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**TIER 1 SCREENING SIDS DOSSIER
ON THE HPV PHASE.. .CHEMICAL**

CYCLOHEXANOL.

CAS NO. 108-93-0

September 26, 2001

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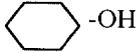
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SIDS PROFILE

DATE: September 26, 2001

1.01 A.	CAS No.	108-93-0
1.01 C.	CHEMICAL NAME	CYCLOHEXANOL
1.01 D.	CAS DESCRIPTOR	Not applicable
1.01 G.	FORMULA & STRUCTURE	C ₆ H ₁₂ O 
1.5	QUANTITY	1240 million pounds for 1998
1.7	USE PATTERN	Mainly used in the production of adipic acid and cyclohexylamine. Also used as an intermediate for pesticides, plasticizers, rubber chemicals, and pharmaceuticals; very limited use as a special process solvent.
1.9	SOURCES AND LEVELS OF EXPOSURE	Process leaks during manufacture of cyclohexanol or conversion to other chemicals such as caprolactam, adipic acid and cyclohexylamine would give rise to some vapor concentrations which may affect exposed personnel. There is also a low probability of skin contact for which maintenance workers would be primarily affected.
TEST PLAN JUSTIFICATION/ISSUES FOR DISCUSSION	SIDS testing required: Repeated exposure study and, depending on results, either a one-generation reproduction study or a developmental toxicity study; also, water stability (hydrolysis) will be measured.	

Tier 1

SIDS SUMMARY

DATE: September 26,200 1

CAS NO: 108-93-o		Information	OECD Study	GLP	Other Study	Estimation Method	Acceptable	SIDS Testing Required
STUDY		Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL-CHEMICAL DATA								
2.1	Melting Point	Y	N	N			Y	N
2.2	Boiling Point	Y	N	N			Y	N
2.3	Density	Y	N	N			Y	N
2.4	Vapor Pressure	Y	N	N			Y	N
2.5	Partition Coefficient	Y	Y	N			Y	N
2.6	a. Water Solubility b. PH and pKa Values	Y					Y	N
2.7	Flash Point	Y						
2.8	Flammability	Y						
2.12	Oxidation: Reduction Potential	N						
2.13	Adsorption/Desorption to Soil	Y						

ENVIRONMENTAL FATE and PATHWAY								
3.1.1	Photodegradation	Y	N		Y	Y	Y	N
3.1.2	Stability in water	Y/N			Y	N	N	Y
3.3	Transport and Distribution	Y	N			Y	Y	N
3.5	Biodegradation	Y	Y			N	Y	N
ECOTOXICITY								
4.1	Acute Toxicity to Fish ¹	Y	N	N			Y	N
4.2	Acute Toxicity to Daphnia ¹	Y	Y	N			Y	N
4.3	Toxicity to Algae ¹	Y	Y	N			Y	N
TOXICITY								
5.1	Acute Toxicity							
5.1.1	Acute Oral	Y	N	N			Y	N
5.1.2	Acute Inhalation	Y	N	N			Y	N
5.1.3	Acute Dermal	Y	N	N			Y	N
5.4	Repeated Dose (General)	N						Y
5.5	Genetic Toxicity <i>in vitro</i>							
	▪ Gene mutation ▪ Chromosomal aberration	Y	N	N			Y	N
5.6	Genetic Toxicity <i>in vivo</i>	Y	N	Y			Y	N
5.7	Reproduction Toxicity	Y	N	N	Y		N	Y*
5.8	Developmental Toxicity/Teratogenicity	N	N	N			N	Y*

*Depending on results from the 90-day study, either a one-generation reproduction study or a developmental toxicity study will be conducted.

1. GENERAL INFORMATION

1.01 SUBSTANCE INFORMATION

- A. CAS-Number 108-93-0
- C. OECD Name Cyclohexanol
- D. CAS Descriptor Not applicable
- G. Structural Formula C₆H₁₁OH (smiles code)



1.5 QUANTITY

Remarks: Cyclohexanol (and cyclohexanone) is primarily consumed either isolated or as a mixture, in the production of adipic acid and caprolactam. According to company confidential data, approximately 1240 million pounds of cyclohexanol was produced in 1998. Less than 2% of this has typically been sold for use in other markets. The manufacturing process starts with either cyclohexane or phenol. (Stahl, W.F., Chemical Economics Handbook, SRI International - CEN Data Summary, Cyclohexanol and Cyclohexanone - United States, May 1998). According to that document, the merchant market for cyclohexanol was 27 million pounds in 1996 with over half (15 million pounds) used in the production of cyclohexylamine. More recently however, the primary manufacturers of cyclohexylamine have apparently switched to aniline as the raw material of choice making the market for cyclohexanol even less on a current basis.

