FOREWORD INTRODUCTION

TRIMETHYL PHOSPHATE

CAS N°: 512-56-1

SIDS Initial Assessment Report

For

SIAM 4

Tokyo, Japan, 20- 22 May 1996

1. Chemical Name: Trimethyl phosphate

2. CAS Number: 512-56-1

3. Sponsor Country: Japan
National SIDS Contact Point in Sponsor Country:
Mr. Yasuhisa Kawamura, Ministry of Foreign Affairs, Japan

4. Shared Partnership with:

5. Roles/Responsibilities of the Partners:

- Name of industry sponsor /consortium
- Process used

6. Sponsorship History

- How was the chemical or category brought into the OECD HPV Chemicals Programme ?

As a high priority chemical for initial assessment, Trimethyl phosphate was selected in the framework of the OECD HPV Chemicals Programme.

SIDS Dossier and Testing Plan were reviewed at a SIDS Review Meeting in 1994, where the following SIDS Testing Plan was agreed:

The original report was already circulated in March 1996, and the report was revised according to the comments from member countries.

No testing ( )

Testing(X) Physical-Chemical Properties
Vapour pressure
Partition coefficient
Environmental fate/Biodegradation
Biodegradation
Photodegradation
Stability in water
Ecotoxicity
Acute toxicity to fish

	Toxicity	Acute toxicity to daphnids Toxicity to algae Chronic toxicity to daphnids Repeated dose toxicity Reproductive/developmental toxicity Gene mutation test Chromosomal aberration in vitro

At SIAM-4, conclusion was approved with comments.

Comments at SIAM-4: Rearrangement of the documents.

7. Review Process Prior to the SIAM:

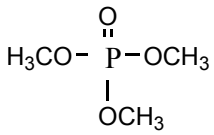
8. Quality check process:

9. Date of Submission: Date of circulation: April 30, 1996

10. Date of last Update:

11. Comments:

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	512-56-1
Chemical Name	Trimethyl phosphate
Structural Formula	

CONCLUSIONS AND RECOMMENDATIONS

A potential hazard to man due to genotoxicity is identified, but exposure throughout OECD is low.

It is currently considered of low potential risk and low priority for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

The production volume of trimethyl phosphate in Japan is ca. 100 - 1,000 tonnes/year in 1990 – 1993, and 500 tonnes/year in the EEC in 1987. This chemical is used as an intermediate for pesticides in closed systems or as a polymerization catalyst in industry. This chemical is stable in neutral, acidic or alkaline solutions, and is considered as "not readily biodegradable".

The potential environmental distribution of trimethyl phosphate obtained from a generic fugacity model (Mackay level III) showed that the chemical will be distributed mainly to water and soil. Predicted environmental concentration (PEC_{local}) of this chemical was estimated to be 1.5×10^{-4} mg/l from a Japanese local exposure scenario.

For the environment, various NOEC and LC_{50} values were gained from test results; LC_{50} = > 1050 mg/l (acute fish); EC_{50} = > 1000 mg/l (acute daphnia); EC_{50} = > 1000 mg/l (acute algae); NOEC = > 1000 mg/l (algae); NOEC = 320 mg/l (long-term daphnia reproduction). The lowest chronic toxicity result, 21d-NOEC (reproduction) of *Daphnia magna* (320 mg/l), was adopted for the calculation of a PNEC. The assessment factor of 100 was used to both acute and chronic toxicity data to determine a PNEC according to the OECD Provisional Guidance for Initial Assessment of Aquatic Effects. Thus, the PNEC of the chemical is 3.2 mg/l in the present report. The PEC is lower than the PNEC, therefore the environmental risk is presumably low.

As trimethyl phosphate is produced in a closed system, exposure during synthesis may be excluded. Since this chemical is used as a polymerization catalyst, the possibility of workplace exposure through dermal route is possible when the product is filled into barrels. Dermal uptake at work place is considered to be the main exposure route while inhalation plays a minor role. Although there is no actual exposure data, using the physical-chemical properties and the EUSES model, exposure levels were calculated to be 0.5 - 3.0 mg/m^3 for inhalation and 0 - 0.1 mg/cm^2/day for the dermal route. However workers wear personal protective equipment (e.g. chemical cartridge respirator with an organic vapour cartridge) during the filling process. Therefore, the exposure at work place is considered to be very low at the present situation. Although the use and resident level of the chemical in consumer products are unknown, because it is an intermediate and under industrial use, the exposure level can also be considered to be negligible. As for indirect exposure via environment, PEC_{local} in surface water was estimated to be 1.5×10^{-4} mg/l from a local exposure scenario. The daily intake through drinking water is estimated as 5.0×10^{-6} mg/kg/day.

Although negative results were obtained both from an Ames test and a chromosomal aberration test *in vitro*, genotoxic effects were shown in a micronucleus test *in vivo*. In a combined repeat dose and reproductive/developmental toxicity screening test, significant decrease of body weight, significant change in haematology and clinical chemistry examines (e.g. decreased erythrocytes) were observed in parental animals. Renal toxic findings and neurotoxic effects were also seen in gross and histopathological examines (e.g. nephropathy,

degeneration of nerve fibre). Increases of kidney weight were observed at the lowest dose level (40 mg/kg/day). For reproductive/developmental end-points, the fertility index and the number of implantation sites were decreased at the lowest dose. In addition, intrauterine mortality of embryos was also increased at that level. Therefore, the NOEL was less than 40 mg/kg/day both for repeated dose and reproductive toxicity.

As for indirect exposure via environment, a PEC_{local} in surface water was estimated to be 1.5×10^{-4} mg/l from local exposure scenario. The daily intake through drinking water is estimated as 5.0×10^{-6} mg/kg/day. For human health, although the NOEL is estimated to be less than 40 mg/kg/day both for repeated dose and reproductive toxicity, the margin of safety is very large. Therefore, health risk through the environment, in general, is considered to be presumably low due to its use pattern and exposure situation.

In conclusion, no further testing is needed at present considering its toxicity and exposure levels.

