concentration : 0.3 to 50.0 µl per plate
Cycotoxic concentr. : 50.0 µl per plate
Metabolic activation : with and without
Result : positive
Method : other
Year : 1979
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Result : Preferential killing of the repair-deficient strains WP100 and TA1538 was observed both with and without metabolic activation. The preferential kill was most apparent in WP100 without activation, where the effect was dose-dependent. Preferential killing of TA1538 without activation was only observed at 50.0 µl per plate.
Toxicity of the test material to all strains was greater in the presence of metabolic activation. Complete toxicity was observed in all strains at 50.0 µl and preferential killing of WP100 and TA1538 was only observed at 30.0 µl.
Test condition : The test compound was tested at doses of 0.3, 3.0, 30.0 and 50.0 ul/plate in tester strains E coli WP2/WP100, S. typhimurium TA1978/TA1538. Test material and bacteria were incubated with and without metabolic activation by liver microsomal enzyme preparations from Aroclor -induced rats for 90 minutes with shaking prior to plating. Dimethylsulphoxide was used as a solvent. Positive and negative controls were used to confirm the validity of the test.
Test substance : Trimethyl phosphite, Distilled Lot# 060991500, 99.51%
Reliability : (1) valid without restriction
Comparable to guideline study.
Flag : Critical study for SIDS endpoint
29.12.2004 (57)

Type : DNA damage and repair assay
System of testing : E coli WP2/WP100, S. typhimurium TA1978/TA1538
Test concentration : 0.3 to 50.0 µl per plate
Cycotoxic concentr. : 50.0 µl per plate
Metabolic activation : with and without
Result : positive
Method : other

Year	:	1979
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Preferential killing of the repair-deficient strains WP100 and TA1538 was observed without metabolic activation. The preferential kill was apparent in WP100 at all dose levels. Significant preferential killing of TA1538 without activation was only observed at 50.0 µl per plate and may have been exaggerated due to a relatively low survival of TA1538 solvent control. No significant preferential kill of repair-deficient strains was observed with metabolic activation except at 50.0 µl, where toxicity to all strains was extensive. No clear dose related response was demonstrated in either test.
Test condition	:	The test compound was tested at doses of 0.3, 3.0, 30.0 and 50.0 ul/plate in tester strains E coli WP2/WP100, S. typhimurium TA1978/TA1538. Test material and bacteria were incubated with and without metabolic activation by liver microsomal enzyme preparations from Aroclor -induced rats for 90 minutes with shaking prior to plating. Dimethylsulphoxide was used as a solvent. Positive and negative controls were used to confirm the validity of the test.
Test substance	:	Trimethyl phosphite, Commercial Lot# 060194800, 98.95%
Reliability	:	(1) valid without restriction Comparable to guideline study.
Flag	:	Critical study for SIDS endpoint

29.12.2004 (58)

Type	:	DNA damage and repair assay
System of testing	:	E coli WP2/WP100, S. typhimurium TA1978/TA1538
Test concentration	:	10.0 µl per plate
Cycotoxic concentr.	:	Not stated.
Metabolic activation	:	with and without
Result	:	negative
Method	:	other
Year	:	1979
GLP	:	no data
Test substance	:	other TS
Result	:	No preferential killing of the repair-deficient strains WP100 and TA1538 was observed with or without metabolic activation.
Test condition	:	The test compound was tested at a single dose of 10.0 ul/plate in tester strains E coli WP2/WP100, S. typhimurium TA1978/TA1538 with and without metabolic activation by liver microsomal enzyme preparations from Aroclor -induced rats. No solvent was used. Positive and negative controls were used to confirm the validity of the test.
Test substance	:	Trimethyl phosphite Lot# 091884800, purity not stated.
Reliability	:	(2) valid with restrictions Study well documented, meets generally accepted scientific principles, acceptable for assessment.

