Rhodia

201-14987

HS&E CORPORATE SERVICES
Toxicology Department

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December 23, 2003

The Honorable Mike Leavitt, Administrator
U.S. EPA
P.O. Box 1473
Merrifield, VA. 22116

Subject: Update - High Production Volume Chemicals Initiative
- CAS # 6294-34-4, Phosphonic acid, (2-chloroethyl)-, bis(2-chloroethyl) ester (BISCEP Monomer)
- CAS # 58823-09-9, Phosphonic acid, [2-[[(2-chloroethoxy)(2-chloroethyl) phosphinyl]oxy]ethyl]-, bis(2-chloroethyl) ester (BISCEP Dimer)

Dear Administrator Leavitt:

As a continuing participant in the High Production Volume (HPV) chemical testing program, Rhodia Inc. is volunteering to support the generation and reporting of data for many HPV chemicals that we produce or import. We have joined consortia with other companies and volunteered individually to perform the tasks requested under the initiative.

Rhodia Inc. submits for review and public comment its test plan, as well as related robust summaries, for CAS # 6294-34-4, Phosphonic acid, (2-chloroethyl)-, bis(2-chloroethyl) ester (BISCEP Monomer), and CAS # 58823-09-9, Phosphonic acid, [2-[[(2-chloroethoxy)(2-chloroethyl)phosphinyl]oxy]ethyl]-, bis(2-chloroethyl) ester (BISCEP Dimer), under the U.S. EPA's HPV Chemical Challenge Program. Please note that our test plan covers the monomer and dimer together as it represents the actual product being produced. Rhodia understands that there will be a 120-day review period for the test plan report and that all comments generated by or provided to EPA will be forwarded to Rhodia for consideration.

While we are voluntarily submitting study summaries of our data for the purposes of the HPV initiative, Rhodia considers the actual study reports and their associated data to be proprietary and does not allow anyone to use or cite them without our expressed written authorization.

I continue to serve as Rhodia Inc.'s technical contact for the HPV initiative. I can be reached at:

Glenn S. Simon, Ph.D., DABT
Rhodia Inc.
5171 Glenwood Avenue, Suite 402
Raleigh, North Carolina 27612

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E-Mail: glenn.simon@us.rhodia.com

Sincerely,

Glenn S. Simon, Ph.D., DABT
Director of Toxicology

Enclosures:

- HPV Test Plan
- Robust Study Summaries (IUCLID)

cc: Charles M. Auer, U.S. EPA
Barbara Leczynski, U.S. EPA
Jim Keith, American Chemistry Council (w/o attachments)
Paul Larson, Rhodia Inc.

Rhodia

HS&E CORPORATE SERVICES
Toxicology Department

201-14987

HIGH PRODUCTION VOLUME (HPV)
CHEMICAL CHALLENGE PROGRAM

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TEST PLAN
for
Phosphonic acid, (2-chloroethyl)-, bis(2-chloroethyl) ester
[BISCEP Monomer]
CAS No. 6294-34-4

and

Phosphonic acid, [2-[[(2-chloroethoxy)(2-chloroethyl) phosphinyl]oxy]ethyl]-, bis(2-chloroethyl) ester
[BISCEP Dimer]
CAS No. 58823-09-9

Submitted to the US EPA
by
Rhodia Inc.

December 23, 2003

5171 Glenwood Avenue, Suite 402, Raleigh, NC 27612
Telephone: (919) 786-9999 Fax: (919) 786-9154

I) INTRODUCTION

Under the U.S. Environmental Protection Agency (EPA) High Production Volume (HPV) Chemical Challenge Program, Rhodia Inc. (formerly Albright & Wilson Americas Inc.) voluntarily committed to compile basic screening data on:

- Phosphonic Acid, (2-chloroethyl)-, bis(2-chloroethyl) ester
  CAS No. 6294-34-4

- Phosphonic Acid, [2-[[(2-chloroethoxy)(2-chloroethyl)phosphinyl]oxy]ethyl]-, bis(2-chloroethyl) ester
  CAS No. 58823-09-9

The material, known as BISCEP, is produced as a mixture of the monomer (CAS No. 6294-34-4) and dimer (CAS No. 58823-09-9). BISCEP contains ca. 55-70% w/w BISCEP monomer and ca. 35-40% w/w BISCEP dimer. Because of this, the existing test data discussed in this test plan have been primarily conducted on this BISCEP mixture and thus the monomer and dimer are addressed and reported in the same test plan. For the remainder of this dossier, we will refer to BISCEP, recognizing we are designating the monomer-dimer mixture.

This test plan follows up on that commitment. Specifically, this test plan sets forth how Rhodia intends to address testing information for BISCEP.

In preparing this test plan the following steps were undertaken:

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

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

II) GENERAL SUBSTANCE INFORMATION

Chemical Name: **Phosphonic acid, (2-chloroethyl)-, bis(2-chloroethyl) ester**

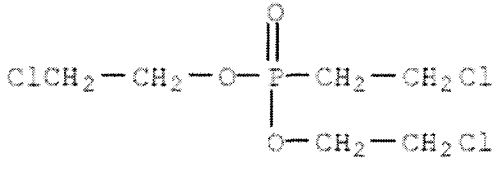
Chemical Abstract Service Registry Number: CAS No.: 6294-34-4

Synomyms: BISCEP Monomer
Bis(2-chloroethyl) 2-chloroethylphosphonate
Bis(2-chloroethyl) (2-chloroethyl)phosphonate
Bis-chloroethyl 2-chloroethanephosphonate

Molecular Formula: $C_6H_{12}Cl_3O_3P$

Molecular Weight: 269.7 g/mol

Structural Diagram:



Phosphonic acid, (2-chloroethyl)-, bis(2-chloroethyl) ester
CAS No. 6294-34-4

Chemical Name: **Phosphonic acid, [2-[[(2-chloroethoxy)(2-chloroethyl) phosphinyl]oxy]ethyl]-, bis(2-chloroethyl) ester**

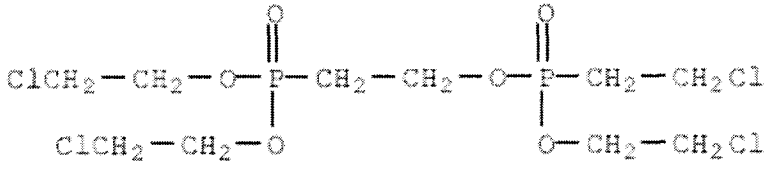
Chemical Abstract Service Registry Number: CAS No.: 58823-09-9

Synomyms: BISCEP Dimer
Bis(2-chloroethyl) [2-[[(2-chloroethoxy)(2-chloroethyl)phosphinyl]oxy]ethyl]phosphonate
[2-[[(2-Chloroethoxy)(2-chloroethyl)phosphinyl]oxy]ethyl]phosphonic acid, bis(2-chloroethyl) ester

Molecular Formula: $C_{10}H_{20}Cl_4O_6P_2$

Molecular Weight: 440.2 g/mol

Structural Diagram:



Phosphonic acid, [2-[[(2-chloroethoxy)(2-chloroethyl) phosphinyl]oxy]ethyl]-, bis(2-chloroethyl) ester
CAS No. 58823-09-9

III) USE AND EXPOSURE INFORMATION

The subject mixture, internally known as BISCEP, consists of the BISCEP monomer (CAS No. 6294-34-4) and BISCEP dimer (CAS No. 58823-09-9). This mixture is manufactured by a single US producer, Rhodia Inc., at a single manufacturing site. BISCEP is used primarily as an internal chemical intermediate to produce a crop protection active ingredient (plant growth regulator) at the same production facility. An extensive EPA database exists on this downstream product -- phosphonic acid, 2-chloroethyl-. There is minimal opportunity for occupational exposure during the manufacture of either BISCEP or the downstream product. In addition, a small amount of BISCEP is commercially sold as a flame retardant. Again, there is limited opportunity for exposure during its use in this application.

IV) REVIEW OF EXISTING DATA AND DEVELOPMENT OF TEST PLAN

Rhodia Inc. has undertaken a comprehensive evaluation of all relevant data on the SIDS endpoints of concern for BISCEP.

The more significant and reliable data are gathered in table 1. The availability of the data on the specific SIDS endpoints is summarized in table 2.

1) Review of existing physicochemical data and proposed testing

Data are available in Rhodia MSDS or in Handbook for melting point, boiling point, density and water solubility. Vapor pressure and octanol/water partition coefficient were estimated with the EPIWIN program. Estimations were performed on BISCEP monomer (CAS No 6294-34-4, the main component of BISCEP) and BISCEP dimer (CAS No 58823-09-9, the other main component of BISCEP (noted as main impurity in

IUCLID as IUCLID was designed to address substances rather than mixtures)). Physico-chemical properties needed individually on BISCEP monomer and BISCEP dimer for the fugacity level III modeling were also estimated with the EPIWIN program.

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

2) Review of existing environmental fate data and proposed testing

Photodegradation in air was calculated to have a half-life of 8.3 hours for BISCEP monomer and 2.7 hours for BISCEP dimer with the AOP program. No data is available on the water stability of BISCEP. A biodegradation study showed that BISCEP is not biodegradable.

Level III fugacity modeling shows that BISCEP monomer and dimer distribute mainly to water and soil when discharged equally in air, water and soil.