Reference: Industrial Health Foundation, Pittsburgh, PA, June 18, 200 1

1.7 USE PATTERN

Remarks: Most of the cyclohexanol produced (-98%) is used in the production of adipic acid and caprolactam during the manufacture of nylon polymer. Other uses include the following:

- a. Intermediate for agricultural chemicals (pesticides).
- b. Intermediate for plasticizers
- c. Intermediate for rubber chemicals.
- d. Intermediate for pharmaceuticals.

Most of these uses involve further processing. Exposure to cyclohexanol in chemical processing is generally low because of the nature of the closed systems employed. Exposure of those using cyclohexanol as a chemical intermediate is expected to be similar to those found in manufacturing.

A limited amount of cyclohexanol is used as a solvent [primarily in special processes]. The high melting and boiling points and low vapor pressure restrict its use as a general solvent. In these applications, appropriate handling guides (OSHA PEL, ACGIH TLV® or equivalent) have been established to assure safe handling. The low vapor pressure (essentially a solid at room temperature) helps in reducing the potential for human exposure by inhalation.

1.9 SOURCES OF EXPOSURE

Process leaks during manufacture of cyclohexanol or conversion to other chemicals such as caprolactam, adipic acid and cyclohexylamine would give rise to some vapor concentrations which may affect exposed personnel. There is also a low probability of skin contact for which maintenance workers would be primarily affected.

2.0 PHYSICAL/CHEMICAL DATA

2.1 Melting Point

Value: 24°C
Decomposition: No Data
Sublimation: No Data
Method: No Data
GLP: Yes[]No[]?[]X[]

Remarks:

Reliability: [4] Not assignable because limited study information was available

Reference: BASF/AG Sicherheitsdatenblatt (MSDS),
Cyclohexanol (6/22/93), Ludwigshafen, Germany

2.2 Boiling Point

Value: 161.1°C
Pressure: at 101.3 kPa
Decomposition: No Data
Method: No Data
GLP: Yes [] No [] ? [X]
Remarks: No additional data
Reliability: [4] Not assignable because limited study information was available
Reference: Budavari, S.(ed.), The Merck Index, 11TH Ed., Rahway, NJ: Merck & Co., Inc., Whitehouse Station, NJ, 1989, p.426.

2.3 Density

Type: Bulk Density [] Density [] Relative Density [X]
Value: 0.9624
Temperature: 20/4°C
Method: No Data
GLP: Yes [] No [] ? [X]
Remarks: No additional data
Reliability: [4] Not assignable because limited study information was available
Reference: Lide, D.R.(ed.), CRC Handbook of Chemistry and Physics, 75th Ed., Boca Raton (FL), CRC Press Inc., 1994-1995, pp. 3 - 125.

2.4 Vapor Pressure

Value: 1.33 kPa (1.0 mmHg)
Temperature: 20°C
Method: calculated [] measured []
GLP: Yes [] No [] ? [X]
Remarks: No additional data
Reliability: [4] Not assignable because limited study information was available
Reference: BASG/AG Sicherheitsdatenblatt (MSDS), Cyclohexanol (6/22/93), Ludwigshafen, Germany.

2.5 Partition Coefficient $\log_{10}Pow$

$\log_{10}Pow$: 1.25
Temperature: 25°C

Method: calculated [] measured [X] according to OECD Guideline 107- "Partition Coefficient (n-octanol/water; Flask-Shaking method

Result: Evaluation of isolated component:
Cyclohexanol log Pow=1.25
Cyclohexanone log Pow= 0.86