29.12.2004 (59)

Type	:	other: Cell Transformation Assay
System of testing	:	C3H/10T½ CL8 cells
Test concentration	:	0.09 to 1.45 µl/ml
Cycotoxic concentr.	:	1.024 µl/ml
Metabolic activation	:	
Result	:	negative
Method	:	other
Year	:	1979
GLP	:	no data
Test substance	:	other TS
Method	:	C3H/10T½ Cell Transformation Assay
Result	:	No indications of transformation were observed in any of the test substance

plates or solvent control. The positive control plates showed extensive development of both Type II and Type III foci. The parallel toxicity study demonstrated attainment of the desired toxic level.

Test condition : Following an initial toxicity test showing 40.90% relative cloning efficiency at 1.024 µl/ml, the test compound was tested at 5 two-fold dilutions of 1.45, 0.73, 0.36, 0.18 and 0.09 µl/ml, concentrations expected to cause 50-75% reduction in cloning efficiency. Acetone was used as the solvent. A toxicity study was carried out in parallel to the assay to demonstrate attainment of the desired toxic level. Positive and solvent controls were used to confirm the validity of the test.

Test substance : Trimethyl phosphite Lot# 091884800, stored under nitrogen, purity not stated.

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

Flag : Critical study for SIDS endpoint

29.12.2004 (60)

5.6 GENETIC TOXICITY 'IN VIVO'

Type : other: Drosophila mutagenicity assays
Species : Drosophila melanogaster
Sex : male/female
Strain :
Route of admin. : inhalation
Exposure period : 1 minute
Doses : 0.07 ml as an aerosol in 25 ml flask (2800 ppm)
Result : negative
Method : other
Year : 1980
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Result : Exposure of flies for 1 minute resulted in anaesthesia of all flies followed by the death of 35-55% of treated flies. Fertility of survivors was sufficient to complete the study.
The test substance did not induce significant genetic damage in Drosophila melanogaster in any of the individual tests.

Test condition : The test substance was examined for mutagenic activity in a battery of assays.
Tests for point mutations:
1) Induction of Sex-linked Lethals
2) White-ivory Somatic Reversions.
Tests for chromosome aberrations and loss:
1) Induction of Dominant Lethal Mutations
2) Y Chromosome Loss
3) Bithorax Test of Lewis
Flies were exposed to 0.07 ml of test substance delivered as an aerosol into a 25 ml flask for 1 minute. Negative and appropriate positive controls were used in all assays.

Test substance : Trimethyl phosphite, Distilled Lot# 060991500, 99.51%

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

Flag : Critical study for SIDS endpoint

29.12.2004 (61)

Type : other: Drosophila mutagenicity assays
Species : Drosophila melanogaster
Sex : male/female

Strain	:	
Route of admin.	:	inhalation
Exposure period	:	30 seconds
Doses	:	0.07 ml as an aerosol in 25 ml flask (2800 ppm)
Result	:	positive
Method	:	other
Year	:	1980
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Exposure of flies to 0.07 ml aerosol into a 25 ml flask for 1 minute resulted in anaesthesia of all flies followed by 50% mortality and an inacceptable level of sterility. The exposure period was reduced to 30 seconds which permitted adequate survival and fertility following anaesthesia. The test substance significantly increased frequency of genetic damage in the dominant lethal, bithorax test of Lewis and sex-linked lethal assay.
Test condition	:	The test substance was examined for mutagenic activity in a battery of assays. Tests for point mutations: 1) Induction of Sex-linked Lethals 2) White-ivory Somatic Reversions. Tests for chromosome aberrations and loss: 1) Induction of Dominant Lethal Mutations 2) Y Chromosome Loss 3) Bithorax Test of Lewis Negative and appropriate positive controls were used in all assays.
Test substance	:	Trimethyl phosphite, Commercial Lot# 060194800, 98.95%
Reliability	:	(2) valid with restrictions Study well documented, meets generally accepted scientific principles, acceptable for assessment.
Flag	:	Critical study for SIDS endpoint

29.12.2004 (62)