NATURE OF FURTHER WORK RECOMMENDED

FULL SIDS SUMMARY

CAS NO: 512-56-1		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point			-10 °C
2.2	Boiling Point			197 °C
2.3	Density			No data available
2.4	Vapour Pressure		OECD TG 104	0.74 Pa at 25 °C
2.5	Partition Coefficient (Log Pow)		OECD TG 107	- 0.46 at 25 °C
2.6 A.	Water Solubility		OECD TG 105	Miscible at 25 °C
B.	pH			No data available.
	pKa			No data available
2.12	Oxidation: Reduction Potential			No data available.
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation			No degradation
3.1.2	Stability in Water		OECD TG 111	Stable (pH 4.0, 7.0, 9.0)
3.2	Monitoring Data			Not detected from surface water and Sediment in Japan in 1984.
3.3	Transport and Distribution		Calculated (Fugacity Level III)	100% released to water, In Air 0.00% In Water 99.80% In Soil 0.00% In Sediment 0.20%
3.5	Biodegradation		OECD TG 301C	Not readily biodegradable: 0 % (BOD) in 28 days, 0 % (GC) in 28 days
3.6	Bioaccumulation	Carp	OECD TG 305C	BCF: 1.5 – 2.4
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	*Oryzias latipes*	OECD TG 203	LC_{50} (96hr): > 1,050 mg/L
4.2	Acute Toxicity to Aquatic Invertebrates (*Daphnia*)	*Daphnia magna*	OECD TG 202	EC_{50} (24hr): > 1,000 mg/l
4.3	Toxicity to Aquatic Plants e.g. Algae	*Selenastrum capricornutum*	OECD TG 201	EC_{50} (72hr): > 1,000 mg/l NOEC: > 1,000 mg/l
4.5.2	Chronic Toxicity to Aquatic Invertebrates (*Daphnia*)	*Daphnia magna*	OECD TG 202	EC_{50} (21d, Immobility): 800 mg/l EC_{50} (21d, Reproduction): 520 mg/l NOEC (21d, Repro): 320 mg/l
4.6.1	Toxicity to Soil Dwelling Organisms			No data available.
4.6.2	Toxicity to Terrestrial Plants			No data available.
(4.6.3)	Toxicity to Other Non-Mammalian Terrestrial Species (Including Birds)	Quail	Unknown	LD_{50}: 750 mg/kg
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat	OECD TG 401	LD_{50}: 840 mg/kg
5.1.2	Acute Inhalation Toxicity			No data available.
5.1.3	Acute Dermal Toxicity			No data available
5.4	Repeated Dose Toxicity	Rat	OECD Combined Test	NOAEL = < 40 mg/kg/day
5.5	Genetic Toxicity In Vitro			

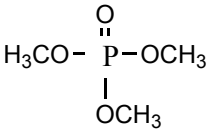
CAS NO: 512-56-1		SPECIES	PROTOCOL	RESULTS
A.	Bacterial Test (Gene mutation)	*S. .typhimurium* *E. coli*	OECD Guidelines No.471 and 472 and Japanese Guidelines	Negative in all strains with and without metabolic activation
B.	Non-Bacterial In Vitro Test (Chromosomal aberrations)	CHL cells	OECD Guideline No.473 and Japanese Guidelines	Negative (With metabolic activation) Negative (Without metabolic activation)
5.6	Genetic Toxicity In Vivo	Mouse	Micronucleus test	Positive
5.8	Toxicity to Reproduction	Rat	OECD Combined Test	NOAEL Parental = < 40 mg/kg/day NOAEL F1 offspring = < 40 mg/kg/day
5.9	Developmental Toxicity/ Teratogenicity			
5.11	Experience with Human Exposure			

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 512-56-1
IUPAC Name: Phosphoric acid, trimethyl ester
Molecular Formula: $C_3H_9O_4P$
Structural Formula:



Synonyms: Trimethyl phosphate

1.2 Purity/Impurities/Additives

Degree of Purity: 99.5 %

Major Impurities: Unknown

Essential Additives: None

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Value
Melting point	-10 °C
Boiling point	197 °C
Vapour pressure	0.74 Pa at 25 °C
Water solubility	miscible at 25 °C
Partition coefficient n-octanol/water (log value)	-0.46

2 GENERAL INFORMATION ON EXPOSURE

Trimethyl phosphate is a stable liquid, and the production volume is ca. 100 - 1,000 tonnes/year in 1990 - 1993 in Japan, and 500 tonnes/year in the EEC in 1987. This chemical is used as an intermediate for pesticides in closed systems or as a polymerization catalyst in industry. Also, this chemical is used as an ignition control agent in gasoline. Release to the environment may occur at the production site, specific industrial sites. All disposal wastes are treated by incineration. Trimethyl phosphate seems to be released into water and air from its production sites after biological treatment. In a Japanese company, about 47 kg/year are released to water from the production site. In a Japanese monitoring program by Environment Agency, this chemical was not detected in the general environment in 1984. This chemical is stable in neutral, acidic or alkaline solutions, and is classified as "not readily biodegradable". Direct photodegradation is not expected because trimethyl phosphate does not absorb UV light.

2.1 Environmental Exposure and Fate

2.1.1 Sources of Environmental Exposure

Global exposure

The potential environmental distribution of trimethyl phosphate obtained from a generic level III fugacity model is shown in Table 2. A problem with the use of a fugacity model for trimethyl phosphate is that it is miscible with water and since no measured Henry's Law constant exists, a high but artificial solubility has to be used (in this case 1000 g/l) in order for the Henry's Law constant to be estimated. The results show that if trimethyl phosphate is released mainly to water, it is unlikely to distribute into other compartments. But, if trimethyl phosphate is released mainly to air or soil, it is likely to be transported both to water and soil. Due to the low vapour pressure of trimethyl phosphate, it is unlikely to distribute into air.

Table 2: Environmental distribution trimethyl phosphate using a generic level III fugacity model.

Compartment	Release: 100% to air	Release: 100% to water	Release: 100% to soil
Air	0.02%	0.00%	0.00%
Water	47.75%	99.80%	45.14%
Soil	52.14%	0.00%	54.77%
Sediment	0.10%	0.20%	0.09%

Local exposure

According to a Japanese manufacturer, 47 kg/y (estimated) of trimethyl phosphate are released with 320,000 t/y of effluent into a bay. Local predicted environmental concentration (PEC_{local}) is 1.5 x 10^{-4} mg/l, employing the following calculation model. In this case, the dilution factor is estimated to be 1000.

$$\frac{\text{Amount of release } (4.7 \times 10^{7} \text{ mg/y})}{\text{Volume of effluent } (3.2 \times 10^{8} \text{ l/y}) \times \text{Dilution factor } (1000)}$$

2.1.2 Photodegradation

Direct photodegradation is not expected because trimethyl phosphate does not absorb UV light.

2.1.3 Stability in Water

The chemical is stable in water at pH 4, 7 and 9 (OECD TG 111).

2.1.4 Biodegradation

If released into water, this substance is not readily biodegraded (MITI (I), corresponding to the OECD TG 301C: 0 % during 28 days based on BOD and 0 % based on GC analysis).

2.1.5 Bioaccumulation

BCF = 1.5 – 2.4 in carp (6 weeks at 25 °C) suggests that the potential for bioconcentration in aquatic organisms is low.