Remarks: Test conditions:
25 ml octanol and 25 ml distilled H₂O, stationary phase: Megabore-capillary (DB-17), thickness of film: 1.0 mm, diameter: 0.53 mm, length: 30 m, stove temperature: 60-160°C, detector temperature: 250°C, sampler temperature: 250°C, carrier gas: N₂, columns heat pressure: 1.5 bar (absolute), total gas flow: 165 ml/min, injection amount: 2.0 ml, instrument: HP 5890 with auto sampler, detector: flame ionization detector average from 3 measurements

Test Substance: test substance= Anolon™ mixture:
53.6% Cyclohexanol
42.0% Cyclohexanone
4.4% other

GLP: Yes [] No [] ? [X]

Reliability: (2) valid with restrictions
Discrepancy between documented test parameters and standard methods, but scientifically, acceptable

Reference: BASF AG Laboratory of Analytical Chemistry. Unpublished Data (J.Nr.101745/01), 7/12/1988.

2.6 Water Solubility

Value: 3.6 wt%

Temperature: 20°C

Description: [] Of very high solubility
[] Of high solubility
[] Soluble
[X] Slightly Soluble
[] Of very low solubility
[] Not soluble

Method: No information

GLP: Yes [] No [] ? [X]

Remarks: No additional data

Reliability: [4] Not assignable because limited study information was available

Reference: Budavari, S. (ed.), The Merck Index, 11th Ed., Rahway, NJ; Merck & Co., Inc., Whitehouse Station, NJ, 1989, p.426.

2.7 Flash Point: 68°C (SF Closed Cup)

2.8 Auto Flammability: 285°C (DIN 5 1794)

2.12 **Oxidation:Reduction Potential-No Data**

2.13 **Adsorption/Desorption to Soil**

Method: Syracuse Research Corporation Model

Remarks: Cyclohexanol is slightly soluble in water with a **value** of 3.6 wt% at 20°C. If released to soil, it is expected to exhibit high-to-very-high mobility in soil. It may leach through soil to groundwater. It will not hydrolyze in moist soil, but it may be subject to volatilization from surface soil based upon estimated rates for its volatilization from water. It may be subject to biodegradation in soil based on results **seen** in laboratory aqueous screening tests.

3.0 **ENVIRONMENTAL FATE AND PATHWAYS**

3.1 **Stability**

3.1.1 **Photodegradation**

A. **Method**

Type: Air [X] Water [] Soil [] other []

Rate Constant: 17.48 E- 12 (cm³/molecules-sec)

Method: Calculated using AOPWIN v1.90 SAR Model

Remarks: Atmospheric photo-oxidation potential was estimated using the **submodel** AOPWIN (Meylan and **Howard**, 2000a). the estimation methods employed **by** AOPWIN are based on the SAR methods developed **by** Dr. Roger Atkinson et al. that rely on structural features of **the** subject chemical. The model calculates a second-order half-life with units of cm³/molecules-sec. Photodegradation based on atmospheric photo-oxidation is based on the second order rate of reaction with hydroxyl radicals (HO₂), (**k**_{phot} with units of cm³/molecules-sec). Default AOPWIN assumptions for calculation of first-order half-lives include an HO₂ concentration of 1.5 E+6 molecules/cm³ and 12 **hours** of daylight each day. Pseudo first-order half-lives (**t**_{1/2}) were then calculated as follows: **t**_{1/2} = 0.693 / **k**_{phot} x HO₂ x 12-hr / 24-hr.

For cyclohexanol, the **k**_{phot} value was calculated to be 17.48 E-12 cm³/molecules-sec and the resulting half-life was **t**_{1/2} = 0.612 days or 14.7 hours.

Reliability: [2] Valid with Restrictions

Reference: Meylan, W. and P.H.Howard. 2000a. User's Guide for AOPWIN, Version I .9, Syracuse Research Corporation, North Syracuse, NY, March. 2000.

3.1.2 Stability in Water

No data for water stability (hydrolysis) is available and EPIWIN models cannot estimate hydrolysis rates for a compound with a structure like cyclohexanol; however cyclohexanol is fairly biodegradable and that information supports not measuring stability in water (hydrolysis).

3.2 Transport and Distribution between Environmental Compartments Including Estimated Environmental Concentrations and Distribution Pathway

Method: Calculation according to Mackay, Level 111, fugacity-based models obtained from Trent University's Modeling Center. Specific model: Equilibrium Concentration Model (EQC) Level 3 Model, Version 1.01.