Type	:	other: Drosophila mutagenicity assays
Species	:	Drosophila melanogaster
Sex	:	male/female
Strain	:	
Route of admin.	:	inhalation
Exposure period	:	Unstated
Doses	:	6000 ppm aerosol (0.3 ml dispersed in a 50 ml volume)
Result	:	positive
Method	:	other
Year	:	1979
GLP	:	no data
Test substance	:	other TS
Result	:	Exposure of flies to 0.3 ml aerosol into a 50 ml flask partally anaesthetised the flies and resulted in about 40% mortality. Fertility of survivors decreased. The test substance induced significant genetic damage in Drosophila melanogaster in all the tests except the test for white-ivory somatic reversions. The most significant increases were observed in the bithorax test of Lewis and the sex-linked lethal test.
Test condition	:	The test substance was examined for mutagenic activity in a battery of assays. Tests for point mutations: 1) Induction of Sex-linked Lethals 2) White-ivory Somatic Reversions. Tests for chromosome aberrations and loss: 1) Induction of Dominant Lethal Mutations 2) Y Chromosome Loss 3) Bithorax Test of Lewis

Negative and appropriate positive controls were used in all assays.

Test substance : Trimethyl phosphite Lot# 091884800, purity not stated.
Reliability : (2) valid with restrictions
Non-guideline study, detailed report
Flag : Critical study for SIDS endpoint
29.12.2004 (63)

5.7 CARCINOGENICITY

Species : rat
Sex : male/female
Strain : other: F344/N
Route of admin. : gavage
Exposure period : 103 weeks
Frequency of treatm. : 5 days/week
Post exposure period : 10-13 days
Doses : 100, 200 mg/kg bw/day males; 50, 100 mg/kg bw/day females
Result : positive
Control group : yes
Method : other: comparable to OECD guideline 451
Year : 1982
GLP : no data
Test substance : other TS

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

Test substance : Dimethyl hydrogen phosphite (CAS: 868-85-9) purity ca. 98%, hydrolysis product of TMP

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

Flag : Critical study for SIDS endpoint

14.12.2004 (64)

Species : mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : gavage
Exposure period : 103 weeks
Frequency of treatm. : 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

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

Test substance : Dimethyl hydrogen phosphite (CAS: 868-85-9) purity ca. 98%, hydrolysis product of TMP

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

Flag : Critical study for SIDS endpoint

14.12.2004 (64)

5.8.1 TOXICITY TO FERTILITY

Type : other
Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : 90 days
Frequency of treatm. : Consecutive days
Premating exposure period
Male :
Female :
Duration of test :
No. of generation studies :
Doses :
Control group :

Method : Results of histopathological examination of gonads in 90-day gavage study. See section 5.4 for full study details.

Result : Histopathologic effects at 160 mg/kg/day:
Testis: Hypoplasia in 11/12 males. Spermatogenesis was reduced, with spermatogonia and other spermatogenic cells reduced in size and number. However, the density of sperm in the epididymis was not greatly or uniformly reduced.

Reliability : (2) valid with restrictions

14.12.2004 (42)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species : rat
Sex : female
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : Gestation Days 6 through 15

Frequency of treatm.	:	Daily
Duration of test	:	Gestation Days 6 through 20
Doses	:	16, 49, 164 mg/kg/day
Control group	:	yes
NOAEL maternal tox.	:	= 49 mg/kg bw
NOAEL teratogen.	:	= 49 mg/kg bw
Result	:	Teratogenic
Method	:	other
Year	:	1979
GLP	:	no data
Test substance	:	other TS

Result :

MORTALITY/CLINICAL SIGNS:
All rats survived the treatment and observation period. No clinical signs were recorded during the in-life portion of the study.

BODYWEIGHT:
At 164 mg/kg/day, maternal bodyweight gain was reduced during Days 6-10 and at Day 20. Dam body weight minus gravid uterus weight was also reduced. None of these differences were statistically significant.

LITTER DATA
Average foetal weight was slightly (10.25%) decreased. The number of resorptions in the high dose group was higher than controls, and comparable to the positive control group, including total resorption of one litter. There were no significant in these parameters for the 16 and 49 mg/kg/day groups.