2.2 Human Exposure

2.2.1 Occupational Exposure

As trimethyl phosphate is produced in a closed system, exposure during synthesis may be excluded. This chemical is used as the polymerization catalyst. The product is filled into barrels under local exhaust ventilation. Dermal uptake considered to be the main exposure route. Inhalation plays a minor role.

The exposure level calculated with the EUSES model, using the physical-chemical properties of the substance and the information above, is as follows:

A. Inhalation 0.5 – 3.0 mg/m^3

B. Dermal 0-0.1 $mg/cm^2/day$

Workers wear safety glasses and gloves during the filling process. Therefore, the exposure to worker is estimated to be negligible.

2.2.2 Consumer Exposure

Unknown

2.2.3 Exposure via the environment

The highest exposure to the general population via the environment would be expected through drinking water processed from surface water. Based on the physical chemical properties of trimethyl phosphate, a significant removal of during processing is not expected. Although PEC_{global} cannot be estimated, the concentration in drinking water is assumed to be less than 1.5×10^{-4} mg/l. Assuming a consumption of drinking water of 2 L/day and an average body weight of 60 kg, a daily intake of 5.0×10^{-6} mg/kg/day can be estimated. The exposure through food is estimated to be negligible as the substance has a low bioaccumulation potential.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Acute Toxicity

The LD_{50} in an acute oral toxicity study with rats was reported as 840 mg/kg. LD_{50} and LC_{50} values from acute inhalation and dermal toxicity studies are not available.

3.1.2 Repeated Dose Toxicity

There is only one key study on repeated dose toxicity of trimethyl phosphate. This chemical was studied for oral toxicity in rats according to the OECD combined repeated dose and reproductive/developmental toxicity test [OECD TG 422]. As the study was well controlled and conducted under GLP, this was appropriate to regard as a key study. Male and female SD rats were orally administered (gavage) at doses of 0, 40, 100 and 250 mg/kg/day. In male rats, the administration period was two weeks prior to mating, 2 weeks of mating and 2 weeks after the completion of mating period. In female, in addition to maximum four weeks pre-mating and mating period, they were given through pregnant period until day 3 of post delivery.

Twelve males and one female that received 250 mg/kg died during the 4th to 6th week of the dosing period. These rats showed progressive paralytic gait and decreased motor activity that became evident after the 2nd week. Body weight gain of males and females given 250 mg/kg were significantly lower than those of the controls. In addition, 12 and 2 pregnant females given 40 and 100 mg/kg revealed a significant decrease in body weight gain during mid- and late-pregnancy. Food consumption of the 250 mg/kg males was significantly lower than that of the controls. By the hematology and clinical chemistry examinations, significant decreased erythrocyte counts, hemoglobin concentration, hematocrit and A/G ratio, and increased platelet counts, percent of segmented neutrophile, cholinesterase activity, total cholesterol and calcium levels were noted in the 100 mg/kg or more males. Similar alteration in hematological and clinical chemistry parameters was observed in the one surviving 250 mg/kg males. At terminal necropsy, compound-related alterations in organ weights included significant increases in the kidney weight of the 40 and 100 mg/kg males and in the thymus weight of the 100 mg/kg males and the 40 mg/kg females, and a significant decrease in the epididymal weight of 100 mg/kg males. In the histopathological examinations, major lesions noted in males and females given 100 mg/kg or more included nephropathy characterized by tubular and papillary alteration such as increased eosinophilic droplets in tubular epithelium, increased regeneration of tubules and papillary necrosis, atrophy of the thymus, liver and testis, increased atretic follicles in the ovary (250 mg/kg female only), and degeneration of nerve fiver in the spinal cord or the peripheral nerves (e.g., sciatic nerve). The incidence and severity of these lesions increased with dose and were greater in males than females. NOEL was less than 40 mg/kg/day for repeated dose toxicity.

3.1.3 Mutagenicity

In vitro Studies

Bacterial test

A reverse gene mutation assay was conducted in line with Guidelines for Screening Mutagenicity Testing of Chemicals (Japan) and OECD Test Guidelines 471 and 472, using the pre-incubation method. This study was well controlled and regarded as a key study. Dimethyl phosphate showed negative results in *Salmonella typhimurium* TA100, TA1535, TA98, TA1537 and *Escherichia coli*

WP2 *uvr*A at concentrations up to 5 mg/plate with or without a metabolic activation system (MHW, 1993).

Non-bacterial test

A chromosomal aberration test in line with Guidelines for Screening Mutagenicity Testing of Chemicals (Japan) and OECD Test Guideline 473 was conducted using cultured Chinese Hamster lung (CHL/IU) cells. This study was well controlled and regarded as a key study. The maximum concentration of the chemical was used within no apparent cytotoxic effect in the continuous treatment. In the short term treatment, it was set to 3.5 mg/ml because the concentration was equivalent to ca. 10 mM as required in test guidelines.

No structural chromosomal aberrations or polyproidy were recognized up to a maximum concentration of 3.5 mg/ml under conditions of both continuous treatment and short-term treatment with or without an exogeneous metabolic activation system (MHW, Japan, 1981).

In vivo Studies

The result of a micronucleus test in mice was reported in 1973. A positive result was obtained in this report, but detailed data are not known (Weber et al., 1973).

3.1.4 Carcinogenicity

There is one result available from a test by the NTP program on carcinogenicity using F344 rats and C6B3F_1 mice (US/NTP, 1978).

The substance was carcinogenic in female B6C3F1 mice, including adenocarcinomas of the uterus/endometrium. Trimethyl phosphate was associated with the induction of benign fibromas of the subcutaneous tissue in male Fischer 344 rats. No evidence of carcinogenicity of the compound was obtained in female rats or in male mice.

3.1.5 Toxicity for Reproduction

Trimethyl phosphate was studied for oral toxicity in rats according to the OECD combined repeated dose and reproductive/developmental toxicity test [OECD TG 422] at doses of 0, 40, 100 and 250 mg/kg/day. Although this combined study was designed to investigate reproductive capability in parental generation as well as development in F_1 offspring, parameters to evaluate developmental toxicity were limited to only body weights at day 0 and day 4 after birth, and autopsy findings at day 4.

The copulation rate of the paired animals was decreased significantly in the 250 mg/kg group and the fertility index and number of implantation sites were decreased significantly in the 40 mg/kg group. Furthermore, intrauterine mortality of embryos was increased significantly in the 40 mg/kg group. However, no significant differences on the pup viability and incidence of the morphological abnormalities of pups were shown in the groups given 40 mg/kg when compared to the controls. Pup weights in the 40 mg/kg group were significantly higher than those in the control group up until terminal necropsy on day 4 of lactation.. The NOAEL values for both parental and F_1 offspring in reproductive toxicity are considered to be less than 40 mg/kg/day.

