201-15755

The Dow Chemical Company
Midland, Michigan 48674

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17 December 2004

Mr Michael O. Leavitt, Administrator
US Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116

Attention: Chemical Right-to-Know Program

On behalf of The Dow Chemical Company, I am pleased to submit the test plan and robust summaries in IUCLID format for Tetrahydrobenzaldehyde (CAS # 100-50-5). All documents are in Adobe Acrobat (pdf) files.

We understand this information will be posted on the internet for comments for a period of 120 days. Please forward comments to me at the address below.

Sincerely,

Kenneth D. Nitschke, D.A.B.T
The Dow Chemical Company
1803 Bldg.
Midland, MI 48674

201-15755A

HIGH PRODUCTION VOLUME (HPV)

CHEMICALS CHALLENGE PROGRAM

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TEST PLAN

For

TETRAHYDROBENZALDEHYDE

CAS NO. 100-50-5

December 2004

Prepared by:

The Dow Chemical Company
Midland, Michigan 48674

EXECUTE SUMMARY

The Dow Chemical Company voluntarily submits the following screening information data and Test Plan covering the chemical Tetrahydrobenzaldehyde, also known as THBA (CAS No. 100-50-5), for review under the Environmental Protection Agency's High Production Volume (HPV) Chemicals Challenge Program. A substantial amount of data exists to evaluate the potential hazards associated with THBA. Use of key studies or estimation models available from data already developed provide adequate support to characterize all but three endpoints in the HPV Chemicals Challenge Program. The three endpoints for which no data presently exists are algal toxicity and developmental and reproduction toxicity. Modeling predicts that algae would be less affected than fish and daphnids by THBA. An algae study is considered to be unnecessary since THBA is a closed system intermediate. Any material accidentally released to the environment would be readily biodegraded. Since THBA is a closed system intermediate there is no need for a reproduction study. Based on the limited exposure of workers to this material and the corrosive nature of THBA which has resulted in a high degree of personal protective equipment, a developmental toxicity study is considered to be unnecessary.

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TEST PLAN FOR TETRAHYDROBENZALDEHYDE

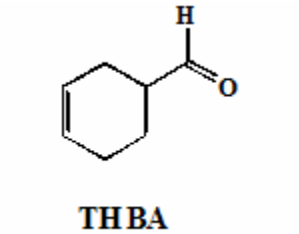
CAS Nos. 100-50-5

I. INTRODUCTION AND IDENTIFICATION OF CHEMICAL

Under EPA's High Production Volume (HPV) Chemicals Challenge Program, The Dow Chemical Company (Dow) has committed to voluntarily compile basic screening data on Tetrahydrobenzaldehyde (THBA). The data included in this Test Plan include physicochemical properties, environmental fate, and human and environmental effects of THBA, as defined by the Organization for Economic Cooperation and Development (OECD). The information provided comes from existing data developed by or on behalf of Dow, or is found in the published scientific literature.

A. Structure and Nomenclature

Following is a structural characterization of THBA and its associated nomenclature.



Tetrahydrobenzaldehyde
CAS No. : 100-50-5
Synonyms: THBA

B. Manufacturing & Use

Union Carbide Corporation, a subsidiary of The Dow Chemical Company, operates a single manufacturing site producing THBA. The manufacturing operation is a closed, batch process. During production, butadiene and acrolein react together using a catalyst to produce THBA. Following the reaction, THBA is piped directly to another plant were it is used as a chemical intermediate. This material has been infrequently transported to a second UCC site (on average approximately once every two years) where it is also used as a chemical intermediate to produce a second product.

The Occupational Safety and Health Administration (OSHA) has set Permissible Exposure Limits (PEL) for the precursors 1,3-butadiene and acrolein of 1 and 0.1 ppm, respectively. Since 1,3-butadiene is a gas at room temperature, any production practices in place to limit exposure to 1,3-butadiene will be equally or more effective for reducing exposure to the relatively non-volatile THBA.

THBA has an odor threshold of approximately 0.22 ppm, and will be detected by smell before air concentrations reach unsafe levels.

Approximately 50 individuals are involved in the manufacture or use of THBA and these individuals have extremely low potential for skin and airborne exposure. Due to the subacute hazards associated with exposure to THBA, an occupational exposure limit of 5 ppm (Union Carbide Occupational Exposure Guideline) has been set. This has resulted in specific manufacturing procedures and practices to minimize the exposure potential to THBA. Between 1988 and 1998, over 300 samples were obtained from the THBA production and use plants. Only two values were greater than 1 ppm, and both of these were below the UCC Occupational Exposure Guideline. A review of more recent industrial hygiene samples from 1999 to the present in both manufacturing and use facilities have also shown that all samples are 1 ppm or lower. Due to the corrosive nature of THBA, personal protective equipment including (self-contained breathing apparatus (SCBA) when vapor exposure is high (considered to be greater than the action level (2.5 ppm) of the UCC Occupational Exposure Guideline), monogoggles, gloves and chemical apron, are worn whenever exposure to THBA is possible. Such operations could include sampling and material transfer operations, shutdown and clean-up activities.

Following the production of THBA, the material undergoes two chemical reactions to produce a single final product. The amount of THBA present in the final product is expected to be very low, probably less than 1 ppm.

The most likely but infrequent route of THBA emission would be via incorporation into wastewaters associated with its manufacture. These wastewaters are treated at an on-site wastewater treatment plant employing secondary biological treatment. Based on the ready biodegradability of THBA, the material is expected to be completely removed from wastewater during such treatment.

II. TEST PLAN RATIONALE

The information included in this Test Plan has come from one or more of the following sources:
1) Internal studies conducted by or on behalf of The Dow Chemical Company
2) Studies that have been extracted from the scientific literature either as primary references, or as reported in well-accepted, peer-reviewed reference books
3) Calculation methods or quantitative structure-activity relationships (QSAR) \which are accepted by the US EPA for such purposes (1999b).

This assessment includes information on physicochemical properties, environmental fate, and human and environmental effects associated with THBA. The data used to support this program include those Endpoints identified by the US EPA (1998). Key studies have been identified for each data Endpoint, and are summarized in Robust Summary form in Section VII of this Dossier.

All studies were reviewed and assessed for reliability according to standards specified by Klimisch *et al* (1997), as recommended by the US EPA (1999a). The following criteria were used for codification:
1. Valid without Restriction - Includes studies which comply with US EPA and/or OECD-accepted testing guidelines, which were conducted using Good Laboratory Practices (GLPs) and for which test parameters are complete and well documented,
2. Valid with Restrictions – Includes studies which were conducted according to national/international testing guidance and are well documented. May include studies conducted prior to establishment of testing standards or GLPs but meet the test parameters and data documentation of subsequent guidance; also includes studies with test parameters which are well documented and scientifically valid but vary

slightly from current testing guidance. Also included are physical-chemical property data obtained from reference handbooks as well as environmental endpoint values obtained from an accepted method of estimation (i.e. EPIWIN).
3. Not Valid – Includes studies in which there are interferences in either the study design or results that provide scientific uncertainty or where documentation is insufficient.
4. Not Assignable – Includes studies in which limited data is provided.

Those studies receiving a Klimisch rating of 1 or 2 are considered adequate to support data assessment needs in this Test Plan?.

III. TEST PLAN SUMMARY AND CONCLUSIONS

Physical-chemical property values (Melting Point, Boiling Point, Vapor Pressure, Partition Coefficient and Water Solubility) were considered to be acceptable. The Vapor Pressure at 25° C (2.97 hPa) was calculated using an accepted estimation method, which accurately estimates the vapor pressure measured at a higher temperature (164° C). The Partition Coefficient was estimated using two different structure-fragment calculation methods, yielding Log Kow values of 1.34 and 1.89. The preferred, more conservative Log Kow value of 1.89 was determined using the accepted EPI Suite method.

Ref for VP is: AIChE. 2002. Design Institute for Physical Properties Research (DIPPR) Database, American Institute of Chemical Engineers, New York, NY.
Ref for EPI Suite is: U.S. EPA. 2003. EPI Suite software, version v3.11. United States Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, D. C. Available at: http://www.epa.gov/oppt/exposure/docs/episuitedl.htm

Environmental Fate values for Hydrolysis, Photodegradation, and Transport (Fugacity) were obtained using computer estimation –modeling programs. The material is not expected to hydrolyze. The fugacity model predicts that emissions to water, the most likely emission scenario, will remain in water (99.9%). Any material that is released to the air will be rapidly photodegraded via reaction with hydroxyl radical and ozone. The predicted half life in the atmosphere is approximately 45 minutes (0.7 hr.). Biodegradation data were considered to be acceptable. THBA was shown to be readily biodegradable, using a test procedure which is equivalent to OECD Test Guideline 301D.

Ecotoxicity of THBA has been evaluated for several aquatic organisms. In the 14-day fish toxicity study the LC_{50} was 1.1 mg/L. The EC_{50} was much higher for daphnids, at 130 mg/L. The predicted EC_{50} value for algae is greater than that predicted for fish and daphnids.

Blinova (2003) has examined freshwater bioassay organisms (e.g., algae, daphnia, and duckweed) and compared their relative acute sensitivities to a variety of water pollutants. She reported (http://www.mantraeast.org/pdf/use_of_bioassays.pdf) that acute studies with the freshwater algae, *Selenastrum capricornutum*, had equal or less sensitivity than acute studies with the daphnid (*Daphnia magna*) for leakage from oil-shale ash, industrial wastewater before treatment, and municipal wastewater before and after treatment; only sludge from the treatment plant was slightly more toxic to the algae than acute studies with the daphnid.

The Danish EPA has recently compared the QSAR vs. measured environmental toxicity data for 180 chemicals evaluated as part of the OECD HPV program. They report that >80, 75 and 65% of the

QSAR values were within a factor of 10 of the actual values for fish, daphnia and algae, respectively. Since the QSAR for THBA predicts the acute toxicity is lowest for algae and the Danish EPA have reported a good correlation between predicted and actual values, this confirms Blinova's assessment.

In consideration of the ready biodegradability of THBA, the low potential for environmental emission, and the less sensitivity predicted for algae, conducting an algae study is unnecessary.

Mammalian Toxicity Endpoints (Acute Toxicity, Repeated Dose Toxicity, Ames Mutagenicity and Chromosomal Aberration Testing) have all been considered adequate. The material is very irritating and is corrosive in the dermal DOT test. When tested with a smaller amount of material than currently required in the eye irritation assay, 0.005 ml, moderately severe corneal injury was observed. Several two week studies have been conducted via two different routes. As part of these studies, the testes and ovaries were weighed and testes examined histopathologically. However, for reproductive toxicity purposes, these studies were of short duration and therefore rated a 4 in the Klimisch rating system. Although the study was of a short duration, there were no significant treatment-related effects noted which would indicate a reproductive effect. No developmental toxicity study was found. Point mutation and chromosomal aberration assays have been conducted and were uniformly negative.

A tabular depiction of data availability and testing recommendations for Tetrahydrobenzaldehyde (THBA) can be found in Table 1.

IV. DATA SET SUMMARY AND EVALUATION

The key studies used in this assessment to fulfill the HPV requirements have been placed in an Endpoint-specific matrix, and are further discussed below. Robust Summaries for each study referenced can be found in Section VII of this dossier.

A. Chemical/Physical Properties

All measurable HPV Endpoints for Chemical/Physical Properties have been completed (Table 2). Widely divergent melting and boiling point values were cited in reputable sources. These values have been evaluated by a group from the American Institute of Chemical Engineers and summarized in the Design Institute for Physical Property Data (DIPPR®) database. A melting point of -96.1^{o} C and a boiling point of 164° C were considered to be the most reliable. A vapor pressure of 2.97 hPa at 25 ^{o}C was calculated from available data. Thus a saturated vapor contains approximately 2930 ppm at 25 ^{o}C and 1000 hPa (750 mm Hg). The partition coefficient (Log Kow) was calculated to be 1.89. The material is reported to be slightly soluble in water (0.5% wt.).

B. Environmental Fate and Biodegradation

All HPV Endpoints for Environmental Fate have been completed (Table 3). THBA has no hydrolysable functional groups. In air, THBA is expected to readily degrade via reaction with hydroxyl radicals and ozone. The half life in air is approximately 45 minutes. THBA is readily biodegradable, and will therefore be rapidly degraded in soil, surface waters, and sediments. A Level III fugacity model, simulating emission of 1,000 kg/hr. to water, predicts that nearly 99.9% of the emitted THBA will remain in the water compartment.

C. Aquatic Toxicity

Aquatic toxicity data is available for the fish and daphnid (Table 4). The 14 day LC_{50} for the guppy is 1.1 mg/L, and the 48 hr EC_{50} for the daphnid is 130 mg/L. Predicted acute ecotoxicity values were calculated using the aldehyde class in the ECOSAR v0.99g program. Predicted 96 hour LC_{50} values in the fish are approximately 10 fold greater than the actual 14 day LC_{50} value. Conversely the predicted 48 hr LC_{50} value in the daphnid is approximately 20 fold lower than the actual 48 hr EC50 value. Although no actual data is available for algae, the predicted value is approximately an order of magnitude greater than for the fish and daphnid. Based on both predicted and measured ecotoxicity, fish are expected to be the most sensitive to THBA. Thus, an algal toxicity study is considered to be unnecessary.

D. Mammalian Toxicity Endpoints

Summaries of available toxicity data used to fulfill the HPV Endpoints for Mammalian Toxicity are found in Tables 5-7. Each of the Key Studies has been further summarized in the Robust Summary section of this Dossier.

1.0 Acute Toxicity

The acute oral and dermal LD_{50} values are 2,385 mg/kg and 1,716 mg/kg, respectively. The 6 hour LC_{50} is >1,679 ppm. The material was corrosive to the skin in a DOT study, and caused moderately severe corneal injury following application of 0.005 ml test material. This is a much lower dose than required in current guidelines. Thus the effect would be expected to be more severe if 0.1 ml test material had been used.

Due in part to the corrosive nature of THBA, protective equipment is required whenever contact with THBA is possible.

2.0 Repeated Dose Toxicity

Two separate two-week inhalation toxicity studies, as well as a two-week dermal toxicity study have been conducted with THBA (Table 6). Doses causing severe irritation at the application site in the dermal study produced only slight effects (mineral deposits) in the kidney. Inhalation exposure to THBA resulted in histopathologic changes in the nasal tissues. In these same animals, clinical changes in kidney function were observed, which included decreases in urine volume, pH and osmolality. However, there was no evidence of histopathologic changes. Thus, following the two most likely routes of exposure for humans, only minimal changes were observed at levels which resulted in severe irritation at the portal of entry.

3.0 Developmental Toxicity

There is no available developmental toxicity study (Table 6). However due to the corrosive nature of the material resulting in an increased level of personal protective equipment required ,the limited number of individuals exposed to THBA and the low concentrations measured in the workplace, a developmental toxicity study is considered to be unnecessary.

4.0 Reproductive Toxicity

There is no available reproduction toxicity study (Table 6). Several two week studies have been conducted via two different routes. As part of these studies, the testes and ovaries were weighed and testes examined histopathologically. However, for reproductive toxicity purposes, these studies were of

short duration and therefore rated a 4 in the Klimisch rating system. Although the study was of a short duration and produced severe irritation at the dermal application site and slight effects in the kidney, there were no significant treatment-related effects noted which would indicate a reproductive effect. Since the material is used solely as a chemical intermediate with limited worker exposure, a reproductive toxicity study is considered unnecessary.