Remarks: Default values were assumed for environmental compartment descriptions, dimensions, and properties, **advective** and dispersive properties. Chemical specific parameters were: molecular weight (100.16 g/mol), Henry's Law Constant (4.44 E-6 atm-m³/mol), vapor pressure (0.65 mm Hg), log Kow (1.23), air half-life (14.7 hr), water and soil half-lives (360 hr), sediment half-life (1440 hr), and equal loadings to air, water, and soil.

Results Distribution was as follows:
Air (2.25%)
Water (50.2%)
Soil (47.5%)
Sediment (<0.1%)

Reliability: [2] valid without restriction

Reference: Meylan, W. and P.H. Howard. 2000a. User's Guide for AOPWIN, Version 1.9 Syracuse Research Corporation. North Syracuse, NY. March, 2000.

Mackay, D. et al. 1996a. Assessing the fate of new and existing chemicals: a live-stage process. *Environ. Toxicol. Chem.* 15(9): 1618-1626.

Mackay, D. et al. 1996b. Evaluating the environmental fate of a variety of types of chemicals using the EQC model. *Environ. Toxicol. Chem.* 15(9): 1627-1637.

3.5 Biodegradation

Type: aerobic [X] anaerobic []

Inoculum: non-adapted

Concentration of the chemical: 398 mg/l related to dissolved organic carbon (DOC)

Medium: activated sludge
Degradation: = 98% after 6 days

Kinetics: 1% after 3 hours
45% after 1 day
98% after 4 days

Method: OECD Guideline 302B. "Inherent biodegradability: Modified Zahn-Wellens Test"

Test Substance: as prescribed by 1.1-1.4

Results: Concentration : 13 1 mg/l
DOC = 398 mg/l, AOX < 1 mg/l
Elimination after 3 hours : 370 mg/l DOC
after 6 days: 24 mg/l

Test Conditions: steam solution: DOC = 3060 mg/l
AOX < 3 mg/l, pH = 7.7 value = 300 ml, inoculum = 150 mg/l

GLP: Yes [] No [] ? [X]

Reliability: [2] valid with restrictions

Reference: BASF AG, unpublished data. LGU 87-758. 2.2/6187, 10/8/1990

4.0 ECOTOXICOLOGICAL DATA

4.1 Acute toxicity to Fish

A. Preferred Result

Type of Test: static [] semi-static [] flow-through [X] other []

Species/Strain: Pimephales **promelas** (fathead minnow) from Environmental Research Laboratory, Diluth culture

Exposure period: 96 hours

Results: 96-hour LC50 = 704 mg/l (CL not relevant)

Analytical monitoring: Yes

Method: Test method of the USEPA Committee on Methods for Toxicity (1975). Approximately 25 fish, about 29 days old, were exposed for 96 hours to nominal cyclohexanol concentrations of 0, 133, 222, 369, 616 and 1026 mg/L; each concentration was run in duplicate. Analytically measured concentrations for each group (and its replicate) were: <0.7 (<0.7), 120 (124), 183 (185), 304 (310), 532 (533) and 942 (952) mg/L. During the exposure period, the average temperature of the test medium was 24.4 °C ± 0.72 °C (mean ± ISD).

Test Substance: Purity 99%

GLP: Yes [] No [] ? [X]

Remarks: At 96 hours, 100% mortality was observed at the highest dose level. No mortality was seen at other doses or in the control group at 96 hours. Affected fish lost equilibrium prior to death. Fish in the tank did not school after 30 hours of exposure. The 96-hr LC50 was calculate using the trimmed Spearman-Karber method on a PDP 11/70 computer.

Reliability: [2] valid with restrictions

References Brooke, L.T., et al. Acute Toxicity of Organic Chemicals to Fathead Minnows. Vol. 1 Center for Lake Superior Environmental Studies, University of Wisconsin, 1982.

B. Supporting Data

The preceding study and 9 to 11 other freshwater fish studies have been conducted on cyclohexanol and are reported in USEPA's ECOTOX Report (November 27, 2000). All show the same low order of acute toxicity to freshwater fish.

4.2 Acute Toxicity to Invertebrates

Type of Test: static semi-static flow-through other ?