3.2 Initial Assessment for Human Health

Although negative results were obtained both from an Ames test and a chromosomal aberration test *in vitro*, genotoxic effects were shown by a micronucleus test *in vivo*. In a combined repeat dose and reproductive/developmental toxicity screening test, significant decrease of body weight,

significant change in haematology and clinical chemistry examines (e.g. decreased erythrocytes) were observed in parental animals. Renal toxic findings and neurotoxic effects were also seen in gross and histopathological examines (e.g. nephropathy, degeneration of nerve fibre). Increases of kidney weight were observed at the lowest dose level (40 mg/kg/day). For reproductive/developmental end-points, the fertility index and the number of implantation sites were decreased at the lowest dose. In addition, intrauterine mortality of embryos was also increased at the level. Therefore, the NOEL was less than 40 mg/kg/day both for repeated dose and reproductive toxicity.

As for indirect exposure via environment, PEC_{local} in surface water was estimated as 1.5×10^{-4} mg/l from local exposure scenario. The daily intake through drinking water is estimated as 5.0×10^{-6} mg/kg/day. The margin of safety is very large. Therefore, health risk through the environment, in general, is considered to be presumably low due to its use pattern and exposure situation.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Trimethyl phosphate has been tested in a limited number of aquatic species (*Selenastrum capricornutum*, *Daphnia magna* and *Oryzias latipes*), under OECD test guidelines [OECD TG 201, 202, 203,]. Acute and chronic toxicity data to test organisms for trimethyl phosphate are summarized in Table 3. No other ecotoxicological data are available.

Various NOEC and LC_{50} values were gained from above tests; LC_{50} = > 1,050 mg/l (acute fish); EC_{50} = > 1,000 mg/l (acute daphnia); EC_{50} = > 1,000 mg/l (acute algae); NOEC = 320 mg/l (long-term daphnia reproduction). Therefore, the chemical is considered to be slightly toxic to daphnids and non-toxic to fish and algae. As the lowest chronic toxicity result, the 21 d-NOEC (reproduction) of *Daphnia magna* (320 mg/l), was adopted. As assessment factor of 100 is applied. Thus the PNEC of trimethyl phosphate is 3.2 mg/l. Since the PEC is lower than the PNEC, environmental risk is presumably low.

Table 3. Acute and chronic toxicity data of trimethyl phosphate to aquatic organisms.

Species	Endpoint[*1]	Conc. (mg/L)	Reference
Selenastrum capricornutum (algae)	Biomass: EC_{50} (72h) NOEC	> 1,000 mg/L > 1,000 mg/L	E.A., Japan. (1994)
Daphnia magna (water flea)	Imm: EC_{50}(24h) Imm: EC_{50}(21d) Rep: EC_{50}(21d) Rep: NOEC(21d)	> 1,000 mg/L 800 mg/L 520 mg/L 320 mg/L	
Oryzias latipes (fish, Medaka)	Mor: LC_{50}(96h)	> 1,050 mg/L	

Notes: [*1] Mor; mortality, Rep; reproduction, Imm; immobilisation

4.2 Initial Assessment for the Environment

For the environment, various NOEC and LC_{50} values were gained from test results; LC_{50} = > 1050 mg/l (acute fish); EC_{50} = > 1000 mg/l (acute daphnia); EC_{50} = > 1000 mg/l (acute algae); NOEC = > 1000 mg/l (algae); NOEC = 320 mg/l (long-term daphnia reproduction). The lowest chronic toxicity result, 21d-NOEC (reproduction) of *Daphnia magna* (320 mg/l), was adopted. The assessment factor of 100 was used to both acute and chronic toxicity data to determine a PNEC according to the OECD Provisional Guidance for Initial Assessment of Aquatic Effects. Thus, the PNEC of the chemical is 3.2 mg/l in the present report. The PEC is lower than the PNEC, therefore the environmental risk is presumably low.

5 RECOMMENDATIONS

The chemical is currently of low priority for further work.

A potential hazard to man due to genotoxicity is identified, but exposure throughout the OECD is low. It is currently considered of low potential risk and low priority for further work.

6 REFERENCES

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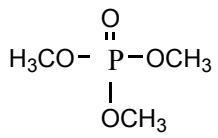
SIDS DOSSIER

Phosphoric acid, trimethyl ester

CAS No. 512-56-1

Sponsor Country : Japan

S I D S P R O F I L E

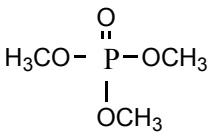
1.01 A.	**CAS No.**	512-56-1
1.01 C.	**CHEMICAL NAME (OECD Name)**	Phosphoric acid, trimethyl ester
1.01 D.	**CAS DESCRIPTOR**	Not applicable
1.01 G.	**STRUCTURAL FORMULA**	
	OTHER CHEMICAL IDENTITY INFORMATION	
1.5	**QUANTITY**	In Japan, 100-1,000 tonnes/year in 1987 – 1992. In EEC, 500 tonnes in 1987.
1.7	**USE PATTERN**	polymerization catalyst, intermediate for pesticides and ignition control agent in gasoline
1.9	**SOURCES AND LEVELS OF EXPOSURE**	In Japan, 1. Amount released from production site to water is 47 kg/year. All of the wastes water is incinerated.
ISSUES FOR DISCUSSION (IDENTIFY, IF ANY)		

S I D S S U M M A R Y

CAS NO: 512-56-1		Information	OECD Study	GLP	Other Study	Estimation Method	Acceptable	SIDS Testing Required
STUDY		**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**
PHYSICAL-CHEMICAL DATA								
2.1	Melting Point	Y	N	N	Y	N	Y	N
2.2	Boiling Point	Y	N	N	Y	N	Y	N
2.3	Density	Y	N	N	Y	N	Y	N
2.4	Vapour Pressure	N						Y
2.5	Partition Coefficient	N						Y
2.6	Water Solubility	N						Y
	pH and pKa values	N						N
OTHER P/C STUDIES RECEIVED								
ENVIRONMENTAL FATE and PATHWAY								
3.1.1	Photodegradation	N						Y
3.1.2	Stability in water	N						Y
3.2	Monitoring data	N						N
3.3	Transport and Distribution	N						N
3.5	Biodegradation	N						Y
3.6	Bioaccumulation	Y	Y	Y	N	N	Y	N
OTHER ENV FATE STUDIES RECEIVED								
ECOTOXICITY								
4.1	Acute toxicity to Fish	N						Y
4.2	Acute toxicity to Daphnia	N						Y
4.3	Toxicity to Algae	N						Y
4.5.2	Chronic toxicity to Daphnia	N						Y
4.6.1	Toxicity to Soil dwelling organisms	N						N
4.6.2	Toxicity to Terrestrial plants	N						N
4.6.3	Toxicity to Birds	N						N
OTHER ECOTOXICITY STUDIES RECEIVED								
TOXICITY								
5.1.1	Acute Oral	N						Y
5.1.2	Acute Inhalation	N						N
5.1.3	Acute Dermal	N						N
5.4	Repeated Dose	N						Y
5.5	Genetic Toxicity *in vitro*							
	. Gene mutation	N						Y
	. Chromosomal aberration	N						Y
5.6	Genetic Toxicity *in vivo*	N						N
5.8	Reproduction Toxicity	N						Y
5.9	Development / Teratogenicity	N						Y
5.11	Human experience	N						N
OTHER TOXICITY STUDIES RECEIVED								