Therefore, an hydrolysis study according to OECD 111 test guideline is proposed to complete the environmental fate data.

3) Review of existing ecotoxicity data and proposed testing

Acute toxicity studies on fish, daphnia and algae are available. Algae was the most sensitive species (72h-ErC50 = 113 mg/l, 96h-ErC50 = 73.5 mg/l, 14d-NOEC = 18 mg/l). Acute toxicity values on fish (96h-LC50) and daphnia (48h-EC50) were above 100 mg/l.

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

4) Review of existing toxicity data and proposed testing

a) Acute oral toxicity :

The acute oral toxicity of BISCEP has been examined in two studies. These studies were not GLP studies (1977 and 1979 studies) but they followed the main requirements of the OECD guideline 401. Both studies were performed on rats, by gavage and the LD50 values were 580 and 810 mg/kg b.w.. The lowest value was selected.
BISCEP is moderately toxic by the oral route. These data fulfill the SIDS endpoint for acute toxicity and no additional testing is proposed.

b) Repeated dose toxicity

BISCEP was tested in a 90-day study in male and female rats. The product was administered orally by gavage at dose levels of 0, 100, 200 and 500 mg/kg bw/day. The predominant toxic effect of the oral administration of the test material was dose-related clonic convulsions in the 200 and 500 mg/kg dose groups. No treatment related toxic change was seen in the 100 mg/kg dose group except some convulsive activity. No NOEL or NOAEL was established for this study.
This study was considered as valid with restrictions as some requirements of the OECD guideline 408 were not followed (urea and creatinin were not measured in blood analyses, uterus, thymus and spleen were not weighted at necropsy and the administered volumes were low as no vehicle was used). However the results are considered as reliable.

Moreover, BISCEP was also studied in a 21-day dermal study on rabbits. Significant lesions which appeared to be related to the test material were present in the liver, kidneys and treated skin. These lesions were of low severity and probably represented mild reversible injury.
This study was considered as valid with restrictions: the main reason was that, due to the oily nature of the test material, it was impossible to clean all the material from the rabbit after the designated daily exposure period. Therefore all high dose group rabbits were entirely contaminated and this contamination decreased with the dose in the other treated groups. Therefore it is difficult to discern whether the observed effects are purely due to dermal exposure or a combination of dermal and oral exposure due to preening. However this study provides valuable information on dermal repeated dose toxicity.

These studies fill the SIDS endpoint for repeated toxicity.

c) Genotoxicity : Gene mutation

BISCEP was negative in a bacterial gene mutation assay with *Saccharomyces cerevisiae* (strain D4) and *Salmonella typhimurium* (strains TA1535, TA1537, TA1538, TA98 and TA100). This study was considered as valid with restrictions as the test was not repeated, the plates were not done in triplicates and the solvent was not indicated.
BISCEP was also negative in another bacterial gene mutation assay (Ames test) with *Salmonella typhimurium* (strains TA1535, TA1537, TA1538, TA98 and TA100). This study was considered as valid with restrictions as the test was not repeated.

BISCEP was negative in a mammalian cell gene mutation assay conducted with L5178Y Mouse lymphoma cells TK $^{+/-}$. This study was GLP. It was considered as valid with restrictions as the test was not repeated, the results mention data on historical controls that are not available and some cultures at low dose levels were lost.
BISCEP was also negative in another mammalian cell gene mutation assay conducted with L5178Y Mouse lymphoma cells TK $^{+/-}$. This study was considered as valid with restrictions as the test was not repeated.

All these studies were conducted both with and without metabolic activation.

Although these studies show some deficiencies (mentioned above), collectively they provided consistent negative results both in bacterial and mammalian systems. Thus they satisfy the requirement for gene mutation data.

d) Genotoxicity : Chromosomal aberration

No data available for BISCEP. A test is proposed.

e) Reproduction toxicity

No data available for BISCEP. A test is proposed.

In a two generation reproduction study conducted on the downstream product (phosphonic acid, 2-chloroethyl-), no effects were observed on fertility, gestation, mating, organ weights or histopathology in any generation (MRID 41508701, EPA 738-R-95-003, April 1995).

f) Developmental toxicity

A teratology study was conducted with BISCEP on rats and did not reveal any teratogenic effect. The NOAEL for developmental effects was 600 mg/kg bw/day (highest dose tested) and the NOAEL for maternal effects was 400 mg/kg bw/day (some deaths occurred at 600 mg/kg). The results are considered reliable and this study fills the SIDS endpoint

g) Conclusion for the toxicology testing

- The SIDS endpoints on acute toxicity, repeated toxicity, genotoxicity as regards gene mutation and developmental toxicity are filled adequately.
- A mammalian erythrocyte micronucleus study according to the OECD guideline 474 is proposed to fill the SIDS endpoint on genotoxicity as regards chromosome aberration.
- A one-generation reproduction study according to the OECD guideline 415 is proposed to fill the SIDS endpoint on reproduction toxicity.

We have located at least one additional study (in Russian) (1), which may be able to address one or more SIDS endpoints. Pending translation and review of this study, Rhodia commits to conducting the above studies, but reserves the right to amend this test plan accordingly.

V) SUMMARY

In summary, the testing proposed in Table 2 will complete the data acquisition requirements for BISCEP under the U.S. Environmental Protection Agency High Production Volume (HPV) Chemical Challenge Program.

VI) ROBUST STUDY SUMMARIES

An IUCLID Data Set for BISCEP is appended.

VII) REFERENCE

(1) Chura, D. A.; Kuz'minov, B. P.; Galushka, A. I.; Nektegaev, I. A.; Kokot, V. R.; Grushka, O. I.; Karatsincheva, M. Yu. Toxicological characterization of bis-(2-chloroethyl)2-chloroethylphosphonate; Original Title: Toksikologicheskaia kharakteristika bis-(2-khloretil)2-khloretilfosfonata, Meditsina Truda i Promyshlennaya Ekologiya, (1993) (2) 21-2. (published in Russian)

Table 1 : Significant Data on BISCEP

BISCEP		
Endpoint	**Result**	**Comment**
Physicochemical		
Melting point	28 °C	Rhodia MSDS
Boiling point	170-172 °C at 6.7 hPa	Handbook (BISCEP monomer)
Density	1.41 g/cm3 at 25°C	Rhodia MSDS
Vapor pressure	1.47 x 10^{-4} hPa at 25°C	Estimation for BISCEP monomer
	2.75 x 10^{-8} hPa at 25°C	Estimation for BISCEP dimer
Log P_{OW}	1.65 at 25°C	Estimation for BISCEP monomer
	1.47 at 25°C	Estimation for BISCEP dimer
Water solubility	1.5 % w/w at 20°C	Rhodia MSDS
Environmental fate and pathway		
Photodegradation	DT50 in air = 8.3 h	Estimation for BISCEP monomer
	DT50 in air = 2.7 h	Estimation for BISCEP dimer
Stability in water	No data	-
Transport/distribution	Air = negligible Water = 51.4% Soil = 48.6% Sediment = 0.03%	Fugacity model level III (BISCEP monomer)
	Air = negligible Water = 56.5% Soil = 43.5% Sediment = 0.03%	Fugacity model level III (BISCEP dimer)
Biodegradation	Not biodegradable	Experimental result
Ecotoxicity		
Acute fish	96h-LC50 > 100 mg/l	Experimental result
Acute daphnia	48h-EC50 = 240 mg/l	Experimental result
Algae	96h-ErC50 = 73.5 mg/l 14d-NOEC = 18 mg/l	Experimental result
Toxicology		
Acute toxicity	oral LD50 = 580 +/- 90.1 mg/kg bw Rat (M&F)	The lowest LD50 among the reliable results.
Repeated dose toxicity	90-day oral study in rats (M&F) : Predominant effects following oral administration were clonic convulsions (observed from the lowest dose of 100 mg/kg bw/day onwards).	Experimental result
	21-day dermal study in rats (M&F). Lesions probably reversible and of low severity in the liver, kidneys and skin (lowest dose tested : 1000 mg/kg bw).	Experimental result
Genetic toxicity *in vitro*		
Gene mutation	Ames tests : negative	Experimental results.
	Mouse lymphoma tests : negative	Experimental results.
Chromosomal aberration	No data.	
Genetic toxicity *In vivo*	No data.	
Toxicity to reproduction	No data.	
Developmental tox/teratogenicity	Teratology study in rats : negative	Experimental result

BISCEP monomer : main component (CAS No 6294-34-4)
BISCEP dimer : other main component (noted as main impurity in IUCLID) (CAS No 58823-09-9)