Species: *Daphnia magna*

Exposure period: 48 hours

Results: EC₀ = 250 mg/l
EC₅₀ >500mg/l
EC₁₀₀ >500 mg/l

Analytical monitoring: Yes No

Method: Directive 84/449/EEC, C.2 "Acute Toxicity for Daphnia" (1998)

Test Substance: Cyclohexanol (C₆H₁₁OH), produced at BASF AG in Ludwigshafen (batch number: B7/11/87, commercial product) with:
purity of >99%
molecular weight: 100.16 g/mol
color: colorless
water solubility: 40 g/l (20° C)
homogeneity: homogeneous

GLP: Yes No ?

Remarks: Test water has a pH of 7.9 a total hardness of 2.55 mmole/l, as alkalinity up to 4.3 of 0.85 mmole/l, a conductivity of 550-650 ms/cm, a test temperature of 292-294°K, and a oxygen content of > 2 mg/l.

Reliability: [2] Valid with restrictions

Reference: BASF AG, Department of Ecology, Unpublished Data (11/1/87), 1/1 511988.

4.3 ACUTE TOXICITY TO AQUATIC PLANTS (e.g. Algae)

Type of test: static semi-static flow-through other

Species: *Scenedesmus subspicatus* (Algae)

Exposure period: 72 hours

Endpoint: growth rate

Results: 72-hr EC20 = 0.11 mg/l
72-hr EC50 = 29.2 mg/l

96-hr EC20 = 0.22 mg/l
96-hr EC50 = 29 mg/l
96-hr EC90 = 470 mg/l

Analytical monitoring: Yes No

Method: DIN 38412, Part 9, "Determination of inhibitory effect on cell multiplication" (1988)

Test substance: Cyclohexanol (C₆H₁₁OH), produced at BASF AG in Ludwigshafen (batch number: B7/1 1/87, commercial product) with:
purity of >99%
molecular weight: 100.16 g/mol
color: colorless
water solubility: 40 g/l (20° C)
homogeneity: homogeneous

GLP: Yes No

Remarks: The duration of the entire test was 96 hours. Inoculum density was 10,000 cells/ml, test temperature was 293°K, initial pH was 9.7 and pH range was 8 to 9.7; illumination: artificial light-permanent illumination, intensity of 120 E/m²a

Reliability: [2] valid with restrictions

Reference: BASF AG. Department of Ecology, unpublished data (111 1/87), 1/22/1988.

5.0 TOXICITY

51.1 Acute Oral Toxicity

A. Preferred Result:

Type of Test: LD50

Species: Sprague-Dawley albino rats

Value: 1550 mg/kg (1390-1710 mg/kg CL)

Method: Consistent with OECD Test Guideline 40 I : single oral dose, undiluted; 2 to 3 rats/sex/dose; average weight at dosing 225 to 240 g; doses of 1000, 1260, 1580, 2000, 2510 and 3160 mg/kg were used

Test substance: cyclohexanol (>90% purity)

GLP: Yes No [X] (See Remarks)

Remarks: Most deaths occurred within 24 hours, a few within 48 hours; no deaths occurred at 1000 or 1260 mg/kg; clinical signs included weight loss, increasing weakness, ocular discharge, salivation, collapse and death. Gross autopsy results showed hemorrhagic lungs, discolored liver, and acute GI inflammation in decedents; no gross findings of toxicity were seen in survivors at 14 days. This study was conducted prior to, but was consistent with, US GLP Guidelines Published in 21 CFR 58, 1978, and effective June 20, 1979.

Reliability: [2] valid with restrictions

Reference: Younger Laboratories. Project No.Y-78-73, OTS053388617 (April 28) (TSCATS/424698), 1978.

B. Supporting Data:

Type: LD50

Species: Carworth-Wistar Rats

Value: 2060 mg/kg
Method: Single oral dose, undiluted; 5 rats/dose; _____ doses ranging from m g i k g to _____ mg/kg.
Test substance: Purity not known
GLP: Yes [] No [X] ? []
Remarks: No additional information
Reliability: [2] valid with restrictions
Reference: H.F. Smyth et al. Am.Ind. Hyg. Assoc. J. 23: 95-107, 1962.