5.0 Mutagenicity and Chromosomal Aberrations

5.1 Mutagenicity Testing (Ames test)

THBA was negative in the Ames test.

5.2 - Chromosomal Aberrations

THBA was negative in the in vitro CHO/HGPRT assay and in the in vivo mouse micronucleus assay.

No additional studies are necessary.

V. REFERENCES

ACGIH TLV (2002). Threshold Limit Values for chemical substances and physical agents and Biological Exposure Indices. American Conference of Governmental Industrial Hygienists.

Klimisch, H.-J., Andreae, M. and Tillman, U. (1997). A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

US EPA, (1998). Guidance for meeting the SIDS requirements (The SIDS Guide). Guidance for the HPV Challenge Program (11/31/98).

US EPA, (1999a). Determining the adequacy of existing data. Guidance for the HPV Challenge Program (2/10/99).

US EPA, (1999b). The use of structure-activity relationships (SAR) in the High Production Volume Chemicals Challenge Program. OPPT, EPA.

VI. ROBUST STUDY SUMMARIES -IUCLID

Data Sets are appended

Table 1. Test Plan Matrix for TETRAHYDROBENZALDEHYDE

	Info available?	OECD?	GLP?	Other study?	Estimated method?	Acceptable?
PHYSICAL CHEMICAL						
Melting Point	Y				N	Y
Boiling Point	Y				N	Y
Vapor Pressure	Y				N	Y
Partition Coefficent	Y				N	Y
Water Solubility	Y				N	Y
ENVIRONMENTAL FATE ENDPOINTS						
Photodegradation	N	-	-	-	Y	Y
Hydrolysis	N	-	-	-	Y	Y
Biodegradation	Y	C	N	N	N	Y
Transport between Environmental Compartmenats (Fugacity)	N	-	-	-	Y	Y
ECOTOXICITY						
Acute Toxicity to Fish	N	N	ND	Y	Y	Y
Acute Toxicity to Aquatic Invertebrates	Y	C	ND	N	Y	Y
Acute Toxicity to Aquatic Plants	N	-	-	-	Y	Y
MAMMALIAN TOXICITY						
Acute Toxicity	Y	Y	Y	N	N	Y
Repeated Dose Toxicity	Y	Y	Y	N	N	Y
Genetic Toxicity - Mutation (Ames)	Y	Y	Y	N	N	Y
Genetic Toxicity - Chromosomal Aberrations	Y	Y	Y	N	N	Y
Developmental Toxicity	N	-	-	-	N	-
Reproductive Toxicity	N	-	-	-	N	-

Y = Yes; N = No; C = Comparable; ND = No Data; S = Supplemental, not required under HPV; - = Not applicable

Table 2. Matrix of Available and Adequate Data on TETRAHYDROBENZALDEHYDE

Physicochemical Properties

Name (CAS No.)	Melting Point (^oC)	Vapor Pressure (hPa @ 25^oC)	Boiling Point (^oC)	Partition Coefficient (log Kow)	Water Solubility (mg/L @ 20C)
TETRAHYDROBENZALDEHYDE (THBA) (100-50-5)	-96.1 (measured)	2.97 (2.225 mm Hg) (calculated)	164 (measured)	1.89 (preferred calc.) 1.34 (other calc.)	0.5% Slightly soluble (measured)

Table 3. Matrix of Available and Adequate Data on TETRAHYDROBENZALDEHYDE

Environmental Fate

Name (CAS No.)	**Hydrolysis**	**Photodegradation** Half life	**Biodegradation**	**Environmental Transport** Level III, 1000 kg/hr released to water
TETRAHYDROBENZALDEHYDE (THBA) (100-50-5)	Not estimatable (Hyrowin 1.67) Does not contain hydrolyzable groups	Hydroxyl Radicals Reaction: 88.6330 E-12 Ozone Reaction: 20.000000 E-17 cm3/molecule-sec Overall half life = 0.7 hours	readily biodegradable 76% in a closed bottle test equivalent to OECD 301D	Air 0.035% Water 99.9% Soil 0.0033% Sediment 0.074%

Table 4. Matrix of Available and Adequate Data on TETRAHYDROBENZALDEHYDE

Ecotoxicity

Name (CAS No.)	Acute Fish 96-hour LC50 (mg/L)	Acute Invertebrate 48-hour EC50 (mg/L)	Algal 72-hour growth inhibition EC50 (mg/L)
TETRAHYDROBENZALDEHYDE (THBA) (100-50-5)	No data for acute study Predicted 96 hr LC50 9.997 mg/L Chronic 14-day LC50 is 1.1 mg/L Predicted 32-day Chronic Value (ChV) is 0.885 mg/L	130 Predicted 48 hr LC50 6.85 mg/L	No data for acute study Predicted 96 hr EC50 68.4 mg/L

Table 5. Matrix of Available and Adequate Data on TETRAHYDROBENZALDEHYDE

Acute Toxicity

Name (CAS No.)	Acute Oral	Acute Dermal	Acute Inhalation	Dermal Irritation	Eye Irritation	Sensitization
TETRAHYDROBENZALDEHYDE (THBA) (100-50-5)	2385 mg/kg	1716mg/kg	>1679 ppm for 6 hour exposure	Corrosive according to DOT test	Moderately severe corneal injury using 0.005 ml test material	No data

Table 6. Matrix of Available and Adequate Data on TETRAHYDROBENZALDEHYDE

Repeat-dose Toxicity

Name (CAS No.)	Repeat Dose	Reproductive	Developmental
TETRAHYDROBENZALDEHYDE (THBA) (100-50-5)	Two week inhalation NOEL – 5 ppm Two week dermal systemic NOEL – 0.10 ml/kg/day	No effect on ovary or testicular weights or testes histopath in two week dermal study	No data

Table 7. Matrix of Available and Adequate Data on TETRAHYDROBENZALDEHYDE

Genotoxicity

Name (CAS No.)	**Genotoxicity (*in vitro* -bacterial)**	**Genotoxicity (*in vitro* - mammalian)**	**Genotoxicity (*in vivo*)**
TETRAHYDROBENZALDEHYDE (THBA) (100-50-5)	Negative	Negative in CHO/HGPRT assay	Negative in mouse micronucleus assay

Table 8 Test Plan Matrix for TETRAHYDROBENZALDEHYDE

	TETRAHYDROBENZALDEHYDE (THBA) (100-50-5)
PHYSICAL CHEMISTRY	
Melting point, °C	-96.1 (measured) A
Boiling point, °C	164 (measured) A
Vapor Pressure, hPa at 25C	2.97 (calculated) A
Water Solubility	0.5% (measured) Slightly soluble A
Log K_{ow}	1.89(calculated) A
ENVIRONMENTAL FATE	
Biodegradation	76% in closed bottle test equivalent to OECD 301D readily biodegradable A
Hydrolysis	Does not contain hydrolysable groups A
Photodegradability	Overall half life = 0.7 hours A
Transport between Environmental Compartments: (**Fugacity Level III Model**) Default assumption: 1000 kg/hr released into water.	Air 0.035% Water 99.9% Soil 0.0033% Sediment 0.074% A
ECOTOXICITY	
Chronic Toxicity to Fish (14 day LC50)	14-day is 1.1 mg/L (measured) A
Acute Toxicity to Aquatic Invertebrates (48hr EC50)	130 (measured) A
Toxicity to Aquatic Plants (72hr EC50)	68.4 (calculated)
TOXICOLOGICAL DATA	
Acute Toxicity (oral), mg/kg	2385 mg/kg A
Acute Toxicity (dermal) mg/kg	1716 mg/kg A
Acute Toxicity (inhalation)	> 1679 ppm for 6 hour exposure A

Acute Eye Irritation	Moderately severe corneal injury using 0.005 ml test material A
Acute Skin Irritation	Corrosive according to DOT test A
Sensitization	No data NR
Repeated Dose Toxicity	Two week NOEL – 5 ppm A
Genetic Toxicity-Mutation	Negative A
Genetic Toxicity- Chromosomal Aberrations	Negative (in vitro) Negative (in vivo) A
Toxicity to Reproduction	No data NR
Developmental Toxicity	No data NA

Legend	
Symbol	**Description**
R	Endpoint requirement fulfilled using category approach, SAR
Test	Endpoint requirements to be fulfilled with testing
Calc	Endpoint requirement fulfilled based on calculated data
A	Endpoint requirement fulfilled with adequate existing data
NR	Not required per the OECD SIDS guidance
NA	Not applicable due to physical/chemical properties

201-15755B

IUCLID

Data Set

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Existing Chemical	:	ID: 100-50-5
CAS No.	:	100-50-5
Generic name	:	tetrahydrobenzaldehyde
Synonym	:	3-cyclohexene-1-carboxaldehyde

Producer related part

Company	:	Dow Chemical, TERC
Creation date	:	27.04.2004

Substance related part

Company	:	Dow Chemical, TERC
Creation date	:	27.04.2004
Status	:	
Memo	:	
Printing date	:	16.12.2004
Revision date	:	
Date of last update	:	16.12.2004
Number of pages	:	64
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

Type	:	manufacturer
Name	:	Dow Chemical
Contact person	:	
Date	:	
Street	:	
Town	:	48674 Midland, MI
Country	:	United States
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	

21.06.2004

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	:	3-cyclohexene-1-carboxaldehyde
Smiles Code	:	O=CC(CCC=C1)C1
Molecular formula	:	C7 H10 O1
Molecular weight	:	110.16
Petrol class	:	

27.04.2004 (1)

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	typical for marketed substance
Substance type	:	organic
Physical status	:	liquid
Purity	:	>= 99.65 % w/w
Colour	:	transparent colorless
Odour	:	mild aldehyde

Reliability : (2) valid with restrictions
26.07.2004 (2)

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

1,2,3,6-tetrahydrobenzaldehyde

27.04.2004

1,2,5,6-tetrahydrobenzaldehyde

27.04.2004

1-cyclohexene -4-carboxaldehyde

27.04.2004

1-formyl-3-cyclohexene

27.04.2004

3-cyclohexene-1-carboxaldehyde

27.04.2004

4-formylcyclohexene

27.04.2004

cyclohexene-4-carboxaldehyde

27.04.2004

delta 1-tetrahydrobenzaldehyde

27.04.2004

1.3 IMPURITIES

Purity	:	typical for marketed substance
CAS-No	:	100-73-2
EC-No	:	202-884-5
EINECS-Name	:	3,4-dihydro-2H-pyran-2-carbaldehyde
Molecular formula	:	
Value	:	<= .25 % w/w

27.04.2004 (3)

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : industrial
Category : Chemical industry: used in synthesis

Reliability : (2) valid with restrictions
21.05.2004

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

Origin of substance : Synthesis
Type : Production

Test substance : Produced by reaction of acrolein and butadiene
Reliability : (2) valid with restrictions
21.05.2004

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit : other: UCC exposure limit
Limit value : 5 ml/m3

Reliability : (2) valid with restrictions
21.05.2004 (4)

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 : = -96.1 °C
Sublimation :
Method :
Year :
GLP : no
Test substance : no data

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment
21.05.2004 (5)

Value : = -100 °C
Sublimation :
Method :
Year :
GLP : no data
Test substance : no data

Reliability : (3) invalid
Rejected by DIPPR Diadem Version 1.5

Additional information on DIPPR can be found at
http://dippr.byu.edu/description.htm
27.04.2004 (6)

Value : = 2 °C
Sublimation :
Method :
Year :
GLP : no data
Test substance : no data

Reliability : (3) invalid
Melting point value is inconsistent with known handling practices and accepted value by DIPPR.

Additional information on DIPPR can be found at
http://dippr.byu.edu/description.htm
27.04.2004 (7)

2.2 BOILING POINT

Value : = 164 °C at 1013 hPa
Decomposition :
Method :
Year : 1948
GLP : no
Test substance : no data

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment
21.05.2004 (5)

Value : = 105 °C at 1013 hPa
Decomposition :
Method :
Year :
GLP : no data
Test substance : no data

Reliability : (3) invalid
3: Rejected by DIPPR Diadem Version 1.5. Additional information on DIPPR can be found at http://dippr.byu.edu/description.htm
27.04.2004 (7)

2.3 DENSITY

Type : density
Value : = .9694 g/cm³ at 20 °C
Method :
Year :
GLP : no data
Test substance : no data

Reliability : (2) valid with restrictions
2g: Data from Handbook or collection of data
27.04.2004 (7)

Type : density
Value : = .977 g/cm³ at 20 °C

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment
27.04.2004 (3)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : = 2.3 hPa at 20 °C

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment
27.04.2004 (3)

Value : = 2.97 hPa at 25 °C
Decomposition :
Method :
Year :
GLP : no data
Test substance : no data

Result : Value is equivalent to 2.225 mm Hg.
Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment
21.05.2004 (8)

2.5 PARTITION COEFFICIENT

Partition coefficient	:	octanol-water
Log pow	:	= 1.34 at °C
pH value	:	
Method	:	
Year	:	1988
GLP	:	no data
Test substance	:	no data
Method	:	Method of Rekker, R.F. (1977). The hydrophobic fragmental constant. Elsevier, Amsterdam was used.
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment

27.04.2004 (9)

Partition coefficient	:	octanol-water
Log pow	:	= 1.89 at °C
pH value	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	KOWWIN v 1.67 estimate
Result	:	Log Kow = 1.89
Reliability	:	(2) valid with restrictions 2f: Accepted calculation method

21.05.2004 (10)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water
Value	:	at °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	no data
Result	:	Slightly soluble
Reliability	:	(2) valid with restrictions 2g: Data from Handbook or collection of data

27.04.2004 (11)

Solubility in	:	Water
Value	:	= .5 vol% at 20 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	

pKa : at 25 °C
Description :
Stable :

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment
27.04.2004 (3)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value : = 47.2 °C
Type :

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment
21.06.2004 (12)

Value : = 46.1 °C
Type : closed cup
Method :
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment
24.05.2004 (4)

Value : = 57.2 °C
Type : open cup
Method :
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment
24.05.2004 (4)

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

Result : Flammability limits are predicted to range from 1.1 to 9.95% at 25C and 1 atm.
Reliability : (2) valid with restrictions
2f: Accepted calculation method
24.05.2004 (13)

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

Memo : Vapor Density is 3.8 (Air = 1).

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment

21.05.2004 (4)

3.1.1 PHOTODEGRADATION

Type : air
Light source :
Light spectrum : nm
Relative intensity : based on intensity of sunlight
Deg. product :
Method :
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

Method : Estimation method using AopWin v1.91
Result : Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 88.6330 E-12 cm3/molecule-sec
Half-Life = 0.121 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 1.448 Hrs
Ozone Reaction:
OVERALL Ozone Rate Constant = 20.000000 E-17 cm3/molecule-sec
Half-Life = 0.057 Days (at 7E11 mol/cm3)
Half-Life = 1.375 Hrs
Overall half life = 0.7 hours
Reliability : (2) valid with restrictions
2f: Accepted calculation method

21.06.2004 (14)

3.1.2 STABILITY IN WATER

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : at °C
t1/2 pH9 : at °C

Method : Estimation method using HYDROWIN v1.67
Result : Currently, this program can NOT estimate a hydrolysis rate constant for the type of chemical structure entered.

