IUCLID

Data Set

Existing Chemical	:	ID: 288-88-0
CAS No.	:	288-88-0
EINECS Name	:	1,2,4-triazole
EC No.	:	206-022-9
TSCA Name	:	1H-1,2,4-Triazole
Molecular Formula	:	C2H3N3

Producer related part

Company	:	Epona Associates, LLC
Creation date	:	26.06.2008

Substance related part

Company	:	Epona Associates, LLC
Creation date	:	26.06.2008
Status	:	
Memo	:	Bayer
Printing date	:	16.10.2008
Revision date	:	
Date of last update	:	16.10.2008
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Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
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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

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	**:**	1H-1,2,4-triazole
Smiles Code	**:**	n1ncnc1
Molecular formula	**:**	C2 H3 N3
Molecular weight	**:**	69
Petrol class	**:**	

14.10.2008

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	**:**	
Substance type	**:**	organic
Physical status	**:**	solid
Purity	**:**	
Colour	**:**	
Odour	**:**	

13.10.2008

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

1,2,4-Triazole

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1H-1,2,4-Triazole

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4H-1,2,4-Triazole

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S-Triazole

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s-Triazole TA

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TA

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1.3 IMPURITIES

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

1.13 REVIEWS

2.1 MELTING POINT

Value	:	= 120.4 °C
Sublimation	:	
Method	:	
Year	:	1983
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Melting point conducted by differential scanning calorimetry (guideline number not provided); DSC thermogram was included in the report. DSC hermogram: Sample weight: 0.421 mg Range: 5 mcal/sec Heating rate: 5 deg/min Chart speed: 20 mm/min Temp range: 360-400 K Heat of fusion: 53.053 cal/g (15.3 kJ/mole; 3664.4 cal/mole) Tm: 393.526 K Calibration: Indium
Result	:	393.526 K = 120.4 deg C
Reliability	:	(2) valid with restrictions Provides basic data.
Flag	:	Critical study for SIDS endpoint

07.07.2008 (18)

Value	:	= 120.5 °C
Sublimation	:	
Method	:	other
Year	:	2007
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(2) valid with restrictions Handbook data

24.07.2008 (21)

2.2 BOILING POINT

Value	:	= 260 °C at
Decomposition	:	
Method	:	other
Year	:	2007
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(2) valid with restrictions Handbook data
Flag	:	Critical study for SIDS endpoint

24.07.2008 (21)

2.3 DENSITY

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value	:	= .0022 hPa at 20 °C
Decomposition	:	
Method	:	OECD Guide-line 104 "Vapour Pressure Curve"
Year	:	2001
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	The vapor pressure curve of 1,2,4-triazole was determined by means of a vapor pressure balance according to OECD TG 104. Duplicate runs were conducted. The vapor pressure was measured between -6 deg C and 46 deg C in the first series and between -14 deg C and 38 deg C in the second series. By interpolating the experimental values to 10, 20 and 25 deg C and by extrapolating them to 50 and 100 deg C, and by taking for each of these temperatures the mean from the two series of measurements, vapor pressures were obtained.
Result	:	The following values for vapor pressure were obtained by intrapolating and extrapolating the experimental values: 10 deg C: 8.1 x 10E-04 hPa 20 deg C: 2.2 x 10E-03 hPa 25 deg C: 3.4 x 10E-03 hPa 50 deg C: 2.9 x 10E-02 hPa 100 deg C: 8.6 x 10E-01 hPa
Reliability	:	(2) valid with restrictions Guideline study, but not GLP.
Flag	:	Critical study for SIDS endpoint

01.07.2008 (4)

2.5 PARTITION COEFFICIENT

Partition coefficient	:	octanol-water
Log pow	:	= -.71 at 25 °C
pH value	:	= 7
Method	:	OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
Year	:	2005
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Also conducted in accordance with: EEC Directive 92/69, Part A, Methods for the determination of physico-chemical properties, A.8 "Partition coefficient", EEC Publication No. L383A, December 1992. EPA Product Properties Test Guidelines, OPPTS 830.7550, Partition Coefficient (n-Octanol/Water), EPA712-C-96-038, August 1996. A shaking flask method was utilized. Test System: The test system consisted of an aqueous phase (pH 5, pH 7 and pH 9, respectively) and an n-octanol phase in the same vessel. A defined amount of test item dissolved in one of the solvents was added. To achieve partition of the test item between both phases the mixture was

shaken intensively for about 21 hours. The equilibration temperature was 25°C and was controlled several times during this period using a calibrated thermometer. The phases of the solvent system were saturated with each other prior to the test by shaking n-octanol and the respective buffer each with a sufficient quantity of the other solvent.

Performance of the Test: For each pH value, three tests were carried out, each in duplicate. The volume ratio of both solvents was 1:1, 2:1 and 1:2 as proposed in the guideline. For each pH value, six test vessels containing the accurately measured amounts of the two solvents, one containing a defined amount of the test item, were prepared. The test vessels were placed on a lab-shaker and shaken for about 21 hours at 25°C. Phase separation of the phases was then obtained by centrifugation (for 10 minutes at about 18100 g).

For the determination of the partition coefficient, it was necessary to analyze the concentrations of the test item in both phases. The aqueous buffer phases were analyzed after 1:10 dilution with a mixture of acetonitrile and water (50:50; v/v). 1 ml of each of the n-octanol phase was diluted to 5 ml with acetonitrile prior to analysis. The quantification of CGA71019 was performed according to a standardized HPLC method.

Result : During the main study three tests were carried out for each pH value, each in duplicate, with volume ratios of both solvents of 1:1, 2:1 and 1:2. After equilibration at 25°C, the concentration of the test item in each phase was determined by HPLC. The log Pow was calculated for each of the vessels and was found to be -0.62 at pH 5, -0.71 at pH 7 and -0.68 at pH 9.

Test substance : Purity 99.9%

Reliability : (1) valid without restriction
Guideline study; GLP

Flag : Critical study for SIDS endpoint

13.10.2008 (25)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : = 700 g/l at 20 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method : other: Guideline OPPTS 830.7840
Year : 2001
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Water solubilities of 1,2,4-triazole at 20 deg C reported in the literature as mole fractions were converted into the unit gram per liter of solution by substituting approximately the partial molar volumes by the ratios of weight fractions and densities neglecting deviations from additivity.

Guideline OPPTS 830.7840
Water solubility:
n=0.268 mole fraction at 20 deg C
n=0.283 mole fraction at 25 deg C (calculated by intrapolation)
n=0.298 mole fraction at 30 deg C
Reference: Vlasov, O.N. and S.I. Sukhova. (1988) Russian Journal of

Physical Chemistry 62: 978-979

Guideline OPPTS 830.7300
Density (crystal):
Density = 1.39 g/cm3
Reference: Jimenez, P., M.V. Roux, and C. Turrion (1989) Journal Chem. Thermodyamics 21: 759-764.

Density = 1.439 g/cm3 and 1.456 g/cm3
Reference: Jeffrey, G.A., J.R. Rubie, and J.H. Yates (1983) Acta Crystallogr. Sect. B 39: 388-394

Result : The resulting values of 700 g/L and 730 g/L were calculated for the water solubilities of 1,2,4-triazole at 20 and 25 deg C, respectively.

Reliability : (2) valid with restrictions
Guideline study, but not GLP.

Flag : Critical study for SIDS endpoint

01.07.2008 (5)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

Memo : Henry's Law Constant

Method : Using the resulting values of 700 and 730 g/L for the water solubilities at 20 and 25 deg C, respectively, and considering the vapor pressures at 20 deg C and 25 deg C of 0.22 Pa and 0.34 Pa (calculated in Bayer Report 200011), respectively, the Henry Law Constants were calculated.

Guideline OPPTS 830.7950
Vapor Pressure:
20 deg C: 2.2 x 10E-03 hPa
25 deg C: 3.4 x 10E-03 hPa
Reference: Bayer AG (1989) Vapor pressure curve of 1,2,4-Triazole.

Report No. 200011.

Result : With vapor pressures of 0.22 Pa and 0.34 Pa at 20 deg C and 25 deg C, respectively, in combination with high water solubilities of 700 g/L and 730 g/L at 20 deg C and 25 deg C, respectively, the Henry Law Constants were calculated to be 2 x 10E-05 Pa x m3/Mole and 3 x 10E-05 Pa x m3/Mole, respectively. These values are in a range where volatilization due to evaporation of water can be excluded.

Reliability : (2) valid with restrictions
Guideline study, but not GLP.

01.07.2008 (5)

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	:	= 0 cm³/(molecule*sec)
Degradation	:	= 50 % after 107 day(s)
Deg. product	:	
Method	:	other (calculated)
Year	:	2008
GLP	:	no
Test substance	:	other TS

Method :

```
AOP Program (v1.92):
==========================
SMILES : n1ncnc1
CHEM   : 1H-1,2,4-Triazole
CAS NUM: 000288-88-0
MOL FOR: C2 H3 N3
MOL WT : 69.07
```

Result :

```
AOP Program (v1.92) Results:
==========================
---- SUMMARY (AOP v1.92): HYDROXYL RADICALS ----------
Hydrogen Abstraction      =   0.0000 E-12 cm3/molecule-sec
Reaction with N, S and -OH =   0.0000 E-12 cm3/molecule-sec
Addition to Triple Bonds   =   0.0000 E-12 cm3/molecule-sec
Addition to Olefinic Bonds =   0.0000 E-12 cm3/molecule-sec
Addition to Aromatic Rings =   0.1000 E-12 cm3/molecule-sec
Addition to Fused Rings    =   0.0000 E-12 cm3/molecule-sec

  OVERALL OH Rate Constant =   0.1000 E-12 cm3/molecule-sec
  HALF-LIFE =   106.960 Days (12-hr day; 1.5E6 OH/cm3)
```

Reliability	:	(2) valid with restrictions Accepted calculation method
Flag	:	Critical study for SIDS endpoint

14.10.2008 (33)

Type	:	water
Light source	:	Sun light
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Deg. product	:	
Method	:	other (measured)
Year	:	1983
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method : The objective of this study was to determine the sunlight photoreactivity of 1,2,4-H-triazole in distilled water and in humic acid solutions, in order to estimate its photoreactivity in actual environmental situations.

Photolysis procedures:
1,2,4-H-Triazole (C14-labeled, 18.9 uCi/mg), was received as a dry film inside a sealed glass container. Three ml of acetonitrile was added to the opened container, and one ml of this solution was added to 20 ml of

distilled water and 20 ml of Fluka humic acid solution. The spectrum of this humic acid approximates several natural water samples. The concentration of triazole in this solution is approximately 80 ppm, assuming all was dissolved in the original acetonitrile. One ml of each of these solutions was added to 1 cm x 10 cm Pyrex glass stoppered test tubes. Since volatilization was of concern, each of the ground glass stoppered joints was wrapped with teflon tape. These solutions were set in the sun on 05-17-83 at a 30 degree angle from the verticle. Samples were taken at periodic intervals over a thirty day period and stored in a refrigerator until the last sample was taken and all were analyzed simultaneously.

Remaining triazole was quantitated in all solutions by spotting 30 microliters of the irradiated solution and 20 microliters of a 20 mg/ml solution of unlabeled triazole on a 3 cm band on a silica gel G TLC plate containing 254 nm phosphor. The plates were developed in 90:10 isopropyl alcohol:water. Visualization was accomplished by irradiating the plates with a medium pressure mercury arc lamp for one hour. The resulting uv quenching bands (Rf = .65 - .75) were scraped into scintillation vials; 1 ml of water and 10 ml of Aguasol were added and the vials counted by liquid scintillation. Total radioactivity in the irradiated solutions was determined by injecting 30 microliters of the irradiated solutions into the scintillation vials which were then treated identically to that described above.

Spectrum: The spectrum of 1,2,4-H-triazole was obtained on a Hitachi Model 100-80 uv-visible spectrometer using 0.145 M aqueous solutions of unlabeled triazole. The spectra was recorded after automatically establishing a flat baseline on the spectrometer.

Result **:** Photolysis:
1. Distilled water: Within experimental error, sunlight degradation of 1,2,4-H-triazole was not observed in distilled water. There was no consistent reduction in the amount of radioactivity from the recovered TLC spots compared to direct addition of irradiated solutions to scintillation vials. Some loss of the starting compound, presumably by volatilization, was evident in several samples, since reductions in radioactivity from both the silica gel and direct counting of the irradiated solutions were similar in each case. Recovery of radioactivity from non-irradiated samples when developed in the TLC system exceeded 90%. The pH of the initial and final solutions were 6.4 and 7.6, respectively.

2. Humic acid solutions: As in the distilled water samples, no photochemical loss of the starting material was observed, within experimental error. The humic acid solution underwent photochemical bleaching during the irradiation. Comparing spectra taken of the starting solution to the spectra of the solution exposed to nearly eight days revealed substantial loss of the visible and ultraviolet absorbing materials. While this presumably generated reactive intermediates, they had no appreciable effect on the triazole. Again, volatilization was observed in some of the samples. Recovery of radioactivity from the TLC system exceeded 90% in these solutions also. The pH of the initial and final solutions was 7.8 and 7.6, respectively.

The concentration of 1,2,4-H-triazole used in these experiments was approximately 80 ppm. The higher concentration was used to insure that analytical aspects of the tests would not be a problem. While this was higher than indicated in the protocol, it would have no effect on the direct photolysis experiments, since the solutions were essentially transparent to sunlight wavelengths. While this is less certain for the humic acid solutions, it would not be expected to exert a major effect.

Spectra:
Extinction coefficients for 1,2,4-H-triazole are presented below. The sunlight absorption of 1,2,4-triazole is extremely low.

Wavelength	Extinction Coefficient
390	0.10
380	0.10
370	0.16
360	0.20
350	0.25
340	0.31
330	0.37
325	0.38
323	0.36
320	0.50
317.5	0.54
315	0.57
312.5	0.62
310	0.67
307.5	0.73
305	0.79
302.5	0.87
300	0.95
297.5	1.03
295	1.12

Conclusion : 1. 1,2,4-H-Triazole does not appreciably absorb sunlight.

2. 1,2,4-H-Triazole does not undergo appreciable direct photolysis in sunlight nor does humic acid have a major effect on increasing the rate of loss by indirect photochemical reactions.

Reliability : (2) valid with restrictions
Provides basic data to evaulate the photolysis of 1,2,4-triazole in water.

01.07.2008 (22)

3.1.2 STABILITY IN WATER

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : > 30 day(s) at 25 °C
t1/2 pH9 : > 30 day(s) at 25 °C
t1/2 pH 5 : > 30 day(s) at 25 °C
Deg. product :
Method : other
Year : 1983
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : The purpose of the study was to determine hydrolysis rate constants and half-lives for 1,2,4-H-Triazole in aqueous buffered solutions of pH 5, 7, and 9 at 25 +/- 1 deg C.

The test chemical was received in crystalline form and was diluted to volume with deionized water. Aliquots of the stock solution (1 mg/ml) were added to the three buffer solutions to achieve a final concentration of 10 ppm. Each dosed buffer solution was split into 2 replicates.

The study monitored the degradation of 1,2,4-H-Trlazole in aqueous solutions of pH 5, 7 and 9 at 25°C. The buffer solutions were sampled regularly (at days 0, 1, 3, 6, 13, and 30) and the loss of 1,2,4-triazole at 25 deg C with respect to time was monitored by quantitation of the test chemical levels present using thin layer chromatography (TLC) and autoradiography. At each sampling interval two samples were removed from each duplicate buffer incubation. One sample was immediately

spotted on thin layer chromatography plates. The second sample was used for radiocarbon counting and pH determination.

Data from the TLC analyses was to be used to evaluate hydrolysis rate constants and half-lives of 1,2,4-H-Triazole.

Result : The pH range had the following results over the 30 day test period:
For pH 5: pH 5.12-5.42
For pH 7: 7.04-7.22
For pH 9: 8.97-9.07

Throughout the study parent molecule accounted for 89.6 to 97.9% of all spotted radioactivity. At all three tested pH values 5, 7, and 9, the test material was found to be stable for 30 days at 25°C. Half-life calculations and rate constants could not be calculated for the hydrolysis of 1,2,4-H-Triazole. The molecule was not observed to hydrolyze at pH 5, 7 or 9 for periods up to 30 days. Therefore, the half-life was in excess of 30 days.

Test substance : The test chemical [U-Ring-14C]-l,2,4-H-Triazole had a specific activity of 18.8 uCi/mg. Purity of the material was determined to be 98.6 percent by TLC.

Reliability : (2) valid with restrictions
Provides basic data to asess the stability of 1,2,4-triazole in water at different pH values; not GLP.