TERATOLOGICAL EFFECTS:
Teratologic effects were seen in the 164 mg/kg/day dose group and in positive controls:
Gross Abnormalities:
Effects seen at 164 mg/kg/day and in positive controls were exencephaly, spina bifida and scoliosis. In addition, a marked incidence of cleft palate was seen in the high dose group only. No gross abnormalities were seen in negative controls or in the low and mid dose groups.
Skeletal Abnormalities:
Abnormalities of long bones were seen in high dose and positive controls only. The incidence of abnormalities of sternebrae, rudimentary ribs and partial ossification of sternebrae and vertebrae was similar to controls at 16 and 49 mg/kg/day. At 164 mg/kg/day the incidence was higher, and comparable to positive controls.
Soft Tissue Abnormalities:
Abnormalities seen at 164 mg/kg/day and in positive controls were a marked increased in dilated ventricles and in undescended testes.

It was concluded that TMP was teratogenic during the period of major organogenesis at 164 mg/kg/day. Teratogenicity appears to be a direct result of exposure to TMP rather than secondary to maternal toxicity, seen as a slight reduction in bodyweight gain.

NOAEL (maternal & foetal): 49 mg/kg/day.

Test condition :

TEST ANIMALS
Mean weight at study initiation: 250 g
Number of animals: 125 (25/group)
ADMINISTRATION / EXPOSURE
Groups consisting of 25 pregnant Sprague-Dawley rats received either 10 ml/kg bw of corn oil (vehicle), acetylsalicylic acid (positive control) at 250 mg/kg/day or TMP at 16, 49 or 164 mg/kg/day via oral gavage from gestation day 6 to day 15.
Animals were observed daily for mortality and clinical signs. Food consumption and bodyweight were recorded on days 6, 10, 15 and 20 of gestation.

The pregnant animals were sacrificed on gestation day 21 and the foetuses were removed, weighed, sexed and examined microscopically for malformations (developmental anomalies).

Test substance : Trimethyl phosphite Lot# 091884800, purity not stated.
Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment.
Flag : Critical study for SIDS endpoint
29.12.2004 (65)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

Endpoint : other: cholinesterase inhibition potential
Study descr. in chapter :
Reference :
Type : other
Species : rat
Sex : male
Strain : other: CD-1
Route of admin. : intravenous
No. of animals : 3
Vehicle : other: undiluted
Exposure period :
Frequency of treatm. : Single injection
Doses : 175 µl/kg, 65 µl/kg, 33 µl/kg
Control group :
Observation period : 3 hours
Result : No significant inhibition
Method : other
Year : 1979
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Result : Rat MRa-1 became unconscious within 15 seconds, without convulsions, and died within 1 minute.
Rat MRa-2 showed discomfort and irritation, but remained upright. There were no signs of cholinesterase inhibition (such as lacrimation, salivation, diarrhea, pupil contraction, bronchospasm, weakness). The blood sample taken after 5 minutes showed a slight decrease in serum cholinesterase which was maintained over the 3 hour observation period.
Rat MRa-3 showed no adverse effects or signs of cholinesterase inhibition. The blood sample taken after 5 minutes showed a 40% decrease in serum cholinesterase which slowly returned to baseline level during the 3 hour observation period.

Serum cholinesterase levels following intravenous injection (expressed as mU/ml)

Rat No	MRa-1	MRa-2	MRa-3
Weight (g)	300	305	300
Dose (µl/kg)	175	65	33
Sample time Minutes			
0	697	835	644
5	dead	625	382
15		631	461

30	662	463
45	574	428
180	602	525

Since the reductions in serum cholinesterase were not dose-related and were not related to any clinical signs of cholinesterase inhibition, it was concluded that TMP did not have any appreciable specific action on cholinesterase.