Table 2 : Availability of data and proposed testing on BISCEP

BISCEP							
Endpoint	**Available**	**GLP**	**OECD study**	**Other study**	**Estim. method**	**Accept-able**	**SIDS testing required**
Physicochemical							
Melting point	Y	N	N	Y	-	Y	N
Boiling point	Y	N	N	Y	-	Y	N
Density	Y	N	N	Y	-	Y	N
Vapor pressure	Y	N	N	N	Y	Y	N
Oct:water partition coef	Y	N	N	N	Y	Y	N
Water solubility	Y	N	N	Y	-	Y	N
Environmental fate and pathway							
Photodegradation	Y	N	N	N	Y	Y	N
Stability in water	N	-	-	-	-	-	**Y**
Transport/distribution	Y	N	N	N	Y	Y	N
Biodegradation	Y	N	N	Y	N	Y	N
Ecotoxicity							
Acute fish	Y	N	N	Y	N	Y	N
Acute daphnia	Y	N	N	Y	N	Y	N
Algae	Y	N	N	Y	N	Y	N
Toxicology							
Acute toxicity	Y	N	N	Y	N	Y	N
Repeated dose toxicity	Y	Y	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	Y	N	Y	N	Y	N
Chromosome aberrat.	N	-	-	-	-	-	**Y**
Toxicity to reproduction	N	-	-	-	-	-	**Y**
Devel. tox/teratogen.	Y	Y	N	Y	N	Y	N

Y : yes
N : no

201-14987

IUCLID

Data Set

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Existing Chemical	:	ID: 6294-34-4
CAS No.	:	6294-34-4
EINECS Name	:	bis(2-chloroethyl) 2-chloroethylphosphonate
EC No.	:	228-557-7
Molecular Formula	:	C6H12Cl3O3P

Producer related part

Company	:	Rhodia Consumer Specialties LTD
Creation date	:	17.10.2003

Substance related part

Company	:	Rhodia Consumer Specialties LTD
Creation date	:	17.10.2003
Status	:	
Memo	:	
Printing date	:	17.12.2003
Revision date	:	
Date of last update	:	17.12.2003
Number of pages	:	38
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	:	manufacturer
Name	:	Rhodia Inc.
Contact person	:	Paul LARSON
Date	:	
Street	:	259 Prospect Plains Road
Town	:	08512 Cranbury, NJ
Country	:	United States
Phone	:	609-860-3913
Telefax	:	609-860-0076
Telex	:	
Cedex	:	
Email	:	paul.larson@us.rhodia.com
Homepage	:	

12.12.2003

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	:	Bis(2-chloroethyl) (2-chloroethyl)phosphonate
Smiles Code	:	O=P(CCCl)(OCCCl)OCCCl
Molecular formula	:	C6 H12 Cl3 O3 P
Molecular weight	:	269.49
Petrol class	:	

04.11.2003

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	typical for marketed substance
Substance type	:	organic
Physical status	:	liquid
Purity	:	ca. 55 - 70 % w/w
Colour	:	Clear, colourless
Odour	:	Characteristic odour

04.11.2003

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

(2-chloroethyl)phosphonic acid bis(2-chloroethyl) ester

05.11.2003

Bis-chloroethyl 2-chloroethanephosphonate

05.11.2003

BISCEP

05.11.2003

Ethanol, 2-chloro-, (2-chloroethyl)phosphonate (2:1)

05.11.2003

Phosphonic acid, (2-chloroethyl)-, bis(2-chloroethyl) ester

04.11.2003

1.3 IMPURITIES

Purity	:	typical for marketed substance
CAS-No	:	58823-09-9
EC-No	:	261-459-2
EINECS-Name	:	bis(2-chloroethyl) [2-[[(2-chloroethoxy)(2-chloroethyl)phosphinyl]oxy]ethyl]phosphonate
Molecular formula	:	C10 H20 Cl4 O6 P2
Value	:	ca. 35 - 40 % w/w
Remark	:	CAS name : Phosphonic acid, (2-(((2-chloroethoxy)(2-chloroethyl)phosphinyl)oxy)ethyl)-, bis(2-chloroethyl) ester SMILE code : O=P(CCCl)(OCCCl)OCCP(=O)(OCCCl)OCCCl MW = 440.02 Named BISCEP dimer as opposed to the main component BISCEP monomer.

26.11.2003

Purity	:	typical for marketed substance
CAS-No	:	107-06-2
EC-No	:	203-458-1
EINECS-Name	:	1,2-dichloroethane
Molecular formula	:	C2 H4 Cl2
Value	:	< .1 % w/w
Remark	:	In site product can contain ca. 0.3% w/w.

12.12.2003

Purity	:	typical for marketed substance
CAS-No	:	107-07-3
EC-No	:	203-459-7
EINECS-Name	:	2-chloroethanol
Molecular formula	:	C2 H5 Cl O
Value	:	ca. .2 % w/w
Remark	:	In site product can contain ca. 0.3% w/w.

12.12.2003

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 : 21.10.2003

05.11.2003

Type of search : Internal and External
Chapters covered : 3, 4, 5
Date of search : 21.10.2003

05.11.2003

1.13 REVIEWS

2.1 MELTING POINT

Value	:	28 °C
Sublimation	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	no data
Reliability	:	(4) not assignable Cited in Rhodia MSDS
Flag	:	Critical study for SIDS endpoint

06.11.2003

Value	:	37 °C
Sublimation	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	no data
Test substance	:	Value refers to Bis(2-chloroethyl) (2-chloroethyl)phosphonate CAS : 6294-34-4
Reliability	:	(2) valid with restrictions Cited in standard data source (Dictionary of Organophosphorus compounds)
Flag	:	Critical study for SIDS endpoint

06.11.2003

2.2 BOILING POINT

Value	:	170 - 172 °C at 6.7 hPa
Decomposition	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	no data
Test substance	:	Value refers to Bis(2-chloroethyl) (2-chloroethyl)phosphonate CAS : 6294-34-4
Reliability	:	(2) valid with restrictions Cited in standard data source (Dictionary of Organophosphorus compounds)
Flag	:	Critical study for SIDS endpoint

06.11.2003

Value	:	339 °C at 1013 hPa
Method	:	Estimation by MPBPWIN programme, v1.41, US-EPA/Syracuse Research
Test substance	:	Estimation performed on molecular structure of bis(2-chloroethyl) 2-chloroethylphosphonate (BISCEP monomer).
Reliability	:	(2) valid with restrictions Accepted calculation method
Flag	:	Critical study for SIDS endpoint

06.11.2003

Value	:	480 °C at 1013 hPa

Method : Estimation by MPBPWIN programme, v1.41, US-EPA/Syracuse Research
Test substance : Estimation performed on molecular structure of bis(2-chloroethyl) [2-[[(2-chloroethoxy)(2-chloroethyl)phosphinyl]oxy]ethyl]phosphonate (BISCEP dimer).
Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint
06.11.2003

2.3 DENSITY

Type : density
Value : 1.41 g/cm³ at 25 °C
Method :
Year :
GLP :
Test substance : no data

Reliability : (4) not assignable
Cited in Rhodia MSDS
Flag : Critical study for SIDS endpoint
06.11.2003

Type : relative density
Value : 1.39 at 20 °C
Method :
Year :
GLP :
Test substance : no data

Method : Relative density at 20 °C compared to water at 4 °C .
Test substance : Value refers to Bis(2-chloroethyl) (2-chloroethyl)phosphonate
CAS : 6294-34-4
Reliability : (2) valid with restrictions
Cited in standard data source (Dictionary of Organophosphorus compounds)
Flag : Critical study for SIDS endpoint
06.11.2003

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : .000147 hPa at 25 °C

Method : Estimation by MPBPWIN programme, v1.41, US-EPA/Syracuse Research
Test substance : Estimation performed on molecular structure of bis(2-chloroethyl) 2-chloroethylphosphonate (BISCEP monomer).
Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint
09.12.2003

Value : .0000000275 hPa at 25 °C

Method : Estimation by MPBPWIN programme, v1.41, US-EPA/Syracuse Research

Test substance	:	Estimation performed on molecular structure of bis(2-chloroethyl) [2-[[(2-chloroethoxy)(2-chloroethyl)phosphinyl]oxy]ethyl]phosphonate (BISCEP dimer).
Reliability	:	(2) valid with restrictions Accepted calculation method
Flag	:	Critical study for SIDS endpoint

06.11.2003

2.5 PARTITION COEFFICIENT

Partition coefficient	:	octanol-water
Log pow	:	1.65 at 25 °C
pH value	:	
Method	:	Estimation by KOWWIN programme, v1.67, US-EPA/Syracuse Research.
Test substance	:	Estimation performed on molecular structure of bis(2-chloroethyl) 2-chloroethylphosphonate (BISCEP monomer).
Reliability	:	(2) valid with restrictions Accepted calculation method
Flag	:	Critical study for SIDS endpoint

09.12.2003

Partition coefficient	:	octanol-water
Log pow	:	1.47 at 25 °C
pH value	:	
Method	:	Estimation by KOWWIN programme, v1.67, US-EPA/Syracuse Research.
Test substance	:	Estimation performed on molecular structure of bis(2-chloroethyl) [2-[[(2-chloroethoxy)(2-chloroethyl)phosphinyl]oxy]ethyl]phosphonate (BISCEP dimer).
Reliability	:	(2) valid with restrictions Accepted calculation method
Flag	:	Critical study for SIDS endpoint

09.12.2003

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water
Value	:	1.5 other: % w/w at 20 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Reliability	:	(4) not assignable Cited in Rhodia MSDS
Flag	:	Critical study for SIDS endpoint