1.01 SUBSTANCE INFORMATION

A.	**CAS-Number**	512-56-1
B.	**Name (IUPAC name)**	Trimethyl phosphate
C.	**Name** *(OECD name)*	Phosphoric acid, trimethyl ester
D.	**CAS Descriptor**	Not applicable
E.	**EINECS-Number**	208-144-8
F.	**Molecular Formula**	$C_3H_9O_4P$
G.	**Structural Formula**	



H.	**Substance Group**	Not applicable
I.	**Substance Remark**	None
J.	**Molecular Weight**	140.1

1.02 OECD INFORMATION

A.	**Sponsor Country:**	Japan
B.	**Lead Organization:**	
	Name of Lead Organization:	Ministry of Health and Welfare (MHW) Ministry of International Trade and Industry (MITI) Environment Agency (EA)
	Contact person:	Mr. Yasuhisa Kawamura Director Second International Organization Bureau Ministry of Foreign Affairs
	Address:	2-2-1 Kasumigaseki, Chiyoda-ku Tokyo 100, Japan TEL 81-3-3581-0018 FAX 81-3-3503-3136
C.	**Name of responder**	
	Name:	Same as above contact person
	Address:	

1.1 GENERAL SUBSTANCE INFORMATION

A. Type of Substance

element **[ ]**; inorganic **[ ]**; natural substance **[ ]**;
organic **[X]**; organometallic **[ ]**; petroleum product **[ ]**

B. Physical State gaseous **[ ]**; liquid **[X]**; solid **[ ]**

C. Purity > 99 %

1.2 SYNONYMS Trimethyl phosphate

1.3 IMPURITIES Unknown

1.4 ADDITIVES Unknown

1.5 QUANTITY

Location	Production (tonnes)	Date
(1) Japan	100-1,000/year	1987-1992
(2) EEC	500	1987

Reference: (1) MITI, Japan (1994a)
(2) ECDIN Database (1994)

1.6 LABELLING AND CLASSIFICATION

None

1.7 USE PATTERN

A. General

Type of Use:	**Category:**
(1) Industry use	Polymerization catalyst
(2) Direct use	Ignition control agent
Industry use	Intermediate for pesticides

Reference: (1) MITI, Japan (1994a)
(2) ECDIN Database (1994)

B. Uses in Consumer Products

Ignition control agent in gasoline

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUE

None

1.9 SOURCES OF EXPOSURE

Source: Media of release: Water from a production site
Quantities per media: 47 kg/year

Reference: MITI, Japan (1994a)

1.10 ADDITIONAL REMARKS

A. Options for disposal Incineration

Reference: MITI, Japan (1994a)

B. Other remarks None

2.1 MELTING POINT

(a)
Value: - 10 °C
Decomposition: Yes **[ ]** No **[X]** Ambiguous **[ ]**
Sublimation: Yes **[ ]** No **[X]** Ambiguous **[ ]**
Method:
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Reference: MITI (1992)

(b)
Value: - 46.2 °C
Decomposition: Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Sublimation: Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Method:
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Reference: Pagal & Schroeder, J. Am. Chem. Soc., 62, 1837 (1940)

(c)
Value: - 70 °C (Freezing point)
Decomposition: Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Sublimation: Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Method:
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Reference: Company data

2.2 BOILING POINT

(a)
Value: 197 °C
Pressure:
Decomposition: Yes **[ ]** No **[X]** Ambiguous **[ ]**
Method:
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Reference: Lange's Handbook of Chemistry (11th edition)

(b)
Value: 180 - 195 °C
Pressure:
Decomposition: Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Method: Unknown
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: None
Reference: Company data

2.3 DENSITY (Relative density)

No data available

2.4 VAPOUR PRESSURE

Value: 7.4×10^{-1} Pa

Temperature:	25°C
Method:	calculated **[ ]**; measured **[X]**
	OECD Test Guideline 104 Dynamic method
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Reference:	MITI, Japan (1994b)

2.5 PARTITION COEFFICIENT $log_{10}P_{ow}$

(a)

Log Pow:	- 0.46
Temperature:	25 °C
Method:	calculated **[ ]**; measured **[X]**
	OECD Test Guideline 107
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Reference:	MITI (1992)

(b)

Log Pow:	- 0.52
Temperature:	25 °C
Method:	calculated **[X]**; measured **[ ]**
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Reference:	Numerica database

2.6 WATER SOLUBILITY

A. Solubility

Value:	Miscible
Temperature:	25 °C
Description:	Miscible **[X]**; Of very high solubility **[ ]**;
	Of high solubility **[ ]**; Soluble **[ ]**;Slightly soluble **[ ]**;
	Of low solubility **[ ]**; Of very low solubility **[ ]**;
	Not soluble **[ ]**
Method:	OECD Test Guideline 105
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Reference:	MITI, Japan (1994b)

B. pH Value, pKa Value

No data available

2.7 FLASH POINT

No data available

2.8 AUTO FLAMMABILITY

No data available

2.9 FLAMMABILITY

No data available

2.10 EXPLOSIVE PROPERTIES

No data available

2.11 OXIDIZING PROPERTIES

No data available

2.12 OXIDATION: REDUCTION POTENTIAL

No data available

2.13 ADDITIONAL DATA

A. Partition co-efficient between soil/sediment and water (Kd)

No data available

B. Other data

None

3.1 STABILITY

3.1.1 PHOTODEGRADATION

Direct photodegradation is not expected because trimethyl phosphate does not absorb UV light.