Test condition : TEST ANIMALS:
3 male CD-1 rats weighing 300-305 g

TEST PROCEDURE:
Blood samples taken during the study were withdrawn from the retro-orbital plexus.
A baseline blood sample was taken from each rat.
The rats were injected intravenously via the tail vein with undiluted TMP. The largest volume injected was 0.1 ml.
DOSES:
MRa-1: 175 µl/kg
MRa-2: 65 µl/kg
MRa-3: 33 µl/kg
The rats were observed for clinical signs of cholinesterase inhibition. Blood samples were withdrawn 5, 15, 30, 45 and 180 minutes post injection.

Test substance : Trimethyl phosphite, purity not stated.
Reliability : (2) valid with restrictions
29.12.2004 (66)

Endpoint : other: cholinesterase inhibition potential
Study descr. in chapter :
Reference :
Type : other
Species : rabbit
Sex : male
Strain : New Zealand white
Route of admin. : intravenous
No. of animals : 3
Vehicle : other: undiluted
Exposure period :
Frequency of treatm. : Single injection
Doses : 42 µl/kg, 99 µl/kg, 107 µl/kg
Control group :
Observation period : 3 hours
Result : No significant inhibition
Method : other
Year : 1979
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Result : Rabbit MRT-1 showed no adverse effects other than local irritation. There were no signs of cholinesterase inhibition (such as lacrimation, salivation, diarrhea, pupil contraction, bronchospasm, weakness). Blood sample taken after 2, 15, 30, 60 and 180 minutes showed no significant change in serum cholinesterase activity.
Rabbit MRT-2 showed mild irritability but remained upright. There were no signs of cholinesterase inhibition. Blood sample taken after 2, 15, 45 and 180 minutes showed no meaningful change in serum cholinesterase activity.
Rat MRa-3 showed signs of vocalised pain, then lost consciousness for about 2 minutes. Afterwards it regained an upright position, remaining unsteady for about 10 minutes. There were no signs of cholinesterase inhibition. Blood sample taken after 1, 15, 30 and 180 minutes showed a slight reduction in serum cholinesterase activity which returned towards baseline during the 3 hour observation period.

Serum cholinesterase levels following intravenous injection
(expressed as mU/ml)

Rabbit No	MRT-1	MRT-2	MRT-3
Weight (kg)	2.4	2.2	2.8
Dose (µl/kg)	42	90	107
Sample time Minutes			
0	663	566	464
1	-	-	392
2	639	605	-
15	615	498	400
30	623	-	430
45	-	531	-
60	623	-	-
180	625	545	428

It was concluded that TMP did not have any appreciable specific action on cholinesterase activity in rabbits.

Test condition : TEST ANIMALS:
3 male New Zealand white rabbits weighing 2.2-2.8 kg

TEST PROCEDURE:
Blood samples taken during the study were withdrawn from the ear veins.
A baseline blood sample was taken from each rabbit.
The rats were injected intravenously via the lateral ear vein with undiluted TMP. The largest volume injected was 0.3 ml.
DOSES:
MRT-1: 42 µl/kg
MRT-2: 90 µl/kg
MRT-3: 107 µl/kg
The rabbits were observed for clinical signs of cholinesterase inhibition.
Blood samples were withdrawn at 4 or 5 time points out of 1, 2, 15, 30, 45, 60 and 180 minutes post injection.

Reliability : (2) valid with restrictions
15.12.2004 (67)

Endpoint : other: cholinesterase activity
Study descr. in chapter :
Reference :
Type : other
Species : dog
Sex : male
Strain : other: mongrel
Route of admin. : intravenous
No. of animals : 2
Vehicle : other: undiluted
Exposure period :
Frequency of treatm. : Single injection
Doses : 100 µl/kg, 50 µl/kg
Control group :
Observation period : 3 hours
Result : No significant inhibition
Method : other
Year : 1979
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Result : Dog MDo-1:
Baseline respiration rate 22, baseline pulse 180.
Pulse rate dropped to 120 within 2 minutes and to zero in 4 minutes.

Respiration ceased at 4 minutes. Artificial respiration did not restore breathing. Blood samples were collected at 2 and 4 minutes. Serum cholinesterase levels decreased 40% within 2 minutes and remained at this level until death at 4 minutes.