06.11.2003

Solubility in	:	Water
Value	:	12.751 g/l at 25 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	

pKa	:	at 25 °C
Description	:	
Stable	:	
Method	:	Estimation by WATERNT programme, v1.01, US-EPA/Syracuse Research.
Test substance	:	Estimation performed on molecular structure of bis(2-chloroethyl) 2-chloroethylphosphonate (BISCEP monomer).
Reliability	:	(2) valid with restrictions Accepted calculation method
Flag	:	Critical study for SIDS endpoint
06.11.2003		
Solubility in	:	Water
Value	:	24.7 g/l at 25 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Method	:	Estimation by WATERNT programme, v1.01, US-EPA/Syracuse Research.
Test substance	:	Estimation performed on molecular structure of bis(2-chloroethyl) [2-[[(2-chloroethoxy)(2-chloroethyl)phosphinyl]oxy]ethyl]phosphonate (BISCEP dimer).
Reliability	:	(2) valid with restrictions Accepted calculation method
Flag	:	Critical study for SIDS endpoint
06.11.2003		

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value	:	143 °C
Type	:	closed cup
Method	:	
Year	:	
GLP	:	
Test substance	:	no data
Reliability	:	(4) not assignable Cited in Rhodia MSDS
06.11.2003		

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

Value	:	200 - mPa s (dynamic) at 10 °C
Result	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	no data
Reliability	:	(4) not assignable Cited in Rhodia MSDS

06.11.2003

Value	:	500 - mPa s (dynamic) at 0 °C
Result	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	no data
Reliability	:	(4) not assignable Cited in Rhodia MSDS

06.11.2003

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

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	:	.0000000000154317 cm³/(molecule*sec)
Degradation	:	50 % after 8.3 hour(s)
Deg. product	:	
Method	:	other (calculated)
Year	:	
GLP	:	
Test substance	:	other TS

Method	:	Estimation by AOPWIN programme, v1.91, US-EPA/Syracuse Research.
Test substance	:	Estimation performed on molecular structure of bis(2-chloroethyl) 2-chloroethylphosphonate (BISCEP monomer).
Reliability	:	(2) valid with restrictions Accepted calculation method
Flag	:	Critical study for SIDS endpoint

26.11.2003

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	:	.0000000000474608 cm³/(molecule*sec)
Degradation	:	50 % after 2.7 hour(s)
Deg. product	:	
Method	:	other (calculated)
Year	:	
GLP	:	
Test substance	:	other TS

Method	:	Estimation by AOPWIN programme, v1.91, US-EPA/Syracuse Research.
Test substance	:	Estimation performed on molecular structure of bis(2-chloroethyl) [2-[[(2-chloroethoxy)(2-chloroethyl)phosphinyl]oxy]ethyl]phosphonate (BISCEP dimer).
Reliability	:	(2) valid with restrictions Accepted calculation method

26.11.2003

3.1.2 STABILITY IN WATER

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 I
Media : other: air - water - soil - sediment
Air : % (Fugacity Model Level I)
Water : 96.1 % (Fugacity Model Level I)
Soil : 3.8 % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: calculation
Year :

Method : Fugacity model Level I, Trent University, Canada, V 2.11 (1999).
Based on: Mackay, Donald (1991), "Multimedia Environmental Models, The Fugacity Approach".

Result : INPUT DATA:
Molecular mass (g/mol) = 269.49
Data temperature (°C) = 25
Log Kow = 1.65
Water solubility (g/m3) = 12 750
Vapour pressure (Pa) = 1.47E-02
Melting point (°C) = 37

RESULTS:
Air (%) : 0.006
Water (%) : 96.1
Soil (%) : 3.8
Sediment (%) : 0.085
Suspended sediment(%) : 0.003
Aerosols (%) : 3.74E-05
Fish (%) : 2.15E-04

Test substance : Calculation performed on bis(2-chloroethyl) 2-chloroethylphosphonate (BISCEP monomer).

Reliability : (2) valid with restrictions
Accepted calculation method

Flag : Critical study for SIDS endpoint
09.12.2003

Type : fugacity model level III
Media : other: air - water - soil - sediment
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
Year :

Method : Fugacity model Level III, Trent University, Canada, V 2.70 (2002).
Based on: Mackay, Donald (2001), "Multimedia Environmental Models, The Fugacity Approach - Second Edition".

Result : INPUT DATA:
Default environment
Molecular mass (g/mol) = 269.49
Data temperature (°C) = 25
Log Kow = 1.65
Water solubility (g/m3) = 12 750

Vapour pressure (Pa) = 1.47E-02
Melting point (°C) = 37
Reaction half-life in air (gaseous) = 16.6 hours (from AOP)
Reaction in all other compartments : negligible
Equal emission rate of chemical in air, water and soil.

RESULTS:
Air (%) : 4.050E-03
Water (%) : 51.4
Soil (%) : 48.6
Sediment (%) : 0.03

Test substance : Calculation performed on bis(2-chloroethyl) 2-chloroethylphosphonate (BISCEP monomer).
Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint
09.12.2003

Type : fugacity model level I
Media : other: air - water - soil - sediment
Air : % (Fugacity Model Level I)
Water : 97.4 % (Fugacity Model Level I)
Soil : 2.5 % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: calculation
Year :

Method : Fugacity model Level I, Trent University, Canada, V 2.11 (1999).
Based on: Mackay, Donald (1991), "Multimedia Environmental Models, The Fugacity Approach".
Result : INPUT DATA:
Molecular mass (g/mol) = 440.03
Data temperature (°C) = 25
Log Kow = 1.47
Water solubility (g/m3) = 24700
Vapour pressure (Pa) = 2.75E-06
Melting point (°C) = 90.27

RESULTS:
Air (%) : 9.62E-07
Water (%) : 97.4
Soil (%) : 2.5
Sediment (%) : 0.06
Suspended sediment(%) : 0.002
Aerosols (%) : 9.50E-06
Fish (%) : 1.44E-04

Test substance : Calculation performed on bis(2-chloroethyl) [2-[[(2-chloroethoxy)(2-chloroethyl)phosphinyl]oxy]ethyl]phosphonate (BISCEP dimer).
Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint
09.12.2003

Type : fugacity model level III
Media : other: air - water - soil - sediment
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

Year :

Method : Fugacity model Level III, Trent University, Canada, V 2.70 (2002).
Based on: Mackay, Donald (2001), "Multimedia Environmental Models, The Fugacity Approach - Second Edition".

Result : INPUT DATA:
Default environment
Molecular mass (g/mol) = 440.03
Data temperature (°C) = 25
Log Kow = 1.47
Water solubility (g/m3) = 24 700
Vapour pressure (Pa) = 2.75E-06
Melting point (°C) = 90.27
Reaction half-life in air (gaseous) = 5.4 hours (from AOP)
Reaction in all other compartments : negligible
Equal emission rate of chemical in air, water and soil.

RESULTS:
Air (%) : 8.09E-06
Water (%) : 56.5
Soil (%) : 43.5
Sediment (%) : 0.03

Test substance : Calculation performed on bis(2-chloroethyl) [2-[[(2-chloroethoxy)(2-chloroethyl)phosphinyl]oxy]ethyl]phosphonate (BISCEP dimer).

Reliability : (2) valid with restrictions
Accepted calculation method

Flag : Critical study for SIDS endpoint
09.12.2003

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : domestic sewage
Concentration : 9.3 mg/l related to Test substance
18.7 mg/l related to Test substance
Contact time : 20 day(s)
Degradation : = 6 (±) % after 20 day(s)
Result : under test conditions no biodegradation observed
Kinetic of testsubst. : 5 day(s) < 2 %
10 day(s) = 5 %
15 day(s) = 5 %
20 day(s) = 6 %
%
Control substance : other: glucose and glucose/glutamic acid
Kinetic : %
%
Deg. product :
Method : other
Year : 1980
GLP : no
Test substance :

Method : Standard Methods for the Examination of Water and Wastewater. 14th Ed.

APHA pp 543-554 (1976).

Result : A COD value of 1.90 mg O2/mg test material was obtained.

The glucose/glutamic acid sample yielded 99.1% of theoretical oxygen demand.

The % biodegradation were :
day 5 : < 2%
day 10 : 5%
day 15 : 5%
day 20 : 6%

BOD5/COD < 0.02

Test condition : COD was determined using 2 µl and 4 µl samples of the test material. A carbon standard yielded 100.9% of theoretical COD.

BOD was determined at two test material concentrations (2 µl and 4 µl per 300 ml test system volume) with four replicates being prepared for each concentration. An apparent specific gravity of 1.4 was used for the calculation. The 5 d test period was extended to 20 d with periodic reaeration to maintain acceptable DO concentrations (> 2 mg/l). Test vessels were seeded with domestic sewage and seed controls were maintained throughout the 20 d test period to correct for oxygen uptake of the seed. A glucose control and a glucose/glutamic acid control were prepared and were analysed after 5 d of incubation to check the activity of the seed and to check for contamination of the BOD dilution water. DO determinations were made using a Yellow Springs oxygen electrode.

Test substance : MCTR-15-79, Lot No. 0120930, Batch analysis not available in the report.

Reliability : (2) valid with restrictions
Meets generally accepted scientific method and is described in sufficient detail.

Flag : Critical study for SIDS endpoint

17.12.2003 (10)

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	:	Lepomis macrochirus (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
NOEC	:	>= 100
LC50	:	> 100
Limit test	:	
Analytical monitoring	:	no
Method	:	other
Year	:	1979
GLP	:	no
Test substance	:	

Method : Committee on Methods for Toxicity Tests with Aquatic Organisms, 1975, Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians, EPA-660/3-75-001.