3.1.2 STABILITY IN WATER

Type:	Abiotic (hydrolysis) **[X]**; biotic (sediment)**[ ]**
Result:	Stable at pH 4, 7 and 9 at 25 °C
Method:	OECD Test guideline 111
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	Trimethyl phosphate
Reference:	MITI, Japan (1994b)

3.1.3 STABILITY IN SOIL

No data available

3.2 MONITORING DATA (ENVIRONMENT)

(a)

Type of Measurement:	Background **[ ]**, At contaminated Site **[ ]**, Other **[ ]**
Media:	Surface water
Results:	ND (Detection limits:0.00002-0.0001ug/ml) in 14 areas in Japan as of 1982
Remarks:	None
Reference:	EA, Japan (1985)

(b)

Type of Measurement:	Background **[ ]**, At contaminated Site **[ ],** Other **[ ]**
Media:	Surface water
Results:	ND (Detection limits:0.00004-0.001ug/ml) in 8 areas in Japan
Remarks:	None
Reference:	EA, Japan (1987)

(c)

Type of Measurement:	Background **[ ]**, At contaminated Site **[ ]**, Other **[ ]**
Media:	Sediment
Results:	ND (Detection limits:0.0005-0.005ug/ml) in 14 areas in Japan
Remarks:	None
Reference:	EA, Japan (1985)

(d)

Type of Measurement:	Background **[ ]**, At contaminated Site **[ ]**, Other **[ ]**
Media:	Sediment
Results:	ND (Detection limits:0.0003-0.005ug/ml) in 8 areas in Japan
Remarks:	None
Reference:	EA, Japan (1987)

3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION PATHWAYS

3.3.1 TRANSPORT

No data available

3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

The potential environmental distribution of trimethyl phosphate obtained from a generic level III fugacity model is shown in Table. A problem with the use of a fugacity model for trimethyl phosphate is that it is miscible with water and since no measured Henry's Law constant exists, a high but artificial solubility has to be used (in this case 1000 g/l) in order for the Henry's Law constant to be estimated. The results show that if trimethyl phosphate is released mainly to water, it is unlikely to distribute into other compartments. But, if trimethyl phosphate is released mainly to air or soil, it is likely to be transported both to water and soil. Due to the low vapour pressure of trimethyl phosphate, it is unlikely to distribute into air.

Environmental distribution Trimethyl phosphate using a generic level III fugacity model.

Compartment	**Release: 100% to air**	**Release: 100% to water**	**Release: 100% to soil**
Air	0.02%	0.00%	0.00%
Water	47.75%	99.80%	45.14%
Soil	52.14%	0.00%	54.77%
Sediment	0.10%	0.20%	0.09%

Reference: EA & MITI, Japan (1994)

3.4 IDENTIFICATION OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE

No data available

3.5 BIODEGRADATION

Type:	aerobic **[X]**; anaerobic **[ ]**
Inoculum:	adapted **[ ]**; non-adapted **[X]**;
Concentration of the chemical:	100 mg/l related to Test Substance **[X]**
Medium:	water**[ ];**water-sediment**[ ];**soil **[ ];**sewage treatment **[ ]** other **[**Japanese standard activated sludge**]**
Degradation:	Degree of degradation after 28 days 0, 0 and 0 % from BOD 0, 0 and 0 % from GC analysis
Results:	Readily biodeg. **[ ];** Inherently biodeg. **[ ]**; under test condition no biodegradation observed **[X]**
Method:	OECD Test Guideline 301 C
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	Trimethyl phosphate
Reference:	MITI (1992)

3.6 BOD_5,COD OR RATIO BOD_5/COD

Not applicable

3.7 BIOACCUMULATION

Species:	Carp
Exposure period:	6 weeks
Temperature:	25 °C
Concentration:	(1) 1 mg/l (2) 0.1 mg/l
BCF:	(1) 1.5 - 2.4 (2) < 1.7
Method:	OECD Test Guideline 305 C
Type of test:	calculated **[ ]**; measured **[X]** static **[ ]**; semi-static **[ ]**; flow-through **[ ]**; other **[ ]**
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	Trimethyl phosphate
Reference:	MITI, Japan (1992)

3.8 ADDITIONAL REMARKS

A. Sewage treatment None

B. Other information None

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type of test:	static **[ ]**; semi-static **[X]**; flow-through **[ ]**; other **[ ]**
	open-system **[X]**; closed-system **[ ]**
Species:	*Oryzias latipes*
Exposure period:	96 hr
Results:	LC_{50} (24h) = > 1050 mg/l
	LC_{50} (48h) = > 1050 mg/l
	LC_{50} (72h) = > 1050 mg/l
	LC_{50} (96h) = > 1050 mg/l
	NOEC =
	LOEC =
Analytical monitoring:	Yes **[ ]** No **[X]** ? **[ ]**
Method:	OECD Test Guideline 203 (1981)
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	Trimethyl phosphate, purity = 99.0 %
Remarks:	A group of 10 fishes were exposed to 5 nominal concentrations (100 - 1050 mg/l).
Reference:	EA, Japan (1994)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

A. Daphnia

Type of test:	static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other **[ ]**;
	open-system **[**X**]**; closed-system **[ ]**
Species:	*Daphnia magna*
Exposure period:	24 hr
Results:	EC_{50} (24h) = > 1000 mg/l
	EC_{50} (48h) =
	NOEC =
	LOEC =
Analytical monitoring:	Yes **[ ]** No **[X]** ? **[ ]**
Method:	OECD Test Guideline 202 (1984)
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	Trimethyl phosphate, purity: = 99.0 %
Remarks:	20 daphnids (4 replicates; 5 organisms per replicate) were exposed to 5 nominal concentrations (100-1000 mg/l).
Reference:	EA, Japan (1994)

B. Other aquatic organisms

No data available

4.3 TOXICITY TO AQUATIC PLANTS e.g. Algae

Species:	*Selenastrum capricornutum* ATCC 22662	
End-point:	Biomass **[X]**; Growth rate **[ ]**; Other **[ ]**	
Exposure period:	72 hours	
Results:	Biomass:	EC_{50} (24h) =
		EC_{50} (72h) = > 1000 mg/l
		NOEC = > 1000 mg/l
		LOEC =

Analytical monitoring: Yes **[ ]** No **[X]** ? **[ ]**
Method: open-system **[**X**]**; closed-system **[ ]**
OECD Test Guideline 201 (1984)
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: Trimethyl phosphate, purity = 99.0 %
Remarks: The EC_{50} values were calculated based on 5 nominal concentrations (100-1000 mg/l).
Reference: EA, Japan (1994)

4.4 TOXICITY TO BACTERIA

No studies located

4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS

4.5.1. CHRONIC TOXICITY TO FISH

Test species: *Poecilia reticulata* (guppy)