Dog MDo-2:
Baseline respiration rate 18, baseline pulse 160.
Pulse rate rose initially, then fell below baseline throughout the observation period. Blood samples were collected at 2, 15, 30 and 60 minutes after injection. . Serum cholinesterase levels decreased by 24% within 2 minutes, gradually returning towards baseline.

Neither dog showed signs of cholinergic activity. TMP does not appear to be a potent cholinesterase inhibitor

Serum cholinesterase levels following intravenous injection (expressed as mU/ml)

Dog No		MDo-1		MDo-2	
Weight (kg)	14.5		14.0		
Dose (µl/kg)	100		50		
Sample time					
Minutes		AChE	pulse	AChe	pulse
0	1930	180	1006	160	
2	1010	120	767	> 160	
4	1096	0	-	160	
15	dead		890	120	
30			932	118	
60			908	146	

Test condition : TEST ANIMALS:
2 male mongrel dogs weighing 14 & 14.5 kg

TEST PROCEDURE:
Dogs were anaesthetised with 25 mg/kg of sodium pentobarbital.
Both femoral veins were exposed for injection and collection of blood samples.
Pulse and respiration rates were measured.
Baseline blood samples were taken from the right femoral vein.
Undiluted TMP was injected through the left femoral vein.
DOSES:
MDo-1: .1.5 ml (100 µl/kg)
MDo-2: 0.7 ml (50 µl/kg)
The dogs were observed for clinical signs of cholinesterase inhibition. Blood samples were withdrawn at intervals post injection.

Reliability : (2) valid with restrictions
16.12.2004 (68)

Endpoint : other: cholinesterase indibition in vitro
Study descr. in chapter :
Reference :
Type : other
Species : rat
Sex : female
Strain : Sprague-Dawley
Route of admin. : ex vivo
No. of animals : 1
Vehicle :
Exposure period :
Frequency of treatm. :
Doses :
Control group :

Observation period :
Result : Some evidence of potential for cholinesterase inhibition.
Method : other
Year : 1981
GLP : no data
Test substance : other TS

Method : Ellman method of colorimetric analysis
Result : Inhibition:

Dose (ppm)	Rate *	Inhibition (%)
am		
0	10.84	-
10	11.61	0.00
100	7.49	30.95
pm		
0	6.86	-
0	6.21	-
ave.	6.53	-
333	6.21	4.95
666	5.17	20.80

* Rate: moles substrate / min / µg tissue

For the afternoon tests, the control rate was lower than the morning control. A second control confirmed this, and an average rate was used. The TMP used for the afternoon tests had been dissolved in water for 5 hours. It is therefore probable that some or all of the TMP had hydrolysed to DMHP.

Test condition : A female Sprague-Dawley rat was sacrificed and the right half of the brain, 0.954 g, was homogenised with 28.6 ml 0.1% Triton X-100 solution. The left half was wrapped in foil and frozen for later use.

A 1% stock solution of TMP was prepared from 5 µl 97% TMP in a 5 ml volume flask q.s. with pH 8.0 phosphate buffer.

Test concentrations were made up for 1000, 10000 and 100000 ppm TMP. On addition of phosphate buffer, 0.4 ml brain homogenate and 100 µl Dithiobisnitrobenzoic acid (DTNB), the solutions turned dark yellow before addition of acetylthiocholine iodide (substrate), making it impossible to analyse these samples.

the left side of the brain (0.7389 g) was homogenised with 22.2 ml 0.1% Triton X-100 solution and additional concentrations were made up at 166.67, 333.33 and 666.67 ppm TMP (97%).

Final concentrations tested were controls, 10, 100, 333 and 666 ppm. For all solutions, including controls, it was difficult to establish a baseline due to reaction before addition of substrate. the solutions were therefore allowed 1.5 minutes to establish a baseline before addition of acetylthiocholine iodide substrate.