Review of the chemical structure also suggests that the material will not undergo hydrolysis.
Reliability : (2) valid with restrictions
2f: Accepted calculation method

21.06.2004 (15)

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 :
Year :

Method : Level III model version 2.70. Obtained from the Canadian Environmental Modeling Centre, Trent University, Peterborough, Ontario, Canada.

Input Parameters for the Level III Model included:

Property	Value	Source
Data Temperature (°C)	25	Default environmental temperature
Chemical Type	1	Type 1 indicates chemical can partition into all environmental compartments
Molecular Mass (g/mol)	110.16	Calculated from molecular structure
Water Solubility (g/m3)	5000	Measured value reported in IUCLID dataset [1]
Vapor Pressure @ 25°C	297	Measured value reported (Pa) in IUCLID dataset [1]
Melting Point (°C)	-96.1	Measured value reported in IUCLID dataset [1]
Estimated Henry's Law	6.54	Calculated by Level I Constant (H)(Pa m3/mol) Fugacity Model [2]
Log Kow Octanol-Water	1.89	Estimated value for Partition Coefficient neutral species [3]
Reaction Half-lives (hr.) Input to Level III Model		
Air (vapor phase)	0.7	Estimated half-life for indirect photolysis [5]
Water (no susp. solids)	360*	Half-lives in water,
Soil	720*	soil, and sediment
Sediment	7200*	extrapolated from measured ready biodegradability [1]
Suspended Sediment	**1.0 x 10(11)	Not expected to adsorb to susp. sediment
Fish	**1.0 x 10(11)	No uptake/bioaccumulation is expected
Aerosol	**1.0 x 10(11)	Aerosol emissions not expected

*Half-lives extrapolated from ready biodegradability classification, according to Technical Guidance Document of the European Commission [6].
**Default value used in Level III model when reaction is expected to be negligible in this compartment

REFERENCES

1. Union Carbide Corporation. 2004. MSDS for Tetrahydrobenzaldehyde, CAS # 100-50-5.
2. AIChE. 2002. Design Institute for Physical Properties Research (DIPPR) Database, American Institute of Chemical Engineers, New York, NY.
3. Shortridge, R. W., Craig, R. A., Greenlee, K. W., Derfer, J. M., and

C. E. Boord. 1948. The synthesis of some cyclopropane and spirane hydrocarbons. J. Am. Chem. Soc. 70:946-949.
4. Mackay, D., 2001. Multimedia Environmental Models: The Fugacity Approach. Lewis Publishers, CRC Press, Boca Raton, FL. Models available at: http://www.trentu.ca/cemc/models.html
5. U.S. EPA. 2003. EPI Suite software, version v3.11. United States Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, D. C. Available at: http://www.epa.gov/oppt/exposure/docs/episuitedl.htm
6. European Commission. 1996. Technical Guidance Documents in support of the commission directive 93/67/EEC on risk assessment for new notified substances and commission regulation. European Commission, Brussels, Belgium.

Remark : The results of Level III fugacity modeling indicate that this material will remain predominantly in the environmental media to which it is emitted. This material is slightly soluble in water, has moderate vapor pressure, and low log Kow. These properties dictate that the material has low potential to volatilize from water to air, or adsorb to soil and sediments. When released to water (the most likely emission scenario), the material will remain dissolved in water and will be rapidly biodegraded. When released to soil, the material will be primarily dissolved in soil pore water (groundwater), and will be rapidly biodegraded. Since this material is susceptible to destructive reactions such as indirect photolysis and biodegradation, it is expected to be short-lived in the environment.

Result : Media: Distribution among air, water, soil, and sediments

Emission Scenario	Percentage and amount distributed to Air	Water	Soil	Sediment	Residence Time (days) [without advection]
1,000 kg/hr to Air					
	88.1%	3.5%	8.4 %	0.0026%	0.03
	670kg	26.7kg	64.0kg	0.02kg	[0.05]
1,000 kg/hr to Water					
	0.035%	99.9%	0.0033%	0.074%	12
	100kg	290000kg	9.7kg	220kg	[18]
1,000 kg/hr to Soil					
	0.039%	12.0%	88.0%	0.0089%	23
	220kg	68000kg	500000kg	50.1kg	[29]
1,000 kg/hr simultaneously to Air, Water, and Soil					
	0.1%	41.9%	58.0%	0.031%	12
	990kg	360000kg	500000kg	270kg	[17]

Reliability : (2) valid with restrictions
2f: Accepted calculation method

30.07.2004

Type : fugacity model level I
Media :
Air : 55.2 % (Fugacity Model Level I)
Water : 41.8 % (Fugacity Model Level I)
Soil : 2.9 % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: Level I Fugacity Model version 2.11
Year : 2004

Method : Level I model version 2.11. Obtained from the Canadian Environmental Modeling Centre, Trent University, Peterborough, Ontario, Canada.

Input Parameters for the Level I Model included:

Property	Value	Source
Data Temperature (°C)	25	Default environmental temperature
Chemical Type	1	Type 1 indicates chemical can partition into all environmental compartments
Molecular Mass (g/mol)	110.16	Calculated from molecular structure
Water Solubility (g/m3)	5000	Measured value reported in IUCLID dataset [1]
Vapor Pressure @ 25°C	297	Measured value reported (Pa) in IUCLID dataset [1]
Melting Point (°C)	-96.1	Measured value reported in IUCLID dataset [1]
Estimated Henry's Law	6.54	Calculated by Level I Constant (H)(Pa m3/mol) Fugacity Model [2]
Log Kow Octanol-Water	1.89	Estimated value for Partition Coefficient neutral species [3]
Simulated Emission (kg)	100,000	Default value for Level I model [2]
Simulated environment		Default Level I environment

REFERENCES

1. Union Carbide Corporation. 2004. MSDS for Tetrahydrobenzaldehyde, CAS # 100-50-5.
2. AIChE. 2002. Design Institute for Physical Properties Research (DIPPR) Database, American Institute of Chemical Engineers, New York, NY.
3. Shortridge, R. W., Craig, R. A., Greenlee, K. W., Derfer, J. M., and C. E. Boord. 1948. The synthesis of some cyclopropane and spirane hydrocarbons. J. Am. Chem. Soc. 70:946-949.

Remark : This material is slightly soluble in water, has moderate vapor pressure, and low log Kow. In the absence of advective and reactive processes, these physical properties dictate that the material will be distributed between the air and water compartments at equilibrium.

Result : Predicted equilibrium distribution among air, water, soil, and sediments

Percentage and amount distributed to

Emission Scenario	Air	Water	Soil	Sediment
100,000 kg	55.2%	41.8%	2.9%	0.064%
	55000kg	42000kg	2900kg	63.9kg

Reliability : (2) valid with restrictions
2f: Accepted calculation method

26.07.2004

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : domestic sewage
Contact time :
Degradation : = 76 (±) % after 20 day(s)

Result	:	
Deg. product	:	
Method	:	
Year	:	1985
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Methods followed Standard Methods for the Examination of Water and Wastewater. This is comparable to the OECD 301D closed bottle test. The source of microorganisms was domestic sewage.
Result	:	The day 5, 10, 15 and 20 BOD values were 23, 65, 69 and 76%, respectively.
Test substance	:	Material was described in report as product.
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment

21.06.2004 (16)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	semistatic
Species	:	Poecilia reticulata (Fish, fresh water)
Exposure period	:	14 day(s)
Unit	:	µmol/l
Limit test	:	
Analytical monitoring	:	yes
Method	:	OECD Guide-line 204 "Fish, Prolonged Toxicity Test: 14-day Study"
Year	:	1988
GLP	:	no data
Test substance	:	no data

Method :

14 day LC50s were determined using a semistatic system with renewal of the test solution daily. Seventeen aldehydes were tested in this paper, including tetrahydrobenzaldehyde, (synonym - 3-cyclohexene-1-carboxaldehyde). Tests were conducted in 1.5 l glass vessels containing 1.4 l solution and were closed with glass lids. At least 5 concentrations, geometrically increasing with a factor of 1.8, were tested for each compound.

Fish (P. reticulate) were laboratory reared, and acclimated to the water used in the tests for at least 12 days prior to initiating the experiment. Fish were 2-3 months of age at the start of the experiment. Ten fish were exposed to each concentration. Control fish were exposed to 72 µl/l acetone which was used as a carrier solvent for most aldehydes. The room had 12 hours artificial light/day and was maintained at 21-23C.

Oxygen content, pH and concentrations of test material were determined four times immediately before and four times immediately after renewal of the solution, for two concentrations of each compound. Water concentration for each compound was determined by gas chromatography with a flame ionization detector.

LC50 data were calculated by logit transformation.

Remark :

10.2 µmoles/L corresponds to 1.1 mg/L.

Since the test material does not contain hydrolyzable groups, hydrolysis is not expected to be of concern. Approximately 23% of the test material was oxidized in the initial 5 days of the BOD exam, thus very little of THBA would be expected to degrade in a solution changed on a daily basis.

Result :

For tetrahydrobenzaldehyde no reliable recovery factor could be determined because of irreproducible results obtained during the analysis of the aqueous solutions. This was probably due to the method of analysis employed. Thus the LC50 value was based on nominal concentration and not corrected for loss of test material.

All measured pH values were in the range of 6.5-7.5. In the rare cases where oxygen levels were found to be low, ~3 mg/L, 24 hr after preparation of the solutions, the data was not used.

Fish showed no obvious toxic symptoms. There was a loss of appetite at higher concentrations. Most deaths occurred during the initial 6 days of exposure.

The log LC50 was 1.01 µmoles/l.

No further information supplied.

Reliability : (2) valid with restrictions

2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment

27.08.2004 (9)

Type : other: estimation
Species :
Exposure period :
Unit :

Method : ECOSAR v 0.99g program was used. Class used was Aldehyde.
Result : 96 hr LC50 - 9.997 mg/L
Reliability : (2) valid with restrictions
2f: Accepted calculation method

21.06.2004 (17)

Type : other: estimation
Species :
Exposure period :
Unit :

Method : ECOSAR v 0.99g program was used. Class used was Aldehyde.
Result : 32-day Chronic Value (ChV) is 0.885 mg/L
Reliability : (2) valid with restrictions
2f: Accepted calculation method

21.06.2004 (17)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
EC50 : = 130 measured/nominal
Analytical monitoring : no
Method :
Year : 1985
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Methods followed EPA/ASTM documents using Daphnia magna less than 24 hours old. The test lasted for 48 hours. The pH of test solutions was not adjusted prior to introducing test organisms.
Result : The 48 hour LC50 was 130 mg/L.

No additional information supplied.
Test substance : Material was described in report as product.
Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment

21.06.2004 (18)

Type : other: estimation
Species :
Exposure period :
Unit :

Method : ECOSAR v 0.99g program was used. Class used was Aldehyde.
Result : 48 hr LC50 - 6.85 mg/L
Reliability : (2) valid with restrictions
2f: Accepted calculation method

21.06.2004 (19)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	other aquatic plant: estimation method
Endpoint	:	
Exposure period	:	
Unit	:	
Method	:	ECOSAR v 0.99g program was used. Class used was Aldehyde.
Result	:	96 hr EC50 - 68.4 mg/L
Reliability	:	(2) valid with restrictions 2f: Accepted calculation method

21.06.2004 (19)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

Species	:	other: estimation
Endpoint	:	
Exposure period	:	
Unit	:	
Method	:	ECOSAR v 0.99g program was used. Class used was Aldehyde.
Result	:	32 day chronic toxicity endpoint was calculated to be 0.885 mg/L
Reliability	:	(2) valid with restrictions 2f: Accepted calculation method

21.06.2004 (17)

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	:	= 2385 mg/kg bw
Species	:	rat
Strain	:	Wistar
Sex	:	male
Number of animals	:	5
Vehicle	:	
Doses	:	1.0, 2.0 or 4.0 ml/kg test material
Method	:	
Year	:	1960
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of 5 male Wistar rats were dosed by oral gavage with 1.0, 2.0 or 4.0 ml/kg test material. Rats were 5-6 weeks of age and 90-120 gram at the time of dosing. Animals were weighed prior to dosing and 14 days after dosing. Animals were observed for 14 days after dosing. The moving average method was used to calculate the LD50.
Remark	:	Since the density at 20C is 0.9694 g/ml, 2.46 ml/kg is equivalent to 2385 mg/kg.
Result	:	One high dose rat died on the day of dosing and all remaining high dose rats and one 2.0 ml/kg rat died the day after dosing. Deaths were preceded by narcosis. All remaining animals survived the 14 day observation period and gained weight. Gross pathologic examination of the animals that died revealed cherry red lungs, congested livers with burned areas from contact with stomachs still containing test material, and congested kidneys and adrenals. Blood was present in the urinary bladder and intestines of several animals. No further details were provided. The oral LD50 was 2.46 ml/kg.
Test substance	:	Described in report as 1,2,3,6-tetrahydrobenzaldehyde. No purity analysis provided.
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment

21.06.2004 (20)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	other: LT50
Value	:	
Species	:	rat
Strain	:	Wistar
Sex	:	female
Number of animals	:	6
Vehicle	:	
Doses	:	
Exposure time	:	
Method	:	
Year	:	1960

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

Method : Groups of 6 female Wistar rats were exposed to nearly saturated vapors of tetrahydrobenzaldehyde for 4 or 8 hours. The nearly saturated atmosphere was generated by passing air at a rate of 2.5 lpm through a fritted glass disc immersed in test material. Animals were weighed prior to dosing and 14 days after dosing. Animals were observed for 14 days after dosing. The moving average method was used to calculate the LC50.

Another group of 6 female rats were exposed to a metered concentration of 2000 ppm for 4 hours. Although not stated, remaining conditions were most likely identical to those used for the previous exposures.

Result : The nominal concentration for nearly saturated vapor exposure was approximately 2600 ppm tetrahydrobenzaldehyde. Rats exposed to the test material for 4 hours appeared normal after the exposure and gained weight during the 2 week observation period. Little gross pathology was noted at sacrifice 14 days after the exposure.

Rats exposed to nearly saturated vapor for 8 hours were alive but prostrate with slow labored breathing. Four animals died the day after exposure with the remainder dying four days after exposure. Gross necropsy examination revealed lung hemorrhage and ruptured lung capillaries and congested livers and kidneys.

All rats exposed to a metered concentration of 2000 ppm survived the 4 hour exposure and gained weight during the subsequent 2-week observation period. No treatment-related effects were noted upon gross pathologic examination 14 days after exposure to test material.

The LT50 is between 4 and 8 hours for a nearly saturated vapor exposure.

No further details were provided.

Test substance : Described in report as 1,2,3,6-tetrahydrobenzaldehyde. No purity analysis provided.

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment

21.06.2004 (20)

Type : other: LT50
Value :
Species : rat
Strain : Sprague-Dawley
Sex : male/female
Number of animals : 10
Vehicle :
Doses :
Exposure time :
Method :
Year : 1991
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : Three groups of 5 male and 5 female Sprague-Dawley rats were exposed under static conditions to the highest attainable concentration of tetrahydrobenzaldehyde for 4, 6 or 8 hours. Test material was placed in an open tray in the top of a sealed 120-liter chamber and the vapor was allowed to equilibrate for approximately 16 or 17 hours prior to introducing animals into the chamber. The test material was not heated to produce a saturated vapor. A gas chromatograph was used to measure chamber concentration. Animals were observed for 14 days post-exposure.