Test method:
Type of test: static **[ ]**, semi-static **[X]**, flow-through **[ ]**, Other (e.g., field test) **[ ]**
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test results: The length of testes showed a significant decrease in length with 2,000 ppm Timethyl phosphate for 100 days.
Test substance: Trimethyl phosphate, purity: unknowm
Remarks:
Reference: Hanna, P.J., Bull. Environm. Contam. Toxicol., 28, 29-32 (1982)

4.5.2. CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Type of test: static **[ ]**; semi-static **[**X**]**; flow-through **[ ]**; other **[ ]**;
open-system **[X]**; closed-system **[ ]**
Species: *Daphnia magna*
End-point: Mortality **[ ]**; Reproduction rate **[X]**; Other **[X]**
Exposure period: 21 day
Results:
Immobility: LC_{50} (24 h) = > 1000 mg/l
LC_{50} (48 h) = > 1000 mg/l
LC_{50} (96 h) = > 1000 mg/l
LC_{50} (7 d) = > 1000 mg/l
LC_{50} (14 d) = 880 mg/l (95% confidence level:810-940 mg/l)
LC_{50} (21 d) = 800 mg/l (95% confidence level:730-860 mg/l)
NOEC =
LOEC =
Reproduction: EC_{50} (14 d) = 280 mg/l (95% confidence level:270-290 mg/l)
EC_{50} (21 d) = 520 mg/l (95% confidence level:510-530 mg/l)
NOEC = 320 mg/l ($p < 0.05$)
LOEC = 560 mg/l ($p < 0.05$)
Analytical monitoring: Yes **[ ]** No **[X]** ? **[ ]**
Method: OECD Test Guideline 202 (1984)
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: Trimethyl phosphate, purity = 99.0 %
Remarks: 40 daphnids (4 replicates; 10 organisms per replicate) were exposed to 5 nominal concentrations (100-1000 mg/l)

Reference: EA, Japan (1994)

4.6 TOXICITY TO TERRESTRIAL ORGANISMS

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

No data available

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

No data available

4.6.3 TOXICITY TO OTHER NON MAMMALIAN TERRESTRIAL SPECIES (INCLUDING AVIAN)

Test species:	Quail
Test method:	Unknown
GLP:	Yes [ ] No [ ] ? [ ]
Test results:	LD_{50}: 750 mg/kg
Test substance:	Trimethyl phosphate
Remarks:	Details toxic effects were not reported
Reference:	J. Reproduction Fertility, 48, 371 (1976)

4.7 BIOLOGICAL EFFECTS MONITORING (INCLUDING BIOMAGNIFICATION)

No studies located

4.8 BIOTRANSFORMATION AND KINETICS IN ENVIRONMENTAL SPECIES

No data available

4.9 ADDITIONAL REMARKS

None

5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

(a)

Type :	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Rat
Value :	840 mg/kg
Method:	Unknown
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance: purity:	Unknown
Remarks:	None
Reference:	NIH-NCI-E-C72-3252 (1973) National Cancer Institute, USA

5.1.2 ACUTE INHALATION TOXICITY

No data available

5.1.3 ACUTE DERMAL TOXICITY

No data available

5.1.4 ACUTE TOXICITY, OTHER ROUTES OF ADMINISTRATION

No data available

5.2 CORROSIVENESS/IRRITATION

5.2.1 SKIN IRRITATION/CORROSION

No data available

5.2.2 EYE IRRITATION/CORROSION

No data available

5.3 SKIN SENSITISATION

No data available

5.4 REPEATED DOSE TOXICITY

(a)

Species/strain:	Rat (Crj:CD(SD))
Sex:	Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**
Route of Administration:	oral gavage
Exposure period:	Males: 42 days including 14 days before mating Females: from 14 days before mating to day 3 of lactation
Frequency of treatment:	7 days/week
Post exposure observation period:	
Dose:	0, 40, 100 or 250 mg/kg (13 animals /group)
Control group:	Yes **[X]**; No **[ ]**; No data **[ ]**;

Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**; Historical **[ ]**
NOEL: < 40 mg/kg/day
LOEL: 40 mg/kg/day
Results: Twelve males and one female that received 250 mg/kg died during the 4th to 6th week of the dosing period. These rats showed progressive paralytic gait and decreased motor activity that became evident after the 2nd week. Body weight gain of males and females given 250 mg/kg were significantly lower than those of the controls. In addition, 12 and 2 pregnant females given 40 and 100 mg/kg revealed a significant decrease in body weight gain during mid- and late-pregnancy. Food consumption of the 250 mg/kg males was significantly lower than that of the controls. By the hematology and clinical chemistry examinations, significant decreased erythrocyte counts, hemoglobin concentration, hematocrit and A/G ratio, and increased platelet counts, percent of segmented neutrophile, cholinesterase activity, total cholesterol and calcium levels were noted in the 100 mg/kg or more males. Similar alteration in hematological and clinical chemistry parameters was observed in the one surviving 250 mg/kg males. At terminal necropsy, compound-related alterations in organ weights included significant increases in the kidney weight of the 40 and 100 mg/kg males and in the thymus weight of the 100 mg/kg males and the 40 mg/kg females, and a significant decreases in the epididymal weight of 100 mg/kg males. In the histopathological examinations, major lesions noted in males and females given 100 mg/kg or more included nephropathy characterized by tubular and papillary alteration such as increased eosinophilic droplets in tubular epithelium, increased regeneration of tubules and papillary necrosis, atrophy of the thymus, liver and testis, increased atretic follicles in the ovary (250 mg/kg female only), and degeneration of nerve fiver in the spinal cord or the peripheral nerves (e.g., sciatic nerve). The incidence and severity of these lesions increased with dose and were greater in males than females.
Method: OECD Combined Repeat dose and reproductive/Developmental Screening Toxicity Test (1992)
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: Commercial, purity: 99.9 %
Reference: MHW, Japan (1994a)

(b)
Species/strain: Rat (Wistar)
Sex: Female **[ ]**; Male **[X]**; Male/Female **[ ]**; No data **[ ]**
Route of Administration: oral (Feeding)
Exposure period:
Frequency of treatment:
Post exposure observation period:
Dose: 0, 0.5 %
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**; Historical **[ ]**
NOEL: < 0.5 %
Results: Body weight of compound-treated rats were significantly lower than controls. Both absolute and relative weight of liver, and those of kidneys of compound-treated rats increased significantly. Erythrocyte counts and hemoglobin concentration, GOT, GPT activities of compound-treated rats were significantly lower than the controls. Slight morphological changes including cytoplasmic vacuolation, increases in the number of binucleated cells and enlargement of cell size were found in the livers of rats treated with trimethyl phosphate.
Method:
GLP: Yes **[ ]** No **[ ]** ? **[X]**

Test substance: Purity: Unknown
Reference: Oishi, H. et al., Toxicol. Lett., 13, 29-34 (1982)