Result : In the definitive test, no mortality was observed through the test period in all the vessels. Abnormal surfacing was observed at 48 h and thereafter in the solvent control and at each test material concentration. It is assumed that this abnormal behaviour is due to lower dissolved oxygen concentrations in these vessels.

Test condition : TEST ORGANISM:
Bluegill sunfish (Lepomis macrochirus Rafinesque) were obtained from a commercial hatchery and maintained in the UCES laboratory at 22°C. Mortality in the stock culture over a one month period was less than 2%. 48 h before starting the test, the fish were taken off feed, and no food was administered thereafter. Fish were selected at random from the stock culture and isolated in a jar of dilution water for 24 h acclimation before testing. In the definitive test, fish were approximately 8-10 months old, with a mean length of 40 (36-43) mm and a mean weight of 0.70 (0.50-0.91) g. Biological loading was 0.47 g/l.

DILUTION WATER:
Dilution water was obtained from a well on the site, treated with reverse osmosis water system and de-ionised. Dilution water was then reconstituted to a pH of 7.43, total hardness of 40 mg/l as $CaCO_3$, total alkalinity of 29 mg/l as $CaCO_3$ and specific conductance of 160 µmhos/cm.

TEST SOLUTIONS:
A stock solution of the test material in reagent grade acetone was prepared by weight to a precision of 0.1 mg. Test concentrations were prepared by adding measured volumes of stock solution to dilution water in the test vessels and mixing thoroughly. Nominal test material concentrations were: 10.0, 18.0, 32.0, 56.0 and 100.0 mg/l. One test vessel was prepared for each test material concentration. An additional vessel with 100 % dilution water served as control, another vessel, with a solution of acetone in dilution water at the same concentration as in the highest test concentration, served as solvent control.

TEST DESIGN:
The definitive test was conducted in chemically clean glass jars, each containing 15 l of test solution and immersed in a constant temperature re-circulating water bath. Ten fish were introduced at random into each of the test, control and solvent control vessels.
At the beginning of the test and every 24 h thereafter, dissolved oxygen and pH in each vessel, and temperature in the water bath, were determined. Mortality and any observable abnormal behaviour were

recorded every 24 h.

Test substance : MCTR-15-79, Lot No. 0120930, Batch analysis not available in the report.

Reliability : (2) valid with restrictions
Meets generally accepted scientific method and is described in sufficient detail.

Flag : Critical study for SIDS endpoint

17.12.2003 (13)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
NOEC : = 180
EC50 : = 240
Analytical monitoring : no
Method : other
Year : 1979
GLP : no
Test substance :

Method : Committee on Methods for Toxicity Tests with Aquatic Organisms, 1975, Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians, EPA-660/3-75-009.

Result : Due to lack of partial kill, the EC50 and 95% confidence limits were calculated by the binomial method:
24 h-EC50 = 240 (180-320) mg/l
48 h-EC50 = 240 (180-320) mg/l
The 48 h-NOEC was observed to be 180 mg/l.

Test condition : TEST ORGANISM:
Daphnia magna came from a UCES laboratory stock culture, the original population having been obtained from the EPA Environmental Research Laboratory in Duluth, Minnesota. 20 h before starting the test, adults with full brood chambers were isolated into UCES well water. Next morning the newly released instars were carefully removed with a wide bore pipette and transferred to a separate holding vessel. One hour before the test they were fed, and no food was administered thereafter.

DILUTION WATER:
Dilution water was obtained from a well on the site. The water was vigorously aerated before use and determined by analysis to have a pH of 8.60, total hardness of 206 mg/l as $CaCO_3$, total alkalinity of 135 mg/l as $CaCO_3$ and specific conductance of 700 µmhos/cm.

TEST SOLUTIONS:
A primary stock solution of 400 mg/ml of the test material in reagent grade acetone was prepared by weight to a precision of 0.1 mg. Test concentrations were prepared by adding measured volumes of stock solution to dilution water in one-litre volumetric flasks and mixing thoroughly. Nominal test material concentrations were: 32, 56, 100 and 180 mg/l. Due to solubility limitations of the test material, two batches of the stock solution (400 mg/ml) and dilution water were combined in two 500 ml volumetric flasks, increasing the obtainable tested concentration to 320 mg/l. Two hundred ml of each concentration was decanted into each of four test beakers. Four beakers, as control, contained 200 ml each of 100 % dilution water, and four beakers, as solvent control, each contained 200 ml solution of acetone in dilution water, at the same acetone level as in the highest test concentration.

TEST DESIGN:
The definitive test was conducted in 250 ml glass beakers, each containing 200 ml of test solution. Four test vessels were prepared for each test material concentration, for the control and the solvent control. Five organisms were introduced at random into each of the 20 test, 4 control and 4 solvent control beakers and held for the duration of the test in a refrigerator incubator at a constant temperature of 21°C.
At the beginning of the test and at 48 h, dissolved oxygen and pH were determined in each beaker. Mortality was recorded at 24 and 48 h.
The EC50 and its 95% confidence limits were determined for the 24 and 48 h exposure periods. Calculations were based on nominal concentrations of the test material. The NOEC was determined by observation at 48 h.

Test substance : MCTR-15-79, Lot No. 0120930, Batch analysis not available in the report.
Reliability : (2) valid with restrictions
Meets generally accepted scientific method and is described in sufficient detail.
Flag : Critical study for SIDS endpoint
17.12.2003 (14)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : Selenastrum capricornutum (Algae)
Endpoint : other: overall growth, maximum specific growth rate, Maximum Standing Crop, algal biomass, duration of lag phase
Exposure period : 14 day(s)
Unit : mg/l
NOEC : = 18
Limit test :
Analytical monitoring : no
Method : other
Year : 1980
GLP : no
Test substance :

Method : Miller W.E. et al., 1978, The Selenastrum capricornutum Printz Algal Assay Bottle Test, EPA-600/9-78-018.
Result : Effect on overall growth : reduced in 56 and 100 mg/l treatments
Effect on maximum specific growth rate : reduced in 56 mg/l treatment
Effect on MSC (cells/ml) : reduced in 32, 56 and 100 mg/l treatments
Effect on algal biomass : reduced in 56 and 100 mg/l treatments
Effect on lag period : lengthened in 32, 56 and 100 mg/l treatments
NOEC = 18 mg/l (relative to the solvent control on any of the above endpoints)

Raw data presented in the test report were used to calculate, by log Probit regression, the ErC50 with 95% confidence limits after 72 h and 96 h of exposition. Results expressed as nominal concentrations of the test material are:
72 h- ErC50 = 113 (64.1 - 200) mg/l
96 h- ErC50 = 73.5 (51.2 - 105) mg/l
Growth of the control cultures were exponential throughout the 96 h test period.
Test condition : TEST ORGANISM:
Selenastrum capricornutum came from UCES stock cultures. Algal stocks were maintained in synthetic algal nutrient medium (Miller et al., 1978) in continuously shaken Erlenmeyer flasks (100 rpm) at 24 ± 2°C under continuous illumination. Transfers were made regularly into fresh medium to provide 7-day old cultures for assay inoculations.

TEST MEDIUM:

Synthetic algal medium according to Miller et al. (1978), passed through a 0.22 µm porosity membrane filter into a sterile container.

TEST SOLUTIONS:
A 200 mg/ml stock solution of the test material in reagent grade N,N-dimethylformamide (DMF) was prepared by weight to a precision of 0.1 mg. Appropriate volumes of stock solutions were added to measured volumes of algal medium to yield final test material concentrations of 10, 18, 32, 56 and 100 mg/l. The control was algal medium only. The solvent control contained an amount of DMF equivalent to the highest DMF concentration in any test treatment, i.e. 0.5 ml/l.

TEST DESIGN:
Test vessels were chemically clean sterile 250 ml Erlenmeyer flasks fitted with foam stoppers. After thorough mixing, 60 ml of each test solution was aseptically added to each of three replicate flasks. An algal inoculum was prepared by centrifuging and re-suspending twice a seven-day old stock culture in a 15 mg/l wash solution of NaHCO3. A 0.88 ml volume of cell suspension was aseptically added to 60 ml test solution in each flask, yielding a nominal inoculum concentration of 3000 cells/ml.
Test flasks were continuously agitated at 100 rpm under continuous cool white fluorescent illumination. Temperature, maintained at 24 ± 2°C, was recorded on counting days.
Cell counts were made with a hemacytometer on days 0, 1, 2, 3, 4, 7, 9, 11 and 14. Four counts per replicate were made each time.
Maximum standing crop (MSC) is defined as the maximum algal biomass (mg dry weight/l culture) attained during incubation. It is considered to have been reached when the rate of increase in biomass, as determined by cell counts, falls below 5% per day.

STATISTICAL ANALYSIS:
Raw data from replicate flasks during the exposure period were subjected to two-way logarithmic analysis of variance (LOGANOVA) and to Duncan's (1955) new multiple range test to locate significant differences among treatment means. All differences were considered statistically significant at $p<0.05$.
Mean cell counts were used to calculate the maximum specific growth rate, defined as the highest specific growth rate occurring at any time during incubation, for each flask. The maximum specific growth rate for a set of replicate flasks, determined by averaging the values of the individual flasks, were subjected to one-way analysis of variance (ANOVA) and to Duncan's test. ANOVA and Duncan's test were applied to mean MSC and to mean dry weights of algal biomass.

Test substance : MCTR-15-79, Lot No. 0120930, Batch analysis not available in the report.
Reliability : (2) valid with restrictions
Meets generally accepted scientific method and is described in sufficient detail.
Flag : Critical study for SIDS endpoint
17.12.2003 (15)

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	:	= 580 mg/kg bw
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	50
Vehicle	:	no data
Doses	:	290.2, 580.4, 870.6, 1160.8, 1451.0 mg/kg
Method	:	other
Year	:	1977
GLP	:	no data
Test substance	:	

Method : The test article was administered orally by intubation (gavage) to groups of fasted male and female rats. The animals were observed for mortality and signs of toxicity at 1, 3, 6, 24, 48 and 72 hours and daily thereafter for a total of 14 days. After 14 days, all surviving animals were killed, autopsied and observed for gross pathological organ changes.

Result : The mortality was as followed: 0/10 at 290.2 mg/kg, 5/10 at 580.4 mg/kg, 7/10 at 870.6 mg/kg, 7/10 at 1160.8 mg/kg, 10/10 at 1451.0 mg/kg.
The test substance produced signs of decreased locomotor activity, ptosis, piloerection, respiratory depression, loss of righting reflex, ataxia, muscle spams, self-inflicted wounds and death. Normal body activity returned within eight days in all surviving animals. Autopsies revealed no gross abnormalities.
The LD50 was determined to be 580.4 +/- 90.1 mg/kg bw.

Test substance : MCTR-30-77; Lot No.0105730; Batch analysis not available in the report.

Reliability : (2) valid with restrictions
Individual data were not provided in the report.

Flag : Critical study for SIDS endpoint

17.12.2003 (3)

Type	:	LD50
Value	:	= 810 mg/kg bw
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	100
Vehicle	:	no data
Doses	:	500 - 590 - 780 - 1000 - 1230 mg/kg bw
Method	:	other
Year	:	1979
GLP	:	no data
Test substance	:	

Method : The test article was administered intragastrically (gavage) to groups of fasted rats. Following a series of range finding doses, a final series of five dose levels were administered to rats (twenty rats per dose levels, ten of each sex). Observations were carried out daily over a 14-day period post treatment.

Result : Clinical signs observed following treatment included labored breathing, depressed activity, clonic convulsions, prostration, clear oral discharge, perianal discharge, ocular discharge, hunching, ataxia and hyperactivity.

The mortality was as follows:
- 500 mg/kg : 0/10 animals.
- 590 mg/kg : 0/10 male, 7/10 females.
- 780 mg/kg : 1/10 male, 4/10 females.
- 1000 mg/kg : 9/10 males, 5/10 females.
- 1230 mg/kg : 9/10 males, 10/10 females.

The calculated acute oral LD50 value for combined sexes was 810 +/- 80 mg/kg body weight.

Test substance : MCTR-243-79; Lot No. 12187906; Batch analysis not available in the report.

Reliability : (2) valid with restrictions
- Time of appearance and duration of symptoms were not specified in the report.
- The calculation method to determine the LD50 was not specified in the report.

17.12.2003 (4)

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

5.2.2 EYE IRRITATION

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Type	:	Sub-chronic
Species	:	rat
Sex	:	male/female
Strain	:	other: Crl:COBS(R)CD(R)(SD)BR
Route of admin.	:	gavage
Exposure period	:	90 days
Frequency of treatm.	:	daily
Post exposure period	:	none.
Doses	:	100, 200, 500 g/kg bw
Control group	:	yes
Method	:	other
Year	:	1980
GLP	:	no data
Test substance	:	

Method : Though it is not specified in the report, the method followed was in accordance with the main requirements of the OECD guideline 408.
A preliminary study was performed to determinate the appropriate dose levels to be administered to the animals (see study #008-001 (Company # MCTR-307-79)).

Groups of sixty rats (thirty males + thirty females per group) were administered the test material daily by gavage at levels of 100, 200 and 500 mg/kg. The test material was undiluted and administered at volumes of 0.071 ml/kg (low dose), 0.142 ml/kg (mid-dose) and 0.355 ml/kg (high dose). A control group of sixty rats (thirty males + thirty females) received 0.355 ml/kg of tap water. The animals were treated for 3 months. An interim sacrifice after one month was included, on the first ten males and ten females of each group, on days 29 and 30 of the study. All remaining animals were sacrificed on days 92 and 93.

Result : Six of sixty rats of the high dose group died before the interim sacrifice and eight of thirty-four rats of the same group died between the interim and final sacrifice. No rats of the mid-dose, low dose or control groups died.

The predominant toxic effect of the oral administration of the test material was characteristic intermittent convulsions. They were dose related in severity, incidence and duration. The convulsive activity disappeared in four to five hours in even the most severe cases so that the rats appeared completely normal in this respect well before the next daily dose. No histologic lesion was found to account for this effect.
Deaths occurred only in the high dose group (14/60) but no consistent pattern of lesions was seen in these rats. For seven of these rats, death was attributed directly to the convulsions, probably through suffocation. Based on lymphocytolysis in their thymus, four others of these rats are considered to have died from a generalised stress syndrome. The remaining three rats had lungs lesions that indicated regurgitation and inspiration of stomach contents or intrapulmonary dosing.
Liver relative weights (organ weight/body weight) were statistically higher in the middle and high dose females in comparison with the controls and kidneys relative weights were statistically higher in the middle and high dose animals (males and females) in comparison with the controls. These effects are considered to be due to metabolism of the test material.
Slight mineralisation at the corticomedullary junction in the kidneys was seen after one and three months of dosing in 4/20, 4/20, 6/20 and 9/20 females of the control, low, middle and high dose groups respectively but not in any of the males. In this study it is considered to be related to a somewhat less than optimal balance of minerals in the animals diet in spite of the fact that only the highest quality feed was used. Moreover, dehydration may have been induced by the treatment-related convulsions which in turn could have caused the slight increase in mineralisation.
Mineralisation of the thalamus (brain) in five high dose and one middle dose rats and not in any control or low dose rats is considered to be treatment related. However the low incidence suggests that it may be a secondary effect rather than the primary site of activity.
The incidence of the natural disease chronic pericarditis, 0/60, 1/60, 1/60 and 6/60 in the control, low, middle and high dose groups respectively, indicates a relationship to treatment. However, the low incidence even in the high dose group suggests this is not a direct effect.
An hypospermatogenesis observed in three high dose rats had the same histologic appearance as is commonly seen in natural disease. A relationship with treatment can not be discarded but this is not a significant toxic effect in comparison to the convulsions observed at the lower middle dose.

Conclusion:
The predominant toxic effect of the oral administration of the test material was dose-related clonic convulsions in the 200 and 500 mg/kg dose groups. No treatment related toxic change was seen in the 100 mg/kg dose group except some convulsive activity. No NOEL or NOAEL was established for this study.

Test substance : MCTR-306-79; Sample No. 12127901; Batch analysis not available in the report.

Reliability : (2) valid with restrictions
- Some requirements of the OECD guideline 408 were not followed (urea and creatinin were not measured in blood analyses, uterus, thymus and spleen were not weighted at necrospy).
- Administered volumes were low as no vehicle was used.

Flag : Critical study for SIDS endpoint

17.12.2003 (7)

Type : Sub-chronic
Species : rat
Sex : male/female
Strain : other: Crl:COBS(R)CD(R)(SD)BR
Route of admin. : gavage
Exposure period : 3 weeks.
Frequency of treatm. : Daily.
Post exposure period : None.
Doses : 125, 250, 500, 1000 mg/kg bw.
Control group : other: tap water.
Method : other
Year : 1980
GLP : no data
Test substance :

Method : The method was adequate to determine the appropriate dose levels for the final 90-day study.

Five male and five female rats per dose levels were administered the test material by gavage at 0, 125, 250, 500 and 1000 mg/kg/d for three weeks (21 consecutive days). The test material was administered undiluted. Dose volumes varied with the dose levels. Controls received tap water by gavage at the largest treatment dosing volume.

Result : Clonic convulsions, hypoactivity and salivation were present in a dose related manner and two females at 500 and two at 1000 mg/kg/d did not survive the study. No convulsions occurred at 125 mg/kg/d but salivation was frequent and one incidence of hypoactivity was observed.
Body weight and food consumption values were similar for the control and treated groups.
No apparent compound related lesions were present at gross necropsy but organ weight analysis revealed a dose related increase in liver weights which was statistically significant for the 500 mg/kg/d males and the 500 and 1000 mg/kg/d females.
On the basis of these results, the dose levels for the 90-day study were chosen to be 0, 100, 200 and 500 mg/kg/d.

Test substance : MCTR-307-79; Batch analysis not available in the report.

Reliability : (2) valid with restrictions
- Some individual data are not available.
- Dose volumes were not indicated in the report.

17.12.2003 (5)

Type : Sub-chronic
Species : rabbit
Sex : male/female
Strain : New Zealand white
Route of admin. : dermal
Exposure period : 21 days
Frequency of treatm. : 6 hours per day
Post exposure period : None
Doses : 1000, 2500, 5000 mg/kg
Control group : other: the control group received water.
Method : other
Year : 1979
GLP : no data

Test substance :

Method : No method was specified in the report.