Animals were weighed prior to exposure and at 7 and 14 days following the day of exposure. A complete necropsy examination was performed on all animals.

There was no control group in this study.

Result : The concentration of test material in the air was 1571, 1939 and 1437 ppm for the 4-, 6- and 8-hour exposure periods, respectively. The average chamber temperature, relative humidity and oxygen levels for each exposure period were between 21.6 and 22.9C, >98% and between 20.0 and 20.4%, respectively. All animals survived the exposure period. For the 6- and 8-hour exposure periods, all of the animals died within 4 days following exposure. Similar clinical signs were observed in each group including ocular irritation, respiratory difficulties and narcosis. During the post-exposure period, clinical signs were only observed in animals exposed for 6- or 8- hours. These clinical signs included periocular/perinasal encrustation, urogenital area wetness, hypoactivity and decreased respiratory rate. Animals in the 4-hour exposure group gained weight at each measured time point. Mottled red or bright pink discoloration of the lungs, yellow staining of the urogenital area and multiple ulcers on the tail, feet and paws were the principle macroscopic lesions observed in animals that died. There were no treatment-related gross lesions found in animals of the 4-hour group sacrificed at the end of the 14 day post-exposure period.

Test substance : Test material was 99.6% pure with two minor impurities noted.

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment

21.06.2004 (21)

Type : LC50
Value : > 1679 ppm
Species : rat
Strain : Sprague-Dawley
Sex : male/female
Number of animals : 10
Vehicle :
Doses : 1679
Exposure time : 6 hour(s)
Method :
Year : 1991
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : A group of 5 male and 5 female Sprague-Dawley rats was exposed under dynamic conditions to the highest attainable concentration of tetrahydrobenzaldehyde for 6 hours. The test material and the airstream were not heated to produce a saturated vapor. A gas chromatograph was used to measure chamber concentration. The chamber used for the exposure to the test material was a 120 liter chamber with a chamber airflow of 25 l/min. Animals were observed for 14 days post-exposure. Animals were weighed prior to exposure and at 7 and 14 days following the day of exposure. A complete necropsy examination was performed on all animals.

The mean and standard deviation of the body weights, body weight changes, and exposure concentrations were calculated. No statistical comparisons were made. The LT50 was determined by the moving average method of Thompson (1947) for males, females, and the combined sexes using the 8-hour and 4-hour static exposure groups.

Result : The mean +/- S.D. vapor concentration of tetrahydrobenzaldehyde over the 6 hour exposure period was 1679 +/- 105 ppm. The chamber airflow was 25 l/min and the chamber relative humidity was 56%. There were no

mortalities during the 6 hour exposure period or the 14 day post-exposure period. Clinical signs observed on the day of exposure and for 1 day following exposure included hypoactivity, blepharospasm, lacrimation, perinasal wetness/encrustation, severe periocular encrustation and unkept fur. In addition, respiratory difficulties, mouth breathing and audible respiration, were observed on the day of exposure. Mean body weight gains were observed for both sexes during the post-exposure period. There were no gross pathologic lesions observed at necropsy.

Test substance : Test material was 99.6% pure with two minor impurities noted.

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment

16.12.2004 (21)

Type : other: RD50
Value : = 59 ppm
Species : mouse
Strain : B6C3F1
Sex : male
Number of animals :
Vehicle :
Doses :
Exposure time :
Method :
Year : 1984
GLP : no data
Test substance : other TS

Method : Groups of three or four B6C3F1 mice were exposed in a 2.7 liter head-only exposure chamber for 10 minutes. Sensory irritation was quantified by measuring respiratory rate depression during the exposure. Respiratory rates were determined by a body plethysmographic method. The animals were sealed in airtight body plethymographs attached to the head-only exposure chamber and allowed to acclimate for approximately 10 minutes. Respiratory rates were recorded during a 5 minute recovery period. The average maximum decrease in respiratory rate for 1 minute was computed from the response of each group of animals and plotted versus the logarithm of the exposure concentration. Usually, five analytically measured concentrations of each aldehyde were used to construct a concentration-response curve from which the RD50 value (concentration eliciting a 50% decrease in respiratory rate) was determined.

Concentration-response curves were constructed by the least-squares method for regression and tested for significance by analysis of variance. Analysis of covariance was used to compare slopes and test for elevation between the concentration-response curves for B6C3F1 mice and between isomers of aldehydes. Results were considered significant when $p<0.05$.

Result : The RD50 (95% CI) value was 59 ppm (52-68 ppm) for B6C3F1 mice.

No additional information was provided.

Test substance : Between 85 to 99% for a number of aldehydes with the remainder being water. No further information provided on the individual chemicals.

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment

21.06.2004 (22)

Type : other: RD50
Value : = 95 ppm
Species : mouse
Strain : Swiss Webster
Sex : male

Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	
Method	:	
Year	:	1984
GLP	:	no data
Test substance	:	other TS

Method : Groups of three or four Swiss Monitor mice were exposed in a 2.7 liter head-only exposure chamber for 10 minutes. Sensory irritation was quantified by measuring respiratory rate depression during the exposure. Respiratory rates were determined by a body plethysmographic method. The animals were sealed in airtight body plethymographs attached to the head-only exposure chamber and allowed to acclimate for approximately 10 minutes. Respiratory rates were recorded during a 5 minute recovery period. The average maximum decrease in respiratory rate for 1 minute was computed from the response of each group of animals and plotted versus the logarithm of the exposure concentration. Usually, five analytically measured concentrations of each aldehyde were used to construct a concentration-response curve from which the RD50 value (concentration eliciting a 50% decrease in respiratory rate) was determined.

Concentration-response curves were constructed by the least-squares method for regression and tested for significance by analysis of variance. Analysis of covariance was used to compare slopes and test for elevation between the concentration-response curves for Swiss-Webster mice and between isomers of aldehydes. Results were considered significant when $p<0.05$.

Result : The RD50 (95% CI) value was 95 ppm (69-168 ppm) for Swiss-Webster mice. Although the RD50 value was 1.6 fold higher for the Swiss-Webster mouse than for the B6C3F1 mouse, this difference was considered to be of questionable biological significance.

No additional information was provided.

Test substance : Between 85 to 99% for a number of aldehydes with the remainder being water. No further information provided on the individual chemicals.

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment

21.06.2004 (22)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	= 1716 mg/kg bw
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male
Number of animals	:	4
Vehicle	:	
Doses	:	1.25 or 2.5 ml
Method	:	
Year	:	1960
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method : Groups of 4 male albino New Zealand rabbits had 1.25 or 2.5 ml/kg test material applied to the skin for 24 hours. Rabbits were 3-5 months of age

and averaged 2.5 kg at the time of dosing. The test material was applied to skin clipped of hair in the trunk region. The test material was covered with polyethylene sheeting to prevent loss of test material. Animals were weighed prior to dosing and 14 days after dosing. Animals were observed for 14 days after dosing. The moving average method was used to calculate the LD50.

Remark : Since the density at 20C is 0.9694 g/ml, the dermal LD50 is equivalent to 1716 mg/kg.

Result : Necrosis of the skin was noted following removal of the polyethylene covering. By the 14th day, scabs had formed on the affected skin areas. Three of the rabbits from the 2.5 ml/kg group died within the 24 hour exposure period; the remaining rabbit died 2 days later. Gross observation at necropsy disclosed some lung congestion, pale mottled livers with prominent acini, off-color brownish kidneys with slight internal congestion and opaque intestinal walls.

No further details were provided.

The dermal 24 hour LD50 is 1.77 ml/kg.

Test substance : Described in report as 1,2,3,6-tetrahydrobenzaldehyde. No purity analysis provided.

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment

21.06.2004 (20)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species : rabbit
Concentration :
Exposure :
Exposure time :
Number of animals : 5
Vehicle :
PDII :
Result :
Classification :
Method :
Year : 1960
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Groups of 5 albino New Zealand rabbits had 0.01 ml test material applied to the skin. The test material was applied to skin clipped of hair on the belly. The test material was uncovered.

Remark : The amount of test material used is 2% of current guideline recommendations. Thus response is less than one would expect if the current recommendations had been used. Although the amount used is much less than recommended, the severity of the effect observed due to the small amount of test material used is relevant and makes the study valid.

Result : Marked irritation was noted on 4 animals and moderate erythema on a fifth. Time point not stated.

Test substance : Described in report as 1,2,3,6-tetrahydrobenzaldehyde. No purity analysis provided.

Reliability : (2) valid with restrictions

2g: Data from Handbook or collection of data

27.08.2004 (20)

Species	:	rabbit
Concentration	:	
Exposure	:	
Exposure time	:	4 hour(s)
Number of animals	:	2
Vehicle	:	
PDII	:	
Result	:	corrosive
Classification	:	
Method	:	other: DOT corrosivity test
Year	:	1972
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Protocol followed 21 CFR 191.11. No additional information provided.
Result	:	Two of 2 rabbits exhibited necrosis after the 4 hour exposure period.
Test substance	:	Test substance is only described as Current Production material.
Reliability	:	(2) valid with restrictions 2g: Data from Handbook or collection of data

21.06.2004 (23)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	
Dose	:	
Exposure time	:	
Comment	:	
Number of animals	:	
Vehicle	:	
Result	:	
Classification	:	
Method	:	
Year	:	1960
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of albino New Zealand rabbits had 0.005 ml test material, or 0.5 ml of a 5 or 15% solution in propylene glycol instilled on the eye.
Remark	:	The amount of test material used is 5% of current guideline recommendations for the neat material. Thus response is less than one would expect if the current recommendations had been used. Although the amount used is much less than recommended, the severity of the effect observed due to the small amount of test material used is relevant and makes the study valid.
Result	:	Moderately severe corneal injury was produced by neat test material or the 15% solution. Minor damage was noted with the 5% solution. All animals exhibited pain reactions as soon as dosing began.
Test substance	:	Described in report as 1,2,3,6-tetrahydrobenzaldehyde. No purity analysis provided.
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment

21.06.2004 (20)

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Type	:	Sub-acute
Species	:	rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	inhalation
Exposure period	:	6 hrs/day
Frequency of treatm.	:	5 days/week
Post exposure period	:	Five rats/sex from control and high dose group were held for a 4 week recovery period.
Doses	:	75, 250 and 500 ppm
Control group	:	yes
LOAEL	:	= 75 ppm
Method	:	other: essentially follows OECD 412
Year	:	1993
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Method :

Four groups, consisting of 15 Fischer 344 rats/sex in the control and high groups and 10 rats/sex in the low and mid level groups, were exposed for 6 hours/day, 5 days/week for 9 exposures during a 2-week period to tetrahydrobenzaldehyde vapor. The additional 5 animals/sex assigned to the control and high exposure groups were held for a 4-week recovery period. Target concentrations were 0 (control), 75, 250 and 500 ppm. The vapor concentration in each chamber was measured approximately 12 times/day by gas chromatography. Routine parameters examined include clinical observations, feed and water consumption, body weights, hematologic and serum clinical chemistry evaluations and urinalysis as per guidelines. A gross necropsy was performed with the following organs weighed, liver, spleen, brain, lungs, kidneys and testes (males). Tissues in excess of those listed in the guideline were collected and retained in 10% neutral buffered formalin. Microscopic evaluations were conducted on all gross lesions, lungs, nasal turbinates (4 sections), trachea, liver, kidneys and larynx.

Statistical analysis
The data for quantitative continuous variables were intercompared for the 3 exposure groups and the control group by use of Levene's test for equality of variances, analysis of variance (ANOVA), and t-tests. The t-tests were used when the F value from the ANOVA was significant. When Levene's test indicated homogeneous variances, and the ANOVA was significant, a pooled t-test was used for pairwise comparisons. When Levene's test indicated heterogeneous variances, all groups were compared by an ANOVA for unequal variances followed, when necessary, by a separate variance t-test for pairwise comparisons.

The data for quantitative continuous variables collected during the recovery period were compared between the control and 500 ppm exposure group using a 2-sample t-test.

Nonparametric data were statistically evaluated using the Kruskal-Wallis test followed by the Mann-Whitney U test when appropriate. For all statistical tests, the probability value of $p < 0.05$ (two tailed) was used as the critical level of significance.

Remark : The urine staining was observed infrequently in this study and is due to a lack of grooming. The irritation observed in the nasal tract and the

decrease in body weight gain probably contributed to this effect.

This study found microscopic changes in the nasal passages in rats exposed to 75, 250 and 500 ppm for 9 exposures. A subsequent study using the identical conditions with rats exposed to 5, 50 and 250 ppm did not observed microscopic changes in the nasal passages at 250 ppm. Thus the findings in this study are inconsistent with the subsequent study.

Result : Mean THBA concentrations were 77.4 (+/-6.0), 244 (+/-18.8) and 479 (+/-38.2) ppm. There were no mortalities prior to the scheduled sacrifices. Urine staining and periocular swelling were observed intermittently in animals from the 500 ppm exposure group during the exposure regimen and the recovery period. Urine staining was observed less than 5% of the time.

On study day 12, body weight was statistically significantly decreased for the male and female animals from the 500 ppm exposure group. Body weight gain was statistically significantly decreased for male and female animals from all exposure groups during the first week of the exposure regimen. During the second week of the exposure regimen, the body weight gain was statistically significantly decreased for the males from the 250 and 500 ppm exposure groups. Also during the second week of the exposure regimen, female animals had statistically significantly decreased body weight gain, except those from the 250 ppm exposure group on day 8. During the recovery period, the female animals from the 500 ppm exposure group had statistically significantly decreased body weight gain until the fourth week of recovery. For the first week of the exposure regimen, male animals from the 250 and 500 ppm exposure groups had statistically significantly decreased feed consumption values. Also for the first week, the female animals from the 75, 250 and 500 ppm exposure groups had statistically significantly decreased feed consumption values. For the second week, female animals from the 500 ppm exposure group still had statistically significantly decreased feed consumption values. Water consumption was essentially unaffected during the exposure portion and the recovery period.

Clinical pathologic findings at the end of the exposure regimen included statistically significantly decreased platelet counts for male animals from the 250 and 500 ppm exposure groups and for female animals from the 500 ppm exposure group. At the end of the recovery period, the platelet counts were comparable to control values. All other hematological parameters were considered to be unaffected by exposure to THBA.

Several clinical chemistry measurements, decreased glucose, and urea nitrogen in 500 ppm males, increased gamma glutamyl transferase in 75 and 500 ppm males, decreased chloride in 75 ppm males, increased creatinine in 75 and 500 ppm females and increased calcium in 250 ppm females, were statistically significantly different from control values. These differences were very slight and considered to be biologically not significant.

After the exposure regimen, total urine volumes were statistically significantly decreased for the male animals from the 250 and 500 ppm exposure groups and females from the 500 ppm exposure group. Male animals from the 500 ppm exposure groups and female animals from the 500 ppm exposure group had statistically significantly increased urine osmolality. In addition osmolality of male rats exposed to 250 ppm THBA was slightly increased. Male animals from the 500 ppm exposure group had statistically significantly decreased urine pH and increased frequency of higher ketone concentrations. Female rats exposed to the same concentration were slightly less affected. At the recovery period sacrifice, these values were not different from control values.