5.5 GENETIC TOXICITY IN VITRO

A. BACTERIAL TEST

(a)
Type : Bacterial reverse mutation assay
System of testing:
Species/strain: *S. typhimurium* TA 98, TA 100, TA 1535, TA1537
E. coli WP2 uvrA
Concentration: 0, 10, 50, 100, 500, 1000, 5000 µg/plate
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**;No data **[ ]**
Results:
Cytotoxicity conc: With metabolic activation: 5000 µg/plate
Without metabolic activation: 5000 µg/plate
Precipitation conc:
Genotoxic effects:

S. typhimurium TA 100, TA1535, TA98, TA1537	+	?	-
With metabolic activation:	**[ ]**	**[ ]**	**[X]**
Without metabolic activation:	**[ ]**	**[ ]**	**[X]**

E. coli WP2 uvrA	+	?	-
With metabolic activation:	**[ ]**	**[ ]**	**[X]**
Without metabolic activation:	**[ ]**	**[ ]**	**[X]**

Method: Japanese Guideline for Screening Mutagenicity testing of chemicals
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Teat substance: Commercial, purity: > 99 %
Remarks: Procedure: Plate incorporation method
Plates/test: 3
Activation system: Liver S-9 fraction from Phenobarbital and 5,6-Benzoflavone pretreated male SD rats with NADPH-generating system
Media:Histidine selective
No. replicates: 2
Reference: Company data in Japan (1981)

B. NON-BACTERIAL IN VITRO TEST

Type : Cytogenetics Assay
System of testing:
Species/strain: Chinese hamster lung (CHL/IU) cells
Concentration: -S9 (continuous treatment) 0, 0.4, 0.7, 1.4 mg/ml
-S9 (short-term treatment) 0, 0.4, 0.7, 1.4 mg/ml
+S9 (short-term treatment) 0, 0.4, 0.7, 1.4 mg/ml
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
Results:
Cytotoxicity conc: With metabolic activation: 1.4 mg/ml
Without metabolic activation: 1.4 mg/ml
Precipitation conc:
Genotoxic effects:

	+	?	-
With metabolic activation:	**[ ]**	**[ ]**	**[X]**
Without metabolic activation:	**[ ]**	**[ ]**	**[X]**

Method:	Japanese Guideline for Screening Mutagenicity testing of chemicals
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	Commercial, purity 99.9 %
Remarks:	Plates/test:2 Activation system: S-9 fraction from the liver of Phenobarbital and 5,6-Benzoflavone induced male SD derived rats with NADPH-generating system Media: RPMI 1640 medium *plus* 10% foetal calf serum *plus* phytohaemagglutinin No. replicates: 1
Reference:	MHW, Japan (1994b)

5.6 GENETIC TOXICITY IN vivo

Test type:	Micronucleus Test
Test species/strain:	Mice ($B_GD_2F_1$)
Method:	i.p., 500, 750, 1000 and 2000 mg/kg b.w.
GLP:	Yes **[ ]**, No **[ ]**, ? **[X]**
Test Results:	Dose related increase in micronuclei was observed.
Genotoxic effects:	

	+	?	-
Micronucleus test	**[X]**	**[ ]**	**[ ]**

Remarks:	
Reference:	Weber, E., Bidwell, k. & Legator, M.S., Mutat. Res., 28, 101-106 (1973)

5.7 CARCINOGENICITY

Test species/strain: Mice/B6C3F1	Rats/Fischer 344
Test method:	US/NTP method gavage studies Rats: 0, 50 or 100 mg/kg, 105 weeks Mice: 0, 250 or 500 mg/kg, 103 weeks
GLP:	Yes **[ ]** No **[ ]**
Test result:	Carcinogenic in female B6C3F1 mice, including adenocarcinomas of the uterus/endometrium. Trimethyl phosphate was associated with the induction of benign fibromas of the subcutaneous tissue in male Fischer 344 rats. No evidence of carcinogenicity of the compound was obtained in female rats or in male mice. a) observation of malignant tumor (type, incidence, location): In the female mice, the incidence of adenocarcinomas of the endometrium was higher (P= 0.004) in the high-dose group than in the vehicle controls (controls 0/16, low-dose 7/40, high-dose, 13/37), and there was a significant dose-related trend (p=0.003) in the incidence of these adenocarcinomas. b) observation of benign tumor (type, incidence, location): In the male rats, the incidence of fibromas of the subcutaneous tissue was higher (P=0.036) in the high-dose group than in the vehicle controls (controls 0/20, low-dose 2/50, high-dose 9/49), and there was a dose-related trend (P=0.006) in the incidence of these fibromas. c) other observations (e.g., time of onset, pathology, rate of survival, etc.):
Test substance:	Trimethyl phosphate
Comments:	

Reference: Bioassay of Trimethyl Phosphate for Possible carcinogenicity. NCI-CG-TR-81, Public Health Service, NIH, USA (1978)

5.8 TOXICITY TO REPRODUCTION

Type: Fertility **[ ]**; One generation study **[ ]**; Two generation study **[ ]**; Other **[X]**
Species/strain: Rat Crj:CD(SD)
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**
Route of Administration: Oral, gavage
Exposure period: Males: 42 days including 14 days before mating
Females: from 14 days before mating to day 3 of lactation.
Frequency of treatment: 7 days/week
Postexposure observation period:
Premating exposure period: male: 14 days, female: 14 days
Duration of the test;
Doses: 0, 40, 100, or 250 mg/kg (13 animals/sex/group)
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**; Historical **[ ]**
NOEL Parental : < 40 mg/kg/day
NOEL F1 Offspring: < 40 mg/kg/day
NOEL F2 Offspring: N/A
Results: The copulation rate of the paired animals was decreased significantly in the 250 mg/kg group and the fertility index and number of implantation sites were decreased significantly in the 40 mg/kg group. Furthermore, intrauterine mortality of embryos was increased significantly in the 40 mg/kg group. However, no significant differences on the pup viability and incidence of the morphological abnormalities of pups were shown in the groups given 40 mg/kg when compared to the controls. Pup weights in the 40 mg/kg group were significantly higher than those in the control group up until terminal necropsy on day 4 of lactation.
Method: OECD Combined Repeat dose and reproductive/Developmental Screening Toxicity Test (1992)
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: Purity 99.9 %
Remarks:
Reference: MHW, Japan (1994b)

5.9 DEVELOPMENTAL TOXICITY/ TERATOGENICITY

See 5.8

5.10 OTHER RELEVANT INFORMATION

A. Specific toxicities

No data available

B. Toxicodynamics, toxicokinetics

No data available

5.11 EXPERIENCE WITH HUMAN EXPOSURE

None

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