13.10.2008 (14)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : fugacity model level III
Media :
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: calculated
Year : 2008

Method : Level III Fugacity Model (Full-Output):
==========
Chem Name : 1H-1,2,4-Triazole
Molecular Wt: 69.07
Henry's LC : 2.14e-010 atm-m3/mole (calc VP/Wsol)
Vapor Press : 0.00165 mm Hg (user-entered)
Liquid VP : 0.0145 mm Hg (super-cooled)
Melting Pt : 120 deg C (user-entered)
Log Kow : -0.71 (user-entered)
Soil Koc : 0.0799 (calc by model)

Result : Level III Fugacity Model (Full-Output):
==========
Mass Amount Half-Life Emissions

	(percent)	(hr)	(kg/hr)
Air	0.00504	2.57e+003	1000
Water	38.9	360	1000
Soil	61	720	1000
Sediment	0.0713	3.24e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	3.1e-013	0.0236	0.876	0.000788	0.0292
Water	1.05e-014	1.3e+003	676	43.4	22.5
Soil	6.05e-013	1.02e+003	0	34	0
Sediment	9.59e-015	0.265	0.0248	0.00883	0.000826

Persistence Time: 579 hr
Reaction Time: 748 hr
Advection Time: 2.57e+003 hr
Percent Reacted: 77.4
Percent Advected: 22.6

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
Air: 2568
Water: 360
Soil: 720
Sediment: 3240
Biowin estimate: 3.047 (weeks)

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

Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint
14.10.2008 (33)

Type : other: adsorption and desorption
Media : soil - air
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
Year : 1988

Method : Conducted in accordance with Guideline 163-1 under GLP.

The adsorptive and desorptive properties of l,2,4-triazole in various soils were measured using radiolabelled triazole in a batch equilibrium experiment. The objective of this study is to estimate the potential for mobility of triazole in soil by studying these properties.

The adsorption properties of triazole on five soils were studied by mixing the soil and solutions of the test material at four concentrations (0.086, 0.043, 0.0085, and 0.0043 ppm) in aqueous calcium chloride (0.01 M). After allowing 95 hours for the mixtures to reach equilibrium the mixtures were centrifuged and the supernatants decanted. The concentration of triazole in the solutions was determined by radioassay. The soils tested were silty clay, clay loam, silty clay loam, sandy loam, and sand. The ratios of solution to soil were 5:1 for the silty clay, 4:1 for the clay loam and the silty clay loam, 3:1 for the sandy loam and 2:1 for the sand.

Desorption was determined by allowing the soils from the adsorption determination to equilibrate with fresh calcium chloride solutions. After 46 hours the mixtures were centrifuged and the supernatants decanted. The concentration of triazole in the solutions was determined by radioassay. Fresh calcium chloride solutions were then added to the remaining soils and the resulting mixtures were shaken for 24 hours before being analyzed in the same manner as the previous mixtures. Samples of the remaining soils were analyzed by combustion radioassay in order to ascertain the recovery of the radioactivity.

Result : The adsorption coefficient, Kd, and the adsorption constants corrected for the amount of organic carbon, Koc, for the five soils were found to be:

Soil		Kd	Koc
Alpaugh Silty Clay		0.833	120
Hollister Clay Loam		0.748	43
Lakeland Sand		0.234	202
Lawrenceville Silty Clay Loam	0.722	104	
Pachappa Sandy Loam		0.719	89

The average of Koc for these soils was found to be 112 +/- 58. On this basis, one would
classify triazole in the high potential mobility category in soil (50-150 being the range for "high mobility").

The Kd's for the desorptions were found to be much higher than those for the adsorptions (an average of 77% higher for the first desorption and 704 % higher for the second), suggesting that some of the triazole may be irreversibly bound to the soils. This would indicate that triazole may not be as mobile as one would predict based upon the adsorption results.

Test substance : The 14C-l,2,4-triazole used in this study was uniformly labelled in the 3 and 5 positions and had a specific activity of 182.4 mCi/g (404900 dpm/ug). The radiopurity of the test material was determined to be >95% by TLC.

Reliability : (1) valid without restriction
Guideline study

13.10.2008 (27)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : activated sludge
Concentration : 100 mg/l related to DOC (Dissolved Organic Carbon)
related to
Contact time : 28 day(s)
Degradation : = 1 (±) % after 28 day(s)
Result : under test conditions no biodegradation observed
Kinetic of testsubst. : 1 day(s) = 3 %
7 day(s) = 1 %
14 day(s) = 0 %
21 day(s) = 1 %
28 day(s) = 1 %
Control substance : Aniline
Kinetic : 7 day(s) = 97 %

14 day(s) = 97 %

Deg. product :

Method : OECD Guide-line 302 B "Inherent biodegradability: Modified Zahn-Wellens Test"

Year : 1990

GLP : yes

Test substance : as prescribed by 1.1 - 1.4

Method : Also conducted in accordance with DIN 38 412 Teil 25.

This test was conducted in accordance with the Zahn-Wellens/EMPA test used to determine inherent biodegradability. A mixture containing the test substance, mineral nutrients and a relatively large amount of activated sludge in aqueous medium was agitated and aerated at 20 - 25 deg C in the dark, for 28 days. Blank controls, containing activated sludge and mineral nutrients but no test substance, were run in parallel. The test was conducted using the reference compound, aniline.

The following vessels were identified in the study:
Inoculum blank: 2 vessels containing inoculum alone (A and B)
Test suspension: 2 vessels containing the test substance and inoculum (G and H)
Procedure control: 2 vessels containing reference compound and inoculum (C and D)

The biodegradation process was monitored by determination of the Dissolved Organic Carbon (DOC) in filtered samples, taken at 0 and 3 hours, and 1, 7, 14, 21, 27 and 28 days. DOC in the test suspensions and procedure controls were monitored in duplicate samples. The ratio of eliminated DOC, corrected for the blank, after each time interval, to the initial DOC value was expressed as the percentage biodegradation at the sampling time. The test was considered valid if the procedural control shows the removal of the reference compound by at least 70% within 14 days.

Result : Percentage degradation over time:

Time	Aniline Net DOC (mg/L)/ % degradation
0 hr	87/0%
3 hr	85/2%
1 d	79/9%
7 d	3/97%
14 d	3/97%
21 d	6/93%
27 d	2/98%
28 d	2/98%

Time	Test material Net DOC (mg/L)/ % degradation
0 hr	104/0%
3 hr	100/4%
1 d	101/3%
7 d	103/1%
14 d	108/0%
21 d	103/1%
27 d	102/2%
28 d	103/1%

Test substance : 1,2,4-Triazole

Reliability : (1) valid without restriction
Guideline study; GLP

Flag : Critical study for SIDS endpoint

13.10.2008 (20)

Type	:	aerobic
Inoculum	:	
Deg. product	:	
Method	:	other: see Methods section
Year	:	2000
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Method :

The study procedures described in this report are based upon the following guidelines:
European Economic Community (EEC), Commission Directive 95/36/EC, Annex I, 7.1.1.2.1., EEC publication No L172 (1995) amending Council Directive 91/414/EEC concerning the placing of plant protection products on the market, Annex II, Part A, 7.1.1., EEC publication No L230 (1991).

Society of Environmental Toxicology and Chemistry (SETAC), Procedures for assessing the environmental fate and ecotoxicity of pesticides, Part 1, 1.1 Aerobic degradation, Ed. M. Lynch (1995).

Dutch Board for the Authorisation of Agrochemicals (CTB). G.1.1: Gegevens over de aard van de omzettingsprodukten en de snelheden waarmee deze worden gevormd (1995).

U.S. Environmental Protection Agency. Pesticide Assessment Guidelines, Subdivision N. Chemistry: Environmental fate. § 162-1 Aerobic soil metabolism studies (1982).

Biologische Bundesanstalt fiir Land- und Forstwirtschaft (BBA). Richtlinien fur die amtliche Prufung von Pflanzenschutzmitteln. Teil IV. 4-1 Verbleib von Pflanzenschutzmitteln im Boden - Abbau, Umwandlung und Metabolismus - (1986).

The objective of this study was to provide data on the degradation kinetics of 1,2,4-Triazole in three different soils under aerobic conditions. [3,5-14C]1,2,4-Triazole was aerobically incubated in three soils (Laacher Hof AXXa, sandy loam; BBA 2.2, loamy sand; Laacher Hof A III, silt loam) at 20°C ± 2°C in the dark at a moisture content of approximately 40% of the water holding capacity. 1,2,4-Triazole was applied at a concentration of about 0.06 mg/kg dry soil. This was equivalent to an application rate of triazole-releasing fungicides of 750 g a.i./ha, reaching the soil for 50%, incorporation in 5 cm of soil and assuming a soil bulk density of 1500 kg/m3, a maximum metabolite formation of 50% and a molar mass ratio of 1,2,4-Triazole to parent of 0.25.

Activity was fractionated into 14CO2, organic volatiles, extracted residues and unextracted residue. The determination of the 1,2,4-Triazole degradation rate was based on its content in the extracted fraction.

Result :

Major end products of [3,5-14C]1,2,4-Triazole degradation in soil were [1,2,4]Triazol-1-yl-acetic acid (7% maximum), 14CO2 (< 33%) and unextracted residue (< 65% after 120 days of incubation). Apart from [1,2,4]Triazol-1-yl-acetic acid in total two other metabolites, one of which was identified as 1,2,4-Triazole-hydroxy, were encountered in minor amounts (i.e. < 2.6%).

1,2,4-Triazole degraded in Laacher Hof AXXa sandy loam soil, BBA 2.2 loamy sand soil and Laacher Hof A III silt loam soil with an average half-life of 8 days (best fit). The DT50 values of the three soils including the kinetic function applied are summarised below.

Soil	Model	DT50 values

Laacher Hof AXXa	FOMC(a)	2.34 days
BBA 2.2	FOMC(a)	9.34 days
Laacher Hof III	First order	12.27 days
MEAN		7.98 days

Where (a) = First order multicompartment.

The DT50 values assuming non-linear first order kinetics in the three soils investigated were: 6.32 days for Laacher Hof AXXa sandy loam soil, 9.91 days for BBA 2.2 loamy sand soil (only first phase was used) and 12.27 days for Laacher Hof A III silt loam soil.Major end products of [3,5-14C]1,2,4-Triazole degradation in soil were [1,2,4]Triazol-1-yl-acetic acid.

Test substance : 1,2,4-Triazole, 14C-labelled:
Radiochemical Purity > 98% (HPLC); > 98% (TLC)
Chemical purity > 99% (GC/FID)
Specific activity 9.65 MBq/mg, 260.9 nCi/mg

1 ,2,4-Triazole, unlabelled
Purity = 99.9%

Reliability : (1) valid without restriction
Guideline study; GLP

13.10.2008 (23)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

Species : other
Exposure period : at °C
Concentration :
BCF : = 3.16
Elimination :
Method : other
Year : 2008
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : BCF Program (v2.17):
==========
SMILES : n1ncnc1
CHEM : 1H-1,2,4-Triazole
MOL FOR: C2 H3 N3
MOL WT : 69.07

Result : BCF Program (v2.17) Results:
==========
---------- Bcfwin v2.17 ----------
Log Kow (estimated) : -0.76
Log Kow (experimental): -0.58
Log Kow used by BCF estimates: -0.71 (user entered)

Equation Used to Make BCF estimate:
Log BCF = 0.50

Correction(s): Value
Correction Factors Not Used for Log Kow < 1

Estimated Log BCF = 0.500 (BCF = 3.162)

Reliability : (2) valid with restrictions

Accepted calculation method

14.10.2008 (33)

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Oncorhynchus mykiss (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
NOEC	:	= 100
LC50	:	> 100
Limit test	:	
Analytical monitoring	:	yes
Method	:	OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year	:	2002
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Also conducted in accordance with EU DIRECTIVE 67/548/EEC, ANNEX V, GUIDELINE C.1. Juvenile fish (mean total length 40 mm, mean wet weight 0.51 g) were exposed under static conditions to the nominal test concentrations 6.3, 13, 25, 50, 100 mg 1,2,4-triazole/L and a negative (dilution water) control. Two replicate test chambers were maintained in each treatment and control group, with 10 trout in each test chamber for a total of 20 trout per concentration. Observations of the fish were made after approximately 3, 24, 48, 72 and 96 hours for dead fish, or any clinical signs of toxicity or abnormal behavior. Measured test concentrations were determined from samples of test water collected from the 6.3, 25 and 100 mg/L treatment groups and the control group at the beginning and end of the test. Chemical analysis, for 1,2,4-triazole, of lowest, middle and highest test concentrations (6.3, 25 and 100 mg/L) was performed at the start (t = 0 h) and end (t = 96 h) of the test using Gas Chromatography with flame ionization detection (GC/FID).
Result	:	Chemical analysis of the test solutions at the start and end of the test period resulted in measured 1,2,4-triazole concentrations ranging from 90 to 125% of nominal values. Therefore, all effect concentrations were based on nominal test concentrations. Fish in the control and all of the 1,2,4-triazole treatment groups appeared healthy and normal throughout the test. Thus, the 24, 48, 72 and 96 h LC50 values were > 100 mg/L, and the concentration without any observed effects (NOEC) was 100 mg/L, the maximum concentration tested.
Conclusion	:	The 96 h LC50 for Oncorhynchus mykiss exposed to 1,2,4-triazole under static conditions was greater than 100 mg/L, thus the compound can be classified as practically non-toxic to fish.
Reliability	:	(1) valid without restriction Guideline study; GLP
Flag	:	Critical study for SIDS endpoint

14.10.2008 (35)

Type	:	static
Species	:	Salmo gairdneri (Fish, estuary, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	> 760
Limit test	:	yes
Analytical monitoring	:	yes
Method	:	OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year	:	1981

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

Method : Juvenile rainbow trout, Onchorynchus mykiss (mean body length 53 mm; mean body weight 1.27 g), were exposed to nominal levels of 100,180, 320, 580 and 1000 mg 1,2,4-triazole/L in a static system for 96 hours. Dechlorinated tap water was used to prepare the test solutions. The test incorporated two replicate tanks of five fish for each exposure concentration and for the untreated water control. Mortalities and symptoms of toxicity were recorded at intervals of 24 hours throughout the test up to 98 hours. Dissolved oxygen, temperature, pH were recorded during the study and the concentrations of 1,2,4-triazole in the test systems were determined by gas chromatography (GC) at 0 and 96 hours.

The LC50 values were calculated according to Spearman-Kaerber, 524-530 in D.J. Finney London (1964).
LC50 (96 hr) was also graphically determined on gausso-logarithmic probability paper.

Remark : The LCso values that were presented in this study report were based on nominal concentrations. However, as some measured concentrations were <80% of nominal, LCso values were re-calculated based on mean measured values (Powley, 2003).

LC50 (mg/L) based on nominal concentrations:
24 hr > 1000
48 hr = 800
72 hr = 760
96 hr = 760

LC50 (mg/L) based on mean measured concentrations (confidence intervals p <= 0.05):
24 hr > 657
48 hr = 528 (n.d.)
72 hr = 498 (378 - 657)
96 hr = 498 (378 - 657)

Based on mean measured concentrations, the 96-hr LC50 for 1,2,4-triazole in rainbow trout was 498 mg/L.

From: Syngenta () 1,2,4-triazole Document M-II, Section 6 Ecotoxicological Studies. Document BASF DocID 2003/1023473.

Result :

Nominal Conc. (mg/L)	Mean Measured (mg/L)
Water	---
100	52
180	132
320	192
580	378
1000	657

Over the test period water temperature was maintained at 15°C, pH ranged between 7.6-8.1 and dissolved oxygen concentrations ranged between 8.2-10.1 mg/L. The test concentrations of 1,2,4-triazole, ranged from 55 to 86% of nominal at study start and from 52 to 73% of nominal in the samples taken after 96 hours. Over the exposure period, abnormal swimming behaviour and loss of equilibrium was observed in fish exposed to 100, 320 and 580 mg 1,2,4-triazole/L and there were slight effects on pigmentation in the 580 mg/L treatment group.

Conc. (mg/L)	Mortality 24h	48h	72h	96h

Control0	0	0	0	
100	0	0	0	0
180	0	0	0	0
320	0	0	0	0
580	0	0	0	0
1000	0	9	10	10

LC50 values calculated:
96-hr: 760 mg/L (confidence limit: none)
72-hr: 760 mg/L (confidence limit: none)
48-hr: 800 mg/L (confidence limit: 800-810 mg/L)
24-hr: > 1000 mg/L

LC50 values graphically determined
96-hr: 760 mg/L

LC0 (96 hr) = 580 mg/L
LC100 (96 hr) = 1000 mg/L
Controls: Moralities blank (0%)

Test substance : Technical 1,2,4-triazole 91.9% content, Batch No. EN38530.
Reliability : (2) valid with restrictions
Guideline study, but not GLP.

14.10.2008 (15)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
EC50 : > 100
Limit Test : yes
Analytical monitoring : yes
Method : OECD Guide-line 202
Year : 1995
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : Also conducted in accordance with EEC Methods for Determination of Ecotoxicity Annex to Directive 92/69/EEC (OJ. No. L383A, 29.12.92) Part C, Method 2 "Acute toxicity to Daphnia".

Based on the results of a range-finding test, Daphnia were exposed to a single concentration of 1,2,4-triazole nominally 100 mg/1 in a limit test. Samples of test solutions were taken for analysis at the start and end of the study to verify exposure concentrations. The test solution was prepared by direct dispersion of the 1,2,4-triazole in dilution water (100 mg of test compound were added to 1 liter of diluent). No auxiliary solvents were used. After 24 and 48 hours exposure the number of mobile and immobile daphnids were recorded. Daphnia were considered to be immobilized if they were unable to swim for approximately 15 seconds after gentle agitation.
The temperature in each vessel was measured daily and the pH and dissolved oxygen levels recorded at the start and at the end of the study. The study was conducted in a constant environment room at 20 ± 2°C under a photoperiod of 16 hours light, 8 hours dark without supplementary aeration or feeding. The test concentration was verified by chemical analysis.

Result : Oxygen concentration remained at or above 7.7 mgO2/l equivalent to >60% saturation throughout the study. Temperature and pH did not vary

significantly across the treatments. Measured concentrations ranged from 94% of nominal at 0 hours to 102% of nominal at 48 hours with a mean measured concentration of 98 mg/1 indicating the test concentration was achieved and adequately maintained over the 48 hour exposure period.

No immobilization of daphnids was recorded after 24 and 48 hours exposure and the following values were therefore determined based on nominal concentrations.

Time (hr)	EC50 (mg/L)
24	>100
48	> 100

NOEC (immobilisation) > 100 mg/L
LOEC (immobilization) >100 mg/L

Test substance : Purity = 100.8%
Conclusion : Based on these results 1,2,4-triazole can be classified as being of low toxicity to Daphnia magna.
Reliability : (1) valid without restriction
Guideline study; GLP
Flag : Critical study for SIDS endpoint
13.10.2008 (19)

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 24 hour(s)
Unit : mg/l
EC50 : = 900
Analytical monitoring : no
Method : OECD Guide-line 202
Year : 1983
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Young daphnia (< 24 hours old) were exposed to test concentrations of 100, 180, 320, 580, and 1000 mg/L (nominal). Twenty daphnia were exposed per concentration and control (4 replicated of 5 daphnia). The test substance appeared dissolved at all test concentrations. Samples for analysis were taken at 0 and 24 hours exposure.

Temperature: 20 +/- 1 deg C
Lighting: Fluorescent light, 16 hours daily
pH, O2 and temperature were measured at the beginning and at the end of the test.

The EC50-value was calculated according to J.BERKSON, JASA 49, (1953),569-599 EC50 (24 hours) was graphically determined on gausso-logarithmic probability paper.

Result : Immobilized Daphnia

Nominal Conc. (mg/L)	after 24 hours (immob/total)	%
Control	0/20	0
100	2/20	5
180	2/20	5
320	0/20	0
580	6/20	30
1000	11/20	55

pH: (7.9-8.4 at 0 hours) (8.1-8.3 at 24 hours)
O2: (8.6-8.7 at 0 hours) (8.2-8.4 at 24 hours)

Temp: (22 at 0 hours) (23 at 24 hours)

24-hr EC50 = 900 mg/L (95% conf. limit = 730 - 2200 mg/L)
24-hr EC50 (determined graphically) = 800 mg/L
24-hr EC100 > 1000 mg/L
24-hr EC0 = 320 mg/L

Test substance : Technical 1,2,4-triazole 91.9% content, Batch No. EN38530.
Reliability : (3) invalid
Not consistent with today's standard methods.

27.06.2008 (17)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : Selenastrum capricornutum (Algae)
Endpoint : other: cell density (most sensitive endpoint), growth rate and biomass
Exposure period : 96 hour(s)
Unit : mg/l
72 hr EC50 : = 12
Limit test :
Analytical monitoring : yes
Method : OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year : 2001
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : Also conducted in accordance with:
EU Directive 92/69/EEC, Method C.3.
U.S. EPA OPPTS Number 850.5400

The freshwater green alga, Selenastrum capricornutum (now known as Pseudokirchneriella subcapitata), was exposed to a geometric series of five test concentrations and a negative (culture medium) control under static conditions for 96 hours. Three "biological" replicate test chambers were maintained in each treatment and control group. One additional "analytical" replicate was maintained in each control and treatment group to provide test solution for verification of test concentrations at 72 hours. One additional abiotic replicate at the highest test concentration was included in the experimental design for concentration verification at 72 and 96 hours. This replicate was used to monitor the effects of the experimental conditions on the stability of the test substance over the exposure period. Nominal test concentrations were selected based upon exploratory range-finding data. Nominal test concentrations selected were 1.9, 3.8, 7.5, 15 and 30 mg active ingredient (a.i.)/L. Mean measured concentrations were determined from samples of test medium collected from each treatment and control group at the beginning and end of the test.

At test initiation an inoculum of algal cells was added to each test chamber to achieve a nominal concentration of approximately 10,000 cells/ml. Samples were collected from each "biological" test chamber at approximately 24-hour intervals during the test to determine cell densities, which were subsequently used to calculate areas under the growth curve and growth rates. Cell densities, areas under the growth curve (biomass) and growth rates were used to calculate percent inhibition values relative to the control over the 96-hour exposure period. EC50, EbC50 and E,C50 values were calculated, when possible, based upon cell density, biomass and growth rate, respectively, for each 24-hour interval of the exposure period. No-observed-adverse-effect-concentrations (NOAEC) were determined at 72 and 96 hours through statistical evaluation of the cell densities, biomass and growth rates, as well as examination of the concentration-response pattern.

Result : Test concentrations:

Nominal	Mean Measured	%nominal
Negative control	<LOQ	--
1.9 mg a.i./L	1.7 mg a.i./L	89
3.8 mg a.i./L	3.1 mg a.i./L	82
7.5 mg a.i./L	6.8 mg a.i./L	91
15 mg a.i./L	14 mg a.i./L	93
30 mg a.i./L	31 mg a.i./L	103

Temperatures ranged from 22.0 to 24.3°C and were within the 23 ± 2°C range established for the test. The test solution pH was 8.0 for all treatment and control groups at 0 hours and ranged from 8.1 to 9.7 at 96 hours. The pH of the abiotic replicate at test termination was 8.0. The pH tended to increase relative to algal population, which was typical for tests conducted with this green algae. The light intensity ranged from 5880 to 7140 lux, which was within the desired range of 6500 lux +/- 10%.

	EC50 (mg a.i./L)	95% C.I. (mg a.i./L)	NOAEC (mg a.i./L)
Cell density			
72-hr	12	9.9-14	3.1
96-hr	18	16-19	6.8
Biomass			
72-hr	13	11-15	3.1
96-hr	14	13-16	3.1
Growth rate			
72-hr	>31	NC*	3.1
96-hr	>31	NC*	6.8

Where NC = Not Calculable

Test substance : Purity = 99%

Conclusion : The conclusions of this study were based on the most sensitive endpoint measured at 72 and 96 hours (i.e., cell density, biomass and/or growth rate). The 72-hour EC50, based on cell density, for Selenastrum capricornutum exposed to 1,2,4-triazole was 12 mg a.i./L, with a 95% confidence interval of 9.9 to 14 mg a.i./L. The 96-hour EC50, based on biomass, was 14 mg a.i./L, with a 95% confidence interval of 13 to 16 mg a.i./L. The 72-hour NOAEC was 3.1 mg a.i./L, based on cell density, biomass and growth rate: The 96-hour NOAEC was 3.1 mg a.i./L based on biomass, and was 6.8 mg a.i./L based on cell density and growth rate.

Reliability : (1) valid without restriction
Guideline study; GLP

Flag : Critical study for SIDS endpoint

13.10.2008 (34)

Species : Scenedesmus subspicatus (Algae)
Endpoint : growth rate
Exposure period : 5 day(s)
Unit : mg/l
EC0 : = .5
EC50 : = 6.3
EC100 : > 40.5
Limit test :
Analytical monitoring : no
Method : other
Year : 1982
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Test system: Scenedesmus subspicatus

Inoculum: 1.0 x 10^5 cells/ml

Exposure:
Water: composition according to AFNOR T 90-304
Light: 16 hours light, 8 hours darkness approx. 4000 LUX cold white fluorescent light
Temp: 24 +/- 2 deg C
Duration: 5 days (120 hours)
Measurement: counting of cells on TOA cell counter
Test concentrations (nominal): 0.5, 1.5, 4.5, 13.5, and 40.5 mg/L
Calculated amounts of stock solution to produce the desired test concentration were mixed with water in the test flasks. Samples for analysis were taken at 0 and 120 hours exposure.
Reference substance: Potassium bichromate at 1.0, 1.5, 2.3, and 3.4 mg/L
Each test concentration and control was tested in 4 replicates.

Result : All results are based on nominal concentrations:

The growth control showed a multiplication factor of 210.

% Inhibition cell growth observed:

Test substance	% Inhibition
0.5 mg/L	0
1.5	14
4.5	38
13.5	75
40.5	93

Potassium bichromate:

1.0	38
1.5	71
2.3	98
3.4	> 100

Test material:
EC50 (5 day) calculated = 6.3 mg/L
95% conf. limit = 5.5 - 7.1 mg/L

Test substance : 1,2,4-Triazol; purity 91.9%
Reliability : (2) valid with restrictions
Comparable to a guideline study, but not GLP.

14.10.2008 (16)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

Species : Oncorhynchus mykiss (Fish, fresh water)
Endpoint : other: growth rate
Exposure period : 28 day(s)
Unit : mg/l
NOEC : = 100
Analytical monitoring : yes
Method : other: OECD 215
Year : 2002
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : Rainbow trout, Oncorhynchus mykiss (mean body length 6.1cm, mean body weight 2.4 g) were exposed to nominal concentrations of 1, 3.2, 10,

32 and 100 mg 1,2,4-triazole/L in a static renewal system for 28 days. The test incorporated five replicate tanks containing ten fish for each exposure concentration and two replicate control tanks in which ten fish were exposed to untreated test water only. Test solutions were changed weekly and water samples were collected on days 0, 7, 14, 21 and 28 for determination of 1,2,4-triazole concentrations. Temperature in the test systems was measured three times a week and recorded hourly in one of the control systems. pH and dissolved oxygen were recorded weekly during the study. Fish were examined on weekdays for mortality and symptoms of toxicity. Fish were weighed on days 0 and 28 to provide specific growth rates (r) for each individual. Growth rate data from the pooled controls were used to estimate significant differences between the treatment groups.

Result : The hardness and conductivity of dilution water were 40-60 CaCOs mg/L and <0.2 uS/cm, respectively. Water temperature, pH and dissolved oxygen concentrations ranged between 10.8-12.8°C, 7.2-7.4 and 90-103% oxygen saturation, respectively, over the test duration. The mean measured concentrations of 1,2,4-triazole ranged from 97 to 99% of nominal values over the test duration. There were no findings of 1,2,3-triazole in the controls with a detection level of 0.096 mg/L.

Effect of 1,2,4-triazole on mean weight and growth rate:

Nominal Conc. (mg/L)	Day 0 weight (g)	Day 28 weight (g)	Growth rate 28 days
Control 1	2.43	4.47	1.027
Control 2	2.51	4.54	0.919
Pooled Controls	2.47	4.64	0.973
1.00	2.44	4.72	1.022
3.20	2.59	4.77	0.936
10.0	2.54	4.62	0.930
32.0	2.53	4.78	0.982
100.0	2.48	4.91	1.053

There were no mortalities in control fish and only one escape-related mortality in the 1 mg/L treatment on day 9. Assuming a daily feeding rate of 3%, the mean 28-day body weight of pooled control fish was 188% of initial weight. Exposure to 1,2,3-triazole did not have a significant effect on day 28 body weight or growth rates (r) relative to pooled control fish in the period of 0-28 days. At concentrations of >10mg/L, 50% of fish were inactive or displayed abnormally low activity and labored respiration. These symptoms did not influence the growth rate of the fish.

Test substance : Technical 1,2,4-triazole, purity 99.9%

Conclusion : Based on nominal concentrations and growth rate calculations, the 28-day NOErC for 1,2,4-triazole in rainbow trout is 100 mg/L, the highest concentration tested.

Reliability : (1) valid without restriction
Guideline study; GLP

Flag : Critical study for SIDS endpoint

13.10.2008 (6)

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	:	= 1648 - 1650 mg/kg bw
Species	:	rat
Strain	:	Wistar
Sex	:	male/female
Number of animals	:	284
Vehicle	:	other: emulsion made with distilled water and Cremophor EL
Doses	:	100, 250, 500, 1000, 1250, 1500, 1750, 1850, 2000, and 2500 mg/kg bw
Method	:	EPA OPP 81-1
Year	:	1982
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method : Conducted in accordance with EPA FIFRA, Subdivision F, §81-1 (equivalentto 92/69 B.I)

1,2,4-triazole was emulsified in distilled water and Cremophor EL. This emulsion was given to male and female Wistar rats by stomach tube such that the animals received 1 ml of emulsion/100 g of body weight. The post-treatment observation period was 14 days. Gross necropsy was performed at study termination.

The calculation of the mean lethal dose (LD50) was carried out using probit analysis (Fink, H. et al., Methods of information in medicine 5, 19, 1966).

Result : The animals exhibited the following toxicity signs: reduction in general well-being, accompanied by sedation and breathing disorders. At higher doses, the animals were lying in the abdominal or side position. The symptoms appeared within an hour of administration and were observed for a maximum of up to 13 days after administration.
Gross pathology examination of the animals revealed no major changes.

Dose (mg/kg)	Result*	Day of death
Males		
250	0/0/15	--
500	0/15/15	--
1000	0/30/30	--
1250	1/15/15	1d
1500	3/15/15	1d
1750	10/15/15	1h - 1d
1850	12/15/15	2h - 7d
2500	14/14/14	1 - 6d
Females:		
100	0/15/15	--
250	0/15/15	--
500	0/15/15	--
1000	0/15/15	--
1250	1/15/15	4h
1500	3/15/15	4h - 1d
1750	9/15/15	1-12d
2000	28/30/30	1 - 9d
2500	15/15/15	3h - 3d

* = number of dead animals/number of animals with symptoms/ number of animals used

Male 14-day LD50 (C.L.) = 1650 mg/kg (1547 - 1744)
Female 14-day LD50 (C.L.) = 1648 mg/kg (1547 - 1737)

Test substance : The test sample was a technically pure substance.
Reliability : (2) valid with restrictions
Guideline study, but not GLP.
Flag : Critical study for SIDS endpoint
30.06.2008 (7) (24)

Type : LD50
Value : > 500 - 5000 mg/kg bw
Species : rat
Strain : Wistar
Sex : male
Number of animals : 6
Vehicle : other: 0.5% methylcellulose
Doses : 0.5 and 5 g/kg bw
Method : EPA OPP 81-1
Year : 1981
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : GLP: Yes (self certification of laboratory)

Conducted in accordance with EPA FIFRA, Subdivision F, §81-1 (equivalent to 92/69 B.I)

1,2,4-triazole was dispersed in 0.5% methylcellulose using a tissue homogenizer and administered as a single gavage dose to two groups of three male rats at doses of 0.5 (2.5 ml/kg) or 5.0 g/kg (25 ml/kg). Animals were observed for mortality and signs of toxicity for 14 days post-dosing. Initial and final body weights were recorded. At study termination necropsies were conducted on all animals.

Remark : Study was conducted in 1981.

GLP: Yes (self-certification of laboratory)

The studies described in this Final Report were conducted in the spirit of the Good Laboratory Practice Standards (1983) of the Pesticide Programs (40 CFR Part 160), the Toxic Substance Control Act (40 CFR Part 792), and Japanese Guidelines 59 NohSan No. 3850 (August 10, 1984), except that the test substance was not analytically characterized prior to initiation of the study, and the concentration of the test substance in any vehicle was not analytically verified. In lieu of analysis, the dose preparations were conducted by experienced researchers and the weights of the dosing components are fully documented. To the best of my knowledge, there were no other deviations from the aforementioned regulations which affected the quality or integrity of the study.

Range-finding studies are preliminary investigations designed to estimate toxicity and/or irritation or to provide information needed for dose selection for subsequent studies. Such data should be considered approximations only, and further extrapolation is not recommended. When screening data are reported, they should be identified as range finding and, if appropriate, an explanatory note such as this should be included. Be aware that these range-finding studies will, in general, not meet regulatory guidelines for numbers of animals per group, inclusion of both sexes of animals, or number of dose levels used.

Result : All rats died in the 5.0 g/kg group within ten minutes after dosing. No test-

substance related clinical signs were observed at 5.0 g/kg prior to death. No deaths occurred and no clinical signs were observed in the 0.5 g/kg group. There were no apparent body weight effects in survivors. Necropsy of decedents (5.0 g/kg) revealed reddened duodenum and reddened glandular portion of stomach. Survivors necropsied at the end of the two week observation period (0.5 g/kg) exhibited no visible lesions.

Test substance : The test substance was a pale brown solid containing 92.8% of the active ingredient 1,2,4-triazole.

Conclusion : 1,2,4-triazole is categorized as SLIGHTLY TOXIC according to Rohm and Haas Company criteria by ingestion of a single dose (i.e. LD50 is between 0.5 and 5.0 g/kg in male rats).

Reliability : (1) valid without restriction
Guideline study; GLP

13.10.2008 (24) (28)

Type : LD50
Value : = 1375 mg/kg bw
Species : rat
Strain : no data
Sex : male
Number of animals : 80
Vehicle : other: distilled water
Doses : 850, 1000, 1200, 1400, 1500, 1750, 2000, and 2500 mg/kg
Method : other
Year : 1978
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : The test material was dissolved in distilled water and administered by oral gavage to male rats (10/dose level) at doses of 850, 1000, 1200, 1400, 1500, 1750, 2000, and 2500 mg/kg. There was a 14 day post exposure observation period.

Result :

850	mg/kg	8.5%	0/10/10
1000	mg/kg	10%	0/10/10
1200	mg/kg	12%	2/10/10
1400	mg/kg	14%	5/10/10
1500	mg/kg	15%	8/10/10
1750	mg/kg	17.5%	9/10/10
2000	mg/kg	20%	10/10/10
2500	mg/kg	25%	10/10/10

LD50 = 1375 (1273-1485) mg/kg

Test substance : 1,2,4-Triazol, batch 16001/78, Eg. 1/78

Reliability : (4) not assignable
Insufficient details to determine reliability.

13.10.2008 (13)

5.1.2 ACUTE INHALATION TOXICITY

Type : LC50
Value :
Species : other: rats and mice
Strain : other: Wistar male rats and NMRI female mice
Sex :
Number of animals : 15
Vehicle :
Doses :
Exposure time :
Method : other
Year : 1982

GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	The inhalation experiments were carried out in a 10 liter inhalation chamber. The chamber contained 5 male Wistar rats and 10 female NMRI mice. The periods of inhalation amounted to 4 hours and 6 hours. The post-treatment observation period was 14 days. Air was passed at 2 liters per minute through 1,2,4-triazole contained in a dust tower. The resulting air, enriched with vapour and dust, was administered to the animals for inhalation.
Result	:	No substance vaporized or atomized in the 4 and 6-hr experiments. Rats and mice tolerated the 4 and 6-hr, inhalation periods without signs. Nor was any irritant effect on the mucous membrane of the eyes and noses of the animals observed.
Test substance	:	The test sample was a technically pure substance.
Reliability	:	(3) invalid Not consistent with today's standard methods (Particle size and analytical concentration were not determined).

27.06.2008 (7)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	= 3129 - 4200 mg/kg bw
Species	:	rat
Strain	:	Wistar
Sex	:	male/female
Number of animals	:	100
Vehicle	:	other: a few drops of Cremophor EL
Doses	:	1000, 2000, 2500, 3500, 4000, and 5000 mg/kg bw
Method	:	EPA OPP 81-2
Year	:	1982
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Conducted in accordance with EPA FIFRA, Subdivision F, 81-2 (equivalent to 92/69/EEC B.3) The studies were carried out on male and female Wistar rats using the occlusive dressing method (NOAKES, D.N., D.M. Sanderson, Brith. J. Ind. Med. 26, 59, 1969). 1,2,4-triazole was applied to the dorsal skin, which was shaven the day before. The substance was weighed out separately for each animal and moistened with a few drops of Cremophor EL so that it could be applied to the skin of the animals. The substance was left on for 24 hours, and was then washed off with water and soap. The post-treatment observation period lasted 14 days. The calculation of the mean lethal dose (LD50) was carried out using probit analysis (Fink, H. et al., Methods of information in medicine 5, 19, 1966).
Result	:	The animals exhibited the following toxicity signs: reduction in general well-being, accompanied by sedation and breathing disorders. At higher doses, the animals were lying in the abdominal or side position. The symptoms appeared within an hour of administration and were observed for a maximum of up to 13 days after administration. Gross pathology examination of the animals revealed no major changes.

Dose (mg/kg)	Result*	Day of death
Males		
1000	0/5/5	--

2500	2/10/10	3-4d
3500	4/10/10	1-3d
5000	6/10/10	2-4d

Females:

1000	0/5/5	--
2000	0/10/10	--
2500	3/10/10	4-9d
3500	6/10/10	2-9d
4000	6/10/10	1-3d
5000	18/20/20	1-4d

* = number of dead animals/number of animals with symptoms/ number of animals used

Male 14-day LD50 (C.L.) = 4200 mg/kg (3081-5725)
Female 14-day LD50 (C.L.) = 3129 mg/kg (2203 - 3648)

Test substance : The test sample was a technically pure substance.
Reliability : (2) valid with restrictions
Guideline study, but not GLP.
Flag : Critical study for SIDS endpoint
13.10.2008 (7) (24)

Type : LD50
Value : > 200 - 2000 mg/kg bw
Species : rat
Strain : New Zealand white
Sex : male
Number of animals : 6
Vehicle : physiol. saline
Doses : .2, 2 and 5 g/kg bw
Method : EPA OPP 81-2
Year : 1981
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : GLP: Yes (self certification of the laboratory)

Conducted in accordance with EPA FIFRA, Subdivision F, 81-2 (equivalent to 92/69/EEC B.3)

1,2,4-triazole was ground in a mortar with a pestle and moistened (1:1 w/v) with saline. 1,2,4-triazole was applied as a single dermal dose at 0.2, 2.0, or 5.0 g/kg to the closely shaved intact skin of two male rabbits per dose level. Each application site was covered with an impervious cuff for a period of 24 hr. After 24 hr, the cuff was removed and the application site wiped with paper towels. Skin irritation was evaluated according to the criteria of Draize et al. (J. Pharmacol. Exp. Therap. 82:377-391, 1944) on days 1 through 14. Animals were observed for mortality and signs of toxicity for 14 days post-dosing. Initial and final body weights were recorded. At study termination necropsies were conducted on all animals.

Remark : Study was conducted in 1981.

The studies described in this Final Report were conducted in the spirit of the Good Laboratory Practice Standards (1983) of the Pesticide Programs (40 CFR Part 160), the Toxic Substance Control Act (40 CFR Part 792), and Japanese Guidelines 59 NohSan No. 3850 (August 10, 1984), except that the test substance was not analytically characterized prior to initiation of the study, and the concentration of the test substance in any vehicle was not analytically verified. In lieu of analysis, the dose preparations were conducted by experienced researchers and the weights of the dosing components are fully documented. To the best of my

knowledge, there were no other deviations from the aforementioned regulations which affected the quality or integrity of the study.

Range-finding studies are preliminary investigations designed to estimate toxicity and/or irritation or to provide information needed for dose selection for subsequent studies. Such data should be considered approximations only, and further extrapolation is not recommended. When screening data are reported, they should be identified as range finding and, if appropriate, an explanatory note such as this should be included. Be aware that these range-finding studies will, in general, not meet regulatory guidelines for numbers of animals per group, inclusion of both sexes of animals, or number of dose levels used.

Result : In the 5.0 and 2.0 g/kg groups, both rabbits in each dose group died by day 4 of the study. The following clinical signs related to the test substance were observed in the 2.0 and/or 5.0 g/kg groups: abdominal breathing, ataxia, clear nasal discharge, gasping, iritis, moribundity, salivation, scant droppings, soft feces, tremors, and yellow nasal discharge. In the 0.2 g/kg group, no deaths occurred and no clinical signs were observed during the study. There were no apparent body weight effects in the survivors. Decedents in the 2.0 and 5.0 g/kg group exhibited numerous gross findings related to the test substance. Necropsy of survivors in the 0.2 g/kg group revealed no visible lesions. No erythema to well-defined erythema and no edema to very slight edema were observed during the study.

Test substance : The test substance was a pale brown solid containing 92.8% of the active ingredient 1,2,4-triazole.

Conclusion : Based on these results 1,2,4-triazole is categorized as MODERATELY TOXIC according to Rohm and Haas Company criteria following acute dermal exposure (i.e., the dermal LD50 is between 0.2 and 2.0 g/kg in male rabbits).

Reliability : (1) valid without restriction
Guideline study; GLP

13.10.2008 (24) (28)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species : rabbit
Concentration : undiluted
Exposure : Occlusive
Exposure time : 24 hour(s)
Number of animals : 2
Vehicle :
PDII :
Result : not irritating
Classification :
Method : EPA OPP 81-5
Year : 1982
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Conducted in accordance with EPA FIFRA, Subdivision F, 81-5 (equivalent to 92/69/EEC B.4)

Small cellulose patches, 1.5 cm x 1.5 cm, to which 500 mg of 1,2,4-triazole had been applied, were attached for 24 hours to the hairless skin of the ears of each of 2 New Zealand white rabbits using an adhesive dressing.

Result : The treated parts of the skin revealed no changes following removal of the

dressing or during the 7-day post-treatment observation period.

Test substance : The test sample was a technically pure substance.

Reliability : (3) invalid
Not consistent with today's standard methods (rabbit ears were used for testing instead of trunk skin).

27.06.2008 (7) (24)

Species : rabbit
Concentration : .5 g
Exposure : Occlusive
Exposure time : 24 hour(s)
Number of animals : 2
Vehicle : other: saline
PDII :
Result : slightly irritating
Classification :
Method : EPA OPP 81-5
Year : 1981
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : Yes (self certification of the laboratory)

Conducted in accordance with EPA FIFRA, Subdivision F, 81-5 (equivalent to 92/69/EEC B.4)

1,2,4-triazole, 0.5 g, was ground in a mortar with a pestle, moistened (1:1 w/v) with saline and applied under two 2.0-in square gauze lined patches to the closely shaved skin of two male rabbits. Each rabbit received one patch on the intact skin and a second patch on abraded skin. Both application sites were covered with an impervious cuff for a period of 24 hr. After 24 hr, the cuff was removed and the application sites on each rabbit were wiped with paper towels. Skin irritation was evaluated according to the criteria of Draize et al. (J. Pharmacol. Exp. Therap. 12, 377-391, 1944) at 24, 72 hrs and at 7 days after patch removal.

Remark : Study was conducted in 1981.

The studies described in this Final Report were conducted in the spirit of the Good Laboratory Practice Standards (1983) of the Pesticide Programs (40 CFR Part 160), the Toxic Substance Control Act (40 CFR Part 792), and Japanese Guidelines 59 NohSan No. 3850 (August 10, 1984), except that the test substance was not analytically characterized prior to initiation of the study, and the concentration of the test substance in any vehicle was not analytically verified. In lieu of analysis, the dose preparations were conducted by experienced researchers and the weights of the dosing components are fully documented. To the best of my knowledge, there were no other deviations from the aforementioned regulations which affected the quality or integrity of the study.

Range-finding studies are preliminary investigations designed to estimate toxicity and/or irritation or to provide information needed for dose selection for subsequent studies. Such data should be considered approximations only, and further extrapolation is not recommended. When screening data are reported, they should be identified as range finding and, if appropriate, an explanatory note such as this should be included. Be aware that these range-finding studies will, in general, not meet regulatory guidelines for numbers of animals per group, inclusion of both sexes of animals, or number of dose levels used.

Result : Mean intact skin irritation scores according to the Draize scheme:
Mean score (24-72 h):
Erythema = 0.5
Edema = 0.0

In the intact skin, one application site exhibited moderate erythema at 24 hr. No edema and no other erythema were observed during the study. In the abraded skins, very slight erythema was observed on two application sites at 24 hr and on one application site at 72 hr. No other erythema and no edema were observed during the study. The Primary Irritation Score (PIS), average of 24 and 72 hr scores, was 0.25 in the intact skins and 0.38 in the abraded skins.

Test substance : The test substance was a pale brown solid containing 92.8% of the active ingredient 1,2,4-triazole.

Conclusion : These range-finding results indicate that 1,2,4-triazole is categorized as SLIGHTLY IRRITATING to the skin (i.e., the Primary Skin Index is between 0 and 2.0 in rabbits). According to EEC classification criteria 1,2,4-triazole does not require a "Xi" label symbol or a "R-38" risk phase (i.e., the mean erythema or edema score is less than 2.0).

Reliability : (3) invalid
Not consistent with today's standard methods (used 24 hour exposure period).

27.06.2008 (24) (28)

Species : human
Concentration : undiluted
Exposure : Occlusive
Exposure time : 8 hour(s)
Number of animals : 5
Vehicle :
PDII :
Result : not irritating
Classification :
Method : other
Year : 1982
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Conducted in accordance with EPA FIFPvA, Subdivision F, 81-5 (equivalent to 92/69/EEC B.4)

1,2,4-triazole was applied to the skin of the forearm of humans, using adhesive dressings. In the preliminary study, the exposure period was 2 hours and 4 hours, and in the main study 8 hours. The substance was washed off afterwards with soap and water. The post-treatment observation period lasted 7 days. In the preliminary study there was one female person for each period of exposure. The 8-hr exposure test was conducted using 5 men.

Result : Both in the preliminary study and in the main study, the treated parts of the skin proved to be physiologically normal following removal of the dressing and during the 7-day post-treatment observation period. 1,2,4-triazole thus has no irritant effect on the skin.

Test substance : The test sample was a technically pure substance.

Reliability : (3) invalid
Not consistent with today's standard methods.

27.06.2008 (7)

5.2.2 EYE IRRITATION

Species : rabbit
Concentration : undiluted
Dose : 50 other: mg
Exposure time :
Comment : not rinsed

Number of animals	:	2
Vehicle	:	
Result	:	highly irritating
Classification	:	
Method	:	EPA OPP 81-4
Year	:	1982
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Conducted in accordance with EPA FIFRA, Subdivision F, 81-4 (equivalent to 92/69/EEC B.5) 1,2,4-triazole was instilled into the conjunctival sac of the left eye of each of two rabbits at a dose of 50 mg/animal.
Result	:	One hour after application, intense reddening and a very intense swelling of the conjunctivae of the treated eyes had developed. Intense reddening and moderate swelling of the conjunctivae could still be observed 24 hours after application. In one animal there was still a slight redness and swelling of the conjunctivae 5 days after application. In the other animal, the conjunctivae were normal. The conjunctivae of both animals were normal 7 days after application. During the first and second days after application, a slight, dispersed, diffuse opacity of the cornea was observed. The iris was slightly reddened and swollen. 1,2,4-triazole thus has a severe irritant effect on the mucous membrane.
Test substance	:	The test sample was a technically pure substance.
Reliability	:	(2) valid with restrictions Although irritation scores were not recorded at 24, 48 and 72 hours, the level of eye irritation was noted; not GLP.

14.10.2008 (7) (24)

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.1 other: g
Exposure time	:	
Comment	:	not rinsed
Number of animals	:	2
Vehicle	:	
Result	:	moderately irritating
Classification	:	
Method	:	EPA OPP 81-4
Year	:	1981
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	GLP: Yes (self certification of the laboratory) Also conducted in accordance with EPA FIFRA, Subdivision F, 81-4 (equivalent to 92/69/EEC B.5) 1,2,4-triazole, 0.1 g, was ground in a mortar with a pestle and applied into the conjunctival sac of the left eye of two male rabbits. The lower eyelid was held open momentarily after the eye was treated and then released to allow the animal to blink freely. Eye irritation was evaluated according to the criteria of Draize et al. (J. Pharmacol. Exp. Therap. 12, 377-391, 1944) at 4, 24, 48, 72 and 96 hr and at 7 and 14 days.
Remark	:	Study was conducted in 1981. The studies described in this Final Report were conducted in the spirit of the Good Laboratory Practice Standards (1983) of the Pesticide Programs (40 CFR Part 160), the Toxic Substance Control Act (40 CFR Part 792), and Japanese Guidelines 59 NohSan No. 3850 (August 10, 1984), except

that the test substance was not analytically characterized prior to initiation of the study, and the concentration of the test substance in any vehicle was not analytically verified. In lieu of analysis, the dose preparations were conducted by experienced researchers and the weights of the dosing components are fully documented. To the best of my knowledge, there were no other deviations from the aforementioned regulations which affected the quality or integrity of the study.

Range-finding studies are preliminary investigations designed to estimate toxicity and/or irritation or to provide information needed for dose selection for subsequent studies. Such data should be considered approximations only, and further extrapolation is not recommended. When screening data are reported, they should be identified as range finding and, if appropriate, an explanatory note such as this should be included. Be aware that these range-finding studies will, in general, not meet regulatory guidelines for numbers of animals per group, inclusion of both sexes of animals, or number of dose levels used.

Result : Mean Score for the two animals tested (24-72 h):
Corneal opacity: 1.7
Iris lesions: 0.8
Conjunctival redness: 2.0
Conjunctival chemosis: 1.8

Corneal, iridal and conjunctival effects were observed at 4 hours. Corneal and conjunctival effects were no longer evident on day 7; iridal effects were no longer evident on day 14. These range-finding results indicate that 1,2,4-triazole is categorized as no more than SUBSTANTIALLY IRRITATING (i.e., ocular effects were reversible within 21 days but not 7 days).

Test substance : The test substance was a pale brown solid containing 92.8% of the active ingredient 1,2,4-triazole.

Conclusion : According to EEC classification criteria 1,2,4-triazole does not require a "Xi" label symbol or a "R-36" risk phase (i.e., the mean score for each of the ocular structures was less than values specified for each structure).

Reliability : (1) valid without restriction
Guideline study; GLP

14.10.2008 (24) (28)

5.3 SENSITIZATION

Type : Guinea pig maximization test
Species : guinea pig
Concentration : 1st: Induction 10 % intracutaneous
2nd: Induction 75 % semiocclusive
3rd: Challenge 75 % semiocclusive
Number of animals : 15
Vehicle : other
Result : not sensitizing
Classification : not sensitizing
Method : OECD Guide-line 406 "Skin Sensitization"
Year : 1998
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : Also conducted in accordance with:
EEC Directive 96/54, L 248, Annex IV C, Test B.6 (dated September 30, 1996)
EEC Directive 93/21, L 110 A, Annex IV (dated May 04, 1993)

Animals: 10 male Dunkin Hartley Crl (HA) guinea pigs in the test group, 5

male guinea pigs in the control group. The choices of doses for the main study were based on the results of a pilot study with 2 male guinea pigs: the intradermal injection of a 10% or 20% solution caused slight to moderate erythema in both animals during the 72-hour observation period, while dermal application of a 75: 25 mixture (w/w) of the test substance in vaseline caused no signs of skin irritation.

A 10% solution of the test article in water or in a 50:50 (v/v) mixture of water and Freund's complete adjuvant was selected for intradermal induction in the main study: The dermal induction and epidermal challenge in the main study was carried out with a 75:25 mixture (w/w) of the test substance in vaseline on days 7 and 21 of the investigation, respectively. The sensitivity and reliability of the experimental technique was demonstrated with benzocaine in April 1998 under the same experimental conditions (7 of 10 animals responded positive at 48 and 72 hours after the start of epidermal challenge).

Result : The test substance caused slight skin irritation with and without Freund's complete adjuvant after intradermal injection. No skin reaction was recorded after dermal induction. At 48 and 72 hours after the start of epidermal challenge (i.e. 24 and 48 hours after removal of the dressings) no signs of allergic skin reactions were noted in test or control animals.

Test substance : 1,2,4-triazole, purity > 98%

Conclusion : 1,2,4-triazole is not sensitising to the skin.

Reliability : (1) valid without restriction
Guideline study; GLP

13.10.2008 (24) (29)

5.4 REPEATED DOSE TOXICITY

Type : Sub-chronic
Species : rat
Sex : male/female
Strain : other: Wistar W.74 SPF
Route of admin. : oral feed
Exposure period : 90 days
Frequency of treatm. : daily
Post exposure period : none
Doses : 100, 500, and 2500 ppm
Control group : yes, concurrent vehicle
NOAEL : = 500 ppm
LOAEL : = 2500 ppm
Method : EPA OPP 82-1
Year : 1979
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : EPA-FIFRA, Subdivision F, § 82-1, OECD 409, 87/302/EEC (B.27Groups of 15 male and 15 female rats received 1,2,4-triazole for three months in the following concentrations in their food: 0 (control), 100, 500, and 2500 ppm. The animals were inspected daily, and a weekly record was kept of any alterations and signs occurring. The animals' body weights were recorded weekly. The weekly food consumption was determined by weighing the uneaten food. Clinical laboratory examinations were carried out one and three months after start of study on 5 males and 5 females in each case. The blood for the test for blood sugar was taken from the vena caudalis, for the measurement of the thromboplastin time by heart puncture, and from the retro-orbital venous plexus under ether anaesthesia for the remaining determinations (NOELLER's method, 1955). Urines were collected over a period of about 17 hours. During this period tap water was available to the animals ad libitum. The body temperatures were taken

rectally for all males and females in all the dose groups, one and three months after start of study. At study termination necropsies were conducted on all the animals. Body weights and organ weights of the thyroid, thymus, heart, lung, liver, spleen, kidneys, adrenals, testicles or ovaries were obtained. The following organ material was fixed in Bouin's fluid (transferred after approx. 30 hours to 70 % ethyl alcohol) from five males and five females from each group of the rats sacrificed at end of study: heart, lung, liver, spleen, kidney, pituitary, thyroid, adrenals, testicles, epididymes, prostate, seminal vesicle, ovaries, uterus, salivary glands, pancreas, esophagus, stomach, intestines, lymph nodes, thymus, urinary bladder, brain, eyes, aorta, trachea, skeletal musculature, bone and bone marrow (sternum). Extra liver specimens (lobus sinister) from all the animals were fixed with formol calcium for the fat demonstration. The organ material from the remaining animals was fixed in 10 % formaldehyde solution.

Statistical methods: The following were calculated: arithmetic group means, standard deviation s, upper and lower confidence limits on the confidence level of 1 - alpha = 95% and 1 - alpha = 99%. The comparison of the values of the test collective with the control collective was made by means of the significance test (U test) after Mann, Whitney and Wilcoxon, on the significance level of alpha = 5% and alpha = 1%.

Remark : 100, 500, or 2500 ppm = (males/females): 7.79/10.27 mg/kg bw, 37.85/54.20 mg/kg bw, or 212.30/266.69 mg/kg bw

Result : Appearance, behaviour, growth, food consumption and mortality were unaffected in the males and females with doses up to 500 ppm. Rectal body temperature was not affected by treatment. Food consumption was reduced at 2500 ppm during the first two weeks of treatment, but in overall terms food intake was similar in all groups. Body weight gains were reduced at 2500 ppm, leading to total weight gain deficits of 12% and 8% for males and females, respectively, relative to untreated controls. 2500 ppm produced temporary slight convulsions in two males and two females.

The blood was not affected by 1,2,4-triazole in the dose groups up to 500 ppm. There were statistically significant changes in red blood cell parameters (reduced hemoglobin, hematocrit, MCV and MCH) after 1 and 3 months in males at 2500 ppm that indicated a slight microcytic hypochromic anemia.

Clinical chemistry, gross pathology and histopathology did not detect any liver damage in the male and female rats receiving up to 500 ppm. After 2500 ppm slight to moderate fat accumulation in liver parenchyma cells was found in three of 15 males examined, and this is attributed to the treatment.

Urinalyses, clinical chemistry, autopsies and histopathology provided no indications of kidney damage in the dose groups up to 2500 ppm.

Blood sugar and cholesterol concentrations were within the normal range in the rats up to the dose group of 2500 ppm.

The test material did not affect functioning of the thyroid up to the dose of 2500 ppm.

There were deviations in absolute organ weights (thymus, heart, lung, spleen, testes) at 2500 ppm, particularly in males, that were attributed to lower terminal body weights.

Necropsies and histopathological examinations did not reveal any indications of treatment-induced organ alterations in the groups up to 2500 ppm, with the exception of the liver findings mentioned.

Test substance : The toxicological study was carried out with batch no. 16001/78 purity 99.6

%). A 90 % pre-mix with Ultrasil VN 3 (precipicated highly dispersed silicic acid, Degussa Co.) was used for the study. In order to compensate the degree of purity, 11 % of the pre-mix was added.

Conclusion : NOAEL: 500 ppm (equivalent to 37.9/54.2 mg/kg bw/day in males/females) based on retarded body weight development, temporary slight CNS effects, lower red blood cell parameters (males, only) and hepatocellular fat accumulation (males only) at 2500 ppm (equivalent to an average test substance intake of 212 and 267 mg/kg bw/day for males and females,

Reliability : (2) valid with restrictions
Guideline study, but not GLP. Diet analyses and ophthalmoscopy were not performed.

Flag : Critical study for SIDS endpoint

16.10.2008 (8) (24)

Type	:	Sub-chronic
Species	:	rat
Sex	:	male/female
Strain	:	other: Wistar Hanover rats (Crl:WI[Glx/BRL/Han] IGS BR)
Route of admin.	:	oral feed
Exposure period	:	90 days
Frequency of treatm.	:	daily
Post exposure period	:	none
Doses	:	250, 500, 3000 or 1000 for 4 weeks/4000 ppm thereafter
Control group	:	yes, concurrent vehicle
NOAEL	:	= 500 ppm
LOAEL	:	= 3000 ppm
Method	:	other: OECD Guideline No. 424 Neurotoxicity Study in Rodents
Year	:	2004
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Method : Also conducted in accordance with:
OPPTS Guideline No. 870.3100: 90-Day Oral Toxicity in Rodents
OECD Guideline No. 408 Subchronic Oral Toxicity - Rodent: 90-day Study
MAFF Guideline 59 NohSan No. 4200 Subchronic Oral Toxicity Study
OPPTS Guideline No. 870.6200: Neurotoxicity Screening Battery

All animals were approximately 8 weeks old when exposure to the chemical was initiated. To initiate the study, animals were randomly distributed into one of five dose groups consisting of 40 animals (20 males and 20 females at each dietary level, for a total of 200 animals). During the study, rats received the test substance for approximately 14 weeks, at nominal dietary concentrations of 0, 250, 500, 3,000 or 1,000/4,000 (1,000 ppm for four weeks and 4,000 ppm thereafter) ppm.

Doses were selected based on the toxicological profile that developed over the course of a 3-month-exposure study that was conducted with the test substance (Bomhard et al., 1979). Dose levels for the present study were set at 0, 250, 500, 1,000, and 3,000 ppm (1,000 ppm later increased to 4,000 ppm). It was anticipated that a low and high dose of 250 and 3,000 ppm would constitute a clear no-observed-effect level and a maximum tolerated dose (predictive goal of reaching a 10% decrement in body weight gain over the course of this 13-week study), respectively, with the intermediate dietary levels of 500 and 1,000 ppm serving to confirm any dose response relationships that may emerge.

The test substance was to be administered continuously in the feed at nominal dietary concentrations of 0, 250, 500, 3,000 or 1,000/4,000 ppm (1,000 ppm for four weeks and 4,000 ppm thereafter) relative to the percentage of purity of the test substance. Ethanol was used to dissolve the test substance prior to mixing in the diet. The control diet (including the

ethanol) was prepared the same as the treated diet, excluding only the test chemical.

The technical grade of 1,2,4-triazole was administered continuously in the feed of the Wistar rat (20 animals/sex/dietary level), for approximately 14 weeks, at nominal dietary concentrations of 0, 250, 500, 3,000 or 1,000/4,000 ppm (1,000 ppm for four weeks and 4,000 ppm thereafter), relative to the percentage of purity of the test substance. Body weight and food consumption determinations, as well as a detailed clinical examination of each animal, were conducted weekly throughout the study.

Selected animals from each dietary group were subjected to a neurobehavioral assessment, using an FOB and automated test of motor activity. Observations for moribundity and mortality were performed at least once daily. Standard hematologic, clinical chemistry, and urinalysis endpoints were evaluated from blood (fasted; drawn via the orbital sinus while under light anesthesia) and urine collected just prior to the respective termination. In addition, selected hepatic enzyme activities were measured. Ophthalmologic exams were conducted on all acclimatized animals prior to exposure, and then again on all surviving animals just prior to termination. All animals placed on study were subject to a postmortem examination, which included (1) documenting and saving all gross lesions, (2) weighing designated organs, and (3) collecting representative tissue specimens for histopathologic evaluation.

Statistical analysis: Continuous data that were examined statistically may have been evaluated for equality or homogeneity of variance using Bartlett's test (Snedecor and Chochran, 1967). Group means were analyzed by a one-way analysis of variance (ANOVA) (Snedecor and Chochran, 1967) followed by Dunnett's test (Dunnett, 1955 and 1964). Frequency data that were examined statistically were evaluated using the Chi-square and/or Fisher exact tests (Hollander and Wolfe, 1973). For the Bartlett test, a probability (p) level < 0.001 was considered significant; for all other statistical tests, differences with p values < 0.05 were considered statistically significant. For the FOB, continuous data were first analyzed using a Repeated-Measures ANOVA, followed by a oneway ANOVA if there was a significant interaction between dose group and test week. For weeks on which there was a significant treatment effect, Dunnett's test was applied to determine which groups, if any, were significantly different from the control group. Categorical data collected in the FOB were analyzed in a similar manner, using General Linear Modeling and Categorical Modeling (CATMOD) Procedures, with post-hoc comparisons using Dunnett's test and an Analysis of Contrasts, respectively (SAS). Motor and locomotor activity (total session activity and activity for each 10-minute interval) were analyzed using ANOVA procedures. Session activity data were first analyzed using a Repeated-Measures ANOVA, followed by a one-way ANOVA if there was a significant interaction with test occasion. For weeks on which there was a significant treatment effect, Dunnett's test was used to determine which, if any, groups were significantly different from the control group. Interval data were subjected to a Repeated-Measures ANOVA, using test interval and test occasion as repeated measures, followed by a Repeated Measures ANOVA to determine on which weeks there was a significant treatment by interval interaction. For those weeks, the data for each interval were subjected to analysis using a one-way ANOVA to determine at which intervals there was a significant treatment effect. For those intervals, Dunnett's test was used to determine which groups, if any, were significantly different from the control group.

Result : The mean daily intake of the test substance (mg 1,2,4-triazole/kg body wt/day) over approximately 14 weeks at nominal dietary concentrations of 250, 500, 3,000 or 1,000/4,000 ppm, respectively, was 16, 33, 183, and 210 for males, and 19, 41, 234, and 275 for females.

Body weight was unaffected in both sexes at doses up to and including 500 ppm. Decreases in body weight (5- 8%) and body weight gain (18-21%) were observed in both sexes at 3,000 and/or 1,000/4,000 ppm.

The FOB revealed several compound-related effects in both sexes at the 3,000 and 1,000/4,000 ppm dietary levels, including ungroomed appearance, muscle fasciculations, tremor, gait in-coordination, decreased activity in the open field, and decreased rearing. The only effect on automated measures of activity was a 30% decreased activity in 3,000 ppm males during week 4 (when that was the highest dietary level). At later measurements this effect was no longer evident.

Serum chemistry indication of treatment-related change was limited to decreased triglyceride concentration in 3,000- and 1,000/4,000-ppm males (97, 80, 80, 52* and 54* mg/kg for the control group and the four dose groups, respectively). Any toxicological relevance of this finding is questionable as no similar effect was evident in females. Treatment-related changes in T4, T3, or TSH concentration were not observed. Analysis of the activity of selected hepatic enzymes indicated slightly increased activities in both sexes at 3,000- and 1,000/4,000-ppm (although effects on total P-450 were not observed). The limited magnitude of the alterations as well as the lack of corresponding morphological evidence indicate an adaptive response by the liver.

No evidence of 1,2,4-triazole-induced toxicity was observed in any other in-life parameter, including food consumption/utilization, ophthalmology, hematology, and urinalysis.

Organ weight change attributable to exposure to 1,2,4-triazole was limited to a slight decrease in absolute brain weight in 3,000- and 1,000/4,000-ppm males and females; the relative brain weights were not affected. Other apparent variations in organ weights relative to controls were best characterized as a secondary response to alterations in body weight gain observed in both sexes at 3,000 and 1,000/4,000 ppm. Gross pathological evidence of toxicity was not observed.

Histopathologic effects were noted in both sexes at 3,000- and 1,000/4,000-ppm. In those animals designated for subchronic (non-neurologic) evaluations, a non-statistical tendency was noted toward a greater number of total and recent-cycle corpora lutea in 3,000- and 1,000/4,000-ppm females. The increase was likely due to an increase in the number of present cycle corpora lutea or those undergoing morphological regression, the extent of which, in conjunction with normal ovarian weights, is interpreted to be within normal physiological limits.

Microscopic findings attributable to exposure to the test substance, in those animals specifically designated and processed for neurologic evaluation, were observed in the brain and nerve tissue at 3,000 and 1,000/4,000 ppm in both sexes. In the brain, the lesions were limited to the more anterior dorsal cerebellum (vermis) and were coded overall as a degeneration/necrosis, which tended to be slightly more prominent in males. Findings were characterized by extensive loss of Purkinje cells, variable white matter degeneration and gliosis. Subtle atrophy of the molecular layer or loss of granule cells was occasionally present.

Individual nerve fiber degeneration, which is a common background change in the peripheral nerves (sciatic, tibial, sural), was increased in incidence and severity over control levels in the 3,000 and 1,000/4,000 ppm groups. Additionally, minimal to mild neuronal chromatolysis and vacuolation of the lumbar dorsal root ganglia was observed at >= 3000 ppm, but no similar change was seen in the cervical dorsal root ganglia.

Tabular Summary (Rats exposed for ca. 13 weeks via the diet at constant dietary concentrations of 0, 250, 500, 3000 or 1000/4000 ppm):

Males:
Doses (mg/kg/day): 0, 16, 33, 183, and 210 mg/kg/day
NOAEL: 33 mg/kg/day (500 ppm)
LOAEL: 183 mg/kg/day (3000 ppm)
Compound-related effects at LOAEL: decrease in body weight, decrease in triglyceride level, increase in several findings in functional observational battery, decrease in motor activity, decrease in absolute brain weight, increase in incidence of brain lesion, increase in incidence of nerve lesion

Females:
Doses (mg/kg/day): 0, 19, 41, 234, and 275 mg/kg/day
NOAEL: 41 mg/kg/day (500 ppm)
LOAEL: 234 mg/kg/day (3000 ppm)
Compound-related effects at LOAEL: decrease in body weight, increase in several findings in functional observational battery, decrease in absolute brain weight, increase in incidence of brain lesion, increase in incidence of nerve lesion

Test substance : 1,2,4-Triazole (test batch No. S13691; CAS Registry No. 288-88-0; white scales or flakes) was obtained from Merck & Co., Inc. The chemical was administered to the animals as a dietary admixture, based on the analytically determined percentage of purity (adjustments were not made for percentage purity of less than 100%). At all times prior to, during, and subsequent to the conclusion of the exposure portion of this study, the test batch of 1,2,4-triazole was stored under room temperature conditions (~ 22 °C). Prior to the experimental start (09/09/03) and then again with conclusion of the in-life portion of the study, the concentration/stability of the test batch, under storage conditions at the test facility, was reconfirmed. Chemical purities of 99.9 and 101% were measured for samples tested 2/03 and 3/04, respectively, thus confirming stability.

Conclusion : Through approximately 14 weeks of continuous and repeated dietary exposure to the test substance, the toxicological response of the rat was principally characterized by retarded body weight gain, clinical symptoms, decreased absolute brain weight and histopathological findings effects in brain and peripheral nerves) at 3,000 and 1,000/4,000 ppm.

Based on the lack of adverse compound-related effects at 500 ppm in males and females, a NOAEL of 33 mg 1,2,4-triazole/kg body wt/day was established for the rat (specifically, 33 and 41 mg 1,2,4-triazole/kg body wt/day for male and female rats, respectively).

Reliability : (1) valid without restriction
Guideline study; GLP

14.10.2008 (10) (24)

Type : Sub-chronic
Species : mouse
Sex : male/female
Strain : CD-1
Route of admin. : oral feed
Exposure period : 90 days
Frequency of treatm. : daily
Post exposure period : none
Doses : 500, 1,000, 3,000, or 6,000 ppm (limit dose)
Control group : yes, concurrent vehicle
NOAEL : = 1000 - 3000 ppm
LOAEL : = 3000 - 6000 ppm
Method : other: not specified
Year : 2004
GLP : yes

Test substance : as prescribed by 1.1 - 1.4

Method : Conducted in general accordance with OPPTS 870.3100, OECD 409, 87/302/EEC (B.27)

All animals were approximately 8 weeks old when exposure to the chemical was initiated (09/17/03). To initiate the study, animals were randomly distributed into one of five dose groups consisting of 40-70 animals (20 males and 20 females at each dietary level, with an additional 15 males and 15 females assigned to Control, 3,000-, and 6,000-ppm groups). A total of 290 animals were placed on study. During the study, mice received the test substance for approximately 13 weeks at nominal dietary concentrations of 0, 500, 1,000, 3,000 or 6,000 ppm. The additional 30 animals per group in the control-, 3,000- and 6,000-ppm levels were sacrificed following 28 days on study.

Doses were selected based principally upon the results of a subacute (4-week) toxicity testing study in the mouse, conducted with the test substance at doses of 0, 50, 250, 500, or 2,000 ppm (Wahle, 2004). Dose levels for the present study were set at 0, 500, 1,000, 3,000 and 6,000 ppm. It was anticipated that the 500- and 3,000-ppm doses would constitute a no-observed-adverse-effect level and a maximum tolerated dose, respectively, with the intermediate dosage of 1,000 ppm serving to evaluate possible dose response relationships. The 6,000 ppm dose level was included as a limit dose (1000 mg/kg), in the event an adequate toxicological response was not observed at 3,000 ppm. The 6,000 ppm dietary concentration was selected based on recent 90-day body weight and food consumption data for the CD-I mouse at the testing facility, which would result in an average active ingredient (ai) intake of at least 1,000 mg ai/kg body weight/day.

Diet preparation and analysis. The test substance was to be administered continuously in the feed at nominal dietary concentrations of 0, 500, 1,000, 3,000, or 6,000 ppm relative to the percentage of purity of the test substance. Ethanol was used to dissolve the test substance prior to mixing in the diet. The control diet (including the ethanol) was prepared the same as the treated diet, excluding only the test chemical.

The technical grade of 1,2,4-triazole was administered continuously in the feed to the CD-1 mouse (20 animals/sex/dose), for approximately 3 months, at nominal dietary concentrations of 0, 500, 1,000, 3,000, or 6,000 ppm (limit dose), relative to the percentage of purity of the test substance. Control, 3,000-, and 6,000-ppm groups included an additional 15 animals/sex/dose that were treated for approximately 4 weeks prior to termination (for hepatic enzyme profile analysis). Body weight and food consumption determinations, as well as a detailed clinical examination of each animal, were conducted weekly throughout the study. Observations for moribundity and mortality were performed at least once daily. Standard hematologic and selected clinical chemistry endpoints were evaluated from non-fasted blood obtained at approximately 4 weeks (drawn via cardiac puncture while under CO2 anesthesia) or just prior to termination (drawn via the orbital sinus). In addition, selected hepatic enzyme activities were measured for control, 3,000, and 6,000 ppm levels at 4 weeks and for control and 6,000 ppm levels at 13 weeks. All animals placed on study for 13 weeks were subject to a postmortem examination, which included (1) documenting and saving all gross lesions, (2) weighing designated organs, and (3) collecting representative tissue specimens for histopathologic evaluation.

Statistical analysis. Continuous data that were examined statistically were evaluated initially for equality or homogeneity of variance using Bartlett's test (Snedecor and Cochran, 1967). Group means were further analyzed

by a one-way analysis of variance (ANOVA) (Snedecor and Cochran, 1967) followed by Dunnett's test (Dunnett, 1955, 1964). In the event of unequal variances, and at the discretion of the study director, data were subjected to non-parametric procedures consisting of a Kruskal-Wallis ANOVA (Hollander and Wolfe, 1973) followed by the Mann-Whitney-U test for between-group comparisons. Frequency data were initially examined for trends; data suggestive of a potential effect were then statistically evaluated using the Fisher exact tests. For the Bartlett test, a probability (p) value < 0.001 was considered significant; for all other statistical tests, differences with p values < 0.05 were considered statistically significant. All statistical evaluations were performed using software obtained from either INSTEM Computer Systems or SAS Institute Inc.

Result : The mean daily intake of the test substance (mg 1,2,4-triazole/kg body wt/day) over approximately 13 weeks at nominal dietary concentrations of 500, 1,000, 3,000, and 6,000 ppm, respectively, was 80, 161, 487, and 988 for males and 105, 215, 663, and 1346 for females.

Alterations in body weight were measured in males at 3,000 ppm and in both sexes at 6,000 ppm relative to controls. Declines in final live body weight of 16% and 9% were noted in 6,000-ppm males and females, respectively; a decline of 6% was noted in 3,000-ppm males. Marked declines in body weight gain (BWG) were noted in these same groups, particularly in males at 6,000 ppm, where the consistent decreases in mean weekly body weight resulted in an overall body weight loss over the course of the study. Importantly, this body weight loss for males at 6000 ppm is indicative of dietary concentrations that exceed the maximum tolerated dose (MTD).

Clinical observations during the study were noted in 6,000-ppm males and included increased incidence of tremors, yellow staining (likely urine stains), and rough coat.

Analysis of the activity of selected hepatic enzymes indicated slight increases in both sexes, at 3,000 and 6,000 ppm following 28 days and at 6,000 ppm following 90 days. However, the magnitude of the alterations as well as the lack of corresponding morphological evidence indicate an adaptive response by the liver.

No evidence of a 1,2,4-triazole-induced toxicity was observed in any other in-life parameter, including food consumption/utilization, mortality, hematology, or clinical chemistry. Gross lesions attributable to exposure to 1,2,4-triazole were limited to 6,000-ppm males and included an increased incidence of rough coat and wet/stained ventrum.

Organ weight changes included decreased testicular weights in 6,000-ppm males and decreased brain weights (absolute only) in 3,000-ppm males and 6,000-ppm males and females. Histopathological findings included an increased incidence of lesions noted in the brain at 6,000-ppm in both sexes, and in the testes of 3,000- and 6,000-ppm males. The finding in the testes at 6,000 ppm was accompanied by a secondary, indirect effect in the epididymis. The lesion identified in the brain consisted of a loss of Purkinje cells in the cerebellum, accompanied by occasional degeneration of the Purkinje cell axons located in the white matter of the cerebellar folia (minimal to slight severity). Although the lack of neurons is considered to be a late-stage lesion, no earlier stages preceding this effect were observed.

In the testes increased incidences of apoptotic-like bodies, tubular atrophy, and abnormalities in spermatid development (spermiogenesis and spermiation) were seen at >= 3000 ppm. The slight effects seen at 1000 ppm are regarded to reflect background findings and not an adverse effect.

The finding in the epididymis, observed at 6,000 ppm only, was considered to be a reflection of the testicular effects which were most pronounced at the highest dose level and consisted of exfoliated germ cells and debris within the lumen of the epididymal duct (the epididymal parenchyma was unchanged compared to controls). Additionally, one of the mice showed an overall decrease in the number of spermatozoa in the epididymal ducts at 6000 ppm.

Tabular Summary (Mice exposed for ca. 13 weeks via the diet at constant dietary concentrations of 0, 500, 1000, 3000 or 6000 ppm):

Males:
Doses (mg/kg/day): 0, 80, 161, 487, 988 mg/kg/day
NOAEL: 161 mg/kg/day (1000 ppm)
LOAEL: 487 mg/kg/day (3000 ppm)
Compound-related effects at LOAEL: decrease in body weight, decrease in brain weight, increase in incidence testes lesion

Females:
Doses (mg/kg/day): 0, 105, 215, 663, and 1346 mg/kg/day
NOAEL: 663 mg/kg/day (3000 ppm)
LOAEL: 1346 mg/kg/day (6000 ppm)
Compound-related effects at LOAEL: decrease in body weight, increase in incidence of brain lesion, decrease in brain weight

Test substance : 1,2,4-Triazole (test batch No. S13691; CAS Registry No. 288-88-0; white scales or flakes) was obtained from Merck & Co., Inc. The chemical was administered to the animals as a dietary admixture, based on the analytically determined percentage of purity (adjustments were not made for percentage purity of less than 100%). At all times prior to, during, and subsequent to the conclusion of the exposure portion of this study, the test batch of 1,2,4-triazole was stored under room temperature conditions (~ 22 °C). Prior to the experimental start (09/09/03) and then again with conclusion of the in-life portion of the study, the concentration/stability of the test batch, under storage conditions at the test facility, was reconfirmed. Chemical purities of 99.9 and 101% were measured for samples tested 2/03 and 3/04, respectively, thus confirming stability.

Conclusion : NOAEL(males): 1000 ppm (equivalent to 161 mg/kg bw/day) based on decreased body weights, decreased absolute brain weight and micropathological finding in the testes at 3000 ppm.

NOAEL(femaies): 3000 ppm (equivalent to 663 mg/kg bw/day) based on decreased body weights, decreased absolute brain weight and micropathological finding in the brain at 6000 ppm

Reliability : (2) valid with restrictions
Comparable to a guideline study; GLP.

Flag : Critical study for SIDS endpoint

13.10.2008 (11) (24)

Type : Sub-acute
Species : mouse
Sex : male/female
Strain : CD-1
Route of admin. : oral feed
Exposure period : 28 days
Frequency of treatm. : daily
Post exposure period : none
Doses : 50, 250, 500 or 2000 ppm
Control group : yes, concurrent vehicle
NOAEL : = 500 - 2000 ppm
Method : other
Year : 2004
GLP : yes

Test substance	:	as prescribed by 1.1 - 1.4
Method	:	The principal objective of this subacute (4-week) toxicity testing study was to establish dose levels of exposure for a subsequent subchronic (13-week) exposure study with 1,2,4-triazole in the mouse. 1,2,4-triazole was administered to groups of 15 male and 15 female CD-1 mice at dietary dose levels of 0, 50, 250, 500 or 2000 ppm for 4 weeks. Feed was available ad libitum at all times; the homogeneity and stability of 1,2,4-triazole as a dietary admixture was confirmed analytically. Mice were observed for moribundity, mortality and general clinical signs at least once per day; detailed clinical examinations, body weights and food consumption were measured weekly. Blood was collected (via orbital plexus) from non-fasted animals just prior to the termination of the in-life phase of the study and used for clinical and haematological determinations. All animals underwent a detailed post mortem examination and selected organs were weighed. Samples of all major organs, tissues and gross lesions were preserved.
Result	:	The mean daily compound intakes were 9, 47, 90 and 356 mg/kg bw/day for males and 12, 60, 120 and 479 mg/kg bw/day for females. Body weight, body weight gain and food consumption were not affected in males and females at dose levels up to 2000 ppm. There were no treatment-related findings or clinical observations in any treatment group. Clinical chemistry and haematology provided no indication of compound-related changes in either sex at any dose level. No treatment-related gross lesions were seen at necropsy and there were no relevant differences in terminal body or organ weights. In the testes of high-dosed males slightly increased incidence and severity of certain background lesions (spermatid degeneration, depletion and asynchrony, and tubular atrophy) were noted in histopathology. Exfoliated germ cells and debris were found in the epididymides at a marginally increased incidence.
Test substance	:	1,2,4-triazole; purity 99.9%
Conclusion	:	NOAEL males: 500 ppm (equivalent to 90 mg/kg bw/day) based on slightly increased incidence and severity of degenerative background lesions in testes and epididymis at 2000 ppm. NOAELfemales: 2000 ppm (equivalent to 479 mg/kg bw/day) / highest dose tested.
Reliability	:	(4) not assignable Range-finding study

14.10.2008 (9) (24)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Bacterial reverse mutation assay
System of testing	:	Salmonella typhimurium TA 98, TA 100, TA 1535 and TA 1537
Test concentration	:	10.0; 33.3; 100.0; 333.3; 1000.0; and 5000.0 ug/plate
Cycotoxic concentr.	:	>= 1000 ug/plate
Metabolic activation	:	with and without
Result	:	negative
Method	:	OECD Guide-line 471
Year	:	1989
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Also conducted in accordance with 84/449/EEC B.14, EPA-TSCA § 798.5265, JMAFF

Vehicle: water.

For the mutagenicity test the histidine-auxotrophic strains of Salmonella typhimurium TA 98, TA 100, TA 1535 and TA 1537 were used. Two sets of independent studies were performed (original and confirmatory study) with and without metabolic activation. The highest concentration applied was determined in the preliminary toxicity test with strains TA 98 and TA 100. Additionally, five lower concentrations spaced by a factor of 3 were tested. After preparation, the plates were incubated for 72 hours at 37 °C in darkness. Thereafter, they were evaluated by counting the number of colonies and determining the background lawn. Positive controls (without metabolic activation: sodium azide; 4-nitro-o-phenylene-diamine; with metabolic activation: 2-aminoanthracene) were included in the test in order to demonstrate the sensitivity of the test system.

Result : In the preliminary toxicity test with S. typhimurium eight concentrations of 1,2,4-triazole ranging from 1.0 to 5000 ug / plate were tested with and without metabolic activation. From the obtained results 5000 ug / plate was selected as highest concentration for the mutagenicity experiments with S. typhimurium. In the original and confirmatory mutagenicity experiments performed without and with metabolic activation, treatment with 1,2,4-triazole at six concentrations in the range of 10 to 5000 ug / plate did not lead to an increased incidence of mutants in comparison with the negative controls. With the positive controls a marked increase of the number of revertant colonies was observed, thus indicating the sensitivity of the test system. Toxic effects, evidenced by a slight or complete reduction in the number of spontaneous revertants, occurred at 1000 and 5000 ug / plate, with and without metabolic activation.

Test substance : lH-l,2,4-triazole., purity 99.7%.

Conclusion : Based on the results of this study and on standard evaluation criteria, it is concluded that 1,2,4-triazole did not induce gene mutations in the strains of S. typhimurium used.

Reliability : (1) valid without restriction
Guideline study; GLP

Flag : Critical study for SIDS endpoint

13.10.2008 (24)

Type : Bacterial reverse mutation assay
System of testing : Salmonella typhimurium TA 98, TA 100, TA 1535 and TA 1537
Test concentration : Exp 1: 100, 500, 2500, 5000, and 7500 ug/plate; Exp 2: 500, 1000, 2000, 3000, and 5000 ug/plate
Cycotoxic concentr. : See results
Metabolic activation : with and without
Result : negative
Method : OECD Guide-line 471
Year : 1981
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Also conducted in accordance with 84/449/EEC B.14, EPA-TSCA § 798.5265, JMAFF

Vehicle: dimethylsulphoxide (DMSO).

For the mutagenicity test the histidine-auxotrophic strains of Salmonella typhimurium TA 98, TA 100, TA 1535 and TA 1537 were used. The highest concentration applied was 7500 ug/plate. Additionally, four lower concentrations (5000, 2500, 500 and 100 ug/plate) were tested. A repeat experiment with 5 concentrations (500, 1000, 2000, 3000, and 5000 ug/plate) was performed with strains TA 98 and TA 100. After preparation and incubation, the plates were evaluated by counting the number of colonies and determining the background lawn. Positive controls (2-

anthramine and 2-acetamidofluorene) were included in the test in order to demonstrate the sensitivity of the test system.

Result : In the original and confirmatory mutagenicity experiments performed without and with metabolic activation treatment with 1,2,4-triazole at concentrations in the range of 100 - 7500 ug/plate did not lead to an increased incidence of histidine-prototrophic mutants in comparison with the negative controls. With the positive controls a marked increase of the number of revertant colonies was observed, thus indicating the sensitivity of the test system. Growth inhibition was observed at 2000 ug/plate and above with strains TA 98 (without activation) and TA 100 (with and without activation), at 5000 ug/plate and above with strain TA 1537 (with activation), and at 7500 ug/plate with strain TA 1535 (without activation).

Test substance : 1,2,4-triazole, purity: 92.8%

Conclusion : Based on the results of this study and on standard evaluation criteria, it is concluded that treatment with 1,2,4-triazole did not induce gene mutations in the strains of S. typhimurium used.

Reliability : (2) valid with restrictions
Confirmatory mutagenicity experiment performed on 2 Salmonella typhimurium strains only; not GLP

13.10.2008 (26)

Type : Chromosomal aberration test

System of testing : rat lymphocytes

Test concentration : Initial assay: 0, 10.8, 21.6, 43.2, 86.4, 172.8, 345.5 and 691 ug/ml; Repeat assay: 0, 43, 87, 173, 346, 519 and 691 ug/ml

Cycotoxic concentr. : > 691 ug/ml

Metabolic activation : with and without

Result : negative

Method : OECD Guide-line 473

Year : 2007

GLP : yes

Test substance : as prescribed by 1.1 - 1.4

Method : Also conducted in accordance with USEPA OPPTS 870.5375 (1998); EC, B. 10 (2000) and JMAFF, Mutagenicity Guidelines (2001)

1,2,4-triazole was evaluated in an in vitro chromosomal aberration assay utilizing rat lymphocytes. Approximately 48 hours after the initiation of whole blood cultures, cells were treated either in the absence or presence of S9 activation with concentrations including 0 (solvent control), 10.8, 21.6, 43.2, 86.4, 172.8, 345.5 and 691 ug 1,2,4-triazole per ml of culture medium. The duration of treatment was 4 or 24 hours without S9 activation and 4 hours with S9 activation. The highest concentration was based on the limit dose of 10 mM in this assay system. Based upon the mitotic indices, cultures treated with targeted concentrations of 0 (solvent control), 172.8, 345.5, and 691 ug/ml in the absence (4 and 24 hour treatment) and presence of S9 activation (4 hour treatment) were selected for determining the incidence of chromosomal aberrations. In a repeat assay in the presence of S9 activation, cultures were treated for 4 hours with concentrations including 0 (solvent control), 43, 87, 173, 346, 519 and 691 ug 1,2,4-triazole per ml of culture medium. Based on mitotic indices, cultures with targeted concentrations of 0 (solvent control), 346, 519, and 691 |ag/ml were selected for determining the incidence of chromosomal aberrations. Positive controls (i.e., mitomycin C without S9 and cyclophosphamide with S9) were used both with and without metabolic activation to verify sensitivity of the assay.

Result : There were no significant increases in the frequencies of cells with aberrations in the presence or absence of metabolic activation. Cultures treated with the positive control chemicals in both assays had significantly higher incidences of abnormal cells in all assays.

Test substance : 1,2,4-triazole, purity 99.3%

Conclusion : 1,2,4-triazole was considered to be non-genotoxic in an in vitro

chromosomal aberration assay utilizing rat lymphocytes.

Reliability : (1) valid without restriction
Guideline study; GLP

Flag : Critical study for SIDS endpoint

13.10.2008 (30)

Type : HGPRT assay
System of testing : Chinese hamster ovary cells
Test concentration : Initial assay: 43.2, 86.4, 172.8, 345.5 and 691 ug/ml; Confirmatory assay: 200, 300, 400, 500 and 691 ug/ml
Cycotoxic concentr. : > 691 ug/ml
Metabolic activation : with and without
Result : negative
Method : OECD Guide-line 476
Year : 2007
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : Also conducted in accordance with USEPA OPPTS 870.5300 (1998); EC, B. 17 (2000)

1,2,4-triazole was evaluated in the in vitro Chinese hamster ovary cell/hypoxanthine-guanine-phosphoribosyl transferase (CHO/HGPRT) forward gene mutation assay. The genotoxic potential of the test material was assessed in two independent assays in the absence and presence of an externally supplied metabolic activation (S9) system with concentrations of 43.2, 86.4, 172.8, 345.5 and 691 ug/ml. The highest concentration was based on the 10 mM limit of the test system. In the confirmatory mutagenicity assay concentrations included 200, 300, 400, 500 and 691 ug/ml in the absence and presence of S9 activation. The adequacy of the experimental conditions for detection of induced mutation was confirmed by employing positive control chemicals, ethyl methanesulfonate for assays without S9 activation and 20-methylcholanthrene for assays with S9 activation. Solvent control cultures were treated with the vehicle used to dissolve the test material (i.e. distilled water).

Result : In the initial mutagenicity assay, in the absence of S9 activation, no toxicity was observed with relative cell survival (RCS) values ranging from 97.2 to 113.7%. In the presence of S9 activation, cultures treated with the test material displaced little to no toxicity with RCS values ranging from 91.1 to 113.9%. The mutant frequencies observed in cultures treated with the test material in the absence and presence of S9 activation were not significantly different from the concurrent solvent control values. All mutant frequencies were within a reasonable range of historical background values.

In the confirmatory mutagenicity assay there was no toxicity observed, as indicated by RCS values, in the absence of S9 activation (99.6 to 129.5%). In the presence of S9 activation varying levels of toxicity were observed with RCS values ranging from 74.4 to 126.0%. The mutant frequencies observed in cultures treated with the test material in the absence and presence of S9 activation were not significantly different from the concurrent solvent control values and were within the range of the laboratory historical background. In both the initial and confirmatory mutagenicity assays, the positive control chemicals induced significant increases in mutant frequencies and these data confirmed the adequacy of the experimental conditions for detecting induced mutations.

Test substance : 1,2,4-triazole; purity 99.3%
Conclusion : 1,2,4-triazole was not mutagenic in the CHO/HGPRT gene mutation assay.
Reliability : (1) valid without restriction
Guideline study; GLP

13.10.2008 (31)

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

Type	:	Two generation study
Species	:	rat
Sex	:	male/female
Strain	:	other: Wistar Hannover
Route of admin.	:	oral feed
Exposure period	:	From 10 weeks premating P-generation through 61 days old for F2-pups
Frequency of treatm.	:	daily
Premating exposure period		
Male	:	10 weeks
Female	:	10 weeks
Duration of test	:	From 10 weeks premating P-generation though day 61 of F2-pups
No. of generation studies	:	2
Doses	:	250, 500, and 3000 ppm
Control group	:	yes, concurrent vehicle
other: paternal NOAEL	:	< 250 ppm
other: maternal NOAEL	:	= 500 ppm
other: reproductive NOAEL	:	= 500 ppm
Method	:	OECD Guide-line 416 "Two-generation Reproduction Toxicity Study"
Year	:	2005
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Method :

Also conducted in compliance with:
OPPTS 870.3800 Reproduction and Fertility Effects
EU Guidelines on Reproductive Toxicity Studies, 91/414/EEC
JMAFF 12 Nousan No. 8147

The principal objective of this study was to evaluate the potential reproductive toxicity of 1,2,4-triazole, including tests to evaluate developmental neurotoxicity. The rat was selected as the test species, based on its general acceptance and suitability as a rodent species for toxicological testing of this type.

1,2,4-triazole was administered continuously via the feed to Wistar Hannover rats (30/sex/dietary level) at nominal dietary concentrations of 0, 250, 500, and 3000 ppm. To maintain a more constant dosage (on basis of mg/kg bw/day) throughout the entirety of the study the dietary levels were reduced for females during lactation. All test diets (including control) were available for ad libitum consumption; the homogeneity and stability of 1,2,4-triazole as a dietary admixture was confirmed analytically.

Animals were observed for clinical signs and monitored for changes in body weight and food consumption. The evaluation of requisite guideline reproductive parameters for adult animals was conducted and included; oestrous cycling, mating, fertility, and gestation length. All animals placed on study underwent a post-mortem examination, which included (1) documenting and saving all gross lesions, (2) weighing designated organs and (3) collecting representative tissue specimens for histo-pathological evaluation and sperm analysis.

In addition to fulfilling standard guideline requirements, this two-generation reproduction study contained the following additional investigations:

(1) in-depth examinations of brain tissue from the P- and F1-generation adults, as well as the F1- and F2-generation 21-day-old pups, which included qualitative microscopic evaluations and gross and microscopic morphometric analyses;
(2) the inclusion of additional microscopic investigative work on the ovarian tissue from the P-generation rats as it related to the identification of infertility in the 3000 ppm group during the conduct of this study;
(3) expansion of the guideline requirements for the F1-generation ovarian counts to include a more
in-depth study of the corpora lutea, based on findings from the P-generation ovarian data; and
(4) determination of the onset of preputial separation and vaginal patency for F2 pups. International experts were consulted to assist with the analysis of the ovary (Dr. Paul Terranova) and to review the slides for neuropathology (Dr. Georg Krinke).

Result **:** The mean daily intake of the test substance (mg 1,2,4-triazole/kg bw/day) throughout this two-generation reproduction study at nominal dietary concentrations of 0, 250, 500 or 3,000 ppm, respectively, is summarised in the following table:

Mean daily intake of 1,2,4-triazole in two-generation reproduction study:

Phase of Study	250 ppm in (mg/kg/d)(a)	500 ppm in (mg/kg/d)(a)	3000 ppm in (mg/kg/d)(a)
Premating (P-gen)			
Male	15.4	30.9	188.6
Female	17.5	36.2	217.9
Premating (F1-gen)			
Male	16	32	NA
Female	18.9	37.5	NA
Gestation (P-gen)			
Female	18.6	38.6	231.7(b)
Gestation (P-gen)			
Female	17.4	34.4	NA

Where:
a) Individual values were based on the means for each particular phase for each generation,
b) Based on only two pregnant females in the 3000 ppm dose group.

There were no test substance-related effects on food consumption or clinical signs in either generation at any dietary level. Compound-related declines in body weight and body weight gain were evident in the P-generation adult males and females of the 3000-ppm dose group. A slight decrease in body weight and weight gain that was attributed to treatment was also evident in F1-generation adult males in both the 250- and 500-ppm dose groups.

A marked reduction in fertility was evident at the 3000 ppm dietary level of the P-generation, with only two females delivering viable offspring (one each) and only three implantation sites (compared to 265 for controls). All high-dose (3000 ppm) P-generation females and pups were sacrificed before weaning, since there were too few pups to provide a second generation. There were no test substance-related effects on the mating, gestation, or fertility indices, number of days to insemination, or gestation

length at any dietary level in either F1- or F2- generation except for decreased fertility in 3000-ppm P-generation females. No effects were observed on the oestrous cycle length or the number of cycles at any dose in either generation, including the 3000-ppm group of the P-generation.

Other than the reduced fertility evident in the 3000 ppm dose group, no other effects were observed on any litter parameter in any dose group in either generation. There was also no effect on any sperm parameter that was attributed to the test substance.

At termination, treatment-related findings were evident only in the P-generation at the 3000 ppm dietary level and included: 1) decreased absolute brain weights in males and females; 2) increased incidence of cerebellar degeneration/necrosis in both genders; 3) statistically increased number of total Corpora lutea measured by quantitative ovarian analysis and increased ovary weights; and 4) increased incidence of uterine horn dilatation. No similar findings were evident in P-generation animals at lower dietary levels or in the offspring from either generation.

The following table summarizes the NOAELs, LOAELs and key findings from the two generation reproductive study with 1,2,4-triazole:

Dosage Levels (mg/kg/d)(a)	NOAEL (mg/kg/d)	LOAEL (mg/kg/d)	Key effects at LOAEL
P-gen Premating: 0, 250, 500, 3000 ppm			
M:0, 15.4, 30.9, 188.6 and BWG	M:30.9	M:188.6	Dec. BW
			Dec. Brain wt
			Cerebellar degeneration and necrosis
F:0, 17.5, 36.2, 217.9	F:36.2	F:217.9	Dec. BW and BWG
			Dec. Brain weight
			Cerebellar degeneration/necrosis
			Inc. Corpora lutea
			Uterine dilatation
F1-gen Premating: 0, 250 and 500 ppm	F1:	F1:	F1:
M:(0, 16.0 and 32.0)	M:<16.0	M:16.0	M:Dec. BW and BWG
F:(0, 18.9 and 37.5)	F:37.5	F:>37.5	
P-gen Gestation: 0, 250, 500, and 3000 ppm	Reproductive	Reproductive	Reproductive
(0,18.6, 38.6 and 231.7((b)	34.4	231.7	Dec. Fertility
			Dec. Implantation sites
F1-gen Gestation: 0, 250, and 500 ppm			
(0, 17.4 and 34.4)			

BW=Body weight
BWG=Body weight gain
(a)=Individual values were based on the means for each particular phase.
(b)=Based on only two pregnant females in the 3000 ppm dose group.

Dec. = Decrease
Inc. = Increase

Paternal NOAEL: < 250 ppm (equivalent to < 16.0 mg/kg bw/day), based on retarded body weight gain at 250 and 500 ppm in F1 males.

Maternal NOAEL: 500 ppm (equivalent to 36.2 mg/kg bw/day) based on lower body weights, degenerative findings in the cerebellum, increased number of Corpora lutea, and uterine horn dilatation at 3000 ppm in P females.

Reproductive NOAEL: 500 ppm (equivalent to 34.4 mg/kg bw/day) based on reduced fertility and decreased implantation sites at 3000 ppm.

Test substance : 1,2,4-triazole, purity 99.9%

Conclusion : 1,2,4-triazole produced considerable evidence of toxicity in P-generation animals at a dietary level of 3,000 ppm (188.6 and 217.9 mg/kg/day for males and females, respectively), including reduced fertility and neuropathology. By comparison, the only evidence of toxicity at lower dietary levels of 250 and 500 ppm was slightly reduced body weight in F1-generation males. Based on these results, the reproductive (fertility) NOAEL is 34.4 mg/kg/day (500 ppm) and the LOAEL is 231.7 mg/kg/day (3000 ppm), based on findings in P-generation animals. No definitive parental NOAEL was established, based on a slight decrease in body weight in the F1-generation males at 16.0 mg/kg/day (250 ppm). However, for females, the parental NOAEL was demonstrated to be 36.2 mg/kg/day (500-ppm).

Reliability : (1) valid without restriction
Guideline study; GLP

Flag : Critical study for SIDS endpoint

14.10.2008 (12) (24) (32)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species : rat
Sex : female
Strain : other: Bor: WISW (SPF Cpb)
Route of admin. : gavage
Exposure period : Gestation days 6 to 15
Frequency of treatm. : Daily
Duration of test : Day 20 of pregnancy
Doses : 10, 30, or 100 mg/kg bw/day in vehicle (0.5% aqueous Cremophor-EL emulsion)
Control group : yes, concurrent vehicle
NOAEL maternal tox. : = 30 mg/kg bw
NOAEL teratogen. : = 30 mg/kg bw
Method : OECD Guide-line 414 "Teratogenicity"
Year : 1989
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : Also conducted in accordance with EPA FIFRA, Subdivision F, §83-3, 87/302/EEC, JMAFF 59 NohSan No. 4200

Test substance/vehicle mixtures were administered by oral gavage to groups of 25 successfully mated and presumably pregnant Bor: WISW (SPF Cpb) rats from day 6 to 15 of pregnancy at daily dose levels of 0, 10, 30, or 100 mg/kg bw/day in vehicle (0.5% aqueous Cremophor-EL emulsion). Maternal observations: viability, clinical signs were recorded daily, body weights were determined on days 0, 6 - 15, and 20. Termination: the dams underwent caesarian section on day 20 of

pregnancy. Determinations: number of nidations, number of fetuses (live and dead), sex of surviving fetuses, weight of each fetus, average fetal weight per litter, runts, total and average placental weight per litter, examination of all fetuses for external malformations, investigation of a number of fetuses (approximately 30% of total) for visceral malformations (modified Wilson technique), remaining fetuses assigned to skeletal and soft tissue evaluations.

Result : Test-article analyses demonstrated stability of the test substance/vehicle mixtures over a period of 8 days. Analyses of each dosing suspension confirmed that all animals received the intended dose within experimental limits of ± 10%.

Maternal data: There were no mortalities. No treatment-related clinical signs were observed. Mean body weight gain was significantly reduced at 100 mg/kg bw.

Body weight gains of dams (mean values, gram):

Time	(mg/kg/day)			
Period	0	10	30	100
Dosing	28.2(100)	25.4(90.1)	26.8(95.0)	21.8*(77.3)
Pregnancy	92.9(100)	86.6(93.2)	90.0(96.9)	79.9*(85.9)

Where:
*=Statistically significant different from control group mean (P<0.05).
Data in brackets express body weight gain as a percentage of that seen in the controls.

Fetal data: Fetal weight was reduced at 100 mg/kg bw/day. The incidence of runts was higher at 100 mg/kg bw/day.

Effects on fetuses (mean values):

Parameter	(mg/kg bw/day)			
	0	10	30	100
No. of implantations/dam	11.6	10.5	11.4	10.6
No. of males/dam	6.5	5.1*	6.0	5.0*
No. of females/dam	4.5	5.0	4.6	4.5
No. of males+females/dam	11.0	10.1	10.6	9.5
No. of losses/dam	0.6	0.4	0.8	1.1
Mean weight of fetuses(g)	3.58	3.59	3.53	3.25**
Mean weight of placenta(g)	0.56	0.56	0.57	0.56
No. of fetuses/litter with minor skeletal deviations	2.0	2.41	2.84	2.42
No. of fetuses with malformations	0.05	0.05	0.05	0.17
No. of runts/litter	0.33	0.23	0.53	2.21**

Where:
*or**=statistically significant at the 5% or 1% level, respectively.

The observed malformations at 100 mg/kg bw/day affected only one fetus each and were considered spontaneous in nature, as noted below.

Rat Teratology study: Malformations:

Type of	(mg/kg bw/day)			
Malformation	0	10	30	100
Microphthalmia, bilateral	1	0	0	0
Microphthalmia, right side	0	1	0	1
Microphthalmia, left side	0	0	0	1
False posture of right hind leg	0	0	1	0
Anophthalmia	0	0	0	1
Dysplasia and asymmetry of body of vertebrae and vertebral arches of thoracic				

spine and abnormal position						
of one rib		0	0	0	1	

Test substance : 1,2,4-triazole; purity: 95.3%
Conclusion : Maternal NOAEL: 30 mg/kg bw/day based on retarded weight gain at 100 mg/kg bw.
Developmental NOAEL: 30 mg/kg bw/day based on an increased incidence of runts and lower fetal weights at 100 mg/kg bw/day.
Reliability : (1) valid without restriction
Guideline study; GLP
Flag : Critical study for SIDS endpoint
13.10.2008 (2) (24)

Species : rabbit
Sex : female
Strain : other: New Zealand White rabbits [Hra: NZW:SPF]
Route of admin. : gavage
Exposure period : Gestation days 6 though 28
Frequency of treatm. : Daily
Duration of test : Gestation day 29
Doses : 5, 15, 30 and 45 mg/kg bw/day in vehicle (0.5% aqueous CMC)
Control group : yes, concurrent vehicle
NOAEL maternal tox. : = 30 mg/kg bw
NOAEL teratogen. : = 30 mg/kg bw
Method : OECD Guide-line 414 "Teratogenicity"
Year : 2004
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : Also conducted in accordance with:
U.S. Environmental Protection Agency (1998). Health Effects Test Guidelines; Prenatal Developmental Toxicity Study. Office of Prevention, Pesticides and Toxic Substances (OPPTS) 870.3700, August, 1998.

U.S. Environmental Protection Agency (1997). Toxic Substances Control Act (TSCA) Test Guidelines; Final Rule. Prenatal Developmental Toxicity, 799.9370 (cross referenced to OPPTS 870.3700). Federal Register, August 15, 1997.

Japanese Ministry of Agriculture, Forestry and Fisheries (1 985). Guidance on Toxicology Study Data for Application of Agricultural Chemical Registration. 59 NohSan No. 4200.

1,2,4-triazole was administered by gavage to groups of twenty-five time-mated New Zealand White rabbits [Hra: NZW:SPF] in 0.5% aqueous CMC at dose levels of 0, 5, 15, 30 and 45 mg/kg bw/day on days 6 though 28. The dosage volume was 10 mL/kg. Viability, clinical observations, body weights and feed consumption were recorded. The animals were sacrificed on day 29 and examined for the number of distribution of Corpora lutea, implantation sites and uterine contents. A gross necropsy of the thoracic, abdominal and pelvic viscera was performed. Fetuses were weighed and examined for gross external, visceral and skeletal alterations and sex.

Result : Five does in the 45 mg/kg/day dosage group were sacrificed due to their moribund condition. All other does survived to day 29 of gestation (GD 29). Adverse clinical observations related to the test substance occurred only in the 45 mg/kg/day dosage group. The number of does with decreased motor activity, clear perinasal substance, ptosis, excess salivation and hyperpnoea was significantly increased in this dosage group. Most of these observations occurred in the does that were sacrificed moribund. Additional observations considered related to the test substance or inter-related with the moribund condition of the doe included: scant feces, ungroomed coat, head tilt, lacrimation, flared nostrils and cold to touch.

Body weight gains were significantly reduced for GDs 9 to 12, 21 to 24 and for the entire dosage period (calculated as GDs 6 to 29) and the entire study period (GDs 0 to 29) in the 45 mg/kg/day dosage group. Body weights did not significantly differ among the other groups. Gravid uterine weights were significantly reduced in the 45 mg/kg/day dosage group. No other statistically significant differences occurred among the groups for either body weight gains, corrected body weights (body weight on DG 29 minus the gravid uterine weight) or corrected body weight gains. Absolute and relative feed consumption values were unaffected by dosages of the test substance as high as 45 mg/kg/day.

Maternal body weight changes (kg) in rabbit development study (values represent mean +/- (SD)):

Dose group (mg/kg bw/d)(a)	0	5	15	30	45
Days 6-29	+0.48 (0.13)	+0.40 (0.21)	+0.37 (0.19)	+0.38 (0.17)	+0.24** (0.21) [20](b)
Days 0-29	+0.65 (0.17)	+0.54 (0.25)	+0.52 (0.26)	+0.55 (0.20)	+0.37** (0.23) [19](b)
Days 6-29C c	-0.07 (0.13)	-0.14 (0.18)	-0.14 (0.16)	-0.15 (0.17)	-0.21 (0.20) [19](b)
Days 0-29C c	+0.09 (0.15)	-0.01 (0.22)	+0.01 (0.01)	+0.02 (0.21)	-0.09 (0.22) [19](b)

Where:
Days = days of gestation
[ ] = number of values averaged
a=Dosage occurred on days 6 through 28 of gestation
b=Excludes values for rabbits that were moribund sacrificed or prematurely delivered
c=29C = corrected maternal body weight [Day 29 of gestation body weight minus the gravid uterine weight]
** Significantly different from the control value (P<0.01)

Fetal weights (male, female and total) were significantly reduced in the 45 mg/kg/day dosage group. No other Caesarean-sectioning or litter parameters were affected by dosages of the test substance as high as 45 mg/kg/day.

Fetal body weight data (g.litter) in rabbit development study (values represent mean +/- (SD)):

Dose group (mg/kg bw/d)(a)	0	5	15	30	45
Total fetuses	44.35 (3.37)	43.42 (5.85)	43.82 (5.70)	42.48 (4.22)	39.36** (5.20)
Male fetuses	44.92 (3.78)	43.91 (6.14)	44.25 (5.72)	42.39 (4.22)	39.65** (4.73)
Female fetuses	42.92 (3.95)	42.79 (5.51) [23](c)	43.64 (6.17)	42.40 (4.34)	38.70* (5.90)

Where:
[ ] = number of values averaged
a=Dosage occurred on days 6 through 28 of gestation
b=Litter 8081 had no male fetuses
c=Litter 8039 had no female fetuses
*Significantly different from the control value (P<0.05
"Significantly different from the control value (P<0.01)

There were a few alterations of the urogenital system (low set, small, absent kidneys and/or an absent ureter) which occurred in several fetuses of the maternally toxic 45 mg/kg/day dosage group. There were no other dosage-dependent and/or significant differences in the litter or fetal incidences of any gross external, soft tissues or skeletal alterations. Skeletal ossification averages per foetus per litter did not differ among the groups.

Rabbits: Fetal Soft Tissue Alterations:

	Dosage [mg/kg bw]				
Parameters	0	5	15	30	45
Litters evaluated		25	24	24	25	19
Fetuses evaluated		217	207	199	219	157
Kidneys: low set					
Litter incidence	0	0	0	0	1
Fetal incidence	0	0	0	0	3a,b,**
Kidneys: small					
Litter incidence	0	0	0	0	1
Fetal incidence	0	0	0	0	3a,b,**
Kidneys: absent					
Litter incidence	0	0	0	0	2
Fetal incidence	0	0	0	0	2b,**
Ureter: absent					
Litter incidence	0	0	0	0	1
Fetal incidence	0	0	0	0	1b

Where:
a: fetuses 8102-1 and 7 had other soft tissue alterations
b: fetus 8102-4 had other soft tissue alterations
p <= 0.01

Test substance : 1,2,4-triazole, purity 99.9%

Conclusion : Maternal NOAEL: 30 mg/kg bw/day based on mortality, reduction in body weight gain, and clinical symptoms at 45 mg/kg bw/day.

Developmental NOAEL: 30 mg/kg bw/day based on lower fetal weights and a slight increase in urogenital alterations for several fetuses at 45 mg/kg bw/day.

Reliability : (1) valid without restriction
Guideline study; GLP

13.10.2008 (1)

Species : rat
Sex : female
Strain : other: Bor: WISW (SPF Cpb)
Route of admin. : gavage
Exposure period : Gestation days 6 to 15
Frequency of treatm. : Daily
Duration of test : Day 20 of pregnancy

Doses	:	100 or 200 mg/kg bw/day in vehicle (0.5% aqueous Cremophor-EL emulsion)
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	< 100 mg/kg bw
NOAEL teratogen.	:	< 100 mg/kg bw
Method	:	OECD Guide-line 414 "Teratogenicity"
Year	:	1989
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Method : Also conducted in accordance with EPA FIFRA, Subdivision F, §83-3, 87/302/EEC, JMAFF 59 NohSan No. 4200

Test article/vehicle mixtures were administered by oral gavage to groups of 25 successfully mated and presumably pregnant Bor: WISW (SPF Cpb) rats from day 6 to 15 of pregnancy at daily dose levels of 0, 100 or 200 mg/kg bw/day in vehicle (0.5% aqueous Cremophor-EL emulsion).

Maternal observations: viability, clinical signs recorded daily, body weights determined on days 0, 6 - 15, and 20, food consumption determined from day 0-6, 6-11,11-16, and 16-20. Termination: the dams underwent caesarian section on day 20 of pregnancy.

Determinations: number of nidations, number of corpora lutea, weight of uterus, number of fetuses (live and dead), sex of surviving fetuses, weight of each fetus, average fetal weight per litter as well as malformations, placental weight, length of fetuses crown to rump, examination of all fetuses for external malformations, investigation of a number of fetuses (approximately 50% of total) for visceral malformations (modified Wilson technique), remaining fetuses assigned to skeletal and soft tissue evaluations.

Result : Test substance analyses demonstrated stability of the test substance/vehicle mixtures over a period of 8 days. Analyses of each dosing suspension confirmed that all animals received the intended dose within experimental limits of ± 10%.

Maternal data: There were no mortalities. No treatment-related clinical signs were observed. Food consumption was not affected by treatment. Mean body weight gain was slightly reduced at 100 mg/kg bw/day and markedly lower at 200 mg/kg bw/day.

Body weight gains of dams (mean values, gram):

Time	(mg/kg/day)		
Period	0	100	200
Dosing	29.3(100)	27.4(93.5)	21.5*(73.4)
Pregnancy	96.9(100)	91.9(94.8)	60.4**(62.3)

Where:
*or**=Statistically significant at the 5% or 1% level, respectively. Data in brackets express body weight gain as a percentage of that seen in the controls.

Fetal data: Fetal weight and placental weight were reduced at 100 and 200 mg/kg bw/day. The incidence of runts was higher at 100 and 200 mg/kg bw/day. The incidence of fetuses with minor skeletal deviations was higher at 100 mg/kg bw/day. The number of surviving fetuses per dam was reduced at 200 mg/kg bw/day. The incidence of fetuses with malformations was higher at 200 mg/kg bw/day.

Effects on fetuses (mean values):

Parameter	(mg/kg bw/day)		
	0	100	200
No. of corpora lutea/dam	13.6	13.9	14.2*

No. of implantations/dam	12.5	12.2	11.8
No. of males/dam	5.9	6.0	3.1**
No. of females/dam	6.1	5.9	2.4**
No. of males+females/dam	12.0	11.9	5.5**
No. of losses/dam	0.5	0.3	6.3**
Mean weight of fetuses(g)	3.55	3.06**	2.35**
Mean weight of placenta(g)	0.59	0.52*	0.49**
No. of fetuses/litter with minor skeletal deviations	2.67	4.32*	2.24
No. of fetuses with malformations	0.29	0.63	0.80*
No. of runts/litter	0.24	2.84**	4.96**

Where:
*or**=statistically significant at the 5% or 1% level, respectively.

The distribution of malformations is summarized below.

Rat Teratology study: Malformations:

Type of	(mg/kg bw/day)			
Microphthalmia, left side	2	0	0	
False posture of hind legs	0	0	1	
Undescended testicle	2	11	6	
Hydronephrosis	1	1	7	
Multiple malformation	1	0	0	
Cleft palate	0	0	4	
Humeral dysplasia	0	0	1	
General edema		0	0	1
Long bone dysplasia	0	0	2	
Diaphragmatic hernia	0	0	1	

Test substance : 1,2,4-triazole; purity: 94%

Conclusion : Maternal NOAEL: < 100 mg/kg bw/day based on retarded weight gain at 100 mg/kg bw.
Developmental NOAEL: < 100 mg/kg bw/day based on an increased incidence of runts, lower fetal and placental weights, and a higher incidence of minor skeletal deviations at 100 mg/kg bw.

Reliability : (1) valid without restriction
Guideline study; GLP

13.10.2008 (3) (24)

Species : rat
Sex : male/female
Strain : other: Wistar Hannover
Route of admin. : oral feed
Exposure period : From 10 weeks premating P-generation through 61 days old for F2-pups
Frequency of treatm. : Daily
Duration of test : From 10 weeks premating P-generation though day 61 of F2-pups
Doses : 250 and 500 ppm
Control group : yes, concurrent vehicle
NOAEL maternal tox. : = 500 ppm
NOAEL teratogen. : > 500 - ppm
Method : other: OECD 416
Year : 2005
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : Also conducted in compliance with:
OPPTS 870.3800 Reproduction and Fertility Effects
EU Guidelines on Reproductive Toxicity Studies, 91/414/EEC
JMAFF 12Nousan No. 8147

1,2,4-triazole was administered continuously via the feed to Wistar Hannover rats (30/sex/dietary level) at nominal dietary concentrations of 0,

250, 500, and 3000 ppm. To maintain a more constant dosage (on basis of mg/kg bw/day) throughout the entirety of the study the dietary levels were reduced for females during lactation. All test diets (including control) were available for ad libitum consumption; the homogeneity and stability of 1,2,4-triazole as a dietary admixture was confirmed analytically. Additional details of this study provided in section 5.8.1.

Developmental toxicity:
Following parturition, the litters were evaluated for effects on pup body weight, litter size, sex ratio, pup viability, onset of preputial separation and vaginal patency and anogenital distance (F2- pups only).

Result : The mean daily intake of the test substance (mg 1,2,4-triazole/kg bw/day) throughout this two-generation reproduction study at nominal dietary concentrations of 0, 250, 500 or 3,000 ppm, respectively, is summarised in the following table:

Mean daily intake of 1,2,4-triazole in two-generation reproduction study:

Phase of Study	250 ppm in (mg/kg/d)(a)	500 ppm in (mg/kg/d)(a)	3000 ppm in (mg/kg/d)(a)
Lactation (P-gen)			
Female	19.3	38.7	NA
Lactation (F1-gen)			
Female	20.3	35.8	NA

Where:
a) Individual values were based on the means for each particular phase for each generation,

The histopathological lesions in the cerebellum were identical to that observed in the sub-chronic and neurotoxicity study in rats and are characterized by variable loss of Purkinje cells, white matter degeneration and gliosis. The white matter tract degeneration presented as nerve fiber (axonal) swelling or fragmentation often with digestion chambers containing debris and macrophage. No similar changes were noted in the 500 ppm animals. The statistical differences associated with certain parameters of F2-pups (pup weights, preputial separation, brain- and spleen weights) are considered to be attributed to an incidental difference in the time of delivery for both the 250- and 500-ppm dietary groups, relative to concurrent controls, rather than exposure to the test substance. The control pups were heavier than the treated group pups and above the range of historic controls because more control dams delivered on gestation day 23 and fewer on day 21 in comparison to the treatment groups.

The following table summarizes the developmental NOAEL and LOAEL and key findings from the two generation reproductive study with 1,2,4-triazole:

Dosage Levels (mg/kg/d)(a)	NOAEL (mg/kg/d)	LOAEL (mg/kg/d)	Key effects at LOAEL
P-gen Lactation: (0, 250, and 500 ppm) (0, 19.3 and 38.7)	Developmental: (F1/F2): 35.8	>35.8	Developmental: (F1/F2):
F1-gen Lactation: (0, 20.3 and 35.8)			

BW=Body weight
BWG=Body weight gain
(a)=Individual values were based on the means for each particular phase.

Developmental NOAEL: > 500 ppm (equivalent to > 35.8 mg/kg bw/day)

based
on lack of treatment-related effects in F1 and F2 pups at 250 and 500 ppm.

Test substance : 1,2,4-triazole, purity 99.9%

Conclusion : These results, including an extensive investigation of brain morphology, provided no evidence of developmental neurotoxicity at a dietary level of 500-ppm.

Reliability : (1) valid without restriction
Guideline study; GLP

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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