At the end of the exposure regimen, urine staining of the urogenital region and swelling of the periocular tissues were observed for both sexes of animals from the 500 ppm exposure group. These findings were resolved upon recovery.

Although several absolute and/or organ weight differences were observed between control and rats exposed to THBA, all of these differences were attributed to decreases in body weight gain.

In the male and female animals from the 250 and 500 ppm exposure groups, mild to moderate injury to the tissues of the nasal mucosa was observed, as evidenced by rhinitis, epithelial necrosis, and a variety of degenerative and/or regenerative lesions of the epithelium including vacuolization, hyperplasia, dysplasia and squamous metaplasia. Minimal or mild epithelial hyperplasia/dysplasia was found in some animals from the 75 ppm group, which was probably related to THBA exposure. Male animals were slightly more affected than female animals. At the recovery period sacrifice, most of the lesions were resolved. All other microscopic lesions observed were considered to be spontaneous, common for this rat strain, and unrelated to exposure to THBA.

Test substance : Test substance was 99.6% pure
Attached document : subacute inhalation.pdf

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TABLE 31
TETRAHYDROBENZALDEHYDE: NINE-DAY VAPOR INHALATION STUDY IN RATS
SUMMARY OF ORGAN WEIGHTS (GRAMS)
ANIMALS SACRIFICED AT DAY 12

MALES

GROUP: PPM	0	75	250	500
FINAL BODY WEIGHT				
MEAN	214.8	210.7	207.1	200.9
S.D.	15.33	12.11	17.93	12.52
N	10	10	10	10
LIVER				
MEAN	9.852	8.995	9.071	8.661
S.D.	1.2532	0.4544	1.4763	1.0841
N	10	10	10	10
LUNGS				
MEAN	0.941	0.930	0.913	0.877
S.D.	0.0752	0.0600	0.0667	0.0724
N	10	10	10	10
KIDNEYS				
MEAN	1.632	1.612	1.569	1.543
S.D.	0.1249	0.0939	0.1690	0.1276
N	10	10	10	10
BRAIN				
MEAN	1.694	1.716	1.704	1.704
S.D.	0.0451	0.0577	0.0530	0.0369
N	10	10	10	10
SPLEEN				
MEAN	0.499	0.507	0.472	0.453**
S.D.	0.0322	0.0292	0.0491	0.0328
N	10	10	10	10
TESTES				
MEAN	2.507	2.484	2.523	2.472
S.D.	0.1245	0.1377	0.1548	0.1180
N	10	10	10	10

** Significantly different from control group (p < .01)

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TABLE 33
TETRAHYDROBENZALDEHYDE: NINE-DAY VAPOR INHALATION STUDY IN RATS
SUMMARY OF ORGAN WEIGHTS AS % OF FINAL BODY WEIGHT
ANIMALS SACRIFICED AT DAY 12

MALES

GROUP: PPM	0	75	250	500
LIVER				
MEAN	4.583	4.273	4.355	4.300
S.D.	0.4501	0.1162	0.4011	0.3044
N	10	10	10	10
LUNGS				
MEAN	0.439	0.441	0.441	0.437
S.D.	0.0273	0.0091	0.0131	0.0320
N	10	10	10	10
KIDNEYS				
MEAN	0.760	0.766	0.757	0.768
S.D.	0.0404	0.0297	0.0234	0.0244
N	10	10	10	10
BRAIN				
MEAN	0.791	0.816	0.827	0.851
S.D.	0.0442	0.0371	0.0574	0.0480
N	10	10	10	10
SPLEEN				
MEAN	0.232	0.241*	0.228	0.226
S.D.	0.0108	0.0066	0.0110	0.0075
N	10	10	10	10
TESTES				
MEAN	1.169	1.180	1.221*	1.232**
S.D.	0.0378	0.0489	0.0513	0.0409
N	10	10	10	10

* Significantly different from control group (p < .05)
** Significantly different from control group (p < .01)

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Conclusion : A no-observed-effect-level (NOEL) could not be established in this study. Decreased body weight gain and possible injury to tissue in the nasal mucosa were observed in the 75 ppm exposure group, the lowest exposure concentration used in this study.

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment

16.12.2004 (24)

Type : Sub-acute
Species : rat
Sex : male/female
Strain : Fischer 344
Route of admin. : inhalation
Exposure period : 6 hrs/day
Frequency of treatm. : 5 days/week
Post exposure period : Five rats/sex from control and high dose group were held for a 4 week recovery period.
Doses : Target concentrations were 5, 50 and 250 ppm.
Control group : yes
NOAEL : = 5 ppm
LOAEL : = 50 ppm
Method : other: essentially follows OECD 412
Year :
GLP : yes
Test substance : other TS

Method : Four groups, consisting of 15 Fischer 344 rats/sex in the control and high groups and 10 rats/sex in the low and mid level groups, were exposed for 6 hours/day, 5 days/week for 9 exposures during a 2-week period to tetrahydrobenzaldehyde vapor. The additional 5 animals/sex assigned to the control and high exposure groups were held for a 4-week recovery period. Target concentrations were 0 (control), 5, 50 and 250 ppm. Concentrations of THBA were measured by gas chromatography approximately 12 times/day for each concentration. Routine parameters examined include clinical observations, feed and water consumption, body and organ weights, hematologic and serum clinical chemistry evaluations, urinalysis, urine and special chemistry evaluations, necropsy and microscopic evaluations as per guideline. Microscopic examination of the control and high groups included nasal turbinates (4 sections), larynx, trachea, lungs (with mainstem bronchi), heart, liver, spleen, kidneys, testes, stomach, lymph nodes (submandibular), sciatic nerve, tibial nerve, thyroid/parathyroid and thymic region.

Statistical analysis
The data for quantitative continuous variables were intercompared for the 3 exposure groups and the control group by use of Levene's test for equality of variances, analysis of variance (ANOVA), and t-tests. The t-tests were used when the F value from the ANOVA was significant. When Levene's test indicated homogeneous variances, and the ANOVA was significant, a pooled t-test was used for pairwise comparisons. When Levene's test indicated heterogeneous variances, all groups were compared by an ANOVA for unequal variances followed, when necessary, by a separate variance t-test for pairwise comparisons.

The data for quantitative continuous variables collected during the recovery period were compared using Levene's test and the appropriate t-test.

Nonparametric data were statistically evaluated using the Kruskal-Wallis test followed by the Mann-Whitney U test when appropriate. Incidence data were compared using the Fisher's Exact Test when appropriate. For all statistical tests, the probability value of $p < 0.05$ (two tailed) was used as the critical level of significance.

Result : Mean analytical concentrations of THBA during the study were 4.9 (+/-0.07), 51.1 (+/-1.30) and 248 (+/-7.81) ppm for target concentrations of 5, 50 and 250 ppm, respectively. There were no mortalities prior to the scheduled sacrifices. Nasal discharge, perioral wetness, and perioral encrustation were observed in the males and females from the 250 ppm exposure group during the exposure period. In addition, periocular wetness was observed in female rats from the 250 ppm exposure group during exposures.

Mean body weight and body weight gain were statistically significantly decreased for the 250 ppm group males and females during some intervals of the exposure period. Mean body weights were statistically significantly decreased on days 5 and 12 of the exposure phase of the study in males exposed to 250 ppm as were females on days 9 and 12. On day 12, mean body weights were reduced 5% in males and 4% in females. During the recovery period, 250 ppm group body weight and body weight gain were approximately the same as controls.

Statistically significantly decreased feed consumption was observed in 250 ppm group males and females on days 1-5 and days 8-10 during the exposure period. During the two days between the exposures as well as the recovery period, feed consumption in males and females from the 250 ppm group was approximately the same as controls.

Water consumption was statistically significantly reduced in 250 ppm group

males during the first week of exposure, but returned to control levels during the remaining exposure and recovery phases of the study. Water consumption in THPA-exposed females was comparable to controls.

There were no exposure related effects on hematological or clinical chemistry parameters noted in rats exposed to THBA.

Exposure-related statistically significant decreases in urinary creatinine clearance values were measured in males and females (not significant in 5 ppm males). Creatinine clearance values returned to control levels during the recovery phase of the study. Following the exposure phase (Day 11), an exposure-related decrease in total urine volume was measured, and was statistically significant for the 50 and 250 ppm group males. Total urine volume was lower in 250 ppm group females at Day 12 and urine pH was statistically significantly decreased. These parameters returned to control levels after a 4-week recovery period. Exposure-related decreases in total urine volume and decreased creatinine clearance values without corresponding decreases in water consumption values tend to suggest that THBA vapor inhalation at 50 and 250 ppm for 9 days produced transient functional changes in the kidney. Both creatinine clearance and total urine volume returned to control levels during the recovery period.

There were no absolute organ weight differences observed in males or females. Relative kidney and adrenal weights were statistically significantly increased in males and females exposed to 250 ppm. In addition, relative testicular weights were statistically significantly increased in male rats exposed to 250 ppm. After four weeks of recovery, there was a statistically significant increase in absolute and relative heart weight noted in male rats previously exposed to 250 ppm THBA.

Gross observation at necropsy and microscopic evaluation revealed no gross or microscopic changes that could be related to THBA exposure.

Test substance : Purity was 99.4% slightly lower than current production material.

Attached document : Subacute inhalation second study.pdf

TABLE 13
TETRAHYDROBENZALDEHYDE (THBA): NINE-DAY VAPOR INHALATION
TOXICITY STUDY IN RATS: SECOND STUDY
SUMMARY OF CLINICAL CHEMISTRY
DAY 12

MALES

GROUP: PPM	0	5	50	250
GLUCOSE (g/l)				
MEAN	1.51	1.52	1.53	1.53
S.D.	0.070	0.047	0.089	0.045
N	10	10	10	10
UREA NITROGEN (mg/l)				
MEAN	170.	169.	182.	159.
S.D.	7.1	25.1	18.3	16.5
N	10	10	10	10
CREATININE (mg/l)				
MEAN	6.	6.	6.	6.
S.D.	0.3	0.0	0.0	0.3
N	10	10	10	10
TOTAL PROTEIN (g/l)				
MEAN	60.	60.	59.	58.
S.D.	1.9	1.9	2.6	2.8
N	10	10	10	10
TOTAL BILIRUBIN (mg/l)				
MEAN	1.	1.	1.	1.
S.D.	0.5	0.4	0.4	0.4
N	10	10	10	10
DIRECT BILIRUBIN (mg/l)				
MEAN	1.	1.	1.	1.
S.D.	0.5	0.5	0.4	0.7
N	10	10	10	10
INDIRECT BILIRUBIN (mg/l)				
MEAN	0.	0.	0.	0.
S.D.	0.0	0.4	0.0	0.4
N	10	10	10	10
CALCIUM (mg/l)				
MEAN	98.	98.	99.	98.
S.D.	1.5	1.3	1.5	2.0
N	10	10	10	10
INORGANIC PHOSPHORUS (mg/l)				
MEAN	70.	68.	70.	70.
S.D.	5.8	3.4	3.6	7.4
N	10	10	10	10
SODIUM (mmol/l)				
MEAN	143.	143.	143.	143.
S.D.	1.2	1.5	1.5	1.2
N	10	10	10	10
POTASSIUM (mmol/l)				
MEAN	4.8	4.8	4.9	4.9
S.D.	0.23	0.18	0.23	0.30
N	10	10	10	10
CHLORIDE (mmol/l)				
MEAN	107.	107.	106.	107.
S.D.	1.9	1.7	2.1	1.3
N	10	10	10	10
ASPARTATE AMINOTRANSFERASE (IU/l)				
MEAN	63.	68.	68.	62.
S.D.	9.3	14.6	10.8	9.1
N	10	10	10	10
ALANINE AMINOTRANSFERASE (IU/l)				
MEAN	33.	36.	37.	33.
S.D.	4.6	9.2	6.8	4.1
N	10	10	10	10

None significantly different from control group

TABLE 13 (continued)
TETRAHYDROBENZALDEHYDE (THBA): NINE-DAY VAPOR INHALATION
TOXICITY STUDY IN RATS; SECOND STUDY
SUMMARY OF CLINICAL CHEMISTRY
DAY 12

MALES

GROUP: PPM	0	5	50	250
γ-GLUTAMYL TRANSFERASE (IU/l)				
MEAN	3.	3.	3.	3.
S.D.	0.6	0.5	0.5	0.5
N	10	10	10	10
CREATINE KINASE (IU/l)				
MEAN	108.	127.	193.	95.
S.D.	39.8	84.2	189.6	25.9
N	10	10	10	10
LACTATE DEHYDROGENASE (IU/l)				
MEAN	56.	48.	61.	39.
S.D.	32.3	22.5	29.9	15.9
N	10	10	10	10
SORBITOL DEHYDROGENASE (IU/L)				
MEAN	7.	8.	9.	7.
S.D.	3.0	5.3	2.4	2.0
N	10	10	10	10
ALKALINE PHOSPHATASE (IU/l)				
MEAN	312.	304.	301.	319.
S.D.	41.3	26.9	22.3	23.9
N	10	10	10	10

None significantly different from control group

TABLE 14
TETRAHYDROBENZALDEHYDE (THBA): NINE-DAY VAPOR INHALATION
TOXICITY STUDY IN RATS: SECOND STUDY
SUMMARY OF CLINICAL CHEMISTRY
DAY 12

FEMALES

GROUP: PPM	0	5	50	250
GLUCOSE (g/l)				
MEAN	1.43	1.39	1.42	1.45
S.D.	0.072	0.137	0.097	0.060
N	10	10	10	10
UREA NITROGEN (mg/l)				
MEAN	157.	154.	162.	164.
S.D.	21.7	9.6	24.5	14.5
N	10	10	10	10
CREATININE (mg/l)				
MEAN	5.	6.	6.	6.
S.D.	0.4	0.7	0.6	0.5
N	10	10	10	10
TOTAL PROTEIN (g/l)				
MEAN	57.	58.	58.	56.
S.D.	1.6	2.3	2.2	1.4
N	10	10	10	10
TOTAL BILIRUBIN (mg/l)				
MEAN	1.	1.	1.	1.
S.D.	0.0	0.0	0.0	0.0
N	10	10	10	10
DIRECT BILIRUBIN (mg/l)				
MEAN	1.	1.	1.	1.
S.D.	0.0	0.0	0.0	0.0
N	10	10	10	10
INDIRECT BILIRUBIN (mg/l)				
MEAN	0.	0.	0.	0.
S.D.	0.0	0.0	0.0	0.0
N	10	10	10	10
CALCIUM (mg/l)				
MEAN	96.	96.	96.	96.
S.D.	1.3	2.1	1.1	2.0
N	10	10	10	10
INORGANIC PHOSPHORUS (mg/l)				
MEAN	77.	77.	78.	76.
S.D.	4.0	5.7	5.8	4.9
N	10	10	10	10
SODIUM (mmol/l)				
MEAN	142.	142.	142.	142.
S.D.	1.1	1.5	1.2	1.1
N	10	10	10	10
POTASSIUM (mmol/l)				
MEAN	4.8	4.8	4.8	4.7
S.D.	0.17	0.27	0.26	0.29
N	10	10	10	10
CHLORIDE (mmol/l)				
MEAN	107.	107.	107.	107.
S.D.	1.2	1.2	0.8	1.0
N	10	10	10	10
ASPARTATE AMINOTRANSFERASE (IU/l)				
MEAN	55.	59.	54.	61.
S.D.	5.0	8.9	5.6	12.1
N	10	10	10	10
ALANINE AMINOTRANSFERASE (IU/l)				
MEAN	26.	27.	26.	30.
S.D.	2.5	3.7	1.8	5.5
N	10	10	10	10