Result : There was no death during the study.
There were no statistical differences in body weight gain between test and control animals. However the animals of the high group lost weight from day 7 onwards. This probably reflects the fact that these animals did not eat or drink normally during the study. By the end of the study these animals were emaciated. The treated animals tended to be lethargic and less responsive to outside stimuli than were the controls.
The mean body weight of animals of the three other groups was slightly lower on day 22 (fasted weight) than on day 14.
The hematology analyses showed that only the poly's of female rabbits in the high dose were significantly higher than the controls.
Blood levels of serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) were elevated in the high dose group, but because of the small number of animals and wide variation, not significantly different from the other groups. Other chemistry values were more similar to the controls and expected values for normal rabbits.
The spleen of males in the high and medium level groups were lighter than those of controls as was also noted visually at the gross necropsy. The weights of the livers relative to the body weights were elevated in the high dose group.
The histology observations showed changes in the liver, kidneys and skin : within the liver, minimal to mild cytoplasmic vacuolisation was present within hepatocytes of all of the high and intermediate dose animals, in four of the six low dose animals and in only one of the controls. It is a common change probably due to the test material.
Minimal to mild cytoplasmic vacuolisation occurred in the convoluted tubules of the kidneys of six high dose rabbits. This change was probably due to the administration of the test material..
Minimal to mild hyperkeratosis was present in the treated skin of five high dose rabbits, four intermediate dose rabbits, four low dose rabbits and in one control animal. This lesion was suggested to be the result of exposure to the test material. The laboratory pathologist considered that these three lesions probably represented mild reversible injury.
Because of the oily nature of the test material, it was impossible to clean all the material from the rabbit after the designated daily exposure period. Therefore all high dose group rabbits were entirely contaminated and this contamination decreased with the dose in the other treated groups. Therefore it is difficult to discern whether the observed effects are purely due to dermal exposure or a combination of dermal and oral exposure due to preening.

Conclusion: Significant lesions which appeared to be related to the test material were present in the liver, kidneys and treated skin. These lesions were of low severity and probably represented mild reversible injury.

Test substance : MCTR-138-78; Lot No. 0629840; Batch analysis not available in the report.

Reliability : (2) valid with restrictions
- Animals grouped consisted in 3 males and 3 females instead of Five males and five females as recommended by the OECD guideline 410.
- Some acclimatisation and housing conditions were not specified in the report.
- Clotting potential was no measured, and some biochemistry analyses were not performed (calcium, phosphorus, albumen, blood creatinin.
- Due to the nature of the test material, it was not possible to ensure that no ingestion of the test material occurred.

17.12.2003 (9)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : other: gene mutation assay with Saccharomyces cerevisiae and Salmonella typhimurium
System of testing : Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98, TA100 and Saccharomyces cerevisiae strain D4.
Test concentration : 0.005, 0.05, 0.5, 5 µl/plate
Cycotoxic concentr. : > 5 µl / plate
Metabolic activation : with and without
Result : negative
Method : other: not specified
Year : 1976
GLP : no data
Test substance :

Method : Five strains of Salmonella typhimurium and one strain of Saccharomyces cerevisiae were used to evaluate the mutagenic activity of the test material, with and without metabolic activation following a plate test method. Negative (solvent) and positive controls were included in the experiment.

Approximately 10E9 cells from a log phase culture of each indicator strain were added to test tubes containing 2.0 ml of molten agar supplemented with biotin and a trace of histidine. For tests without metabolic activation, the four dose levels of the test compound were added to the contents of the appropriate tubes and poured over the surfaces of selective agar plates. For tests with metabolic activation, the activation system (prepared from liver of Sprague Dawley rats) and required co-factors were added to the overlay tubes. Four dose levels of the test chemical were added to the appropriate tubes, which were then mixed and the contents poured over the surface of a minimal agar (selective medium) plate and allowed to solidify.
The plates were incubated for 48 to 72 hours at 37°C and scored for the number of colonies growing on each plate. Positive and solvent controls were run with each assay (with and without activation).
Result : The results of the test were negative in both the absence or presence of a metabolic activation system.
Test substance : MCTR-21-76; Sample No. 120553000; Batch analysis not available in the report.
Reliability : (2) valid with restrictions
- The test was not repeated.
- Plates were not done in triplicates.
- The solvent was not indicated in the report.

Flag : Critical study for SIDS endpoint
17.12.2003 (1)

Type : Ames test
System of testing : Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538
Test concentration : 0.2, 1.0, 5.0, 10.0, 20.0 µl/plate
Cycotoxic concentr. : 10 µl/plate
Metabolic activation : with and without
Result : negative
Method : other
Year : 1979
GLP : yes
Test substance :

Method : The protocol followed was a modification of that described by Ames, B. N., et al. "Methods for detecting carcinogens and mutagens with the Salmonella/mammalian-microsome mutagenicity test", Mutation Research 31:347-364, 1975.

A preliminary toxicity determination was performed with the TA100 strain without metabolic activation, at dose levels of 0.003, 0.01, 0.03, 0.1, 0.3, 1.0, 3.1, 10 µl/plate (and a control plate with DMSO) and resulted in a slight cytotoxicity at the highest dose level showed by a reduced viable count. There was no reduction in revertants per plate at any dose level. No precipitate was observed.
The main test was then performed with all strains at dose levels of 0.2, 1.0, 5.0, 10.0 and 20.0 with and without metabolic activation, and with solvent control (DMSO) and positive controls. All plates were done in triplicate.

Result : Toxicity was observed at the highest dose level, 20 µl/plate, in all strains, showed by a decrease in the number of revertants per plate. No significant increase of the revertants per plate was observed, in any of the strains, with or without metabolic activation.

Test substance : MCTR-233-79; Lot No. 0917940; Batch analysis not available in the report.

Reliability : (2) valid with restrictions
The test was not repeated.

Flag : Critical study for SIDS endpoint

17.12.2003 (11)

Type : Mouse lymphoma assay
System of testing : L5178Y Mouse lymphoma cells
Test concentration : 0.13 to 5.6 µl/ml without metabolic activation and 0.013 to 1.00 µl/ml with metabolic activation.
Cycotoxic concentr. : 10 µl/ml (-S9) and 1 µl/ml (+S9)
Metabolic activation : with and without
Result : negative
Method : other
Year : 1980
GLP : yes
Test substance :

Method : The experimental protocol was a modification of that described by Clive D. and Spector J.F.S. "Laboratory procedure for assessing specific locus mutations at the TK locus in cultured L5178Y Mouse Lymphoma cells", Mutation Research 31:17-29, 1975.

An initial toxicity test was conducted at dose levels of 0.001, 0.01, 1.0, 10 and 100 µL /ml, with and without metabolic activation. The toxicity was almost complete (almost no growth) from 10.0 µl/ml onwards without metabolic activation and from 1.0 µl/ml onwards with metabolic activation.
On the basis of these results the dose levels for the main test were :
- 0.13 to 5.6 µl/ml without metabolic activation,
- 0.013 to 1.00 µl/ml with metabolic activation.
The cells were exposed to the test material for a four-hour period, then washed, re-suspended and incubated for the expression period.
After the three-day expression period, eight cultures without activation and ten cultures with activation were selected for cloning based on their degree of toxicity, i.e. exhibiting from approximately 5 to 90% of growth inhibition during the expression period :
- 0.13, 0.18, 0.24, 0.32, 0.42, 0.56, 0.75, 1.00 µl/ml without metabolic activation,
- 0.075, 0.10, 0.13, 0.18, 0.24, 0.32, 0.42, 0.56, 0.75, 1.00 µl/ml with metabolic activation.
Six plates per test material concentration were prepared, three of which were done with selective medium to reveal the mutant cells and three others on non-selective medium to evaluate the viability. After a ten-day incubation period, the plates were scored for the total number of colonies per plate.
Positive and negative controls were added to the experiments.

Result : The total growth was 83 to 134% of the control for the cultures treated without metabolic activation and 32 to 131% of the controls for cultures

treated with metabolic activation.
Cultures with and without metabolic activation showed no increase in the mutant frequency in comparison with the negative controls.

Test substance : MCTR-234-79; Lot No. 0917940; Batch analysis not available in the report.

Reliability : (2) valid with restrictions
- The test was not repeated.
- The results mention data on historical controls but they are not available in the report.
- All cutures at the lowest dose level and half of the cultures at the following dose level (0.18 µl/ml) were lost (in both cases, without metabolic activation). No explanation was provided in the report.

Flag : Critical study for SIDS endpoint

17.12.2003 (12)

Type : Mouse lymphoma assay
System of testing : L5178Y Mouse lymphoma cells.
Test concentration : 0.16, 0.32, 0.65, 1.25, 1.88, 2.50 µl/ml without activation and 0.32, 0.65, 1.25, 1.88, 2.50, 5.00 µl/ml with activation.
Cycotoxic concentr. : 2.50 µl/ml (-S9) and 5.00 µl/ml (+S9).
Metabolic activation : with and without
Result : negative
Method : other
Year : 1977
GLP : no data
Test substance :

Method : The procedure used was a modification of that reported by Clive and Spector (Mutation Research, 31:17-29, 1975).