Test substance : Trimethyl phosphite, Aldrich Chemical Co. Lot #0103ME. No information on purity is available.
Reliability : (2) valid with restrictions
29.12.2004 (69)

Endpoint : other: in vitro cholinesterase inhibiiton
Study descr. in chapter :
Reference :
Type : other
Species : rat
Sex : male
Strain : Sprague-Dawley

Route of admin. : ex vivo
No. of animals : 1
Vehicle :
Exposure period :
Frequency of treatm. :
Doses :
Control group : yes
Observation period :
Result :

Method : Modified Ellman colorimetric method
Result :

Dose (ppm)	Rate *	Inhibition (%)
0	0.245	-
2	0.231	5.7
50	0.253	0.00
100	0.267	0/00

* Rate: O.D. units / 30 sec . / gram (average of duplicate assays)

No significant inhibition.

Test condition : TMP was incorporated into fresh rat brain homogenates derived from a male SD rat.

The homogenates (approximately 1 gram brain tissue per 20 ml buffer) were fortified at 2, 50 and 100 ppm and allowed to equilibrate at 4 deg C for 5 minutes prior to assay.

29.12.2004 (70)

5.10 EXPOSURE EXPERIENCE

Type of experience : Health records from industry

Method : Occupational Exposure Monitoring Data
Result : TWA samples ranged from 0.1 to 10 mg/m3 with a weighted average of 3.0 mg/m3 for 15 samples.
STEL range was from 1 to 132 mg/m3 with an average of 34 mg/m3 for 8 samples.
The sampling range in the work area was from 1 to 61 mg/m3 with an average of 10 mg/m3 for 7 samples.
Test condition : The TWA was generally the time-weighted average of an approximately 3 hour sample taken in the morning and a 3 hour sample taken in the afternoon.
Area samples were taken for 10 minute periods.
Short term exposure (STE) samples were taken while the operation (taking samples or work in the booth) was taking place.
Analysis was by an in-house gas chromatography method.
Reliability : (2) valid with restrictions
10.12.2004 (71)

Type of experience : Health records from industry

Method : Health effect study.
Remark : A special eye examination programme looking for evidence of lens opacities was conducted on all the employees at the Mobil Chemical Company plant at Charleston following a series of 28-day inhalation toxicity studies in rats which concluded that TMP caused irreversible cataracts at 100 ppm (NOEC 10 ppm).
Result : No clinical cataracts were present in either the exposed (n=117) or non-exposed (n=63) employee groups. Numerous subclinical

non-progressive congenital opacities and early progressive senile opacities were identified. No association was found between TMP exposure and cataract formation.

Test condition : Without knowledge of previous TMP exposure history, an eye examination was carried out on every employee at the Mobil Chemical Company plant at Charleston. Following test of visual acuity, with and without glasses, applanation tonography, external eye examination and preliminary split lamp examination were performed. After full pupillary dilation, cornea and lens were visually examined, fundus, retina, optic nerve and macula were examined by direct and indirect ophthalmoscope. Clarity of vitreous was verified.
Using recent plant monitoring data, employee work histories and recollections, each employee was assigned either a zero (no exposure) or a level 1 (low = 0.3-5 ppm TWA), 2 (medium = 5-10 ppm TWA) or 3 (high = >10 ppm) exposure for each year of employment.

Reliability : (2) valid with restrictions

Flag : Critical study for SIDS endpoint

14.12.2004 (72)

Type of experience : Health records from industry

Method : Medical surveillance

Remark : Pregnancy outcome history was investigated following a teratogenicity study in rats which concluded that TMP was teratogenic at an oral dose of 164 mg/kg/day (NOEL 49 mg/kg/day)

Result : Only one out of the six female employees, an office worker, indicated any attempt at conception while employed at the plant. She reported no difficulties in conception and delivered, on three separate occasions, without difficulties or abnormalities.

Test condition : As part of the routine medical surveillance examination given to Mobil Chemical Corporation employees on the Charleston plant, a special pregnancy outcome history was taken in 1979 on the six female employees.

Reliability : (4) not assignable
The sample population was not large enough to draw any conclusions. Females only studied.

30.12.2004 (73)

5.11 ADDITIONAL REMARKS

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

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10. Summary and Evaluation

10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT