

**FOREWORD**

**INTRODUCTION**

**BENZENE, 1,4-DICHLORO-2-NITRO-**

**CAS N°: 89-61-2**

## SIDS Initial Assessment Report

### For

### SIAM 4

Tokyo, Japan, 20-22 May 1996

- 1. Chemical Name:** Benzene, 1,4-dichloro-2-nitro-
- 2. CAS Number:** 89-61-2
- 3. Sponsor Country:** Japan  
  
National SIDS Contact Point in the Sponsor Country:  
Mr. Yasuhisa Kawamura,  
Ministry of Foreign Affairs, Japan
- 4. Shared Partnership with:**
- 5. Roles/Responsibilities of the Partners:**
  - Name of industry sponsor /consortium
  - Process used
- 6. Sponsorship History**
  - How was the chemical or category brought into the OECD HPV Chemicals Programme ?  
As a high priority chemical for initial assessment, 2,5-dichloronitrobenzene was selected for assessment in the framework of the HPV Programme.
- 7. Review Process Prior to the SIAM:**  
SIDS Dossier and Testing Plan were reviewed at a SIDS Review Meeting in 1994, where the following SIDS Testing Plan was agreed:  
  
no testing [ ]  
  
testing [X]  
  
Physical Chemical Properties  
Vapour Pressure  
Partition Coefficient  
Water solubility  
  
Environmental fate / Biodegradation  
Photodegradation  
Stability in water  
Biodegradation

## Ecotoxicity

- Acute toxicity to fish
- Acute toxicity to daphnids
- Acute toxicity to algae
- Chronic toxicity to daphnids

## Toxicity

- Reproductive/developmental toxicity
- Gene mutation test
- Chromosomal aberration in vitro

At SIAM-4, the conclusions of the Report were approved with comments. Comments at SIAM-4: The documents should be rearranged. The original report was already circulated in March 1996, and was revised according to the comments from member countries.

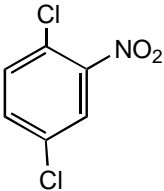
**8. Quality check process:**

**9. Date of Submission:** 30 April 1996

**10. Date of last Update:**

**11. Comments:**

**SIDS INITIAL ASSESSMENT PROFILE**

<b>CAS No.</b>	89-61-2
<b>Chemical Name</b>	Benzene, 1,4-dichloro-2-nitro- (2,5-Dichloronitrobenzene)
<b>Structural Formula</b>	
<b>CONCLUSIONS AND RECOMMENDATIONS</b>	
<p>A potential hazard to man due to genotoxicity is identified, but exposure is low in the sponsor country.</p> <p>Unless further information on exposure in other Member countries presents evidence to the contrary, it is currently considered of low potential risk and low priority for further work.</p>	
<b>SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS</b>	
<b>Exposure</b>	
<p>The production volume of 2,5-dichloronitrobenzene in Japan was ca. 200 - 1,200 tonnes/year in 1988 – 1992, and 2,400 - 2,800 tonnes/year in Germany. This chemical is used as an intermediate for pigments, pesticides and UV absorbents in closed systems in Japan. This chemical is stable in neutral, acidic or alkaline solutions, and is considered as “not readily biodegradable”.</p> <p>The potential environmental distribution of the chemical obtained from a generic fugacity model (Mackey level III) showed that the chemical would be distributed mainly to water and soil. The Predicted Environmental Concentration (PEC<sub>local</sub>) of this chemical was estimated as <math>8.0 \times 10^{-4}</math> mg/l in a Japanese local exposure scenario</p> <p>As 2,5-dichloronitrobenzene is produced in a closed system, exposure during synthesis may be excluded. Workers wear personal protective equipment (e.g. a chemical cartridge respirator with an organic vapour cartridge) when filling barrels with the product. Therefore, the exposure in the workplace is considered to be negligible in the present situation. In addition, this chemical is not contained in consumer products, because it is an intermediate in industrial use. As for indirect exposure via the environment, the daily intake through drinking water is estimated to be <math>2.6 \times 10^{-5}</math> mg/kg/day and through fish is calculated as <math>1.2 \times 10^{-3}</math> mg/kg/day.</p>	
<b>Environment</b>	
<p>For the environment, various NOEC and LC<sub>50</sub> values were gained from test results; 96h-LC<sub>50</sub> = 5.4 - 8.5 mg/l (acute fish); 24h-EC<sub>50</sub> = 8.0 mg/l (acute daphnia); 72h-EC<sub>50</sub> = 5.0 mg/l (acute algae); 72h-NOEC = 2.0 mg/l (algae); 21d-NOEC = 1.0 mg/l (long-term daphnia reproduction). The lowest chronic toxicity result for daphnia [21d-NOEC (reproduction) of <i>Daphnia magna</i> (1.0 mg/l)] was used with an assessment factor of 100 to determine the PNEC according to the OECD Provisional Guidance for Initial Assessment of Aquatic Effects. Thus, the PNEC of the chemical is 0.01 mg/l. The PEC is lower than the PNEC. The environmental risk is presumed to be low.</p>	
<b>Human Health</b>	
<p>The chemical showed genotoxic effects in the Ames test and the chromosomal aberration test <i>in vitro</i>. In a repeated dose toxicity test, a slight effect to the liver (e.g. increased liver weight) and damage in the reproductive system (e.g.</p>	

necrosis of germ epithelium, azoospermia) were observed. The NOEL was 10 mg/kg/day. In a preliminary reproductive/ developmental screening toxicity test, one dam, receiving 60 mg/kg/day, delivered dead pups. In the highest dose group (200 mg/kg/day), one dam died on day 20 of the pregnancy, one during the delivery period and four during the lactation period. A lack of care behaviour was also found in dams at the highest dose level. At that level, many pups died during the lactation period and a reduced body weight of the pups was observed. In this study, suppression of body weight gains and food consumption and an effect to the testes were also observed in adult rats at the highest dose. The NOEL for reproductive toxicity was 20 mg/kg/day.

For human health, the NOEL is estimated as 10 mg/kg/day for repeated dose and 20 mg/kg/day for reproductive toxicity. As for indirect exposure via the environment, the PEC was estimated as  $8.0 \times 10^{-4}$  mg/l in a local exposure scenario. The daily intake through drinking water is estimated as  $2.6 \times 10^{-5}$  mg/kg/day and through fish is calculated as  $1.2 \times 10^{-3}$  mg/kg/day. The margin of safety is large. Therefore, the health risk through the environment, in general, is considered to be low due to its use pattern and exposure.

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

#### **NATURE OF FURTHER WORK RECOMMENDED**

## FULL SIDS SUMMARY

CAS NO: 89-61-2		SPECIES	PROTOCOL	RESULTS
<b>PHYSICAL-CHEMICAL</b>				
2.1	Melting Point			54.6 °C
2.2	Boiling Point			261 °C at 1,013 hPa
2.3	Density			1.669 at 22°C
2.4	Vapour Pressure		OECD TG 104	0.51 Pa at 25 °C
2.5	Partition Coefficient (Log Pow)		OECD TG 107	2.93 at 25 °C
2.6 A.	Water Solubility		OECD TG 105	95 mg/L at 25 °C
B.	pH			6.9 (80 mg/l water) at 20°C
	pKa			No data available
2.12	Oxidation: Reduction Potential			No data available.
<b>ENVIRONMENTAL FATE AND PATHWAY</b>				
3.1.1	Photodegradation		AOP Win v 1.86	$T_{1/2} = 9.32 \times 10^{-2}$ y (sensitizer: OH radical)
3.1.2	Stability in Water		OECD TG 111	Stable at pH 4.0, 7.0, 9.0 at 25°C
3.2	Monitoring Data			Not detected from surface water and Sediment in Japan in 1982.
3.3	Transport and Distribution		Calculated (Fugacity Level III)	100% released to water, In Air 0.85% In Water 91.27% In Soil 5.60% In Sediment 2.28%
3.5	Biodegradation		OECD TG 301C	Not readily biodegradable: 0 – 8% (BOD) in 28 days, 0 - 1% (HPLC) in 28 days
3.7	Bioaccumulation	Guppy		BCF: 820
<b>ECOTOXICOLOGY</b>				
4.1	Acute/Prolonged Toxicity to Fish	<i>Oryzias latipes</i>	OECD TG 203	LC <sub>50</sub> (72hr): 7.0 mg/L LC <sub>50</sub> (96hr): 5.4 mg/L
4.2	Acute Toxicity to Aquatic Invertebrates ( <i>Daphnia</i> )	<i>Daphnia magna</i>	OECD TG 202	EC <sub>50</sub> (24hr): 8.0 mg/l
4.3	Toxicity to Aquatic Plants e.g. Algae	<i>Selenastrum capricornutum</i>	OECD TG 201	EC <sub>50</sub> (72hr): 5.0 mg/l NOEC: 2.0 mg/l
4.5.2	Chronic Toxicity to Aquatic Invertebrates ( <i>Daphnia</i> )	<i>Daphnia magna</i>	OECD TG 202	EC <sub>50</sub> (21d, Immobility): 2.3 mg/l EC <sub>50</sub> (21d, Reproduction): 2.5 mg/l NOEC (21d, Repro): 1.0 mg/l

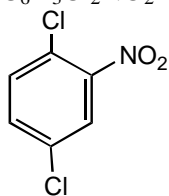
CAS NO: 89-61-2		SPECIES	PROTOCOL	RESULTS
4.6.1	Toxicity to Soil Dwelling Organisms			No data available.
4.6.2	Toxicity to Terrestrial Plants			No data available.
(4.6.3)	Toxicity to Other Non-Mammalian Terrestrial Species (Including Birds)			No data available.
<b>TOXICOLOGY</b>				
5.1.1	Acute Oral Toxicity	Rat		LD <sub>50</sub> : 2,503 mg/kg
5.1.2	Acute Inhalation Toxicity			No data available.
5.1.3	Acute Dermal Toxicity	Rat		LD <sub>50</sub> : > 2,000 mg/kg
5.4	Repeated Dose Toxicity	Rat	28-days Repeated Toxicity Test Oral (gavage)	NOEL = 10 mg/kg/day
5.5	Genetic Toxicity <i>in vitro</i>			
A.	Bacterial Test (Gene mutation)	<i>S. typhimurium</i> <i>E. coli</i>	OECD TG 471 and 472 and Japanese Guidelines	TA 100: Positive with and without metabolic activation TA 1535: Positive without metabolic activation Other bacterial strains: Negative (With and without metabolic activation)
B.	Non-Bacterial <i>in vitro</i> Test (Chromosomal aberrations)	CHL cells	OECD TG 473 and Japanese Guidelines	Positive (Without metabolic activation) Negative (With metabolic activation)
5.6	Genetic Toxicity <i>in vivo</i>			No data available
5.8	Toxicity to Reproduction	Rat	OECD Preliminary Reproductive Toxicity Test	NOEL Parental = 20 mg/kg/day NOEL F1 offspring = 60 mg/kg/day
5.9	Developmental Toxicity/ Teratogenicity			See 5.8
5.11	Experience with Human Exposure			

## SIDS Initial Assessment Report

### 1 IDENTITY

#### 1.1 Identification of the Substance

CAS Number: 89-61-2  
IUPAC Name: Benzene, 1,4-dichloro-2-nitro-  
Molecular Formula:  $C_6H_3Cl_2NO_2$   
Structural Formula:



Synonyms: 2,5-Dichloronitrobenzene

#### 1.2 Purity/Impurities/Additives

Degree of Purity: 98 %  
Major Impurities: Unknown  
Essential Additives: None

#### 1.3 Physico-Chemical properties

**Table 1** Summary of physico-chemical properties

Property	Value
Melting point	56.6 °C
Boiling point	261 °C
Vapour pressure	0.51 Pa at 25 °C
Water solubility	95 mg/l at 25 °C



## 2 GENERAL INFORMATION ON EXPOSURE

### 2.1 Production Volumes and Use Pattern

The production volume of 2,5-dichloronitrobenzene in Japan was ca. 200 - 1,200 tonnes/year in 1988 - 1992. The majority of this amount was sold and handled in Japan. This chemical is used as an intermediate for pigments, pesticides and UV absorbents in closed systems in Japan. This chemical is stable in neutral, acidic or alkaline solutions, and is considered to be "not readily biodegradable". Direct photodegradation is expected because 2,5-dichloronitrobenzene absorbs UV light. The half-life is estimated to be about a week.

### 2.2 Environmental Exposure and Fate

#### 2.2.1 Sources of Environmental Exposure

The potential environmental distribution of 2,5-dichloronitrobenzene obtained from a generic level III fugacity model is shown in Table 2. The results show that if 2,5-dichloronitrobenzene is released mainly to water and soil, it is unlikely to distribute into other compartments. But, if 2,5-dichloronitrobenzene is released mainly to air, it is likely to be transported both to water and soil.

**Table 2:** Environmental distribution of 2,5-dichloronitrobenzene using a generic level III fugacity model.

Compartment	Release: 100% to air	Release: 100% to water	Release: 100% to soil
Air	12.16%	0.85%	0.12%
Water	7.68%	91.27%	2.61%
Soil	79.97%	5.60%	97.21%
Sediment	0.19%	2.28%	0.07%

### Local exposure

According to a Japanese manufacturer, 8000 kg/year (estimated) of 2,5-dichloronitrobenzene are released with  $1.0 \times 10^7$  t/y of effluent into a bay. The local predicted environmental concentration ( $PEC_{local}$ ) is  $8.0 \times 10^{-4}$  mg/l, employing the following calculation model. In this case, the dilution factor is estimated to be 1000.

$$\text{Amount of release (8.0 x 10}^9 \text{ mg/y)}$$

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$$\text{Volume of effluent (1.0 x 10}^{10} \text{ l/y) x Dilution factor (1000)}$$

### 2.3 Human Exposure

The highest exposure to the general population via the environment would be expected through drinking water processed from surface water. Based on the physical chemical properties of 2,5-dichloronitrobenzene, a significant removal during processing is not expected. Although  $PEC_{global}$  cannot be estimated, the concentration in drinking water is assumed to be  $8.0 \times 10^{-4}$  mg/l, as the worst case.

### **2.3.1 Occupational Exposure**

As 2,5-dichloronitrobenzene is produced in a closed system, exposure during synthesis may be excluded. This chemical is used as an intermediate for pigments, pesticides and UV absorbents. Workplace exposure is possible when the product is filled into barrels, with inhalation uptake considered to be the main exposure route. Skin contact plays a minor role. Workers wear a chemical cartridge respirator with an organic vapour cartridge during the filling process. Therefore, the exposure to workers is estimated to be negligibly small in the present situation.

### **2.3.2 Consumer Exposure**

2,5-Dichloronitrobenzene is not contained in consumer products because this substance is used as an intermediate for pigments, pesticides and UV absorbents. No further information on consumer use is available.

### 3 HUMAN HEALTH HAZARDS

#### 3.1 Effects on Human Health

##### 3.1.1 Acute Toxicity

Oral and dermal LD<sub>50</sub> values of 2,5-dichloronitrobenzene for male rats was reported to be 2,503 mg/kg and > 2,000 mg/kg, respectively.

##### 3.1.2 Irritation

Two reports on irritation tests are available. The results were that 2,5-dichloronitrobenzene was not irritating to the skin and eyes of rabbits.

##### 3.1.3 Repeated Dose Toxicity

An Oral 28-Days repeated dose study of 2,5-Dichloronitrobenzene in Wistar rats at doses of 0, 10, 50, 250 mg/kg/day was reported (Hoechst AG, 1990). Impairment of body weight gain, increased hepatic weight and bilirubin value, and damaging of the forestomach were observed in the 50 mg/kg or more groups. The high dose group showed distinct increases of water consumption and clinical symptoms (salivation, crouching position, crural walk). Also, hepatocellular hypertrophy and testicle damage (necrosis of germ epithelium, azoospermia, depression of spermatogenesis) were observed in the high dose group. The NOEL for 28 days repeated dose toxicity was considered to be 10 mg/kg/day from this study.

##### 3.1.4 Mutagenicity

###### In vitro Studies

###### *Bacterial test*

A reverse gene mutation assay was conducted in line with Guidelines for Screening Mutagenicity Testing of Chemicals (Japan) and OECD Test Guidelines 471 and 472, using the pre-incubation method. This study was well controlled and regarded as a key study. Although 2,5-dichloronitrobenzene showed positive results in *S. typhimurium* TA 100 with and without metabolic activation and TA 1535 without metabolic activation, negative results were obtained in TA98, TA 1537 and *Escherichia coli* WP2 *uvrA* with and without metabolic activation at concentrations up to 5 mg/plate (MHW, 1994b).

###### *Non-bacterial test in vitro*

A chromosomal aberration test in line with the Guidelines for Screening Mutagenicity Testing of Chemicals (Japan) and the OECD Test Guideline 473 was conducted using cultured Chinese Hamster lung (CHL/IU) cells. This study was well controlled and regarded as a key study. The maximum concentration of the chemical was used with no apparent cytotoxic effect in continuous treatment. The chemical showed positive results in Chinese hamster CHL cells without metabolic activation. (MHW, 1994b).

###### In vivo Studies

No data are available on *in vivo* mutagenicity tests.

### 3.1.5 Toxicity for Reproduction

2,5-Dichloronitrobenzene was studied for its oral toxicity in rats in an OECD preliminary reproductive toxicity test at doses of 0, 6, 20, 60, 200 mg/kg/day (MHW, 1994a). One dam receiving 60 mg/kg delivered only dead pups. In the 200 mg/kg group, one dam died on day 20 of pregnancy, one during the delivery period and four during the lactation period. A lack of care behaviour was also found in seven dams receiving 200 mg/kg. A lower value for the viability index on day 4 of lactation was obtained with 200 mg/kg because many pups died during the lactation period. With the pups of the 200 mg/kg group, reduced body weight values were obtained for both sexes on day 0 and 4 of lactation. It is concluded that the chemical exerts effects on dams during the perinatal period at 60 mg/kg or more and the dams during the lactation period at 200 mg/kg. In addition, there are indications that the chemical affects growth of new born pups at 200 mg/kg.

Regarding repeated dose toxicity, the chemical exhibited influence on general signs (yellowish urine and salivation at 60 mg/kg or more, and perigenital soiling, decrease in locomoter activity and extension of the hind limbs at 200 mg/kg in both sexes), suppressed body weight gains in both sexes at 200 mg/kg, and lower values for food consumption in females at 200 mg/kg. Degeneration of seminiferous epithelium in the testes and debris in ducts of the epididymides were found at 200 mg/kg. Atrophy of the thymus and decreased cellularity of white pulps in the spleen were found in surviving females, whereas atrophy/hemorrhage in the thymus, lymphoid atrophy and decreased cellularity of the marginal zone in the spleen, congestion in the lungs and liver, and glandular stomach ulcers were found in females receiving 200 mg/kg which died. The NOEL for reproductive toxicity was considered to be 200 mg/kg/day and 20 mg/kg/day for reproductive performance of male and females, respectively, and 60 mg/kg/day for development of pups.

### 3.2 Initial Assessment for Human Health

2,5-Dichloronitrobenzene showed genotoxic effects in the Ames test and the chromosomal aberration test *in vitro* using CHL cells. The NOEL is estimated to be 10 mg/kg/day for repeated dose toxicity and 20 mg/kg/day for reproductive toxicity. As for indirect exposure via the environment, the PEC was estimated to be  $8.0 \times 10^{-4}$  mg/l in a local exposure scenario. The daily intake through drinking water is estimated to be  $2.6 \times 10^{-5}$  mg/kg/day and through fish is calculated as  $1.2 \times 10^{-3}$  mg/kg/day. The margin of safety is large. Therefore, the health risk through the environment, in general, is considered to be low due to its use pattern and exposure.

## 4 HAZARDS TO THE ENVIRONMENT

### 4.1 Aquatic Effects

#### Acute and Chronic Toxicity Test Results

2,5-Dichloronitrobenzene has been tested in a limited number of aquatic species (*Selenastrum capricornutum*, *Daphnia magna* and *Oryzias latipes*) according to OECD test guidelines [OECD TG 201, 202 (part I and II), and 203]. Acute and chronic toxicity data to test organisms for the chemical are summarized in Table 3. No other ecotoxicological data are available. Various NOEC and LC<sub>50</sub> values were gained from the above tests; LC<sub>50</sub> (96h) = 5.4 mg/l (acute fish); EC<sub>50</sub> (24h) = 8.0 mg/l (acute daphnia); EC<sub>50</sub> (72h) = 5.0 mg/l (acute algae); NOEC (72h) = 2.0 mg/l; EC<sub>50</sub> (21d) = 2.5 mg/l (long-term daphnia reproduction); NOEC (21d) = 1.0 mg/l. Therefore, the chemical is considered to be moderately toxic to, fish, daphnids and algae. The lowest chronic toxicity result [21d-NOEC (reproduction) of *Daphnia magna* (1.0 mg/l)] was used with an assessment factor of 100 to determine the PNEC according to the OECD Provisional Guidance for Initial Assessment of Aquatic Effects. Thus, the PNEC of the chemical is 0.01 mg/l. The PEC is lower than the PNEC. The environmental risk is presumed to be low.

**Table 3:** Acute and chronic toxicity results of 2,5-dichloronitrobenzene with aquatic organisms.

Species	Endpoint* <sup>1</sup>	Conc. (mg/L)	Reference
<i>Selenastrum capricornutum</i> (algae)	Biomass: EC <sub>50</sub> (72h)	5.0 mg/L	MOE, Japan. (1992)
	Biomass: NOEC	2.0 mg/L	
<i>Daphnia magna</i> (water flea)	Imm: EC <sub>50</sub> (24h)	8.0 mg/L	
	Imm: LC <sub>50</sub> (21d)	2.3 mg/L	
	Rep: EC <sub>50</sub> (21d)	2.5 mg/L	
	Imm: NOEC(21d)	1.0 mg/L	
<i>Oryzias latipes</i> (fish, Medaka)	Mor: LC <sub>50</sub> (48h)	8.2 mg/L	
	Mor: LC <sub>50</sub> (72h)	7.0 mg/L	
	Mor: LC <sub>50</sub> (96h)	5.4 mg/L	

Notes: \*<sup>1</sup> Mor = mortality; Rep = reproduction.

### 4.2 Initial Assessment for the Environment

Various NOEC and LC<sub>50</sub> values were gained from test results; LC<sub>50</sub> = 5.4 - 8.5 mg/l (acute fish); EC<sub>50</sub> = 8.0 mg/l (acute daphnia); EC<sub>50</sub> = 5.0 mg/l (acute algae); NOEC = 2.0 mg/l (acute algae); NOEC = 1.0 mg/l (long-term daphnia reproduction). The lowest chronic toxicity result [21d-NOEC (reproduction) of *Daphnia magna* (1.0 mg/l)] was used with an assessment factor of 100 to determine the PNEC according to the OECD Provisional Guidance for Initial Assessment of Aquatic Effects. Thus, the PNEC of the chemical is 0.01 mg/l. The PEC is lower than the PNEC. The environmental risk is presumed to be low.

## **5 RECOMMENDATIONS**

The chemical is currently of low priority for further work.

A potential hazard to man due to genotoxicity is identified, but exposure is low in the sponsor country.

Unless further information on exposure in other Member countries presents evidence to the contrary, it is currently considered of low potential risk and low priority for further work.

## 6 REFERENCES

EA, Japan (1994) "Investigation of the Ecotoxicological Effects of OECD High Production Volume Chemicals", Office of Health Studies, Environmental Health Department, Environment Agency, Japan (HPV/SIDS Test conducted by EA, Japan)

EA & MITI, Japan (1993) Unpublished Report on Exposure Estimation (HPV/SIDS Test conducted by EA and MITI, Japan)

EA, Japan (1985) Chemicals in the Environment: Report on Environmental Survey and Wildlife Monitoring in F.Y. 1982 and 1983, and Chemicals in the Environment: Report on Environmental Survey and Wildlife Monitoring in F.Y. 1984 and 1985. (Test was conducted by Office of Health Studies, Environmental Health Department, EA, Japan)

ECDIN database (1994)

Hanna, P.J., Bull. Environm. Contam. Toxicol., 28, 29-32 (1982)

Lange's Handbook of Chemistry (11th edition)

Lyman, W.J, W. F. Reehl and D. H. Rosenblatt (1981) "Handbook of Chemical Property Estimation Method", McGraw Hill Book Co.

MHW, Japan (1994a) Unpublished Report on Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test of 2,5-dichloronitrobenzene. (HPV/SIDS Test conducted by MHW, Japan)

MHW, Japan (1994b) Unpublished Report on Mutagenicity Test of 2,5-dichloronitrobenzene. (HPV/SIDS Test conducted by MHW, Japan)

MITI, Japan (1994a): Unpublished data

MITI, Japan (1994b) Unpublished Report (HPV/SIDS Test conducted by MITI, Japan. Test was performed in Chemicals Inspection and Testing Institute, Japan)

# **SIDS DOSSIER**

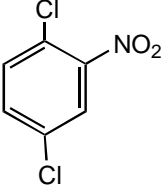
**Benzene, 1,4-dichloro-2-nitro-**

**CAS No. 89-61-2**

Sponsor Country: Japan



## SIDS PROFILE

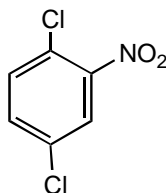
1.01 A.	<b>CAS No.</b>	89-61-2
1.01 C.	<b>CHEMICAL NAME ( OECD Name)</b>	Benzene, 1,4-dichloro-2-nitro-
1.01 D.	<b>CAS DESCRIPTOR</b>	Not applicable
1.01 G.	<b>STRUCTURAL FORMULA</b>	
	<b>OTHER CHEMICAL IDENTITY INFORMATION</b>	
1.5	<b>QUANTITY</b>	In Japan, 200-1,200 tonnes/year in 1988 - 1992.
1.7	<b>USE PATTERN</b>	Intermediate for pigments, pesticides and UV absorbents.
1.9	<b>SOURCES AND LEVELS OF EXPOSURE</b>	In Japan, Amount released from production site to water is 8 tonnes/year. All of the waste water is incinerated.
	<b>ISSUES FOR DISCUSSION (IDENTIFY, IF ANY)</b>	

## SIDS SUMMARY

CAS NO: 89-61-2		Information	OECD Study	GLP	Other Study	Estimation Method	Acceptable	SIDS Testing Required
STUDY		Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
<b>PHYSICAL-CHEMICAL DATA</b>								
2.1	Melting Point	Y	N	N	Y	N	Y	N
2.2	Boiling Point	Y	N	N	Y	N	Y	N
2.3	Density	Y	N	N	Y	N	Y	N
2.4	Vapour Pressure	N						Y
2.5	Partition Coefficient	N						Y
2.6	Water Solubility	N						Y
	pH and pKa values	N						N
OTHER P/C STUDIES RECEIVED								
<b>ENVIRONMENTAL FATE and PATHWAY</b>								
3.1.1	Photodegradation	N						Y
3.1.2	Stability in water	N						Y
3.2	Monitoring data	N						N
3.3	Transport and Distribution	N						N
3.5	Biodegradation	N						Y
3.6	Bioaccumulation	Y	Y	Y	N	N	Y	N
OTHER ENV FATE STUDIES RECEIVED								
<b>ECOTOXICITY</b>								
4.1	Acute toxicity to Fish	N						Y
4.2	Acute toxicity to Daphnia	N						Y
4.3	Toxicity to Algae	N						Y
4.5.2	Chronic toxicity to Daphnia	N						Y
4.6.1	Toxicity to Soil dwelling organisms	N						N
4.6.2	Toxicity to Terrestrial plants	N						N
4.6.3	Toxicity to Birds	N						N
OTHER ECOTOXICITY STUDIES RECEIVED								
<b>TOXICITY</b>								
5.1.1	Acute Oral	Y	N	N	Y	N	Y	N
5.1.2	Acute Inhalation	N						N
5.1.3	Acute Dermal	Y	N	N	Y	N	Y	N
5.4	Repeated Dose	Y	N	N	Y	N	Y	N
5.5	Genetic Toxicity <i>in vitro</i>							
	. Gene mutation	N						Y
	. Chromosomal aberration	N						Y
5.6	Genetic Toxicity <i>in vivo</i>	N						N
5.8	Reproduction Toxicity	N						Y
5.9	Development / Teratogenicity	N						Y
5.11	Human experience	N						N
OTHER TOXICITY STUDIES RECEIVED								

**1. GENERAL INFORMATION****1.01 SUBSTANCE INFORMATION**

- A. CAS-Number** 89-61-2
- B. Name (IUPAC name)** 1,4-Dichloro-2-nitrobenzene
- C. Name (OECD name)** Benzene, 1,4-dichloro-2-nitro
- D. CAS Descriptor** Not applicable
- E. EINECS-Number** 201-923-3
- F. Molecular Formula** C<sub>6</sub>H<sub>4</sub>Cl<sub>2</sub>NO<sub>2</sub>
- G. Structural Formula**



- H. Substance Group** Not applicable
- I. Substance Remark** None
- J. Molecular Weight** 192.00

**1.02 OECD INFORMATION**

- A. Sponsor Country:** Japan

**B. Lead Organisation:**

Name of Lead Organisation: Ministry of Health and Welfare (MHW)  
Ministry of International Trade and Industry (MITI)  
Environment Agency (EA)

Contact person: Mr. Yasuhisa Kawamura  
Director

Address: Second International Organization Bureau  
Ministry of Foreign Affairs  
2-2-1 Kasumigaseki, Chiyoda-ku  
Tokyo 100, Japan  
TEL 81-3-3581-0018  
FAX 81-3-3503-3136

**C. Name of responder**

Name: Same as above contact person

**1.1 GENERAL SUBSTANCE INFORMATION****A. Type of Substance**

element [ ]; inorganic [ ]; natural substance [ ];

		organic [X]; organometallic [ ]; petroleum product [ ]		
<b>B.</b>	<b>Physical State</b>	gaseous [ ]; liquid [ ]; solid [X]		
<b>C.</b>	<b>Purity</b>	98 %		
<b>1.2</b>	<b>SYNONYMS</b>	2,5-Dichloronitrobenzene		
<b>1.3</b>	<b>IMPURITIES</b>	Unknown		
<b>1.4</b>	<b>ADDITIVES</b>	Unknown		
<b>1.5</b>	<b>QUANTITY</b>	Location	Production (tonnes)	Date
		Japan	200-1,200/year	1988-1992
	Reference:	MITI, Japan (1994a)		
<b>1.6</b>	<b>LABELLING AND CLASSIFICATION</b>	None		
<b>1.7</b>	<b>USE PATTERN</b>			
<b>A.</b>	<b>General</b>	<b>Type of Use:</b>	<b>Category:</b>	
		Industry use	Intermediate for pigments, Pesticides and UV absorbents	
	Reference:	MITI, Japan (1994a)		
<b>B.</b>	<b>Uses in Consumer Products</b>	None		
<b>1.8</b>	<b>OCCUPATIONAL EXPOSURE LIMIT VALUE</b>	None		
<b>1.9</b>	<b>SOURCES OF EXPOSURE</b>			
	Source:	Media of release: Water from a production site Quantities per media: 8 tonnes/year		
	Reference:	MITI, Japan (1994a)		
<b>1.10</b>	<b>ADDITIONAL REMARKS</b>			
<b>A.</b>	<b>Options for disposal</b>	Incineration		
	Reference:	MITI, Japan (1994a)		
<b>B.</b>	<b>Other remarks</b>	None		

**2. PHYSICAL-CHEMICAL DATA**

**2.1 MELTING POINT**

(a)  
Value: 54.6 °C  
Decomposition: Yes [ ] No [**X**] Ambiguous [ ]  
Sublimation: Yes [ ] No [**X**] Ambiguous [ ]  
Method:  
GLP: Yes [ ] No [ ] ? [**X**]  
Reference: MITI (1992)

(b)  
Value: 52.8 °C  
Decomposition: Yes [ ] No [ ] Ambiguous [ ]  
Sublimation: Yes [ ] No [ ] Ambiguous [ ]  
Method:  
GLP: Yes [ ] No [ ] ? [**X**]  
Reference: Company (Hoechst) data (1889)

**2.2 BOILING POINT**

(a)  
Value: 261.3-261.7 °C  
Pressure: 1013 hPa  
Decomposition: Yes [ ] No [**X**] Ambiguous [ ]  
Method:  
GLP: Yes [**X**] No [ ] ? [ ]  
Reference: MITI (1994b)

(b)  
Value: 267 °C  
Pressure: 1013 hPa  
Decomposition: Yes [ ] No [ ] Ambiguous [ ]  
Method: Unknown  
GLP: Yes [ ] No [ ] ? [**X**]  
Remarks: None  
Reference: Company (Hoechst) data (1989)

**2.3 DENSITY (Relative density)**

Type: Bulk density [ ]; Density [**X**]; Relative Density [ ]  
Value: 1.669  
Temperature: 22 °C  
Method: Unknown  
GLP: Yes [ ] No [ ] ? [ ]  
Remarks: None  
Reference: ECDIN Database (1994)

**2.4 VAPOUR PRESSURE**

(a)  
Value: 0.51 Pa  
Temperature: 25°C

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

(b)  
Value: < 0.7 hPa  
Temperature: 20°C  
Method: calculated [ ]; measured [X]  
GLP: Yes [ ] No [ ] ? [X]  
Reference: Company (Hoechst) data (1989)

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

(a)  
Log Pow: 2.93  
Temperature: 25 °C  
Method: calculated [ ]; measured [X]  
OECD Test Guideline 107  
GLP: Yes [X] No [ ] ? [ ]  
Reference: MITI (1994b)

(b)  
Log Pow: 3.3  
Temperature:  
Method: calculated [X]; measured [ ]  
GLP: Yes [ ] No [X] ? [ ]  
Reference: Company (Hoechst) data (1991)

## 2.6 WATER SOLUBILITY

### A. Solubility

(a)  
Value: 95 mg/l  
Temperature: 25 °C  
Description: Miscible [ ]; Of very high solubility [ ];  
Of high solubility [ ]; Soluble [ ];Slightly soluble [ ];  
Of low solubility [X]; Of very low solubility [ ];  
Not soluble [ ]  
Method: OECD Test Guideline 105  
GLP: Yes [X] No [ ] ? [ ]  
Reference: MITI, Japan (1994b)

(b)  
Value: 0.83 mg/l  
Temperature: 20 °C  
Description: Miscible [ ]; Of very high solubility [ ];  
Of high solubility [ ]; Soluble [ ];Slightly soluble [ ];  
Of low solubility [ ]; Of very low solubility [X];  
Not soluble [ ]  
Method: Unknown  
GLP: Yes [ ] No [ ] ? [X]  
Reference: Company (Hoechst) data (1991)

**B. pH Value, pKa Value**

Value: pH 6.9 (80 mg/l water)  
Temperature: 20 °C  
Method: Unknown  
GLP: Yes [ ] No [ ] ? [X]  
Reference: Company (Hoechst) data (1991)

**2.7 FLASH POINT**

No data available

**2.8 AUTO FLAMMABILITY**

No data available

**2.9 FLAMMABILITY**

No data available

**2.10 EXPLOSIVE PROPERTIES**

No data available

**2.11 OXIDIZING PROPERTIES**

No data available

**2.12 OXIDATION: REDUCTION POTENTIAL**

No data available

**2.13 ADDITIONAL DATA**

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

No data available

**B. Other data**

None

**3. ENVIRONMENTAL FATE AND PATHWAYS****3.1 STABILITY****3.1.1 PHOTODEGRADATION**

Type: Air [ ]; Water [X]; Soil; Other [ ]  
 Light source: Sunlight [X]; Xenon lamp [ ]; Other [ ]  
 Spectrum of substance: epsilon = 1.26 x 10<sup>-3</sup> at 300 nm  
 Estimated parameter for calculation:  
 Quantum yield 0.01  
 Concentration 5 x 10<sup>-5</sup> M  
 Depth of water body 500 cm  
 Conversion constant 6.023 x 10<sup>20</sup>  
 Result: Degradation rate 1.18 x 10<sup>-11</sup> mol / l / s  
 Half life 9.32 x 10<sup>-2</sup> years  
 Reference: W. J. Lyman, W. F. Reehl and D. H. Rosenblatt,  
 "Handbook of Chemical Property Estimation Method",  
 McGraw Hill Book Co., 1981.

**3.1.2 STABILITY IN WATER**

Type: Abiotic (hydrolysis) [X]; biotic (sediment)[ ]  
 Result: Stable at pH 4, 7 and 9 at 25 °C  
 Method: OECD Test guideline 111  
 GLP: Yes [X] No [ ] ? [ ]  
 Test substance: 2,5-Dichloronitrobenzene  
 Reference: MITI, Japan (1994b)

**3.1.3 STABILITY IN SOIL**

No data available

**3.2 MONITORING DATA (ENVIRONMENT)**

(a)  
 Type of Measurement: Background [ ], At contaminated Site [ ], Other [X]  
 Media: Surface water  
 Results: ND (Detection limits:0.02 ug/ml) in 21 areas in Japan  
 as of 1982  
 Remarks: None  
 Reference: EA, Japan (1985)

(b)  
 Type of Measurement: Background [ ], At contaminated Site [ ], Other [ ]  
 Media: Sediment  
 Results: ND (Detection limits: 0.001 ug/ml) in 21 areas in Japan  
 as of 1982  
 Remarks: None  
 Reference: EA, Japan (1985)

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



### 3.3.1 TRANSPORT

No data available

### 3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

The potential environmental distribution of 2,5-dichloronitrobenzene obtained from a generic level III fugacity model is shown in Table. The results show that if 2,5-dichloronitrobenzene is released mainly to water or soil, it is unlikely to distribute into other compartments. But, if 2,5-dichloronitrobenzene is released mainly to air, it is likely to be transported both to water and soil.

Environmental distribution of 2,5-dichloronitrobenzene using a generic level III fugacity model.

Compartment	Release: 100% to air	Release: 100% to water	Release: 100% to soil
Air	12.16%	0.85%	0.12%
Water	7.68%	91.27%	2.61%
Soil	79.97%	5.60%	97.21%
Sediment	0.19%	2.28%	0.07%

Reference: EA & MITI, Japan (1994)

### 3.4 IDENTIFICATION OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE

No data available

### 3.5 BIODEGRADATION

Type: aerobic [**X**]; anaerobic [ ]  
 Inoculum: adapted [ ]; non-adapted [**X**];  
 Concentration of the chemical: 100 mg/l related to Test Substance [**X**]  
 Medium: water [ ]; water-sediment [ ]; soil [ ]; sewage treatment [ ]  
 other [Japanese standard activated sludge]  
 Degradation: Degree of degradation after 28 days  
 8, 4 and 0 % from BOD  
 0.1, and 1 % from HPLC analysis  
 Results: Readily biodeg. [ ]; Inherently biodeg. [ ]; under test  
 condition no biodegradation observed [**X**]  
 Method: OECD Test Guideline 301 C  
 GLP: Yes [**X**] No [ ] ? [ ]  
 Test substance: 2,5-Dichloronitrobenzene  
 Reference: MITI (1994b)

### 3.6 BOD<sub>5</sub>, COD OR RATIO BOD<sub>5</sub>/COD

Not applicable

### 3.7 BIOACCUMULATION

Species: Guppy

Exposure period:  
Temperature: 21-23 °C  
Concentration: 1 mg/l  
BCF: 820  
Method:  
Type of test: calculated [ ]; measured [**X**]  
static [ ]; semi-static [ ]; flow-through [ ]; other [ ]  
GLP: Yes [ ] No [ ] ? [**X**]  
Test substance: Purity 98 %  
Reference: Denner, J.W. et al., Aquit. Toxicol. 10, 115 - 129 (1987)

### 3.8 ADDITIONAL REMARKS

- A. Sewage treatment** None
- B. Other information** None

**4. ECOTOXICOLOGICAL DATA**

**4.1 ACUTE/PROLONGED TOXICITY TO FISH**

Type of test: static [ ]; semi-static [X]; flow-through [ ]; other [ ]  
open-system [ ]; closed-system [X]

Species: *Oryzias latipes*

Exposure period: 96 hrs

Results: LC<sub>50</sub> (24h) = 8.5 mg/l (95% confidence limits: 7.2-10 mg/l)  
LC<sub>50</sub> (48h) = 8.2 mg/l (95% confidence limits: 6.8-9.8 mg/l)  
LC<sub>50</sub> (72h) = 7.0 mg/l (95% confidence limits: 5.1-10 mg/l)  
LC<sub>50</sub> (96h) = 5.4 mg/l (95% confidence limits: 4.5-6.6 mg/l)  
NOEC = mg/l  
LOEC = mg/l

Analytical monitoring: Yes [ ] No [X] ? [ ]

Method: OECD Test Guideline 203 (1981)

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

Test substance: 1,4-Dichloro-2-nitrobenzene, purity = 98 %

Remarks: A group of 10 fish were exposed to each of 5 nominal concentrations (3.0-15 mg/l). Stock solution was prepared with Tween 80:acetone = 1:1 (100 mg/l). Controls with and without this vehicle were taken for the test. The vessel was sealed with a Parafilm.

Reference: EA, Japan (1994)

**4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES**

**A. Daphnia**

Type of test: static [X]; semi-static [ ]; flow-through [ ]; other [ ]  
open-system [X]; closed-system [ ]

Species: *Daphnia magna*

Exposure period: 24 hr

Results: EC<sub>50</sub> (24h) = 8.0 mg/l (95% confidence limits: 6.1-11 mg/l)

Analytical monitoring: Yes [ ] No [X] ? [ ]

Method: OECD Test Guideline 202 (1984)

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

Test substance: 1,4-Dichloro-2-nitrobenzene, purity: = 98 %

Remarks: 20 daphnids (4 replicates; 5 organisms per replicate) were exposed to each of 7 nominal concentrations (1.0-32 mg/l). Stock solution was prepared with DMSO:HCO = 9:1 (1000 mg/l). Controls with and without this vehicle were taken for the test.

Reference: EA, Japan (1994)

**B. Other aquatic organisms**

No data available

**4.3 TOXICITY TO AQUATIC PLANTS e.g. Algae**

Species: *Selenastrum capricornutum* ATCC 22662

End-point: Biomass [X]; Growth rate [ ]; Other [ ]

Exposure period: 72 hours

Results: Biomass: EC<sub>50</sub> (72h) = 5.0 mg/l  
NOEC = 2.0 mg/l (p<0.05)  
LOEC =

Analytical monitoring: Yes [ ] No [X] ? [ ]

Method: open-system [X]; closed-system [ ]  
OECD Test Guideline 201 (1984)

GLP: Yes [ ] No [X] ? [ ]  
Test substance: 1,4-Dichloro-2-nitrobenzene, purity = 98 %  
Remarks: The EC<sub>50</sub> values for biomass were calculated based on 5 nominal concentrations (2-10 mg/l). Stock solution was prepared with DMSO (1000 mg/l). Controls with and without this vehicle were taken for the test.  
Reference: EA, Japan (1994)

#### 4.4 TOXICITY TO BACTERIA

No studies located

#### 4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS

##### 4.5.1 CHRONIC TOXICITY TO FISH

Test species: *Poecilia reticulata* (guppy)  
Test method:  
Type of test: static [ ], semi-static [ ], flow-through [ ]  
Other (e.g., field test) [X]  
GLP: Yes [ ] No [ ] ? [X]  
Test results: LC<sub>50</sub>: 4.9 mg/l  
Test substance: purity: 98 %  
Remarks:  
Reference: Denner. J.W. et al., Aquat. Toxicol. 10, 115-129 (1987)

##### 4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Type of test: static [ ]; semi-static [X]; flow-through [ ]; other [ ];  
open-system [X]; closed-system [ ]  
Species: *Daphnia magna*  
End-point: Mortality [ ]; Reproduction rate [X]; Other [X]  
Exposure period: 21 day  
Results:  
Immobility: LC<sub>50</sub> (48 h) = 17 mg/l (95% confidence limits: 12-66 mg/l)  
LC<sub>50</sub> (21 d) = 2.3 mg/l (95% confidence level: 730-860 mg/l)  
NOEC =  
LOEC =  
Reproduction: EC<sub>50</sub> (21 d) = 2.5 mg/l (95% confidence level: 2.1-3.1 mg/l)  
NOEC = 1.0 mg/l (p < 0.05)  
LOEC = 3.2 mg/l (p < 0.05)  
Analytical monitoring: Yes [ ] No [X] ? [ ]  
Method: OECD Test Guideline 202 (1984)  
GLP: Yes [ ] No [X] ? [ ]  
Test substance: 1,4-Dichloro-2-nitrobenzene, purity = 98 %  
Remarks: 40 daphnids (4 replicates; 10 organisms per replicate) were exposed to each of 5 nominal concentrations (0.10-10 mg/l). Stock solution was prepared with DMSO:HCO-40=9:1 (500 mg/l). Controls with and without this vehicle were taken for the test.  
Reference: EA, Japan (1994)

#### 4.6 TOXICITY TO TERRESTRIAL ORGANISMS

##### 4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

No data available

**4.6.2 TOXICITY TO TERRESTRIAL PLANTS**

No data available

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

No data available

**4.7 BIOLOGICAL EFFECTS MONITORING (INCLUDING BIOMAGNIFICATION)**

No studies located

**4.8 BIOTRANSFORMATION AND KINETICS IN ENVIRONMENTAL SPECIES**

No data available

**4.9 ADDITIONAL REMARKS**

None

**5. TOXICITY****5.1 ACUTE TOXICITY****5.1.1 ACUTE ORAL TOXICITY**

(a)  
Type : LD<sub>0</sub> [ ]; LD<sub>100</sub> [ ]; LD<sub>50</sub> [X]; LDL<sub>0</sub> [ ]; Other [ ]  
Species/strain: Rat  
Value : 2,503 mg/kg  
Method: Unknown  
GLP: Yes [ ] No [ ] ? [X]  
Test substance: purity: Unknown  
Remarks: None  
Reference: Company data (Hoechst AG)

**5.1.2 ACUTE INHALATION TOXICITY**

No data available

**5.1.3 ACUTE DERMAL TOXICITY**

Type : LD<sub>0</sub> [ ]; LD<sub>100</sub> [ ]; LD<sub>50</sub> [X]; LDL<sub>0</sub> [ ]; Other [ ]  
Species/strain: Rat  
Value : > 2,000 mg/kg  
Method: Unknown  
GLP: Yes [ ] No [ ] ? [X]  
Test substance: purity: Unknown  
Remarks: None  
Reference: Company data (Hoechst AG, 1988)

**5.1.4 ACUTE TOXICITY, OTHER ROUTES OF ADMINISTRATION**

No data available

**5.2 CORROSIVENESS/IRRITATION****5.2.1 SKIN IRRITATION/CORROSION**

(a)  
Species/strain: Rabbit  
Method: Barail-test  
GLP: Yes [ ] No [ ] ? [X]  
Results: No irritation  
Test substance: purity: Unknown  
Remarks: None  
Reference: Company data (Hoechst AG, 1968)

(b)  
Species/strain: Rabbit  
Method: Patch-test, semi-okkulative  
GLP: Yes [ ] No [ ] ? [X]  
Results: No irritation  
Test substance: purity: Unknown  
Remarks: None  
Reference: Company data (Hoechst AG, 1989)

**5.2.2 EYE IRRITATION/CORROSION**

(a)  
Species/strain: Rabbit  
Method:  
GLP: Yes [ ] No [ ] ? [X]  
Results: No irritation  
Test substance: purity: Unknown  
Remarks: None  
Reference: Company data (Hoechst AG, 1968)

(b)  
Species/strain: Rabbit  
Method: Standard Draized method  
GLP: Yes [ ] No [ ] ? [X]  
Results: 100 mg/24 h Moderate  
Test substance: purity: Unknown  
Remarks: None  
Reference: RTECS Database

**5.3 SKIN SENSITISATION**

Species/strain: Guinea Pigs  
Method: Maximization test  
GLP: Yes [ ] No [ ] ? [X]  
Results: No sensitization  
Test substance: purity: Unknown  
Remarks: None  
Reference: Company data (Hoechst AG, 1968)

**5.4 REPEATED DOSE TOXICITY**

Species/strain: Rat (Wistar)  
Sex: Female [ ]; Male [ ]; Male/Female [X]; No data [ ]  
Route of Administration: oral gavage  
Exposure period: 28 days  
Frequency of treatment:  
Post exposure observation period:  
Dose: 0, 10, 50 or 250 mg/kg  
Control group: Yes [X]; No [ ]; No data [ ];  
Concurrent no treatment [ ]; Concurrent vehicle [X];  
Historical [ ]  
NOEL: 10 mg/kg/day  
LOEL: 50 mg/kg/day  
Results: Impair pf body weight gain, increased hepatic weight and bilirubin value, and damaging of the forestomach were observed in the 50 mg/kg or more groups. High dose group showed distinct increases of water consumption and clinical symptoms (salivation, crouching position, crural walk). Also, hepatocellular hypertrophy and testicle damaging (necrosis of germ epithelium, azoospermia, depression of spermatogenesis) were observed in the high dose group.  
Method: not described  
GLP: Yes [ ] No [ ] ? [X]  
Test substance: Commercial, purity: Unknown  
Reference: Company data (Hoechst AG, 1990)

**5.5 GENETIC TOXICITY *IN VITRO***

**A. BACTERIAL TEST**

Type : Bacterial reverse mutation assay

System of testing:

Species/strain: *S. typhimurium* TA 98, TA 100, TA 1535, TA1537  
*E.coli* WP2 uvrA

Concentration: 0, 78.13, 156.3, 312.5, 625, 1250, 2500, 5000 µg/plate

Metabolic activation: With [ ]; Without [ ]; With and Without [X]; No data [ ]

Results:

Cytotoxicity conc: With metabolic activation: 1250 µg/plate  
Without metabolic activation: 1250 µg/plate

Precipitation conc:

Genotoxic effects:

<i>S. typhimurium</i> TA 100	+ ? -
With metabolic activation:	[X] [ ] [ ]
Without metabolic activation:	[X] [ ] [ ]
 <i>S. typhimurium</i> TA 1535	+ ? -
With metabolic activation:	[ ] [ ] [X]
Without metabolic activation:	[X] [ ] [ ]
 <i>S. typhimurium</i> TA 98 and TA1537	+ ? -
With metabolic activation:	[ ] [ ] [X]
Without metabolic activation:	[ ] [ ] [X]
 <i>E. coli</i> WP2 uvrA	+ ? -
With metabolic activation:	[ ] [ ] [X]
Without metabolic activation:	[ ] [ ] [X]

Method: Japanese Guideline for Screening Mutagenicity testing of chemicals

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

Test substance: Commercial, purity: > 99.5 %

Remarks: Procedure: Plate incorporation method  
Plates/test: 3  
Activation system: Liver S-9 fraction from Phenobarbital and 5,6-Benzoflavone pretreated male SD rats with NADPH-generating system  
Media: Histidine selective  
No. replicates: 2

Reference: MHW, Japan (1994)

**B. NON-BACTERIAL *IN VITRO* TEST**

Type : Cytogenetics Assay

System of testing:

Species/strain: Chinese hamster lung (CHL/IU) cells

Concentration: -S9 (continuous treatment) 0, 0.04, 0.08, 0.15 mg/ml  
-S9 (short-term treatment) 0, 0.024, 0.047, 0.094 mg/ml  
+S9 (short-term treatment) 0, 0.024, 0.047, 0.094 mg/ml

Metabolic activation: With [ ]; Without [ ]; With and Without [X]; No data [ ]

Results:

Cytotoxicity conc: With metabolic activation:



Precipitation conc: Without metabolic activation: 0.15 mg/ml  
 Genotoxic effects: + ? -  
 With metabolic activation: [ ] [ ] [X]  
 Without metabolic activation: [X] [ ] [ ]  
 Method: Japanese Guideline for Screening Mutagenicity testing of chemicals  
 GLP: Yes [X] No [ ] ? [ ]  
 Test substance: Commercial, purity 99.9 %  
 Remarks: Plates/test: 2  
 Activation system: S-9 fraction from the liver of  
 Phenobarbital and 5,6-Benzoflavone induced male SD  
 derived rats with NADPH-generating system  
 Media: RPMI 1640 medium *plus* 10% foetal calf serum  
*plus* phytohaemagglutinin  
 No. replicates: 1  
 Reference: MHW, Japan (1994b)

**5.6 GENETIC TOXICITY *IN VIVO***

No data available

**5.7 CARCINOGENICITY**

No data available

**5.8 TOXICITY TO REPRODUCTION**

Type: Fertility [ ]; One generation study [ ]; Two generation study [ ]; Other [X]  
 Species/strain: Rat Crj:CD(SD)  
 Sex: Female [ ]; Male [ ]; Male/Female [X]; No data [ ]  
 Route of Administration: Oral, gavage  
 Exposure period: Males: 42 days including 14 days before mating  
 Females: from 14 days before mating to day 3 of lactation.  
 Frequency of treatment: 7 days/week  
 Postexposure observation period:  
 Premating exposure period: male: 14 days, female: 14 days  
 Duration of the test;  
 Doses: 0, 6, 20, 60 or 200 mg/kg (12 animals/sex/group)  
 Control group: Yes [X]; No [ ]; No data [ ]; Corn oil  
 Concurrent no treatment [ ]; Concurrent vehicle [X];  
 Historical [ ]  
 NOEL Parental: 20 mg/kg/day  
 NOEL F1 Offspring: 60 mg/kg/day  
 NOEL F2 Offspring: N/A  
 Results: One dam receiving 60 mg/kg delivered only dead pups. In the 200 mg/kg group, one dam died on Day 20 of pregnancy, one during the delivery period and four during the lactation period. A lack of care behaviour was also found in seven dams receiving 200 mg/kg. A lower value for the viability index on Day 4 of lactation was obtained with 200 mg/kg because many pups died during the lactation period. With the pups of the 200 mg/kg group, reduced body weight values were obtained for both sexes on Day 0 and 4 of lactation. It is concluded that the chemical exerts effects on dams during the perinatal period at 60 mg/kg or more and the dams during the lactation period at 200 mg/kg. In addition, there are indications that the chemical affects growth of new born pups at 200 mg/kg. With the repeated dose toxicity, the chemical exhibited influence on general signs (yellowish urine and salivation at 60 mg/kg or more, and perigenital soiling, decrease in locomoter activity and extension of the hind limbs at 200 mg/kg in both sexes), suppressed body weight gains in both sexes at 200 mg/kg, and lower values for food

consumption in females at 200 mg/kg. Degeneration of seminiferous epithelium in the testes and debris in the ducts of the epididymides were found at 200 mg/kg. Atrophy of the thymus and decreased cellularity of white pulps in the spleen were found in surviving females, whereas atrophy/hemorrhage in the thymus, lymphoid atrophy and decreased cellularity of the marginal zone in the spleen, congestion in the lungs and liver, and glandular stomach ulcers were found in females receiving 200 mg/kg which died.

Method: OECD Preliminary Reproductive Toxicity Test (1992)  
GLP: Yes [**X**] No [ ] ? [ ]  
Test substance: Purity > 99.5 %  
Remarks:  
Reference: MHW, Japan (1994b)

**5.9 DEVELOPMENTAL TOXICITY/ TERATOGENICITY**

See 5.8

**5.10 OTHER RELEVANT INFORMATION**

**A. Specific toxicities**

No data available

**B. Toxicodynamics, toxicokinetics**

No data available

**5.11 EXPERIENCE WITH HUMAN EXPOSURE**

None

**6. REFERENCES**

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