5.1.2 Acute Inhalation Toxicity

Type: LC50
Species: Sprague-Dawley rats (M/F)
Value: >3.63 mg/l
Method: A dynamic inhalation exposure involving head and nose was used. The dose was nominally 7.5 mg/l but was analytically determined to be 3.63 mg/l by gas chromatography. Cyclohexanol was administered as an aerosol (particle size unknown) to 10 male and 10 female rats. Body weight at the start averaged 185g ± 1.5g and rats were weighed 7 and 14 day after dosing.
Test substance: cyclohexanol with a purity of 99.9%
GLP: Yes [] No [X] ? []
Remarks: No animals died during the 14-day observation period. The only clinical sign was "unkempt fur" and it occurred only during the exposure. At 14 days post-dosing, gross autopsies were unremarkable. Body weight gain was similar for control and test rats.
Reliability: [2] valid with restrictions
Reference: BASF AG, Department of Toxicology, unpublished studies (78/791), 4/19/79.

5.1.3 Acute Dermal Toxicity

Type: LD50
Species: New Zealand albino rabbits
Value: >50 l <794 mg/kg
Method: Cyclohexanol was applied undiluted to the skin of rabbits for 24 hours, 1 male or 1 female rabbit/dose, at 7 doses ranging from 3.16 to 5010 mg/kg. Body weights ranged from 1.9 to 2.6 kg.
Test substance: cyclohexanol (>90% purity)
GLP: Yes [] No [X] ? []
Remarks: All deaths occurred within 24 hours. Weakness, collapse, and death. Gross autopsy of decedents showed lung hyperemia, liver and spleen discoloration, enlarged gall bladder, darkened kidneys and GI inflammation. Survivors at 14 days showed no remarkable findings at gross autopsy.

Reliability: [2] valid with restrictions
Reference: Younger Laboratories. Project No.Y-78-37, OTS0538617 (April 20).
TSCATS/424698, 1978.

5.4 REPEATED DOSE TOXICITY (Inadequate Information)

Remarks:

Several limited repeated-exposure toxicity studies have been conducted by the oral route (Weitzer 1950, Lake 1982, Messiha 1985, Lox 1985, and Wakabayashi 1991), the inhalation route (Pohl 1924, DiPrisco 1932, Treon 1943, and Dobrinski 1964) and the **dermal** route (Pohl 1924 and Treon 1943). However, none of the preceding studies have adequate technical or scientific merit to be used to define the toxic hazard associated with repeated exposure to cyclohexanol.

Reliability: Inadequate Information

References:

- ❖ DiPrisco, L. (1932). Minerva Med. **II**: 432-426 (CA27:339).
- ❖ Dobrinski, A. A. (1964). Gig. Sanit. **29** (12): 8-13 (CA62:9683f)
- ❖ Lake, B. G., et al. (1982). Acta Pharmacol. Toxicol. **51** (3): 217-226 (CA97:209833w).
- ❖ Lox, C. (1995). J. Cellular Biochem. Suppl. **19A**: 197 (Abstract No. A50308)(Biosis/95/15424).
- ❖ Messiha., F.S., et al. (1985). Neurobehav. Toxicol. Teratol. **7** (2): 207-208.
- ❖ Pohl, J. (1924). Z. Gewebehyg. Unfallverh. **1**:91 (Cited in Treon et al. 1943).
- ❖ Treon, J. F., et al. (1943). J. Ind. Hyg. Toxicol. **25**: 323-347 (CA39: 5002).
- ❖ Treon, J. F., et al. (1943). J. Ind. Hyg. Toxicol. **25**: 199-214 (CA39: 5002).
- ❖ Wakabayashi. T. et al. (1991). Acta Pathol. Jpn. **41**(6): 405-413 (BIOSIS/91/28271).
- ❖ Weitzel, K.G. et al. (1950). Z. Physiol. Chem. **285**: 58-77 (CA44: 6527h).

5.5 GENETIC TOXICITY IN VITRO

A. Bacterial Test

(1) Type: Bacterial reverse mutation assay

System of testing: Standard plate method

Concentration: cyclohexanol concentrations ranged from 500 µg/plate to 10,000 µg/plate (without metabolic activation) or 15,000 µg/plate (with metabolic activation)

Method of Activation: With [] Without [] With and Without [X] No Data []

Results: "Not mutagenic"

Test Substance: Purity unknown

Cytotoxicity Concentration: 7500 µg/plate, with and without metabolic activation

Precipitation Concentration: Not applicable

Genotoxic Effects: Negative, with and without metabolic activation

Method: Four histidine-requiring strains of *Salmonella typhimurium* bacteria were used (TA 1535, TA 1537, TA 1538 and TA 98). Two replicates were used at each test substance concentration and all tests were performed in the presence and absence of a rat-liver homogenate (S.9) Approximately 10⁸ bacteria were used in each plate and all plates were incubated at 37°C for 48 hours. Both positive

(ethanol) and negative controls (2 AA, MNNG, et al.) were used in these studies.

GLP: Yes [] No [X] ? []

Reliability: [2] valid with restrictions

Reference: DuPont Company, unpublished studies, Haskell Laboratory Report No. 755-75, 1975.

(2) Type: Other Point Mutation Assays in Bacteria (Supporting Data)

Summary:

Three other *in vitro* studies using Salmonella typhimurium bacteria were conducted on cyclohexanol. In two assays (Frantz 1981; Rowe and McCollister 1982), there was no evidence of mutagenicity but details were limited. In a third study (Haworth 1983), cyclohexanol tested at 3300 µg/plate and 9100 µg/plate, with and without metabolic activation, produced results relative to mutagenicity potential.

References:

- ❖ Frantz, S.W., and J.E. Sinsheimer. Mutation Research 90: 67-78. 1981.
- ❖ S. Haworth et al: Salmonella Test Results for 250 chemicals. Environ. Mutagen. Suppl. I : 3-142. 1983.
- ❖ Rowe. V.K. and S.B. McCollister. Patty's Ind. Hyg. Toxicology, 3rd ed. pp. 4644-4649, 1982.

B. Non-Bacterial In Vitro Test

Type: cytogenetic assay (chromosome aberration)

System of testing: human leukocytes

Concentration: 0.01, 0.001 and 0.0001 moles/l cyclohexanol were tested

Method of Activation: With [] Without [X] With and Without [] No Data []

Results: "Positive"

Cytotoxicity Concentration: unknown

Precipitation Concentration: unknown

Genotoxic Effects: without metabolic activation, cyclohexanol was reported to induce achromatic regions, breaks and deletions in chromosomes.

Method: Human Leukocyte Assay described by Morhead (1960).

GLP: Yes [] No [X] ? []

Test Substance: no data

Remarks: limited technical details; non-validated protocol; non-GLP

Reliability: [4]

References: Morhead, P.S., et al. Exper. Cell. Res. 20: 613-616, 1960.
Collins, J.P. Diabete 19 (4): 215-221, 1971 (CA77:1583u).

5.6 GENETIC TOXICITY *IN VIVO*

A. Type: Micronucleus Assay

Species/strain: NMRI Mice

Sex: Female [] Male [] Male/Female [X] No Data []

Route of Administration: oral gavage

Exposure Period: 16, 24 and 48 hours for the high dose group; 24 hours for the lower doses

Doses: 500, 1000, and 1500 mg/kg bw

Results: "Negative"
Animals receiving the positive and negative control treatments showed no signs of toxicity, but mice given cyclohexanol did have toxic signs. The frequency of erythrocytes containing micronuclei was similar between negative controls and the 3 cyclohexanol dose groups (including all time points for the high-dose group).

Effect on Mitotic Index or P/N Rate: No information

Genotoxic Effects: Not an *in vivo* mutagen

Method: According to Schmid, W.: The Micronucleus Test, In: Kilbey et al. (eds.). Handbook of Mutagenicity Test Procedures. Amsterdam-New York, Elsevier, 1977.
The test substance was suspended in an aqueous 0.5% carboxymethyl cellulose (CMC) formulation. It was given to male and females in a volume of 10 ml/kg. The negative control received merely the carrier solution. The positive control for clastogenicity was 20 mg/kg bw of cyclophosphamide in distilled water using a volume of 10 ml/kg. The positive control for spindle poisoning effects was 0.15 mg/kg bw of vincristine in distilled water using a volume of 10 ml/kg. Five males and five females were used per dose. Animals were sacrificed at the times indicated and bone marrow from both femurs was prepared. After staining, 1000 polychromatic erythrocytes were evaluated per animal and examined for micronuclei. The normocytes with and without micronuclei occurring per 1000 polychromatic erythrocytes were also recorded.

GLP: Yes [X] No [] ? []

Test Substance: 98.8% pure cyclohexanol

Remarks: Under these experimental conditions, cyclohexanol has no chromosome-damaging (clastogenic) effects, nor does it lead to any impairment of chromosome distribution in mitosis.

Reliability: [I] valid without restrictions

Reference: BASF AG, Department of Toxicology, unpublished studies (89/843), I 0/29/9 1.

B. Type: Gene Mutation *In Vivo* (Supporting Data)

Summary: Cyclohexanol at 0.1 ml/100ml was given to *Drosophila melanogaster* (fruit flies) for 3 days as part of an SLRL Test. The results of this non-GLP test were negative, i.e. the frequency of recessive lethal mutations was not affected by treatment with cyclohexanol. even when followed by gamma and x-ray (1500R) irradiation.

Reference: R.I. Goncharova. Genetic Activity of Some Cyclohexane Derivatives. Genet. Tsito., pp. 137-142, 1970 (CA76:54780s).

5.7 TOXICITY TO REPRODUCTION

Remarks: In a study by Tyagi et al. (1979), 20 adult male gerbils and 20 male rats were subcutaneously injected with 15 mg cyclohexanol/kg/day for a period of 21 and 37 days, respectively. A significant reduction in the weights of the testes, epididymides, seminal vesicles and ventral prostate was detected. In addition, the authors indicated, based on their histological evaluation, that spermatogenesis in both species was arrested. Recovery was not investigated. In another study (Dixit et al. 1980), groups of 15 male rabbits received 25 mg cyclohexanol/kg/day by gavage for a period of 40 days. One group was allowed a 70-day recovery period following cessation of cyclohexanol administration. Similar to the preceding gerbil and rat findings, a significant reduction in the weights of the testis and epididymides was observed. Additionally, marked degenerative changes were noted upon microscopic examination of the testes. The changes were consistent with those previously described for the gerbil and the rat. Normal spermatogenesis was seen after 70 days following cessation of cyclohexanol treatment. The organ weights were also comparable to the controls. In a third study (Lake et al. 1982), male rats were given 455 mg cyclohexanol/kg/day by gastric intubation for 7 days. Cyclohexanol increased liver size and stimulated certain parameters of hepatic xenobiotic metabolism in the rat but had no effect on testis weight.

Reliability: Inadequate Information (No study meets HPV requirements.)

References:

- ❖ Dixit, V.P. et al (1980). Reversible Chemical Sterilization: Effects of Cyclohexanol Administration on the Testes and Epididymides of the Rabbits. Indian J. Physiol. Pharmacol. 24: 278-286.
- ❖ Lake, B. G. et al. (1982). Studies on the Effects of Orally Administered Dicyclohexyl Phthalate in the Rat. Acta Pharmacol. Toxicol. 5 1: 2 17-226.
- ❖ Tyagi, A, et al. (1979). Antispermatic Activity of Cyclohexanol in the Gerbil and House Rat. Indian Journal of Experimental Biology 17: 1305-1307.

5.8 DEVELOPMENTAL TOXICITY

No Information

5.11 EXPERIENCE WITH HUMAN EXPOSURE (WORKPLACE)

Remarks: The five US producers of cyclohexanone/cyclohexanol have, on various occasions between 1994-2000, taken area and/or personal samples for determination of possible exposure to cyclohexanol. Information has been submitted to IHF as Agent for the Consortium. To preserve the confidentiality of individual Company data, the details may be summarized as follows:

1. Samples were collected on either charcoal tubes or charcoal badges and analyzed by gas chromatography using flame ionization detection methodology.
2. The lower limits of detection varied from about 0.01 ppm for the longer-term samples (8 hours) to 0.4 ppm for short-term samples (15 minutes to one hour)
3. Area samples (n>200) and personal samples (n=200) ranged from averages of 0.01-3.5 ppm for longer sampling intervals and averages of 0.4-29 ppm for short sampling intervals.
4. Area samples tended to be of long duration with results only slightly above the appropriate detection limits for the majority of samples.
5. None of the samples taken suggested the probability of exposure in excess of the current OSHA PEL/ACGIH TLV® of 50 ppm.

Reference: Industrial Health Foundation, Pittsburgh, PA. June 15, 2001