None significantly different from control group

TABLE 14 (continued)
TETRAHYDROBENZALDEHYDE (THBA): NINE-DAY VAPOR INHALATION
TOXICITY STUDY IN RATS: SECOND STUDY
SUMMARY OF CLINICAL CHEMISTRY
DAY 12

FEMALES

GROUP: PPM	0	5	50	250
γ-GLUTAMYL TRANSFERASE (IU/l)				
MEAN	4.	4.	4.	4.
S.D.	0.5	0.5	0.8	0.6
N	10	10	10	10
CREATINE KINASE (IU/l)				
MEAN	116.	108.	153.	103.
S.D.	42.5	58.9	97.4	33.2
N	10	10	10	10
LACTATE DEHYDROGENASE (IU/l)				
MEAN	56.	55.	54.	50.
S.D.	19.1	13.6	20.4	11.9
N	10	10	10	10
SORBITOL DEHYDROGENASE (IU/l)				
MEAN	7.	8.	8.	8.
S.D.	1.3	1.6	1.3	2.0
N	10	10	10	10
ALKALINE PHOSPHATASE (IU/l)				
MEAN	243.	242.	252.	259.
S.D.	17.4	28.0	19.8	19.8
N	10	10	10	10

None significantly different from control group

TABLE 21
TETRAHYDROBENZALDEHYDE (THBA): NINE-DAY VAPOR INHALATION
TOXICITY STUDY IN RATS: SECOND STUDY
SUMMARY OF URINE CHEMISTRY
DAY 11

MALES

GROUP: PPM	0	5	50	250
N-ACETYL-B-D-GLUCOSAMINIDASE (IU/L)				
MEAN	6.56	5.72	7.41	6.24
S.D.	4.404	4.345	3.591	4.208
N	10	10	10	10
ALPHA 2U-GLOBULIN (g/l)				
MEAN	1.62	1.38	1.56	1.58
S.D.	0.337	0.258	0.482	0.386
N	10	10	10	9
URINE TOTAL PROTEIN (g/l)				
MEAN	5.51	4.95	5.87	5.95
S.D.	1.169	0.741	1.010	1.182
N	10	10	10	10
URINE CREATININE (mg/l)				
MEAN	1181.	1094.	1236.	1276.
S.D.	206.4	136.2	144.9	217.2
N	10	10	10	10
CREATININE CLEARANCE (ml/15hr)				
MEAN	1059.4	980.7	875.4**	857.3**
S.D.	94.35	141.96	96.14	184.91
N	10	10	10	10

** Significantly different from control group (p < .01)

TABLE 22
TETRAHYDROBENZALDEHYDE (THBA): NINE-DAY VAPOR INHALATION
TOXICITY STUDY IN RATS: SECOND STUDY
SUMMARY OF URINE CHEMISTRY
DAY 12

FEMALES

GROUP: PPM	0	5	50	250
N-ACETYL-B-D-GLUCOSAMINIDASE (IU/L)				
MEAN	5.05	5.28	5.37	6.26
S.D.	0.862	1.505	1.116	1.417
N	10	10	10	10
URINE TOTAL PROTEIN (g/l)				
MEAN	2.20	2.15	2.41	2.61
S.D.	0.571	0.702	0.422	0.452
N	10	10	10	10
URINE CREATININE (mg/l)				
MEAN	910.	919.	920.	1015.
S.D.	211.9	246.1	246.2	166.3
N	10	10	10	10
CREATININE CLEARANCE (ml/15hr)				
MEAN	873.2	748.0*	754.5*	673.9**
S.D.	116.54	102.96	137.15	97.44
N	10	10	10	10

* Significantly different from control group ($p < .05$)
** Significantly different from control group ($p < .01$)

TABLE 23
TETRAHYDROBENZALDEHYDE (THBA): NINE-DAY VAPOR INHALATION
TOXICITY STUDY IN RATS: SECOND STUDY
SUMMARY OF URINE CHEMISTRY
DAY 39

MALES

GROUP: PPM	0	5	50	250
N-ACETYL-B-D-GLUCOSAMINIDASE (IU/L)				
MEAN	9.90			9.35
S.D.	1.033			1.073
N	5			5
ALPHA 2U-GLOBULIN (g/l)				
MEAN	1.42			1.38
S.D.	0.237			0.266
N	5			5
URINE TOTAL PROTEIN (g/l)				
MEAN	5.27			5.14
S.D.	0.565			0.568
N	5			5
URINE CREATININE (mg/l)				
MEAN	1296.			1333.
S.D.	185.6			159.8
N	5			5
CREATININE CLEARANCE (ml/15hr)				
MEAN	1040.7			954.1
S.D.	78.82			115.68
N	5			5

None significantly different from control group

TABLE 24
TETRAHYDROBENZALDEHYDE (THBA): NINE-DAY VAPOR INHALATION
TOXICITY STUDY IN RATS: SECOND STUDY
SUMMARY OF URINE CHEMISTRY
DAY 39

FEMALES

GROUP: PPM	0	5	50	250
N-ACETYL-B-D-GLUCOSAMINIDASE (IU/L)				
MEAN	5.03			6.35
S.D.	1.127			0.956
N	5			5
URINE TOTAL PROTEIN (g/l)				
MEAN	2.45			2.39
S.D.	0.268			0.965
N	5			5
URINE CREATININE (mg/l)				
MEAN	1005.			987.
S.D.	172.1			265.5
N	5			5
CREATININE CLEARANCE (ml/15hr)				
MEAN	759.9			746.8
S.D.	108.39			42.72
N	5			5

None significantly different from control group

TABLE 29
TETRAHYDROBENZALDEHYDE (THBA): NINE-DAY VAPOR INHALATION
TOXICITY STUDY IN RATS: SECOND STUDY
SUMMARY OF ORGAN WEIGHTS (GRAMS)
ANIMALS SACRIFICED AT DAY 12

MALES

GROUP: PPM	0	5	50	250
FINAL BODY WEIGHT				
MEAN	199.7	197.8	201.8	188.7
S.D.	10.11	11.10	15.73	12.42
N	10	10	10	10
LIVER				
MEAN	7.727	7.697	7.975	7.627
S.D.	0.7169	0.7642	0.8274	0.6672
N	10	10	10	10
LUNGS				
MEAN	0.871	0.912	0.887	0.856
S.D.	0.0431	0.0521	0.0616	0.0495
N	10	10	10	10
KIDNEYS				
MEAN	1.473	1.505	1.509	1.480
S.D.	0.0543	0.0751	0.1359	0.0812
N	10	9	10	10
BRAIN				
MEAN	1.729	1.723	1.714	1.713
S.D.	0.0457	0.0588	0.0833	0.0551
N	10	10	10	10
SPLEEN				
MEAN	0.456	0.460	0.481	0.427
S.D.	0.0414	0.0382	0.0397	0.0360
N	10	10	10	10
HEART				
MEAN	0.685	0.670	0.679	0.654
S.D.	0.0364	0.0409	0.0510	0.0340
N	10	10	10	10
ADRENAL GL				
MEAN	0.031	0.032	0.029	0.035
S.D.	0.0038	0.0025	0.0070	0.0048
N	10	10	10	10
TESTES				
MEAN	2.365	2.350	2.422	2.427
S.D.	0.1419	0.1706	0.1801	0.1932
N	10	10	10	10

None significantly different from control group

TABLE 30
TETRAHYDROBENZALDEHYDE (THBA): NINE-DAY VAPOR INHALATION
TOXICITY STUDY IN RATS: SECOND STUDY
SUMMARY OF ORGAN WEIGHTS (GRAMS)
ANIMALS SACRIFICED AT DAY 12

FEMALES

GROUP: PPM	0	5	50	250
FINAL BODY WEIGHT				
MEAN	144.2	143.7	146.8	137.1*
S.D.	6.18	7.02	8.96	6.65
N	10	10	10	10
LIVER				
MEAN	5.000	5.037	5.172	4.944
S.D.	0.3103	0.3654	0.2823	0.2786
N	10	10	10	10
LUNGS				
MEAN	0.719	0.751	0.735	0.690
S.D.	0.0424	0.0368	0.0256	0.0375
N	10	10	9	10
KIDNEYS				
MEAN	1.071	1.103	1.107	1.092
S.D.	0.0463	0.0675	0.0707	0.0624
N	10	10	10	10
BRAIN				
MEAN	1.629	1.643	1.638	1.613
S.D.	0.0394	0.0705	0.0502	0.0373
N	10	10	10	10
SPLEEN				
MEAN	0.344	0.355	0.359	0.320
S.D.	0.0265	0.0353	0.0275	0.0251
N	10	10	10	10
HEART				
MEAN	0.516	0.548	0.542	0.527
S.D.	0.0230	0.0609	0.0444	0.0247
N	10	10	10	10
ADRENAL GL				
MEAN	0.038	0.040	0.039	0.041
S.D.	0.0033	0.0045	0.0047	0.0044
N	10	10	10	10
OVARIES				
MEAN	0.089	0.085	0.087	0.078
S.D.	0.0126	0.0094	0.0143	0.0098
N	10	10	10	10

* Significantly different from control group ($p < .05$)

TABLE 31
TETRAHYDROBENZALDEHYDE (THBA): NINE-DAY VAPOR INHALATION
TOXICITY STUDY IN RATS: SECOND STUDY
SUMMARY OF ORGAN WEIGHTS AS % OF FINAL BODY WEIGHT
ANIMALS SACRIFICED AT DAY 12

MALES

GROUP: PPM	0	5	50	250
LIVER				
MEAN	3.867	3.885	3.948	4.039
S.D.	0.2634	0.2262	0.2042	0.1627
N	10	10	10	10
LUNGS				
MEAN	0.437	0.462	0.440	0.455
S.D.	0.0166	0.0221	0.0262	0.0280
N	10	10	10	10
KIDNEYS				
MEAN	0.738	0.752	0.748	0.785**
S.D.	0.0173	0.0225	0.0291	0.0295
N	10	9	10	10
BRAIN				
MEAN	0.867	0.873	0.854	0.911
S.D.	0.0370	0.0578	0.0732	0.0507
N	10	10	10	10
SPLEEN				
MEAN	0.228	0.232	0.239	0.226
S.D.	0.0151	0.0102	0.0178	0.0078
N	10	10	10	10
HEART				
MEAN	0.343	0.339	0.337	0.347
S.D.	0.0100	0.0137	0.0159	0.0166
N	10	10	10	10
ADRENAL GL				
MEAN	0.016	0.016	0.015	0.019*
S.D.	0.0027	0.0016	0.0032	0.0028
N	10	10	10	10
TESTES				
MEAN	1.185	1.188	1.202	1.286**
S.D.	0.0653	0.0559	0.0765	0.0555
N	10	10	10	10

* Significantly different from control group ($p < .05$)
** Significantly different from control group ($p < .01$)

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TABLE 32
TETRAHYDROBENZALDEHYDE (THBA): NINE-DAY VAPOR INHALATION
TOXICITY STUDY IN RATS: SECOND STUDY
SUMMARY OF ORGAN WEIGHTS AS % OF FINAL BODY WEIGHT
ANIMALS SACRIFICED AT DAY 12

FEMALES

GROUP: PPM	0	5	50	250
LIVER				
MEAN	3.469	3.505	3.527	3.608
S.D.	0.1996	0.1792	0.1647	0.1688
N	10	10	10	10
LUNGS				
MEAN	0.499	0.523	0.504	0.504
S.D.	0.0242	0.0300	0.0254	0.0295
N	10	10	9	10
KIDNEYS				
MEAN	0.743	0.768	0.755	0.797**
S.D.	0.0336	0.0407	0.0359	0.0405
N	10	10	10	10
BRAIN				
MEAN	1.131	1.146	1.118	1.178
S.D.	0.0362	0.0711	0.0533	0.0461
N	10	10	10	10
SPLEEN				
MEAN	0.238	0.247	0.245	0.233
S.D.	0.0118	0.0202	0.0122	0.0117
N	10	10	10	10
HEART				
MEAN	0.358	0.381	0.369	0.384
S.D.	0.0179	0.0361	0.0197	0.0187
N	10	10	10	10
ADRENAL GL				
MEAN	0.027	0.028	0.027	0.030*
S.D.	0.0022	0.0031	0.0034	0.0036
N	10	10	10	10
OVARIES				
MEAN	0.062	0.060	0.060	0.057
S.D.	0.0074	0.0049	0.0116	0.0076
N	10	10	10	10

* Significantly different from control group ($p < .05$)
** Significantly different from control group ($p < .01$)

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Conclusion : Exposure of rats to THBA vapor for 9 exposures at 50 and 250 ppm produced a limited number of effects on body weight, feed consumption, urine chemistry and urinalysis parameters. Although creatinine clearance in female rats exposed to 5 ppm THBA was less than control animals, urine creatinine and serum creatinine values were comparable. Since serum creatinine values were comparable to control values and there were no renal histopathologic effects noted at 5 ppm THBA, the no-observed-effect level (NOEL) was considered to be 5 ppm.

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment

16.12.2004 (25)

Type : Sub-acute
Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : dermal
Exposure period : 6 hours/day
Frequency of treatm. : 5 days/week
Post exposure period : Five rats/sex in the control and high level group were sacrificed 4 weeks following the last exposure.

Doses	:	0.10, 0.25 and 0.75 ml/kg/day
Control group	:	yes, concurrent no treatment
NOAEL	:	= .1 ml/kg bw
LOAEL	:	= .25 - ml/kg bw
Method	:	
Year	:	1999
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Method : Four groups, consisting of 15 Sprague Dawley rats/sex in the control and high groups and 10 rats/sex in the low and mid level groups, were dosed topically at 0 (control), 0.10, 0.25 and 0.75 ml/kg/day. Rats were dosed for 6 hours/day, 5 days/week for a total of 9 applications in two weeks. Ten rats/sex/dose level were sacrificed the day following the last exposure. The remaining 5 rats/sex in the control and high level group were sacrificed 4 weeks following the last exposure. Test material was applied to the dorsal region of skin, gauze was applied over the application site followed by impervious plastic. Following 6 hours of exposure, the wrappings were removed and the test site wiped free of excess test material. Control animals were sham treated. Due to excessive tissue damage noted in the high dose male rats, the dose site of all high dose animals was moved to untreated skin beginning on day 9. All other animals were dosed at the same site throughout the study. Routine parameters examined include skin evaluation at the application site, clinical observations, neurobehavioral screen, feed and water consumption, body and organ weights, hematologic and serum clinical chemistry evaluations, urinalysis, and necropsy and microscopic evaluations of selected tissues. With the exception of serum clinical chemistry ornithine decarboxylase activity, all endpoints specified in OECD 410 for 21/28 day dermal subchronic toxicity studies were evaluated. Histopathologic examination included adrenal, bone marrow, brain, heart, kidneys, liver, lungs, muscle, nerve, skin (treated and untreated), spinal cord, spleen, testes and any macroscopic changes.

Statistical evaluation:
Statistical evaluation of equality of means was made by the appropriate one way analysis of variance technique, followed by a multiple comparison procedure if needed. First, Bartlett's test was performed to determine if groups had equal variance. If the variances were equal, parametric procedures were used; if not, nonparametric procedures were used. The parametric procedures were the standard one way ANOVA using the F distribution to assess significance. If significant differences among the means were indicated, Dunnett's test was used to determine which means were significantly different from the control. If a nonparametric procedure for testing equality of means was needed, the Kruskal-Wallis test was used, and if differences were indicated Dunn's summed rank test was used to determine which treatments differed from control.

A statistical test for trend in the dose levels was also performed. In the parametric case (i.e., equal variance) standard regression techniques with a test for trend and lack of fit were used. In the nonparametric case Jonckheere's test for monotonic trend was used.

The Bartlett's test was conducted at the 1% two-sided risk level. All other tests were conducted at the 5% and 1%, two-sided risk level. Statistical evaluations were not performed when the standard deviation for the control group was zero. Dose groups were eliminated from analyses if their standard deviation was zero.

Two-Group Analyses
The variances of the two groups were tested for equality using the F-test. If the variances were equal, a standard independent two sample t-test was

used to determine equality of means. If the variances differed at the 1% level of significance, Welch's t-test was used to determine equality of means. T-tests were conducted at the 5% and 1% 2-sided risk level.

The test for equal variance (Bartlell's) was conducted at the 1%, two-sided risk level. All other statistical tests were conducted at the 5% and 1%, two-sided risk level.

Result : At the 0.75 ml/kg/day dose, two of the fifteen females were found dead during the first week of the study; based on an assessment of morphologic abnormalities, a cause of death was not determined. The remaining females and all fifteen males survived. The survivors in this group had decreased weight gains and increased water consumption, compared to the control values. Histopathology of the kidneys of the females revealed focal mineral deposits. Severe, reversible skin irritation was seen at the dose site of all 0.75 ml/kg/day animals. Histopathology of the site of topical application of THBA revealed surface accumulations of inflammatory cells/cell debris and/or necrotic debris, squamous cell hyperplasia, hyperkeratosis, dermal necrosis and ulcers and acute to subacute-chronic inflammation, edema and hypertrophy/hyperplasia of sebaceious glands. No evidence of THBA induced toxicity was seen in the feed consumption, physical evaluations, neurobehavioral studies, hematology, clinical chemistry, urinalysis or organ weight values of these animals.

All 0.25 ml/kg/day animals survived to the end of the treatment period, and were free of test material related clinical signs. However, mild to moderate skin irritation was seen at the dose site; histopathology of the dose site revealed changes similar to those seen in the 0.75 ml/kg/day group but were less severe. Histopathology of the kidneys (females only) also revealed changes which were similar to those seen in the 0.75 ml/kg/day group, but were less severe. No evidence of THBA induced toxicity was seen in the body weights, feed consumption, water consumption, neurobehavioral studies, hematology, clinical chemistry, urinalysis or organ weight values of the 0.25 ml/kg/day animals.

There were no treatment-related deaths in the 0.10 ml/kg/day animals, and all animals were free of clinical signs and significant skin irritation. Histopathology of the dose site revealed changes similar to those seen in the 0.75 ml/kg/day group but were minimal to slight in severity. No evidence of THBA induced toxicity was seen in the body weights, feed consumption, water consumption, neurobehavioral studies, hematology, clinical chemistry, urinalysis or organ weight values of the 0.10 ml/kg/day animals. Except for the skin lesions discussed previously, there were no significant microscopic changes seen in these animals which could be attributed to administration of THBA.

Test substance : Test material is reported to be 100% pure.

Attached document : Subacute dermal tables.pdf

TREATED SKIN: INCIDENCE AND SEVERITY OF MICROSCOPIC FINDINGS

Group - ml/kg/day		MALES 0	MALES 0.10	MALES 0.25	MALES 0.75	FEMALES 0	FEMALES 0.10	FEMALES 0.25	FEMALES 0.75
TERMINATION									
Number Examined		10	10	10	10	10	10	10	12
Squamous Cell Hyperplasia	Total	2	10	10	10	0	9	10	9
	MN	1.00	2.00	2.30	2.50	0.00	1.56	2.00	2.56
Hyperkeratosis	Total	3	10	10	10	2	9	10	10
	MN	1.00	1.50	2.00	1.90	1.00	1.56	1.70	2.00
Ulcers	Total	1	1	1	3	0	2	4	7
	MN	1.00	2.00	2.00	2.00	0.00	1.50	2.25	2.14
Dermis: Necrosis	Total	0	1	2	4	0	2	4	7
	MN	0.00	2.00	2.00	2.75	0.00	1.50	2.25	2.14
Dermis: Acute Inflammation	Total	1	1	2	4	0	2	5	7
	MN	1.00	2.00	2.00	2.75	0.00	1.50	2.00	2.29
Surface: Inflammatory Cells/ Cellular and/or Necrotic Debris	Total	1	3	8	10	0	4	5	10
	MN	1.00	1.67	2.38	2.60	0.00	1.50	2.80	2.90
Dermis: Subacute/Chronic Inflammation	Total	0	8	10	10	0	6	9	10
	MN	0.00	1.50	2.00	2.00	0.00	1.83	1.89	2.00
Sebaceous Glands: Hypertrophy/ Hypertrophy/Hyperplasia	Total	1	7	10	8	0	4	9	10
	MN	1.00	2.00	2.00	2.00	0.00	1.75	1.78	2.00
RECOVERY									
Number Examined		5	-	-	5	5	-	-	3
Dermis: Increased Dermal Collagen	Total	0	-	-	5	0	-	-	3
	MN	0.00	-	-	1.80	0.00	-	-	1.67

Severity Grades:
1=Minimal; 2=Slight; 3=Moderate; 4=Moderately Severe; 5=Severe
MN=Mean Severity; Total=Total number of animals with positive entries

Males	Mean Organ Weights Terminal Sacrifice	Table 12

	TERMINAL BODY WT. (G)	WT. (G)	TEST/EPID ORG/TBW (X 100)	ORG/BRN (X 1)
GROUP I - 0 ML/KG/DAY				
MEAN	240	3.407	1.42	1.71
S.D.	11	0.282	0.10	0.15
N	10	10	10	10
GROUP II - 0.10 ML/KG/DAY				
MEAN	224	3.465	1.55	1.81
S.D.	19	0.408	0.15	0.18
N	10	10	10	10
GROUP III - 0.25 ML/KG/DAY				
MEAN	223	3.435	1.54	1.78
S.D.	17	0.327	0.13	0.12
N	10	10	10	10
GROUP IV - 0.75 ML/KG/DAY				
MEAN	** 209	3.189	1.53	1.73
S.D.	15	0.255	0.14	0.15
N	10	10	10	10

*Significantly different from control mean; p≤0.05.
**Significantly different from control mean; p≤0.01.
If no asterisks, no statistically significant differences from control mean.

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Females	Mean Organ Weights Terminal Sacrifice	Table 12

	TERMINAL BODY WT. (G)	OVARIES WT. (G)	ORG/TBW (X 10000)	ORG/BRN (X 100)
GROUP I - 0 ML/KG/DAY				
MEAN	206	0.0960	4.64	5.08
S.D.	15	0.0174	0.64	0.89
N	10	10	10	10
GROUP II - 0.10 ML/KG/DAY				
MEAN	199	0.0839	4.22	4.51
S.D.	20	0.0123	0.63	0.72
N	9	9	9	9
GROUP III - 0.25 ML/KG/DAY				
MEAN	200	0.0893	4.49	4.75
S.D.	15	0.0124	0.73	0.71
N	10	10	10	10
GROUP IV - 0.75 ML/KG/DAY				
MEAN	197	0.0887	4.50	4.64
S.D.	13	0.0114	0.50	0.62
N	10	10	10	10

*Significantly different from control mean; p≤0.05.
**Significantly different from control mean; p≤0.01.
If no asterisks, no statistically significant differences from control mean.

Conclusion : Under the conditions of this study, the cutaneous administration of THBA to rats for 9 days at doses up to 0.75 ml/kg/day produced reversible changes in the skin at the application site for all groups and changes (mineral deposits) in the kidneys of female rats at 0.25 and 0.75 ml/kg/day. The no-observed-effect-level (NOEL) for systemic toxicity was 0.10 ml/kg/day.

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment

16.12.2004 (26)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Ames test
System of testing :
Test concentration :
Cycotoxic concentr. :
Metabolic activation : with and without
Result : negative
Method : other:
Year : 1994
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : The test material was dissolved in dimethylsulfoxide based on solubility of the test article and compatibility with the target cells.

For a probe study, tetrahydrobenzaldehyde was used at dose levels

ranging from 0.001 to 10.0 mg/plate on strain TA100 with and without S9 metabolic activation. The preincubation procedure was used. The metabolic activation system was an Aroclor 1254-induced rat liver S9 fraction.

Salmonella thyphimurium strains TA98, TA100, TA1535, TA1537 and TA1538 were treated in triplicate with the vehicle control, an appropriate positive control substance, and 5 dose levels of tetrahydrobenzaldehyde both in the absence and in the presence of a rat liver S9 metabolic activation system using the preincubation method. Dose levels used without metabolic activation ranged from 0.01 to 1.0 mg/plate and with metabolic activation ranged from 0.03 to 3.0 mg/plate. The positive controls, 4-nitro-o-phenylenediamine was used without S9 in strains TA98 and TA1538, sodium azide was used without S9 in strains TA100 and TA1535, 9-aminoacridine was used without S9 in strain TA1537 and 2-aminoanthracene was used in all strains with S9. Treated cultures were incubated at 37C for 48-72 hours. Two independent repetitions of the complete assay were performed.

A response was considered to be positive if it consistently produced a dose-related increase in the mean reversion frequency of at least one bacterial strain as compared to the vehicle control for that strain. At least one of those doses must have produced a mean reversion frequency at least twice that of the vehicle control. Alternatively, a test substance was considered a bacterial mutagen if there was a reproducible increase in the mean number of revertant colonies at a single dose level of at least 2-fold compared to the vehicle control. Increases in the mean reversion frequency that were not dose related, or could not be reproduced, were considered negative test results.

Methods cited were:
Ames, B.N., McCann, J. and Yamasaki, F. (1975). Methods for detecting carcinogens and mutagens with the Salmonella/mammalian-microsome mutagenicity test. Mutation Research 31:347-364.

Kier, L.D., Brusick, D.J., Auletta, A.E., VonHalle, E.S., Brown, M.M., Simmon, V.F., Dunkel, V., McCann, J., Mortelmans, K., Prival, M., Rao, T.K. and Ray, V. (1986). The Salmonella typhimurium/mammalian microsomal assay. A report of the U.S. Environmental Protection Agency Gene-Tox Program. Mutation Research 168: 69-240.

Maron, D.M. and Ames, B.N. (1983). Revised methods for the Salmonella mutagenicity test. Mutation Research 113:173-215.

Result : In the probe study, tetrahydrobenzaldehyde was nontoxic to strain TA100 at doses of 0.30 mg/plate or less in the absence of an S9 rat liver metabolic activation system and at doses of 1.0 mg/plate or less in the presence of S9 activation. Complete absence of background lawn growth was observed at tetrahydrobenzaldehyde doses of 1.0 mg/plate or greater in the absence of metabolic activation and at doses of 3.0 mg/plate or greater in the presence of metabolic activation.

For the definitive mutagenicity study using the Ames test, there was no mutagenic activity observed in strains TA98, TA100, TA1537 or TA1538 with or without metabolic activation either by evidence of a dose-response relationship or a doubling of the mean number of colonies over the mean vehicle control value. An increase of approximately 2-fold was observed in the mean number of colonies/plate in strain TA1535 in the presence of S9 activation at 1.0 mg/plate (Table 1). However, this increase did not appear to be dose-related, was within the normal range of variability for this strain and was not observed in an independent experiment.

Table 1
Results in strain TA1535 in the Ames test with metabolic activation

Dose Level	Mutants/plate Initial	Replicate
Control	11+/-2.0	4+/-1.7
0.03	11+/-1.0	7+/-5.5
0.10	11+/-1.5	5+/-2.0
0.30	9+/-2.9	6+/-1.5
1.0	9+/-3.0	9+/-4.6
3.0	Toxic	Toxic
2-AA	176+/-8.5	144+/-13.6

Each value was conducted in triplicate.
2-AA - 2-aminoanthracene

Test substance : Purity of the test substance was 99.5%
Attached document : Salmonella E coli results.pdf
Conclusion : Tetrahydrobenzaldehyde did not produce consistent, dose-related mutagenic effects in any of the Salmonella strains tested, either in the absence or in the presence of an S9 metabolic activation system. These results were observed in two independent tests. Under the conditions of this Salmonella/microsome mutagenicity assay, tetrahydrobenzaldehyde was not considered mutagenic.
Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment

30.08.2004 (27)

Type : Bacterial reverse mutation assay
System of testing :
Test concentration :
Cycotoxic concentr. :
Metabolic activation : with and without
Result :
Method : OECD Guide-line 471
Year : 1997
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : The test material was dissolved in dimethylsulfoxide based on solubility of the test article and compatibility with the target cells.

For a probe study, tetrahydrobenzaldehyde was used at dose levels ranging from 6.7 to 5000 µg/plate on Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and Escherichia coli strain WP2 uvrA with and without S9 metabolic activation. The plate incorporation methodology was used. The metabolic activation system was an Aroclor 1254-induced rat liver S9 fraction.

Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and Escherichia coli strain WP2 uvrA were treated in triplicate with the vehicle control, an appropriate positive control substance, and 6 dose levels of tetrahydrobenzaldehyde both in the absence and in the presence of a rat liver S9 metabolic activation system using the plate incorporation method. Dose levels used with and without metabolic activation ranged from 33 to 5000 µg/plate. The positive controls, 2-nitrofluorene was used without S9 in strains TA98, sodium azide was used without S9 in strains TA100 and TA1535, 9-aminoacridine was used without S9 in strain TA1537, methyl methanesulfonate was used in strain WP2 uvrA and 2-aminoanthracene

was used in all strains with S9. Treated cultures were incubated at 37C for 48-72 hours. Two independent repetitions of the complete assay were performed.

For the test material to be considered to be positive in this assay, it must cause a dose-related increase in the mean revertants/plate of at least one tester strain with a minimum of two increasing concentrations of test material. Data sets for strains TA1535 and TA1537 were judged positive if the increase in mean revertants at the peak of the dose responseis equal to or greater than three times the mean vehicle control value. Data sets for strains TA98, TA100 and WP2uvrA were judged positive if the increase in mean revertants at the peak of the dose response is equal to or greater than two times the mean vehicle control value.

Remark : The results of these two Ames studies conducted by slightly different methods have resulted in slight increases in different strains in each study. None of the results have been reproducible between and/or within studies and thus the results are considered to be chance findings and the overall conclusion is that this material is negative in the Ames test.

Result : For the probe study, the maximum dose tested was 5000 µg/plate. No precipitate was observed but toxicity was observed at >3333 µg and 5000 µg/plate with strains TA98 and TA1537 in both the presence and absence of S9 activation. Based on the findings of the toxicity assay, the maximum dose plated in the mutagenicity assay was 5000 µg/plate.

For the definitive studies, no precipitate was observed but toxicity was generally observed at 5000 µg/plate with tester strains TA98 and TA1537 with and without metabolic activation.

In the first study, experiment B1, a positive response was observed with tester strain TA100 (2.2-fold, maximum increase) in the presence of S9 activation. A slight increase of 1.8-fold above control value was observed in strain TA100 in the absence of S9 activation. No other positive responses were observed with any of the remaining test strains/activation combinations.

In the second study, experiment B2, the independent repeat assay, a positive response was observed in strain TA98 (3.1-fold maximum increase) in the absence of S9. A slight increase of 1.7-fold above control value was observed in strain TA100 in the presence of S9 activation. Due to a plating error in which two dose levels (1000 and 3333 µg/plate) did not receive aliquots of strain TA100 in the absence of S9 activation was not evaluated but was retested in experiment B3. No positive responses were observed with the remaining strain/activation combinations.

In the third study, experiment B3, no positive response was observed with strain TA100 in the absence of S9 activation. A slight increase, 1.7x, was observed in strain TA100 in the absence of S9.

Test substance : The test material was reported to be 99.7% pure. Subsequent purity by capillary GC was 98.6%.

Conclusion : Tetrahydrobenzaldehyde did not cause reproducible positive responses with any of the tester strains in the presence and absence of Aroclor-induced rat liver S9. However, the dose responsive increases observed with strain TA100 in the presence and absence of S9 activation suggest the presence of low level mutagenic activity.

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment

30.08.2004 (28)

Type : HGPRT assay

System of testing :

Test concentration	:	
Cycotoxic concentr.	:	
Metabolic activation	:	
Result	:	negative
Method	:	OECD Guide-line 476
Year	:	1997
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Method : The test material was dissolved in dimethylsulfoxide based on solubility of the test article, >500 mg/ml, and compatibility with the target cells.

For a probe study, CHO cells were exposed for 5 hours to the vehicle alone and 9 concentrations of test material ranging from 0.5 to 5000 µg/ml with and without metabolic activation. For metabolic activation, Aroclor 1254-induced rat liver S9 was used.

For the definitive study, CHO cells were exposed for 5 hours to the vehicle alone, appropriate positive controls and 50, 100, 150, 200 and 250 µg/ml of test material without metabolic activation and 250, 500, 600, 750 and 1000 µg/ml with metabolic activation in duplicate. The positive controls, ethyl methanesulfonate and benzo(a)pyrene, were used without and with metabolic activation, respectively.

The doses chosen for the independent repeat mutagenesis assay ranged from 100 to 400 µg/ml for the non-activated and 500 to 900 µg/ml for the S9-activated cultures.

The assay will be considered positive in the event of a dose-dependent increase in mutant frequencies with at least two consecutive doses showing mutant frequencies which are elevated above 40 mutants/10(6) clonable cells. If a single point above 40 mutants per 10(6) clonable cells is observed at the highest dose, the assay will be considered suspect. If no culture exhibits a mutant frequency of >40 mutants per 10(6) clonable cells, the test material will be considered negative.

Result : For the probe study, visible precipitate was observed in treatment medium at concentrations of 1500 and 5000 µg/ml. Treatment medium was cloudy but with no visible precipitate at a concentration of 500 µg/ml. Concentrations of <150 µg/ml were soluble in treatment medium. The osmolality of the solvent control was 442 mmol/kg and the osmolality of the highest soluble dose, 500 µg/ml, was 427 mmol/kg. Cloning efficiency relative to the solvent controls (RCE) was 0% at 500 µg/ml without activation and 0% at 1500 µg/ml with S9 activation. Based on the results of the toxicity test, the doses chosen for the initial mutagenesis assay ranged from 50 to 250 µg/ml for the non-activated cultures and 250 to 1000 µg/ml for the S9-activated cultures.

For the definitive study, cultures treated with concentrations of 50, 100, 150, 200 and 250 µg/ml test material without metabolic activation and concentrations of 250, 500, 600, 750 and 1000 µg/ml test material with metabolic activation were cloned. No test material precipitate was observed at any dose level in treatment medium. Relative cloning efficiency was 66% and 4% at the highest dose tested in the non-activated and S9-activated systems, respectively. None of the treated cultures exhibited mutant frequencies of greater than 40 mutants per 10(6) clonable cells.

For the independent repeat mutagenesis assay, cultures treated with 100, 200, 250, 300 and 400 µg/ml for the non-activated and 500, 600, 750, 800 and 900 µg/ml for the S9-activated cultures were cloned. No test material precipitate was observed at any dose level in treatment medium. Relative

cloning efficiency was 4 and 16% at the highest dose tested in the non-activated and S9-activated systems, respectively. None of the treated cultures exhibited mutant frequencies of greater than 40 mutants per 10(6) clonable cells.

Test substance : The test material was reported to be 99.7% pure. Subsequent purity by capillary GC was 98.6%.

Conclusion : Tetrahydrobenzaldehyde did not cause a positive response in the non-activated and S9-activated systems and was concluded to be negative

Reliability : (1) valid without restriction
1a: GLP guideline study

30.08.2004 (29)

5.6 GENETIC TOXICITY 'IN VIVO'

Type : Micronucleus assay
Species : mouse
Sex : male/female
Strain : ICR
Route of admin. : i.p.
Exposure period :
Doses :
Result : negative
Method : OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"
Year : 1997
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : The test material was dissolved in corn oil which was determined to be the solvent of choice based on solubility and compatibility of the solvent with the test system. The test article was soluble in corn oil at 500 mg/ml, the maximum concentration tested.

As part of a probe study, groups of 5 male and 5 female ICR mice were dosed ip with 1, 10, 100, 1000, 1300, 1600, 2200 or 3000 mg active ingredient (AI) test material/kg body weight. All animals died at doses of 1600 mg/kg or greater. At 1300 mg/kg, 3 of 5 males and 5 of 5 females died within 3 days of dose administration.

For the micronucleus assay, groups of 15 male and 15 female mice were dosed with tetrahydrobenzaldehyde by a single ip injection of 0, 250, 500 or 1000 mg AI/kg which was administered in a total volume of 20 ml corn oil/kg body weight. At 1000 mg AI/kg body weight an additional group of 5 male and 5 female mice dosed with tetrahydrobenzaldehyde were designated as replacement animals in the event of mortality prior to the scheduled sacrifice time. Another group of 5 male and 5 female mice were dosed with the positive control, cyclophosphamide at 60 mg/kg. Mortality, clinical signs and body weight gains were recorded.

Groups of 5 male and 5 female mice from each treatment group were sacrificed 24-, 48- or 72-hours, bone marrow cells were collected and slides were prepared. The positive control group was sacrificed only after 24 hours. The incidence of micronucleated polychromatic erythrocytes/1000 polychromatic erythrocytes was determined for each mouse and treatment group. Statistical significance was determined using the Kastenbaum-Bowman tables which are based on binomial distribution (Kastenbaum M.A. and Bowman K.O. (1970). Tables for determining the statistical significance of mutation frequencies. Mutation Research 9:527-549). All analyses were performed separately for each sex and sampling time.

The test material was considered to induce a positive response if a treatment-related increase in micronucleated polychromatic erythrocytes was observed and one or more doses were statistically elevated relative to the vehicle control ($p \leq 0.05$) at any sampling time.

Result : The LD50 for the probe studies was calculated by probit analysis to be approximately 1263.6 mg AI/kg for male mice and female mice. The high dose for the micronucleus test was set at 1000 mg AI/kg which was estimated to be approximately 80% of the LD50.

For the micronucleus assay, male and female mice were dosed with a single intraperitoneal injection of 250, 500 or 1000 mg tetrahydrobenzaldehyde/kg body weight.

The number of micronucleated polychromatic erythrocytes/1000 polychromatic erythrocytes in test material treated groups was not statistically increased relative to their prespective vehicle control in either male or female mice, regardless of dose level or bone marrow collection time.

Test substance : The test material was reported to be 99.7% pure. Subsequent purity by capillary GC was 98.6%.

Conclusion : Tetrahydrobenzaldehyde was considered to be negative in the micronucleus test using male and female ICR mice.

Reliability : (1) valid without restriction
1a: GLP guideline study

30.08.2004 (30)

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

Type :
In vitro/in vivo : In vivo
Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : dermal
Exposure period : 6 hrs/day
Frequency of treatm. : 5 days/week for 9 exposures in two weeks
Duration of test : two weeks
Doses : 0.10, 0.25 and 0.75 ml/kg/day
Control group : yes, concurrent vehicle
Method :
Year :
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : As part of the two week dermal toxicity study, the ovaries and testes/epididymides were weighed and testes were examined histopathologically. Mean values of all dose groups were compared to the mean value for the control group at each time interval.

Multiple Group Analyses
Statistical evaluation of equality of means was made by one-way ANOVA, followed by a multiple comparison method if needed. Bartlett's test was performed to determine equal variances. If variances were equal, parametric procedures were used; if not, non-parametric methods were used. The parametric procedures were the standard one-way ANOVA using the F distribution to assess significance. If significant differences among the means was detected, Dunnett's test was used to determine which means were significantly different from the control. If nonparametric procedures for testing equality of means was needed, the Kruskal-Wallis test was used, and if differences were indicated, Dunn's summed rank test was used to determine which treatments differed from control. A statistical test for trend in the dose levels was also performed. In the parametric case, standard regression techniques with a test for trend and lack of fit were used. In the nonparametric case, Jonckheere's test for monotonic trend was used. The Bartlett's test was conducted at the 1% two-sided risk level. All other tests were conducted at the 5% and 1%, two-sided risk level. Statistical evaluations were not performed when the standard deviation for the control group was zero. Dose groups were eliminated from analyses if their standard deviation was zero.

Two-Group Analyses
The variances of the two groups were tested for equality using the F-test. If the variances were equal, a standard independent two sample t-test was used to determine equality of means. If the variances differed at the 1% level of significance, Welch's t-test was used to determine equality of means. T-tests were conducted at the 5% and 1% 2-sided risk level.

Result : Ovary and testes/epididymides weights were unaffected in the two week study. There were no treatment related histopathologic changes noted in the testes of males from the 0.75 ml/kg/day groups.

Reliability : (2) valid with restrictions
2h - Although the dosing period was shorter than typically used for OECD 421 studies, gross examination at the end of the study, organ weights for the major reproductive organs and histopathological examination of the testes in this study were within normal limits. In a similarly designed study via the inhalation route, gross examination of the reproductive organs and testicular weights were within normal limits. Collectively, these two studies provide no indication of a reproductive concern.

16.12.2004 (26)

Type :
In vitro/in vivo : In vivo
Species : rat
Sex : male/female
Strain : Fischer 344
Route of admin. : inhalation
Exposure period : 6 hrs/day
Frequency of treatm. : 5 days/week for 9 exposures in two weeks
Duration of test : 2 weeks
Doses : 5, 50 and 250 ppm
Control group : yes
Method :
Year :
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : As part of the two week inhalation toxicity study, the testes and ovaries were weighed following 6 hr/day, 5 day/week for 9 exposures to 0, 5, 50 or 250 ppm tetrahydrobenzaldehyde. Gross examination of each organ was conducted on each rat at the scheduled necropsy. Body weights, testes and brain weights were obtained and absolute and relative values calculated. Histopathologic examination of the testes was conducted from

the control and high dose group.

The data for quantitative continuous variables were intercompared for the 3 exposure groups and the control group by the use of Levene's test for equality of variances, ANOVA, and t-tests. The t-tests were used when the F value from the ANOVA was significant. When Levene's test indicated homogenous variances, and the ANOVA was significant, a pooled t-test was used for pairwise comparisons. When Levene's test indicated heterogeneous variances, all groups were compared by an ANOVA for unequal variances followed, when necessary, by a separate variance t-test for pairwise comparisons. The data for quantitative continuous variables collected during the recovery period were compared between the control and 500 ppm exposure group using a 2-sample t-test. Non-parametric data were evaluated using the Kruskal-Wallis test followed by the Mann-Whitney U test when appropriate. Incidence data were conpared using the Fisher's exact test when appropriate. For all tests, the probability value of $p < 0.05$ (two-tailed) was used as the level of significance.

Result : Absolute and relative ovary and absolute testicular weights were unaffected. However, due to a slight decrease in body weight along with a slight increase in testicular weight, the relative testicular weight was statistically significantly increased from control values. The difference was approximately 8.5% greater for the high dose animals than for the control group. Values for the 5 and 50 ppm male rats were comparable to control values. As a percent of final brain weight, the ovary and testicular weights for the high dose group were comparable to control values. There were no gross or microscopic (testes only) lesions noted at concentrations as high as 250 ppm.

Reliability : (2) valid with restrictions
2h - Although the dosing period was shorter than typically used for OECD 421 studies, gross examination at the end of the study, organ weights for the major reproductive organs and histopathological examination of the testes in this study were within normal limits. In a similarly designed study via the inhalation route, gross examination of the reproductive organs and testicular weights were within normal limits. Collectively, these two studies provide no indication of a reproductive concern.

16.12.2004 (25)

Type :
In vitro/in vivo : In vivo
Species : rat
Sex : male/female
Strain : Fischer 344
Route of admin. : inhalation
Exposure period : 6 hours/day
Frequency of treatm. : 5 days/week for 9 exposures
Duration of test : two weeks
Doses : 75, 250 and 500 ppm
Control group : yes
Method :
Year :
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : As part of the two week inhalation toxicity study, the testes were weighed following 6 hr/day, 5 day/week for 9 exposures to 0, 75, 250 or 500 ppm tetrahydrobenzaldehyde. Gross examination of each organ was conducted on each rat at the scheduled necropsy. Body weights, testes and brain weights were obtained and absolute and relative values calculated. Histopathologic examination of the testes was conducted from the control and high dose group.

The data for quantitative continuous variables were intercompared for the 3

exposure groups and the control group by the use of Levene's test for equality of variances, ANOVA, and t-tests. The t-tests were used when the F value from the ANOVA was significant. When Levene's test indicated homogenous variances, and the ANOVA was significant, a pooled t-test was used for pairwise comparisons. When Levene's test indicated heterogeneous variances, all groups were compared by an ANOVA for unequal variances followed, when necessary, by a separate variance t-test for pairwise comparisons. The data for quantitative continuous variables collected during the recovery period were compared between the control and 500 ppm exposure group using a 2-sample t-test. Non-parametric data were evaluated using the Kruskal-Wallis test followed by the Mann-Whitney U test when appropriate. Incidence data were conpared using the Fisher's exact test when appropriate. For all tests, the probability value of $p < 0.05$ (two-tailed) was used as the level of significance.

Result : Absolute and as a percentage of final brain weights, testicular weights were unaffected in the two week study at concentrations as high as 500 ppm. Relative testicular weights, as a percentage of final body weight, were increased from control values for males from the 250 and 500 ppm exposure groups. There were no gross or microscopic (testes only) lesions noted at concentrations as high as 500 ppm.

Reliability : (2) valid with restrictions
2h - Although the dosing period was shorter than typically used for OECD 421 studies, gross examination at the end of the study, organ weights for the major reproductive organs and histopathological examination of the testes in this study were within normal limits. In a similarly designed study via the inhalation route, gross examination of the reproductive organs and testicular weights were within normal limits. Collectively, these two studies provide no indication of a reproductive concern.

16.12.2004 (24)

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