The solvent used was DMSO. The solubility, toxicity and doses were determined prior to screening. The cells were exposed to a wide range of the test substance concentrations in complete growth medium. Toxicity was measured as loss in growth potential of the cells induced by a five-hour exposure to the test material followed by a 72 hours expression period in growth medium. Six dose levels were selected.
Prior to each treatment, cells were cleansed of spontaneous TK-/-.
The test compound was then added to the cleansed cells in growth medium at the predetermined doses for five hours. In the activation assay, the metabolic activation system was added to the growth medium.
Then the cells were washed and allowed to express in growth medium for three days. At the end of this expression period, the mutant cells were detected by cloning the cells in the selection medium for ten days.
Surviving cell populations were determined by plating diluted aliquots in non selective growth medium.
Negative and positive controls were added to the assays.

Result : There was no dose-related increase or other patterns indicative of mutagenesis in either the series with metabolic activation or the series without metabolic activation, even though considerable toxicity was achieved at the highest levels.
The test compound did not induce mutagenic activity at the TK locus in L5178Y mouse lymphoma cells.

Test substance : MCTR-30-77; Lot No. 015073000; Batch analysis not available in the report.

Reliability : (2) valid with restrictions
The test was not repeated.

Flag : Critical study for SIDS endpoint

17.12.2003 (2)

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	female
Strain	:	other: Charles River COBS CD
Route of admin.	:	gavage
Exposure period	:	From day 6 to day 19 of gestation
Frequency of treatm.	:	Single daily dose
Duration of test	:	Surviving animals were sacrificed on day 20 of gestation.
Doses	:	100, 400, 600 mg/kg bw/day
Control group	:	other: the control group received distilled water.
Result	:	negative
Method	:	other
Year	:	1981
GLP	:	yes
Test substance	:	

Method : Although it is not specified in the report, the study was performed according to a method comparable to the OECD guideline 414.

The study used four groups of twenty-five female rats that were mated with males of the same strain and source. The day that evidence of mating was detected was designated day 0 of gestation.
The test substance was administered orally by gavage, as a single dose daily on days 6 through 19 of gestation, undiluted, at dose levels of 100, 400 and 600 mg/kg bw/day at total dosage volumes of 0.071, 0.284 and 0.426 ml/kg bw/day respectively. The control group received distilled water on a comparable regimen at a volume of 0.426 ml/kg bw/day.
Females not surviving to scheduled sacrifice were necropsied in an attempt to determine the cause of death. The normally developing implantations from these dams were examined to the fullest possible extent.
All surviving animals on gestation day 20 were sacrificed for gross examination as well as caesarean sections.

Result : Seven deaths occurred in the 600 mg/kg group between days 9 and 13 of gestation. The cause of death could not be determined for any of the dams. No abnormalities were noted among the normally developing implantations in any of these dams. Survival was 100% in the 100 and 400 mg/kg groups and in the control group.
The number of gravid females were 22/25, 25/25, 23/25 and 18/25 respectively in the control group, 100, 400 and 600 mg/kg groups.
Yellow and orange staining (primarily of the limbs and facial regions) was observed in eleven animals in the 600 mg/kg group, two animals in the 400 mg/kg group and one animal in the 100 mg/kg group. No staining was observed in the control group. Hair loss (primarily of the head, limbs and posterior regions) was observed in fifteen animals in the 600 mg/kg group, seven animals in the 400 mg/kg group and in two animals each in the 100 mg/kg group and control group. Lethargic behaviour was observed in seven animals in the 600 mg/kg group and one animal each in the 400 and 100 mg/kg groups. Additional observations found only in the 600 mg/kg group included two animals with laboured breathing and red or black anogenital staining (each occurred once). At caesarean sections, one animal of the control group had hydrometra and one animal of the 400 mg/kg group had hydronephrosis. All other animals were found to be

internally normal.
Mean maternal body weight gains (gestation days 6 to 20) and mean adjusted (exclusive of the mean gravid uterus weight) body weight gains (gestation days 0 to 20) in all treated groups were comparable to the control group.
The mean number of viable foetuses per dam was significantly lower in the 600 mg/kg group when compared with the control group. This was attributed largely to an increase in mean post-implantation loss, which was due primarily to one animal with early resorptions only. There were no biologically meaningful or statistically significant differences in mean foetal body weights or foetal sex distribution in any treatment group or in the mean numbers of corpora lutea, total implantations, early resorptions, late resorptions or viable foetuses in the 100 or 400 mg/kg groups when compared to the control group. Non viable foetuses were not observed in any group.
Moreover, there were no biologically meaningful or statistically significant differences in the number of litters with malformations in any of the treated groups when compared with the control group. No malformations occurred in the 600 mg/kg group.
The developmental and genetic variations observed in the treated groups were also comparable to the control group.

Conclusion : treatment with the test material did not produce a teratogenic response when administered orally to pregnant rats at a dosage level of 600 mg/kg/day or less.
The NOAEL for developmental effects can be set at 600 mg/kg and the NOAEL for maternal effect at 400 mg/kg.

Test substance : MCTR-301-79; Sample No. 12127901; Batch analysis not available in the report.

Reliability : (2) valid with restrictions
- Administered volumes were low as no vehicle was used.
- Some results were lost by the laboratory : observations of eight foetuses in one litter at the high dose level and six foetuses in one litter at the low dose level.

Flag : Critical study for SIDS endpoint

17.12.2003 (8)

Species : rat
Sex : female
Strain : other: Charles River COBS CD
Route of admin. : gavage
Exposure period : From day 6 to day 19 of gestation.
Frequency of treatm. : Single daily dose.
Duration of test : Surviving animals were sacrificed on day 20 of gestation.
Doses : 120, 250, 500, 1000, 2000 mg/kg bw/day.
Control group : other: the control group received distilled water.
Result : Negative.
Method : other
Year : 1980
GLP : yes
Test substance :

Method : This study was a preliminary study to determine appropriate dose levels for a teratology study (see report M3010-79)

The study used six groups of five female rats that were mated with males of the same strain. The day that evidence of mating was detected was designated day 0 of gestation.
The test substance was administered orally by gavage, as a single dose daily on days 6 through 19 of gestation, undiluted, at dose levels of 120, 250, 500, 1000 and 2000 mg/kg bw/day at total dosage volumes of 0.085, 0.177, 0.355, 0.709 and 1.418 ml/kg bw respectively. The control group

received distilled water on a comparable regimen at a volume of 10 ml/kg bw/day.
Females not surviving to scheduled sacrifice were necropsied in an attempt to determine the cause of death. All surviving animals on gestation day 20 were sacrificed and the number and location of viable and non viable foetuses, early and late resorptions and the number of total implantations and corpora lutea were recorded. The abdominal and thoracic cavities and organs of the dams were examined for grossly evident morphological changes.

Result : The number of gravid females were 4/5, 5/5, 5/5 , 3/5, 5/5 and 5/5 respectively in the control group, 120, 250, 500, 1000 and 2000 mg/kg groups.
Conjunctivis was noted among rats in the control, 120, 250 and 500 mg/kg groups. There were no biologically meaningful differences in the appearance or behaviour of rats in the 120 or 250 mg/kg groups when compared to the control group. In the 500 mg/kg group, staining of the anogenital area was noted in one rat between days 9 and 15 of gestation and rattled breathing was noted in three rats within the last week of gestation (two of these also had milky urine). Convulsions and matting and staining of the anogenital area were observed in several of the rats prior to the scheduled sacrifice in the 1000 and 2000 mg/kg groups. An oral discharge was noted in two rats in the 1000 mg/kg group prior to death.
All rats in the 1000 and 2000 mg/kg groups died. These deaths occurred between gestation days 7 and 10 in the 1000 mg/kg dosage group and on gestation day 7 in the 2000 mg/kg group. Causes of death could not be determined for any of these animals at necropsy. Reddened intestinal and/or stomach mucosa were noted at necropsy in four rats in the 1000 mg/kg group and in four rats in the 2000 mg/kg group.
Hydronephrosis was noted in two rats, one in the 250 mg/kg group and one in the 2000 mg/kg group. Pitted kidneys were observed in two rats, one in the control group and one in the 500 mg/kg group.
There were no biologically meaningful differences in mean maternal body weight gain in the 120, 250 and 500 mg/kg groups in comparison with the control group. The body weight gains of the dams in 1000 and 2000 mg/kg was comparable to that of the controls from days 0 to 6. Only one animal was weighted afterwards as it died on day 10, after the next weighing session (day 9). This animal showed a severe body weight loss. The other animals died between days 7 and 9 and were not weighted.
There were no biologically meaningful differences in the mean number of viable foetuses, postimplantation loss (early or late resorptions), total implantations or corpora lutea in the 120, 250, or 500 mg/kg groups when compared to the control group means. A slight decrease in the mean number of total implantations and viable foetuses in the 120 mg/kg group was due to one dam with one implantation only.

Conclusion : A dose level of 1000 mg/kg was considered excessive for a teratology study. No developmental toxicity was observed at 120, 250 and 500 mg/kg. No developmental data are available for the two highest groups (all animals died) except that all females were gravid.

Test substance : MCTR-308-79; Sample No. 12127901; Batch analysis not available in the report.

Reliability : (2) valid with restrictions
- No individual data are available for clinical and gross examinations in the report.
- Administered volumes were low as no vehicle was used.

17.12.2003 (6)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

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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10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT