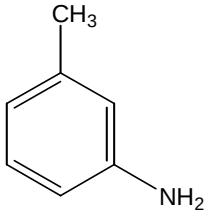
FOREWORD INTRODUCTION

M-TOLUIDINE

CAS N°: 108-44-1

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	108-44-1
Chemical Name	m-Toluidine
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Although the metabolites, 2-amino-4-methylphenol and 4-amino-2-methylphenol were identified in the rat urine with a small amount of the parent compound, there is not sufficient information on metabolism and toxicokinetics. Acute toxicity of m-toluidine is low because the oral LD50 values in rat, mouse and rabbit are from 450 to 1,430 mg/kg. This chemical is slightly irritating to skin and moderately irritating to eyes. There is no information available on skin sensitisation.

In accordance with an OECD combined repeat dose and reproductive/developmental toxicity screening test [TG 422], m-toluidine was given to Crj: CD (SD) male and female rats by gavage at doses of 0, 30, 100, 300 mg/kg/day for at least 41 days. The critical effect at 100 and 300 mg/kg is a hemolytic anemia, revealed by reduction of erythrocyte counts and hemoglobin concentration, and histological changes such as pigment deposit and extramedullary hematopoiesis in liver and spleen. Other toxicity is renal tubular epithelium lesions accompanied with pigment deposit in kidney. As there is suggestive evidence of hemolytic anemia such as marginal pigment deposit and extramedullary hematopoiesis in spleen at the lowest dose of 30 mg/kg, probably caused by methemoglobin formation, LOAEL for repeat dose toxicity was 30mg/kg/day.

In the above screening test [OECD TG 422], m-toluidine was given from 14 days before mating to 14 days after mating in males and from 14 days before mating to day 3 of lactation in females. As implantation losses were found in all animals at 300 mg/kg and two of ten at 100 mg/kg but not at 30 mg/kg, NOAEL for reproductive toxicity is 30 mg/kg/day. The death of all pups or more than half the number of pups observed at 30 and 100 mg/kg/day is considered as the result of maternal toxicity because there is clear evidence of the lack of the nursing activity, probably due to anemia, and all live offsprings of 30 and 100 mg/kg had normally developed up to 4 days. Therefore the NOAEL for developmental toxicity is considered to be 100 mg/kg/day.

Bacterial genotoxicity studies show negative results in *S. typhimurium* and *E. coli* with and without metabolic activation. In chromosomal aberration test conducted in cultured Chinese hamster lung (CHL/IU) cells by OECD TG 473, clastogenicity was not observed but significant increase of polyploidy (0.9 to 1.25 %) was found at the highest concentration. However, this result was

considered not to be positive because it was within historical control and generally accepted criteria of significance (5 %). Two kinds of *in vivo* studies, sister chromatid exchange and inhibition of DNA-synthesis, also show negative results. Therefore m-toluidine is considered not to be genotoxic. Tumors were not observed in dietary study of male rats at 9,400ppmand male and female mice at 14,700 and 20,400 ppm, respectively. However, the carcinogenicity in rodents is inconclusive because the experimental conditions were insufficient compared to a current carcinogenicity testing protocol.

Environment
This chemical is mainly persistent in water and it will be transported to water compartment when released to other environmental compartments. The chemical is not readily biodegradable, and its bioaccumulation potential is low.

This chemical has been tested in a limited number of aquatic species. For algae, 72 h EC50 (biomass change in *Selenastrum capricornutum*) is 17.7 mg/L. For *Daphnia*, the lowest acute toxicity value is 0.73 mg/L (48 h EC50 for immobilization), and the lowest chronic value is 0.01 mg/L (21d NOEC for reproduction). For fish, only acute data were available, the lowest of which is 34 mg/L (96 h LC50, *Oryzias latipes*).

PNEC of 0.0001 mg/L for the aquatic organisms was calculated from the lowest chronic value (NOEC for *Daphnia;* 0.01 mg/L) using an assessment factor of 100. Toxicity of this chemical to aquatic organisms, specially against *Daphnia*, is high.

Exposure
The production volume of m-toluidine in Japan was less than 100 tonnes in 1990 - 1992, and imported volume was 97-285 tonnes/year in 1988-1992, however both the production volume and imported volume in Japan in 1998 was 0 ton. This chemical is used as intermediates for pigments, photography agents and others. This chemical is stable in neutral or alkaline solutions, and is classified as "not readily biodegradable". Direct photodegradation is expected. The half-life is estimated to be about 4 months. A generic fugacity model (Mackey level III) shows this chemical would be distributed mainly to water. In the monitoring study of the general environment in Japan in 1977, m-toluidine was detected from surface water and sediment, but in the monitoring study in 1999, it was not detected in water, sediment or air. According to a Japanese manufacturer, 400 kg/year (estimated) of m-toluidine are released with 1×10^{7} tonnes/year of effluent into bay. Local predicted environmental concentration (PEClocal) is 4.0×10^{-5} mg/l, employing the calculation model. The highest exposure to the general population via the environment would be expected through drinking water processed from surface water. The concentration in drinking water is assumed to be less than 4.0×10^{-5} mg/l. Consumer exposure is negligible because m-toluidine is not contained in consumer products. As m-toluidine is mainly produced in a closed system, occupational exposures at production sites may occur by the inhalation and dermal route. Estimated human exposure for a worker who operates sampling (0.1 hr/day), drum filling (1.5 hr/day), and reaction vessel cleaning (2 day/year) without protective equipment is less than 0.21 mg/kg/day. By wearing chemical cartridge respirator during these operations, and ventilation systems during the filling process, exposure level is lower than the estimation.

NATURE OF FURTHER WORK RECOMMENDED

Local exposure assessment should be considered given the aquatic toxicity of the chemical.

FULL SIDS SUMMARY

CAS NO: 108-44-1		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point		Unknown	-31.2 °C
2.2	Boiling Point		Unknown	203.3 °C
2.3	Density		Unknown	0.993 g/cc at 15 °C
2.4	Vapour Pressure		OECD TG 104	17 Pa at 25 °C
2.5	Partition Coefficient (Log Pow)		OECD TG 107	1.53 at 25 °C
2.6 A.	Water Solubility		OECD TG 105	10 g/L at 25 °C
B.	pH			None
	pKa			None
2.12	Oxidation: Reduction Potential			None
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation		Estimation	T1/2=3.07E-1 years (in surface water at 5 m depth)
3.1.2	Stability in Water		OECD TG 111	Stable at pH 7 and 9 at 25°C $T_{1/2}$=72.1 days at pH 4 at 25°C
3.2	Monitoring Data			In air = ND (Japan, 1986) In surface water = ND (Japan, 1998) In sediment = ND (Japan, 1998) In biota = None
3.3	Transport and Distribution		Calculated (Level III Fugacity Model)	(Release 100% to air) Air Water Soil Sediment 18.06% 30.95% 50.91% 0.08% (Release 100% to water) Air Water Soil Sediment 0.15% 99.15% 0.43% 0.27% (Release 100% to soil) Air Water Soil Sediment 0.56% 28.01% 71.35% 0.08%
			(local exposure)	PEC_{local} =4.0E-5 mg/L
3.5	Biodegradation		OECD TG 301C	No biodegradation
3.7	Bioaccumulation			None
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	*Oryzias latipes*	OECD TG 203	LC_{50} (96h)= 34 mg/L
			Other	LC_{50} (14d)= 36.31 mg/L
4.2	Acute Toxicity to Aquatic Invertebrates	*Daphnia magna*	OECD TG 202	EC_{50} (24hr, Imm)= 3.8 mg/L
			Other (Dutch Standard)	LC_{50} (48h)=0.73 mg/L
4.3	Toxicity to Aquatic Plants e.g. Algae	*Selenastrum capricornutum*	OECD TG 201	EC_{50} (72hr, Bms)= 17.7 mg/L NOEC (72hr, Bms)<6.8 mg/L
4.5.2	Chronic Toxicity to Aquatic	*Daphnia magna*	OECD TG 202	EC_{50} (21d, Rep)= 0.026 mg/L

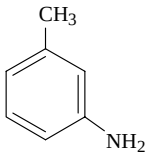
CAS NO: 108-44-1		SPECIES	PROTOCOL	RESULTS
	Invertebrates		Other (Dutch Standard)	NOEC (21d, Rep)= 0.01 mg/L NOEC (16d, Gro)=0.012 mg/L EC_{50} (16d, Rep)= 0.043 mg/L
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat	Other (unknown)	LD_{50} = 450 - 1,160 mg/kg b.w.
5.1.3	Acute Dermal Toxicity	Rabbit	Other (unknown)	LD_{50} = 3,250 mg/kg b.w.
5.2.1	Skin Irritation	Rabbit	Other (unknown)	Slightly irritating
5.2.2	Eye Irritation	Rabbit	Other (unknown)	Moderately irritating
5.3	Skin Sensitisation			No data
5.4	Repeated Dose Toxicity	Rat	OECD TG 422	LOAEL = 30 mg/kg/day
5.5	Genetic Toxicity In Vitro			
A.	Bacterial Test (Gene mutation)	*S. typhimurium* *E. coli*	Other (unknown)	- (With metabolic activation) - (Without metabolic activation)
B.	Non-Bacterial In Vitro Test (Chromosomal aberrations)	Chinese hamster CHL cells	Japanese TG and OECD TG 473	- (With metabolic activation) - (Without metabolic activation)
5.6	Genetic Toxicity In Vivo	Sister chromatid exchange	Other	Negative
5.7	Carcinogenicity	Rat & Mouse	Other	No tumorigenesis
5.8	Toxicity to Reproduction	Rat	OECD TG 422	NOAEL = 30 mg/kg/day
5.9	Developmental Toxicity/ Teratogenicity	Rat	OECD TG 422	NOAEL = 100 mg/kg/day No teratogenicity
5.11	Experience with Human Exposure			None

SIDS INITIAL ASSESSMENT REPORT (SIAR)

m-Toluidine

1. Identity

OECD Name: *m*-Toluidine
Synonym: Benzenamine, 3-methyl-
CAS Number: 108-44-1
Empirical Formula: C_7H_9N
Structural Formula:



Degree of Purity: Unknown
Major Impurities: Unknown
Essential Additives: Unknown
Physical and chemical properties

	Protocol	Results
Melting Point	Unknown	< - 31.2 °C
Densitity	Unknown	0.993 g/cc at 15 °C
Vapour Pressure	OECD TG 104	17 Pa at 25 °C
Partition Coefficeint (Log Pow)	OECD TG 107	1.53 at 25 °C
Water Solubility	OECD TG 105	10 g/L at 25°C

2. Exposure

2.1 General discussion

The production level of *m*-toluidine in Japan was less than 100 tonnes/year in 1990-1992. The imported volumes of *m*-toluidine were 97-285 tonnes/year in 1988-1992. However, both the imported volume and production volume in Japan in 1998 is 0 ton.

m-Toluidine is not readily biodegradable (OECD 301C: 1 % after 28 days).

m-Toluidine is unstable at pH 4, but stable 7 and 9. Direct photodegradation is expected. The half-life is estimated to be about 4 months in furface water at 5 m depth.

2.2 Environmental exposure

a. Global exposure

The potential environmental distribution of *m*-toluidine obtained from a generic level III fugacity model is shown in Table 1. The results show that if *m*-toluidine is released mainly to water, it is

unlikely to distribute into other compartments. But, if *m*-toluidine is released mainly to air, it is likely to be transported both to water and soil.

Table 1 Environmental distribution of *m*-toluidine using a generic level III fugacity model

Compartment	Release: 100% to air	Release: 100% to water	Release: 100% to soil
Air	18.06%	0.15%	0.56%
Water	30.95%	99.15%	28.01%
Soil	50.91%	0.43%	71.35%
Sediment	0.08%	0.27%	0.08%

In the monitoring study of general environment in Japan at 1977, *m*-toluidine was detected from surface water and sediment, but in monitoring study in 1999, it was not detected from water, sediment and air.

b. Local exposure

According to a Japanese manufacturer, 400 kg/year (estimated) of *m*-toluidine are released with 1.0 x 10^7 tonnes/year of effluent into bay. Local predicted environmental concentration (**PEC_{local}**) is 4.0 x 10^{-5} mg/l, employing the following calculation model. In this case, the dilution factor is estimated to be 1000.

$$\frac{\text{Amount of release } (4.0 \times 10^8 \text{ mg/y})}{\text{Volume of effluent } (1.0 \times 10^{10} \text{ l/y}) \times \text{Dilution factor } (1000)}$$

In Germany, m-toluidine is used as intermediate only, and there are seven known industrial sites, which are processing m-toluidine. At some major processing sites, the concentration of m-toluidine was determined analytically in the effluent of the respective wwtp. The following concentrations were calculated in the receiving streams:

- River Rhine (at Leverkusen) PEC_{local} is < 0.072 ug/L
- River Rhine (at Uerdingen) PEC_{local} is 0.005 ug/L
- River Main (at Offenbach) PEC_{local} is 0.04 ug/L

At three other industrial sites in Germany, the processing of m-toluidine is a dry process and m-toluidine is not released to wwtps.

2.3 Consumer Exposure

m-Toluidine is not contained in consumer products, because *m*-toluidine is the intermediates for pigment, photography agents and others.

2.4 Exposure via the environment

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 *m*-toluidine, a significant removal of during processing is expected. Although PEC_{global} cannot be estimated, the concentration in drinking water is assumed to be less than 4.0 x 10^{-5} mg/l.

2.5 Occupational exposure

- Occupational exposures at production sites may occur by the inhalation and dermal route.
- The atmospheric concentration was measured at one production site. The monitored data are shown in Table 2.

Table 2: Available workplace monitoring data for m-Toluidine

Occupation (Country)	Activity	Monitoring data	Comment	Source
m-Toluidine manufacture (Japan)	Sampling (quality control)	<0.5 mg/m^3	Analyzed by GC. Determination Limit was 0.5 mg/ m^3.	Report from Manufacturer
	Drum filling	< 0.5 mg/m^3		
	Reaction Vessel Cleaning	<0.5 mg/m^3		

- Based on the atmospheric concentration of 0.5 mg/m^3, $EHE_{inhalation}$ for a worker who operates sampling (0.1 hr/day), drum filling (1.5 hr/day), and reaction vessel cleaning (2 day/year) without protective equipment is 0.014 mg/kg/day.
- Dermal exposure during sampling work estimated using the EASE model as non-dispersive, direct handling was 0.1-1 mg/cm^2/day. The EHE_{dermal} for 8 minutes sampling work was 0.2 mg/kg/day, assuming both hands were exposed.
- Combined EHE was 0.21 mg/kg/day. Since workers wear chemical cartridge respirator during all these operations. The actual exposure could be much lower than this.
- This chemical is used as the intermediates for pigments and dyes.
- Time weighted average of 2 ppm (8.8-9 mg/m^3) is adopted as occupational exposure limit in USA, Australia, Belgium, Denmark and Switzerland.

3 EFFECTS ON THE ENVIRONMENT

3.1 Toxicity to Aquatic Organisms

m-Toluidine has been tested in a limited number of aquatic species. Results are summarized in Table 3. The experimental conditions and results were well documented in these studies, although the chemical concentrations in the medium had not been measured during the course of the experiments in two different studies.

Daphnia was the most sensitive among the organisms tested. The lowest value shown in Table 3 seemed to be plausible, because long-term toxicity values for *Daphnia* were within the same range.

Table 3: Summary of effects of m-Toluidine on aquatic organisms

Organism	Test duration	Result (mg/L)	Reference
Aquatic plants, e.g. algae			
Green alga (*Selenastrum capricornutum*)	72 h (s)	EC_{50} (Bms) = 17.7 (nc)	Japan EA (1994)
	72 h (s)	NOEC(Bms) < 6.8 (nc)	Japan EA (1994)

Invertebrates			
Water flea (*Daphnia magna*)	24 h (op, s)	EC_{50} (Imm) = 3.8 (nc)	Japan EA (1994)
	48 h (op, s)	LC_{50} = 0.73 (nc)	Hermens J. et al (1984)
	21 d (op, ss)	EC_{50} (Rep) = 0.026 (nc)	Japan EA (1994)
	21 d (op, ss)	NOEC(Rep) = 0.010 (nc)	Japan EA (1994)
	16 d (nr)	NOEC(Gro) = 0.012 (nc)	Deener J. W. et al (1988)
	16 d (nr)	EC_{50} (Rep) = 0.043 (nc)	Deener J. W. et al (1988)
Fish			
Medaka (*Oryzias latipes*)	96 h (op, ss)	LC_{50} = 34 (nc)	Japan EA (1994)
Guppy (*Poecilia reticulata*)	14 d (ss)	LC_{50} = 36.31(nc)	Hermens J. et al (1984)

cl = closed system
m = measured concentration
f = flow through
op = open system
s = static
ss = semi-static
nr=Not described for test type
nc = nominal
Bms = biomass
Imm = immobilization
Rep = reproduction
Gro=Growth

3.2 Toxicity to Terrestrial Organisms

There is no available information.

3.3 Other

There is no available information.

3.4 Initial Assessment for the Environment

When m-Toluidine is released to water, it will stay in water. When this chemical is released to air or soil, it will be transported to water compartment to a certain extent. Since this chemical is not biodegradable, aquatic environment is the most likely to be affected.

The lowest acute and chronic values were 0.73 mg/L (*Daphnia* 48h LC_{50}) and 0.01 mg/L (*Daphnia* 21 d NOEC, reproduction), respectively. This chemical is moderately toxic to fish and algae, but highly toxic to *Daphnia*. The predicted no effect concentration (PNEC) of 0.0001 mg/L for the aquatic organisms was calculated from the 21 d-NOEC for *Daphnia* (reproduction) using an assessment factor of 100, because only two chronic data (*Daphnia* and *Selenasatrum*) were available.

4. HUMAN HEALTH HAZARD

4.1 EFFECTS ON HUMAN HEALTH

b) Toxicokinetics and metabolism

After a single oral administration of 500 mg m-toluidine to rats, only 2.5 % of the unchanged compound was recovered from the urine for 24 hrs and two metabolites, 2-amino-4-methylphenol and 4-amino-2-methylphenol were identified after hydrolysis of the urine extract [Cheever et al.: 1980]. However, there is no information on the quantitative metabolism and excretion. After dermal application to rats, m-toluidine was dose-dependently detected in the blood [Senczuk et al.: 1984]. In the case of a single iv injection of 111.1 mg m-toluidine-HCl/kg b.w. to dogs, the metabolite, m-nitrosotoluene in blood reached to a maximum concentration of 3.5 µg/ml at 30 min and still remained in ca. 1 µg/ml at 5 hrs [Kiese: 1963].

b) Acute toxicity

Many acute toxicity data are reported for rats, mice and rabbits as shown in Table 4. Although there is no detailed information on all cases, the oral acute toxicity seems low because of oral LD_{50} values ranging from 450 to 1,430 mg/kg.

Table 4: Acute toxicity of m-toluidine in experimental animals

Route	Animals	Values	Type	References
Oral				
	Rat	450 mg/kg	LD_{50}	Dieke et al.: 1947
	Rat	974 mg/kg	LD_{50}	Marhold et al.: 1986
	Rat	1160 mg/kg	LD_{50}	Trenel and Kuehn: 1982
	Rat	1430 mg/kg	LD_{50}	Vasilenko et al.: 1981
	Mouse	740 mg/kg	LD_{50}	Vasilenko et al.: 1981
	Rabbit	750 mg/kg	LD_{50}	All-Union Institute of Scientific and Technical Information
Dermal				
	Rabbit	3250 mg/kg	LD_{50}	National Tech. Inf. Service

Human data

An exposure of 40 ppm (176 mg/m^3) in atomosphere for 60 min produced severe intoxication in persons [Goldblatt: 1955]. But the detailed information including isomer specification is not given.

Conclusions*:*

Acute toxicity of m-toluidine is low because LD_{50} values are from 450 to 1,430 mg/kg by oral route and 3,250 mg/kg by dermal route.

c) Repeated dose toxicity

There are two reported studies, showing that the major toxicity of m-toluidine is anemia. MHW oral study was identified as the key study because it was well conducted using OECD TG 422 [MHW, Japan: 1995]. In the other study, rats were received orally at dose of 280 mg/kg/day for 30 and 90 days, but there was no detailed information such as strain, sex, histopathological data and so on [Vasilenko: 1977].

SD (Crj: CD) rats were received m-toluidine by gavage at doses of 0, 30, 100 and 300 mg/kg/day. Males were dosed for 42 days and females were dosed from 14 days before mating, throughout pregnancy to day 3 of lactation. Haematological and biochemical analysis was conducted only for males.

Compound-related clinical signs were low locomotor activity and pale skin at 300 mg/kg. Erythrocyte counts, blood hemoglobin concentration and hematocrit were decreased at 100 and 300 mg/kg of males. Histopathological lesions of both sexes were deposit pigmentation and extramedullary hematopoiesis in the liver at 100 and 300 mg/kg, and in the spleen at 30 mg/kg and more. Other histological findings were very slight hepatocyte swelling at 100 mg/kg males and 300 mg/kg males and females, and changes in renal tubular epithelium with pigment deposit at 100 and 300 mg/kg of both sexes.

At the lowest dose of 30 mg/kg, marginal deposit pigmentation and extramedullary hematopoiesis in spleen were observed, suggesting that a slight hemolysis occurred. Additionally, there are sufficient evidences that this chemical induces methemoglobinemia, but methemoglobin content was not determined in this study. Therefore, the dose of 30 mg/kg should be considered to be adverse effect level because of suggestive evidence of hemolytic anemia. LOAEL for repeat dose toxicity was 30 mg/kg/day.

There is no information available on humans.

Conclusions:
The critical effect in repeat dose toxicity of m-toluidine is a hemolytic anemia, revealed by reduction of erythrocyte counts and hemoglobin concentration, and histological changes such as pigment deposit and extramedullary hematopoiesis in liver and spleen. Other toxicity is renal tubular epithelium lesions accompanied with pigment deposit in kidney. As there is suggestive evidence of hemolytic anemia at the lowest dose of 30 mg/kg, probably caused by methemoglobin formation, LOAEL for repeat dose toxicity was 30 mg/kg/day.

d) Reproduction/developmental toxicity

The only available study is an OECD combined repeat dose and reproductive/ developmental toxicity screening test [OECD TG 422]. This study was identified as a key study because it was well conducted and reported. Details of this study are as follows.

m-Toluidine was administered to SD (Crj: CD) rats by gavage at doses of 0, 30, 100 and 300 mg/kg from 14 days before mating to 14 days after mating in males and from 14 days before mating to day 3 of lactation in females [MHW, Japan: 1995].

No compound-related adverse effects were detected with regard to the mating performances at any dose levels. However, two of ten pregnant females receiving 100 mg/kg and all the eleven receiving 300 mg/kg showed total implantation losses in utero. Therefore, the NOAEL for reproductive toxicity is considered to be 30 mg/kg/day. Two of eleven pregnant females receiving 30 mg/kg and three of ten recieving 100 mg/kg did not show the nursing activity obviously and all or more than half number of their pups died after birth, while all live offsprings of other dams in 30 and 100 mg/kg groups had normally developed up to 4 days. Therefore, this death of pups is considered as a result of maternal toxicity, probably due to anemia. Furthermore, change of pup weights and incidence of morphological abnormalities of pups were not significant in 30 and 100 mg/kg. The NOAEL for developmental toxicity is considered to be 100 mg/kg/day.

There is no information available on humans.

Conclusions:

m-Toluidine induced implantation losses in rats at 100 and 300 mg/kg by gavage. Any developmental toxicity including teratogenicity was not observed. The NOAELs for reproductive and developmental toxicity are considered to be 30 mg/kg/day and 100 mg/kg/day, respectively.

e) Genotoxicity

Bacterial in vitro test

Reverse gene mutation assay in bacteria was conducted in many laboratories as shown in Table 5. Among them, Thompson 's study was identified as a key study because it was well conducted and the sufficient testing strains were used [Thompson et al.: 1983].

Table 5 Summary of reverse mutation assay

Type of test	Test system	Dose of m-toluidine	Result	Reference
GENE MUTATION ASSAYS				
Ames test *(reverse mutation)*	*S. typh.* (strains TA1535, TA1537, TA98, TA100, TA1538, G46, C3076, D3052) *E. coli* WP2, WP2 uvr A	Up to 1,000 µg/plate	**Negative** (+ & - MA*)	Thompson et al.: 1983
Ames test *(reverse mutation)*	*S. typh.* (strains TA98, TA100, TA1535, TA1537, WP2 uvr A)	Up to 5,000 µg/plate	**Negative** (+ & - MA)	MHW: unpublished
Ames test *(reverse mutation)*	*S. typh.* (strains TA102)	Up to 5,000 µg/plate	**Negative** (+ MA)	Jung et al.: 1992
Ames test *(reverse mutation)*	*S. typh.* (strains TA98, TA100)	No data	**Negative** (+ & - MA) in presence of co-mutagen Norharman	Gupta et al.: 1989
Ames test *(reverse mutation)*	*S. typh.* (strains TA98)	Up to 200 µg/plate	**Negative** (+ MA)	Sugimura et al.: 1982
Ames test *(reverse mutation)*	*S. typh.* (strains TA1538)	Up to 100 µg/plate	**Negative** (+ & - MA)	Garner and Nutman: 1977
Ames test *(reverse mutation)*	*S. typh.* (strains TA98, TA100,)	535.8 or 1071.6 µg/plate (5, 10 mM)	**Negative** (+ & - MA)	Nohmi et al.: 1984
Ames test *(reverse mutation)*	*S. typh.* (strains TA 100, TA 1537, TA98)	Not data	**Negative** (+ MA)	Zimmer et al.: 1980
Ames test *(reverse mutation)*	*S. typh.* (strains TA98, TA100, TA1535, TA 1537)	321.5 µg/plate	**Negative** (+ & - MA)	Florin et al.: 1980
Ames test *(reverse mutation)*	*S. typh.* (strains TA 98, TA 100)	Up to 107 µg/plate	**Negative** (+ & - MA)	Mori et al.: 1980

*MA: Metabolic activation

All results were negative in *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538, G46, C3076, D3052, *Escherichia coli* WP2 and WP2 *uvr*A with or without an exogenous metabolic activation system.

Non-bacterial in vitro test

Two studies were reported as a non-bacterial *in vitro* test. Chromosomal aberration test was conducted in cultured Chinese hamster lung (CHL/IU) cells by Japanese test guideline equivalent to OECD TG 473 [MHW, Japan: 1995] and unscheduled DNA synthesis test was conducted in rat liver hepatocyte [Thompson et al.: 1983]. Both studies showed negative results. Chromosomal aberration test was identified as a key study because it was well conducted and reported.

Structural chromosomal aberrations were not induced on continuous treatment, and on short-term treatment with and without metabolic activation. Polyploidy was increased at the highest concentration of 0.52 mg/ml on continuous treatment, and 1.1 mg/ml on short-term treatment with and without metabolic activation. However, these results (0.9 or 1.25 %) were considered to be negative by the jugdement based on generally accepted criteria of significance: 5 % and compared with historical control.

Genetic in vivo test
Four studies were found as *in vivo* genotoxicity study. But they could not be adopted as the robust study due to the lack of the detailed data. Their test types were sister chromatid exchange assay and inhibition of DNA-synthesis. All results were negative.

Conclusions:
This chemical is not genotoxic because of negative results in bacterial and mammalian *in vitro* tests as well as *in vivo* experiments.

f) Carcinogenicity

Only one study was reported as one of early National Cancer Institute program, the current name of National Toxicology Programs in US [Weisburger et al.: 1978]. Therefore, the experimental conditions were insufficient compared to a current carcinogenicity testing protocol. m-Toluidine was given to male SD rats, and male and female HaM/ICR mice in diet for 18 months.

In rat study, the initial doses of 8,000 and 16,000 ppm were reduced to 4,000 and 8,000 ppm after 3 months, the time weighted average doses being 4,700 and 9,400 ppm (233 and 467 mg/kg/day, respectively). There were no significantly increased incidences of neoplasm in thirteen major oragans.

In mouse study, the initial doses of 16,000 and 32,000 ppm were reduced to 4,000 and 8,000 ppm for males and, 8,000 and 16,000 ppm for females after 5 months, the time weighted average doses being 7,300 and 14,700 ppm (1,100 and 2,200 mg/kg/day, respectively) for males and 10,200 and 20,400 ppm (1,533 and 3,067 mg/kg/day, respectively) for females. Only significant increase of hepatic tumors was observed in male mice at the low dose (high dose: 1/16, low dose: 4/16, control: 1/18).

There is no information available on humans.

Conclusions:
Tumors were not observed in dietary study of male rats at 9,400 ppm, and male and female mice at 14,700 and 20,400 ppm, respectively. However, the carcinogenicity in rodents is inconclusive because the experimental conditions were insufficient compared to a current carcinogenicity testing protocol.

g) Other human health related information

Irritation and sensitisation

- Application of 500 mg/24 hr of m-toluidine induced slight skin irritation in rabbits [Marhold: 1986].
- Moderate irritating to eyes in rabbits at 20 mg/24 hr were reported [Marhold: 1986].

- There is no data available on skin sensitization.

Conclusions*:*
This chemical is slightly irritating to skin and moderately irritating to eyes in rabbits. There is no information available on skin sensitisation.

Methemoglobin formation

Major reports of methemoglobin formation are shown in Table 6. They show that a single adiministration of m-toluidine induces severe methemoglobinemia in rats, cats and dogs. Although species differences in methemoglobin reductase activity *in vitro* were reported [Stolk et al.: 1966], there is no information on species differences of chemical-induced methemoglobinemia *in vivo*, including m-toluindine.

Table 6: Methemoglobin induction in experimental animals

Route	Animals	Doses	Methemoglobin ratio	References
Oral	Rat	200 mg/kg b. w.	36.4 %	Senczuk and Rucinska: 1984a
Dermal	Rat	2.5-12.5 mg/ml	40 %	Senczuk and Rucinska: 1984a
Dermal	Rat	700 mg/kg b.w.	32.6 %	Vasilenko et al.: 1977
i.v.	Cat	26.79 mg/kg b.w.	60.2 %	McClean et al.: 1967, 1969
i.v.	Dog	111.1 mg/kg b.w.	56 %	Kiese: 1963

Information on structurally related chemicals

o-Toluidine
Oral LD_{50} value in rodents is from 515 to 940 mg/kg. This chemical has a moderate to strong irritating effect on skin and eyes of rabbits. The major toxic effect is a hemolytic anemia with methemoglobinemia [Lunkin 1967]. This chemical induces a variety of tumors in mice and rats [Weisburger et al.: 1978].

p-Toluidine
Oral LD_{50} value in rodents is from 656 to 1,285 mg/kg. This chemical has a moderate to strong irritating effect on skin and eyes of rabbits. The major toxic effect is methemoglobinemia [Mclean et al.: 1969]. This chemical is a hepatic carcinogen in mice but not in male rats [Weisburger et al.: 1978].

4.2 Initial Assessment for Human Health

Although the metabolites, 2-amino-4-methylphenol and 4-amino-2-methylphenol were identified in the rat urine with a small amount of the parent compound, there is no sufficient information on metabolism and toxicokinetics. Acute toxicity of m-toluidine is low because the oral LD50 values in rat, mouse and rabbit are from 450 to 1,430 mg/kg. This chemical is slightly irritating to skin and moderately irritating to eyes. There is no information available on skin sensitisation.

In accordance with an OECD combined repeat dose and reproductive/developmental toxicity screening test [TG 422], m-toluidine was given to Crj: CD (SD) male and female rats by gavage at doses of 0, 30, 100, 300 mg/kg/day for at least 41 days. The critical effect at 100 and 300 mg/kg is a hemolytic anemia, revealed by reduction of erythrocyte counts and hemoglobin concentration, and

histological changes such as pigment deposit and extramedullary hematopoiesis in liver and spleen. Other toxicity is renal tubular epithelium lesions accompanied with pigment deposit in kidney. As there is suggestive evidence of hemolytic anemia such as marginal pigment deposit and extramedullary hematopoiesis in spleen at the lowest dose of 30 mg/kg, probably caused by methemoglobin formation, LOAEL for repeat dose toxicity was 30mg/kg/day.

In the above screening test [OECD TG 422], m-toluidine was given from 14 days before mating to 14 days after mating in males and from 14 days before mating to day 3 of lactation in females. As implantation losses were found in all animals at 300 mg/kg and two of ten at 100 mg/kg but not at 30 mg/kg, NOAEL for reproductive toxicity is 30 mg/kg/day. As death of all pups or more than half number of pups observed at 30 and 100 mg/kg/day is considered as the result of maternal toxicity because there is clear evidence of the lack of the nursing activity probably due to anemia, and all other live offsprings of 30 and 100 mg/kg had normally developed up to 4 days. Therefore NOAEL for developmental toxicity is considered to be 100 mg/kg/day.

Bacterial genotoxicity studies show negative results in S. typhimurium and E. coli with and without metabolic activation. In chromosomal aberration test conducted in cultured Chinese hamster lung (CHL/IU) cells by OECD TG 473, clastogenicity was not observed but significant increase of polyploidy (0.9 to 1.25 %) was found at the highest concentration. However, this result was considered not to be positive because it was within historical control and generally accepted criteria of significance (5 %). Two kinds of in vivo studies, sister chromatid exchange and inhibition of DNA-synthesis show also negative. Therefore m-toluidine is considered not to be genotoxic. Tumors were not observed in dietary study of male rats at 9,400 ppm, and male and female mice at 14,700 and 20,400 ppm, respectively. However, the carcinogenicity in rodents is inconclusive because the experimental conditions were insufficient compared to a current carcinogenicity testing protocol.

5. CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

Physical/chemical property, production, use and distribution

The production volume of m-toluidine in Japan is less than 100 tonnes in 1990 - 1992, and imported volume is 97-285 tonnes/year in 1988-1992. This chemical is used as intermediates for Pigments, photography agents and others. This chemical is stable in neutral or alkaline solutions, and is classified as "not readily biodegradable". Direct photodegradation is expected. The half-life is estimated to be about 4 months. A generic fugacity model (Mackey level III) shows this chemical would be distributed mainly to water. In the monitoring study of general environment in Japan at 1977, m-toluidine was detected from surface water and sediment, but in monitoring study at 1999, it was not detect from water, sediment and air. According to a Japanese manufacturer, 400 kg/year (estimated) of m-toluidine are released with 1×10^{7} tonnes/year of effluent into bay. Local predicted environmental concentration (PEClocal) is 4.0×10^{-5} mg/l, employing the calculation model. The highest exposure to the general population via the environment would be expected through drinking water processed from surface water. The concentration in drinking water is assumed to be less than 4.0×10^{-5} mg/l. Consumer exposure is negligible because m-toluidine is not contained in consumer products. As m-toluidine is produced in a closed system, occupational exposures at production sites may occur by the inhalation and dermal route. Estimated human exposure for a worker who operates sampling (0.1 hr/day), drum filling (1.5 hr/day), and reaction vessel cleaning (2 day/year) without protective equipment is less than 0.21 mg/kg/day. By wearing

chemical cartridge respirator during these operations, and ventilation systems during the filling process, exposure level is lower than the estimation.

Environment
This chemical is mainly persistent in water and it will be transported to water compartment when released to other environmental compartments. The chemical is not readily biodegradable, and its bioaccumulation potential is low.

This chemical has been tested in a limited number of aquatic species. For algae, 72 h EC_{50} (biomass change in *Selenastrum capricornutum*) is 17.7 mg/L. For *Daphnia,* the lowest acute toxicity value is 0.73 mg/L (48 h EC_{50} for immobilization), and the lowest chronic value is 0.01 mg/L (21d NOEC for reproduction). For fish, only acute data were available, the lowest of which is 34 mg/L (96 h LC_{50}, *Oryzias latipes*).

PNEC of 0.0001 mg/L for the aquatic organisms was calculated from the lowest chronic value (NOEC for *Daphnia;* 0.01 mg/L) using an assessment factor of 100. Toxicity of this chemical to aquatic organisms, specially against *Daphnia*, is high.

Human health
Oral LD_{50} value is from 450 to 1,430 mg/kg. This chemical is slightly irritating to skin and moderately irritating to eyes. There is no information available on skin sensitisation. In a repeat dose toxicity study of m-toluidine, the critical effect is a hemolytic anemia, revealed by reduction of erythrocyte counts and hemoglobin concentration, and histological changes such as pigment deposit and extramedullary hematopoiesis in liver and spleen. Other toxicity is renal tubular epithelium lesions accompanied with pigment deposit in kidney. As there is suggestive evidence of hemolytic anemia at the lowest dose of 30 mg/kg, probably caused by methemoglobin formation, LOAEL for repeat dose toxicity was 30 mg/kg/day. m-Toluidine induced implantation losses in rats at 100 and 300 mg/kg. Any developmental toxicity including teratogenicity was not observed. The NOAELs for reproductive and developmental toxicity are considered to be 30 mg/kg/day and 100 mg/kg/day, respectively. This chemical is not genotoxic because of negative results in bacterial and mammalian *in vitro* tests as well as *in vivo* experiments.

5.2 Recommendations

None

REFERENCES

All-Union Institute of Scientific and Tech. Information (Moscow, USSR) #4035-77.

Cheever, K.L. et al. (1980) Toxicol. Appl. Pharmacol., 56, 361-369.

Deener J. W. et al. (1988) Ecotoxicol. Environ. Safety, 15, 72-77.

Dieke, S.H. et al. (1947) J. Pharmakol. Exper. Ther., 90, 260-270.

Environment Agency of Japan (1994)

Florin, I. et al. (1980) Toxicology, 15, 219-232.

Garner, R.C. and Nutman, C.A. (1977) Mutat. Res., 44, 9-19.

Goldblatt, M.W. (1955) Brit. J. Industr. Med., 12, 1-20.

Gupta, R.L. et al. (1989) Toxicol. Lett., 48, 75-81.

Jung, R. et al. (1992) Mutat. Res., 278, 265-270.

Kiese, M. (1963) Naunyn Schmiedeberg's Arch. exp. Path. Und Pharmak., 244, 387-404.

Lunkin, V.N. (1967) Ref. Zh. Otd. Vyp. Farmakol. Khiomiter Sredstva. Toksikol., No.12.54.1096.

Marhold, J. (1986) Prehled Prumyslove Toxikol. Org. Latky, 459-460.

McClean, S. et al. (1967) J. Pharm. Pharmacol., 19, 146-154.

McClean, S. et al. (1969) J. Pharm. Pharmacol., 21, 441-450.

Ministry of Health and Welfare: Japan (1995) *Toxicity Testing Reports of Environmental Chemicals*, 2, 79-102.

Ministry of Health and Welfare: Japan, unpublished

Mori, Y. et al. (1980) Carcinogenesis, 1, 121-127.

National Technical Information Service, Springfield, VA22161, Formerly U.S. Clearinghouse for Scientific and Technical Information, AD691-490.

Nohmi, T. et al. (1984) Mutat. Res., 136, 159-168.

Senczuk, W. and H. Rucinska (1984a) Bromat. Chem. Toksykol., 17, 241-243.

Stolk, J.M. et al. (1966) Biochem. Pharmacol., 15, 343-351.

Sugimura, T. et al. (1982) Adv. Exp. Med. Biol., 136, 1011-1025.

Thompson, C.Z. et al. (1983) Environ. Mutag., 5, 803-811.

Trenel, J. and Kuehn,R. (1982) Bewertung wassergefaehrdender Stoffe im Hinblick auf Lagerung, Umschlag und Transport und Untersuchung zur Abklaerung substanz- und bewertungsmethodenspezifischer Grenzfaelle bei der Bewertung wassergefaehrdender Stoffe, UFOPLAN des Bundesministers des Innern im Auftrag des Umweltbundesamtes, Juli 1982

Vasilenko, N.M. et al. (1977) Deposited Doc. ISS Viniti, 4035-4077.

Vasilenko, N.M. et al. (1981) Gig. Tr. Prof. Zabol., 25(8), 50.

Weisburger, E.K. et al. (1978) J. Environ. Pathol. Toxicol., 2, 325-356.

Zimmer D, et al. (1980) Mutat. Res., 77, 317-326.

REVISED OECD HPV FORM 1

SIDS DOSSIER
ON THE HPV PHASE 3 CHEMICAL

m-Toluidine

CAS No. 108-44-1

Sponsor Country: Japan

DATE: September, 2000

CONTENTS

2.11 OXIDISING PROPERTIES
2.12 † OXIDATION: REDUCTION POTENTIAL
2.13 ADDITIONAL REMARKS
A. PARTITION CO-EFFICIENT BETWEEN SOIL/SEDIMENT AND WATER (Kd)
B. OTHER REMARKS

3. ENVIRONMENTAL FATE AND PATHWAYS

3.1 STABILITY
3.1.1 * PHOTODEGRADATION
3.1.2 * STABILITY IN WATER
3.1.3 STABILITY IN SOIL
3.2 * MONITORING DATA (ENVIRONMENT)
3.3 * TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION PATHWAYS
3.3.1 TRANSPORT
3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)
3.4 MODE OF DEGRADATION IN ACTUAL USE
3.5 * BIODEGRADATION
3.6 BOD-5, COD OR RATIO BOD-5/COD
3.7 BIOACCUMULATION
3.8 ADDITIONAL REMARKS
A. SEWAGE TREATMENT
B. OTHER

4. ECOTOXICITY

4.1 * ACUTE/PROLONGED TOXICITY TO FISH
4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES
* A. DAPHNIA
B. OTHER AQUATIC ORGANISMS
4.3 * TOXICITY TO AQUATIC PLANTS e.g., ALGAE
4.4 TOXICITY TO BACTERIA
4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS
4.5.1 CHRONIC TOXICITY TO FISH
4.5.2 (*) CHRONIC TOXICITY TO AQUATIC INVERTEBRATES (e.g., DAPHNIA REPRODUCTION)
4.6 TOXICITY TO TERRESTRIAL ORGANISMS
4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS
4.6.2 TOXICITY TO TERRESTRIAL PLANTS
4.6.3 TOXICITY TO OTHER NON-MAMMALIAN TERRESTRIAL SPECIES (INCLUDING BIRDS)
4.7 BIOLOGICAL EFFECTS MONITORING (INCLUDING BIOMAGNIFICATION)
4.8 BIOTRANSFORMATION AND KINETICS
4.9 ADDITIONAL REMARKS

5. TOXICITY

5.1 * ACUTE TOXICITY
5.1.1 ACUTE ORAL TOXICITY

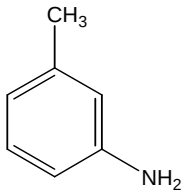
5.1.2 ACUTE INHALATION TOXICITY
5.1.3 ACUTE DERMAL TOXICITY
5.1.4 ACUTE TOXICITY BY OTHER ROUTES OF ADMINISTRATION
5.2 CORROSIVENESS/IRRITATION
5.2.1 SKIN IRRITATION/CORROSION
5.2.2 EYE IRRITATION/CORROSION
5.3 SKIN SENSITISATION
5.4 ***** REPEATED DOSE TOXICITY
5.5 ***** GENETIC TOXICITY IN VITRO
A. BACTERIAL TEST
B. NON-BACTERIAL IN VITRO TEST
5.6 ***** GENETIC TOXICITY IN VIVO
5.7 CARCINOGENICITY
5.8 ***** TOXICITY TO REPRODUCTION
5.9 ***** DEVELOPMENTAL TOXICITY / TERATOGENICITY
5.10 OTHER RELEVANT INFORMATION
A. SPECIFIC TOXICITIES (NEUROTOXICITY, IMMUNOTOXICITY etc.)
B. TOXICODYNAMICS, TOXICOKINETICS
5.11 ***** EXPERIENCE WITH HUMAN EXPOSURE

6. REFERENCES

Note: *; Data elements in the SIDS
†; Data elements specially required for inorganic chemicals

1. GENERAL INFORMATION

1.01 SUBSTANCE INFORMATION

***A.**	**CAS-Number**	108-44-1
B.	**Name (IUPAC name)**	3-Methylaniline
***C.**	**Name** *(OECD name)*	m-Toluidine
†D.	**CAS Descriptor**	
E.	**EINECS-Number**	208-144-8
F.	**Molecular Formula**	C_7H_9N
***G.**	**Structural Formula**	
H.	**Substance Group**	Not applicable
I.	**Substance Remark**	None
J.	**Molecular Weight**	107.17

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)
Ministry of Labor (MOL)

Contact person: Mr. Akitaka Saiki
Director
Second International Organization Bureau
Ministry of Foreign Affairs

Address: 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

Address:

1.1 GENERAL SUBSTANCE INFORMATION

A. Type of Substance

element **[ ]**; inorganic **[ ]**; natural substance **[ ]**;
organic **[X]**; organometallic **[ ]**; petroleum product **[ ]**

B. Physical State gaseous **[ ]**; liquid **[X]**; solid **[ ]**

C. Purity 99 %

1.2 SYNONYMS *m*-Toluidine

1.3 IMPURITIES Unknown

1.4 ADDITIVES Unknown

***1.5 QUANTITY**

Location	Production	Date
Japan	60 tonnes/year	1990-1992
	97-285 tonnes/year (Import)	1988-1992
	0 ton	1998

Reference: MITI, Japan (1994a, 1998)

1.6 LABELLING AND CLASSIFICATION

None

***1.7 USE PATTERN**

A. General

Type of Use:	**Category:**
(1) Industry use	Intermediate for pigments (40%), photographic agents (50%) and others (10%)

Reference: (1) MITI, Japan (1994a)

B. Uses in Consumer Products

None

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUE

None

***1.9 SOURCES OF EXPOSURE**

Source: Media of release: Water from a production site
Quantities per media: 400 kg/year

Reference: MITI, Japan (1994a)

1.10 ADDITIONAL REMARKS

A. Options for disposal Incineration

Reference: MITI, Japan (1994a)

B. Other remarks None

2. PHYSICAL-CHEMICAL DATA

*2.1 MELTING POINT

(a)
Value: - 31.2 °C
Decomposition: Yes **[ ]** No **[X]** Ambiguous **[ ]**
Sublimation: Yes **[ ]** No **[X]** Ambiguous **[ ]**
Method:
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Reference: Encyclopaedia Chimica; Kyoritu Shuppan (1963)

(b)
Value: - 30.4 °C
Decomposition: Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Sublimation: Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Method:
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Reference: Weast, R..C. Handbook of Chemistry and Physics. The Chemical Rubber Co., 18901 Cranwood Parkway, Cleveland, Ohio, 44128. 1970-1971

*2.2 BOILING POINT

(a)
Value: 203.3 °C
Pressure:
Decomposition: Yes **[ ]** No **[X]** Ambiguous **[ ]**
Method:
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Reference: Encyclopaedia Chimica; Kyoritu Shuppan (1963)

(b)
Value: 203.4 °C
Pressure: 760 mmHg
Decomposition: Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Method: Unknown
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: None

Reference: Herrington, E.F.G., Physical Constants of Some Constituents of Coal Tar, NPL Report No. Chem.102

(c)
Value: 203.0 - 204.0 °C
Pressure:
Decomposition: Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Method: Unknown
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: None
Reference: The Merck Index 9th Edition

†2.3 DENSITY (Relative density)

Type: Bulk density **[ ]**; Density **[X]**; Relative Density **[ ]**
Value: 0.993 g/cc
Temperature: 15 °C
Method: Unknown
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: None
Reference: ECDIN database

*2.4 VAPOUR PRESSURE

Value: 17 Pa
Temperature: 25°C
Method: calculated **[ ]**; measured **[X]**
OECD Test Guideline 104 Dynamic method
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Reference: MITI, Japan (1994b)

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

(a)
Log Pow: 1.53
Temperature: 25 °C
Method: calculated **[ ]**; measured **[X]**
OECD Test Guideline 107
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Reference: MITI (1992)

(b)
Log Pow: 1.40
Temperature:
Method: calculated **[X]**; measured **[ ]**
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Reference: Numerica database

(c)
Log Pow: 1.41

Temperature:
Method: calculated **[ ]**; measured **[?]**
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Reference: Company data

***2.6 WATER SOLUBILITY**

A. Solubility

Value: 10 g/l
Temperature: 25 °C
Description: Miscible **[ ]**; Of very high solubility **[ ]**;
Of high solubility **[ ]**; Soluble **[X]**; Slightly soluble **[ ]**;
Of low solubility **[ ]**; Of very low solubility **[ ]**;
Not soluble **[ ]**
Method: OECD Test Guideline 105
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Reference: MITI, Japan (1994b)

B. pH Value, pKa Value

pKa = 4.66 at 25 °C

2.7 FLASH POINT

Value: 85 °C
Method: Unknown
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Reference: Catalog Handbook of Fine Chemicals, Aldrich Chem. Co. (1992)

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 = 1.38×10^3 at 300 nm	
	Estimated parameter for calculation:	
	Quantum yield	0.01
	Concentration	5×10^{-5} M
	Depth of water body	500 cm
	Conversion constant	6.023×10^{20}
Result:	Degradation rate	3.57×10^{-12} mol/l/ s
	Half life	3.07×10^{-1} 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 7 and 9 at 25 °C Half-life: 72.1 days at pH 4
Method:	OECD Test guideline 111
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	*m*-Toluidine
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:	0.096 - 0.26 ng/ml (Detection limits: 0.08-0.2 ng/ml) in detected in 4 of 68 samples analyzed in Japan.
Remarks:	None

Reference: EA, Japan (1977)

(b)
Type of Measurement: Background **[ ]**, At contaminated Site **[ ]**, Other **[X]**
Media: Surface water
Results: ND (Detection limits: 0.09 ng/ml) in 13 areas (0 of 39 samples analyzed; 3 samples collected per area) in Japan in 1998
Remarks: None
Reference: EA, Japan (1999)

(c)
Type of Measurement: Background **[ ]**, At contaminated Site **[ ]**, Other **[X]**
Media: Ground water
Results: 3.3 µg/l in 2 of 3 wells analysed in USA.
Remarks: None
Reference: Stuermer, D.H. et al.: Environmental Science and Technology 16, 582-7 (1982)

(d)
Type of Measurement: Background **[ ]**, At contaminated Site **[ ]**, Other **[X]**
Media: Sediment
Results: 0.002-0.056 µg/g (Detection limits: 0.001-0.004 µg/g) in 32 of 68 samples Analyzed in Japan in 1976
Remarks: None
Reference: EA, Japan (1977)

(e)
Type of Measurement: Background **[ ]**, At contaminated Site **[ ]**, Other **[X]**
Media: Sediment
Results: ND (Detection limits: 0.01 µg/g) in 13 areas (0 of 39 samples analyzed; 3 samples collected per area) in Japan in 1998
Remarks: None
Reference: EA, Japan (1999)

(f)
Type of Measurement: Background **[ ]**, At contaminated Site **[ ]**, Other **[ ]**
Media: Air
Results: ND (Detection limits: 0.02-100 ng/m^3) in 72 samples in Japan in 1986. in 1985
Remarks: None
Reference: EA, Japan (1987)

3.4 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 *m*-Toluidine obtained from a generic level III fugacity model is shown in Table. The results show that if *m*-Toluidine is released mainly to water, it is unlikely to distribute into other compartments. But, if *m*-Toluidine is released mainly to air, it is likely to be transported both to water and soil.

Environmental distribution *m*-toluidine using a generic level III fugacity model.

Compartment	Release: 100% to air	Release: 100% to water	Release: 100% to soil
Air	18.06%	0.15%	0.56%
Water	30.95%	99.15%	28.01%
Soil	50.91%	0.43%	71.35%
Sediment	0.08%	0.27%	0.08%

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	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 0, 1 and 0 % from BOD 3, 0 and 4 % from TOC 5, 1 and 3 % 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:	*m*-toluidine
Reference:	MITI (1992)

3.6 BOD_5, COD OR RATIO BOD_5/COD

Not applicable

3.7 BIOACCUMULATION

No data available

3.8 ADDITIONAL REMARKS

A. Sewage treatment

None

B. Other information

None

4. ECOTOXICOLOGICAL DATA

*4.1 ACUTE/PROLONGED TOXICITY TO FISH

(a)

Type of test:	static **[ ]**; semi-static **[X]**; flow-through **[ ]**; other **[ ]** open-system **[X]**; closed-system **[ ]**
Species:	*Oryzias latipes*
Exposure period:	96 hr
Results:	LC_{50} (24h) = 190 mg/L LC_{50} (48h) = 81 mg /L LC_{50} (72h) = 46 mg/ L LC_{50} (96h) = 34 mg/ L
Analytical monitoring:	Yes **[ ]** No **[X]** ? **[ ]**
Method:	OECD Test Guideline 203 (1981)
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	m-Toluidine, purity = 99 %
Remarks:	A group of 10 fish were exposed to each of 7 nominal concentrations (10-320 mg/ L). Stock solution was prepared with DMSO:HC-40 = 9:1 (Final concentration: 500 mg/ L). Controls with and without this vehicle were taken for test.
Reference:	EA, Japan (1994)

(b)

Type of test:	static **[ ]**; semi-static **[X]**; flow-through **[ ]**; other **[ ]** open-system **[ ]**; closed-system **[ ]**
Species:	*Poecilia reticulata*
Exposure period:	14 d
Results:	LC_{50} = 36.31 mg/ L
Analytical monitoring:	Yes **[ ]** No **[ ]** ? **[X]**
Method:	Other
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance:	
Remarks:	
Reference:	Hermens, J. et al. (1984)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

***A. Daphnia**

(a)

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

Exposure period: 24 hr
Results: $EC_{50\ (24h)}$ = 3.8 mg/ L (95% confidence limits:1.3-6.7 mg/ L)
Analytical monitoring: Yes **[ ]** No **[X]** ? **[ ]**
Method: OECD Test Guideline 202 (1984)
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: m-Toluidine, purity: = 99 %
Remarks: 20 daphnids (4 replicates; 5 organisms per replicate) were exposed to each of 8 nominal concentrations (1.8-100 mg/ L). Stock solution was prepared with DMSO:HCO-40 = 9:1 (Final concentration: 200 mg/ L). Controls with and without this vehicle were taken for test.
Reference: EA, Japan (1994)

(b)
Type of test: static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other **[ ]**; open-system **[**X**]**; closed-system **[ ]**
Species: *Daphnia magna*
Exposure period: 24 hr
Results: $LC_{50\ (48h)}$ = 0.73 mg/ L
Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**
Method: The concept NEN reports 6501 or 6502 (Dutch Standard Organization (1980) and Canton et al. (1975))
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance:
Remarks: 50 daphnids (2 replicates; 25 organisms per replicate) were exposed to each of nominal concentrations. Although the common factor was 3.2, nominal concentration was not described.
Reference: Hermens J. et al., Aquatic Toxicology 5, 315-322 (1984)

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: $EC_{50\ (72h)}$ = 17.7 mg / L
NOEC < 6.8 mg/L
Analytical monitoring: Yes **[ ]** No **[X]** ? **[ ]**
Method: open-system **[ ]**; closed-system **[X]**
OECD Test Guideline 201 (1984)
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: m-Toluidine, purity = 99 %
Remarks: The EC_{50} values for biomass were calculated based on 5 nominal concentrations (6.8-72 mg/L). Stock solution was prepared with DMSO (Final concentration: 61.2-648 mg/L). Controls with and without this vehicle were taken for test. The vessel was sealed with an aluminum film.
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

No data available

(*)4.5.2. CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

(a)

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 days
Results:
Immobility: EC_{50} (48 h) = 0.15 mg/L (95% confidence limits:0.12 - 0.18mg/L)
EC_{50} (7 d) = 0.11 mg/L
EC_{50} (14 d) = 0.11 mg/L
EC_{50} (21 d) = 0.08 mg/L (95% confidence limits:0.06-0.10 mg/L)
Reproduction: EC_{50} (21 d) =0.026mg/L (95% confidence limits:0.021-0.034 mg/L)
NOEC = 0.010 mg/L ($p < 0.05$)
LOEC = 0.032 mg/L ($p < 0.05$)
Analytical monitoring: Yes **[ ]** No **[X]** ? **[ ]**
Method: OECD Test Guideline 202 (1984)
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: m-Toluidine, purity = 99 %
Remarks: 40 daphnids (4 replicates; 10 organisms per replicate) were exposed to each of 5 nominal concentrations (0.010-1.0 mg/L). Stock solution was prepared with DMSO:HCO-40 = 9:1 (Final concentration: 200 mg/L). Controls with and without this vehicle were taken for test.
Reference: EA, Japan (1994)

(b)

Type of test: static **[ ]**; semi-static **[ ]**; flow-through **[ ]**; other **[ ]**; open-system **[ ]**; closed-system **[ ]**
Species: *Daphnia magna*
End-point: Mortality **[ ]**; Reproduction rate **[ ]**; Other **[X]**
Exposure period: 16 days
Results:
Growth rate: NOEC (16 days) = 0.012 mg/L
Analytical monitoring: Yes **[ ]** No **[ ]** ? **[X]**
Method: The concept NEN report 6502 (Dutch Standard Organization)
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: m-Toluidine, purity = Not described
Remarks: 40-50 daphnids (2 replicates; 20-25 organisms per replicate) were exposed to each of nominal concentrations Although the common factor was 1.8, nominal concentration was not described.

Reference: Deener J. W. et al. Ecotoxicol. Environ. Safety 15, 72-77 (1988)

(c)
Type of test: static **[ ]**; semi-static **[ ]**; flow-through **[ ]**; other **[ ]**; open-system **[ ]**; closed-system **[ ]**
Species: *Daphnia magna*
End-point: Mortality **[ ]**; Reproduction rate **[X]**; Other **[ ]**
Exposure period: 16 days
Results:
Reproduction: $EC_{50\ (16\ d)}$ = 0.043 mg/L
Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**
Method: The concept NEN reports 6501 or 6502 (Dutch Standard Organization (1980) and Canton et al. (1975))
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: m-Toluidine, purity = Not described
Remarks: 30 daphnids (2 replicates; 15 organisms per replicate) were exposed to each of nominal concentrations Although the common factor was 3.2, nominal concentration was not described.
Reference: Hermens J. et al. Aquatic Toxicology 5, 315-322 (1984)

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_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Rat
Value:	974 mg/kg
Method:	Unknown
GLP:	Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance:	purity: Unknown
Remarks:	None
Reference:	Marhold: 1986

(b)

Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Rat
Value:	1160 mg/kg
Method:	Unknown
GLP:	Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance:	purity: Unknown
Remarks:	None
Reference:	Trenel and Kuehn: 1982

(c)

Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Rat
Value:	1430 mg/kg
Method:	Unknown
GLP:	Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance:	purity: Unknown
Remarks:	None
Reference:	Vasilenko et al.: 1981

(d)

Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Rat
Value:	450 mg/kg
Method:	Unknown
GLP:	Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance:	purity: Unknown
Remarks:	None
Reference:	Dieke et al.: 1947

(e)

Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Mouse
Value:	740 mg/kg
Method:	Unknown
GLP:	Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance:	purity: Unknown
Remarks:	None
Reference:	Vasilenko et al.: 1981

(f)
Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Rabbit
Value: 750 mg/kg
Method: Unknown
GLP: Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance: purity: Unknown
Remarks: None
Reference: All-Union Institute of Scientific and Technical Information (Moscow, USSR)

(g)
Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Cat
Value: > 50 mg/kg
Method: Unknown
GLP: Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance: purity: Unknown
Remarks: None
Reference: National Technical Information Service

5.1.2 ACUTE INHALATION TOXICITY

No data available

5.1.3 ACUTE DERMAL TOXICITY

(a)
Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Rabbit
Value: 3250 mg/kg
Method: Unknown
GLP: Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance: purity: Unknown
Remarks: None
Reference: National Technical Information Service

5.1.4 ACUTE TOXICITY, OTHER ROUTES OF ADMINISTRATION

(a)
Type: LC_0 **[ ]**; LC_{100} **[ ]**; LC_{50} **[ ]**; LCL_0 **[ ]**; Other **[ ]**
LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Rat
Route of Administration: i.m. **[ ]**; i.p. **[X]**; i.v. **[ ]**; infusion **[ ]**; s.c. **[ ]**; other **[ ]**
Exposure time: No data available
Value: males 690 mg/kg; females 660 mg/kg
Method: Unknown
GLP: Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance: purity: Unknown
Remarks:
Reference: Weisburger et al.: 1978

(b)
Type: LC_0 **[ ]**; LC_{100} **[ ]**; LC_{50} **[ ]**; LCL_0 **[ ]**; Other **[ ]**
LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Mouse
Route of Administration: i.m. **[ ]**; i.p. **[X]**; i.v. **[ ]**; infusion **[ ]**; s.c. **[ ]**; other **[ ]**
Exposure time: No data available
Value: 116 mg/kg bw
Method: Unknown
GLP: Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance: purity: Unknown
Remarks:
Reference: Citroni: 1951

(c)
Type: LC_0 **[ ]**; LC_{100} **[ ]**; LC_{50} **[ ]**; LCL_0 **[ ]**; Other **[ ]**
LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: mouse
Route of Administration: i.m. **[ ]**; i.p. **[X]**; i.v. **[ ]**; infusion **[ ]**; s.c. **[ ]**; other **[ ]**
Exposure time: No data available
Value: males 714 mg/kg; females 650 mg/kg
Method: Unknown
GLP: Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance: purity: Unknown
Remarks:
Reference: Weisburger et al.: 1978

(d)
Type: LC_0 **[ ]**; LC_{100} **[ ]**; LC_{50} **[ ]**; LCL_0 **[ ]**; Other **[ ]**
LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: mouse
Route of Administration: i.m. **[ ]**; i.p. **[X]**; i.v. **[ ]**; infusion **[ ]**; s.c. **[ ]**; other **[ ]**
Exposure time: No data available
Value: 150 mg/kg bw
Method: Unknown
GLP: Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance: purity: Unknown
Remarks:
Reference: National Technical Information Service

5.2 CORROSIVENESS/IRRITATION

5.2.1 SKIN IRRITATION/CORROSION

(a)
Species/strain: Rabbit
Results: Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[X]**; Not irritating **[ ]**
Classification: Irritating **[ ]**; Not irritating **[ ]**; Risk of serious damage to eyes **[ ]**
Method: Standard Draize test
GLP: Yes **[ ]**; No **[ ]**; ? **[X]**

Test substance: purity: Unknown
Remarks: 500 mg/24 hr
Reference: Marhold: 1986

(b)
Species/strain: Rabbit
Results: Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[X]**; Slightly irritating **[ ]**; Not irritating **[ ]**
Classification: Irritating **[ ]**; Not irritating **[ ]**; Risk of serious damage to eyes **[ ]**
Method: No data
GLP: Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance: purity: Unknown
Remarks: 24 h exposure
Reference: Marhold: 1972

5.2.2 EYE IRRITATION/CORROSION

(a)
Species/strain: Rabbit
Results: Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[X]**; Slightly irritating **[ ]**; Not irritating **[ ]**
Classification: Irritating **[ ]**; Not irritating **[ ]**; Risk of serious damage to eyes **[ ]**
Method: Standard Draize test
GLP: Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance: purity: Unknown
Remarks: 20 mg/24 hr
Reference: Marhold: 1986

(b)
Species/strain: Rabbit
Results: Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[X]**; Slightly irritating **[ ]**; Not irritating **[ ]**
Classification: Irritating **[ ]**; Not irritating **[ ]**; Risk of serious damage to eyes **[ ]**
Method: No data
GLP: Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance: purity: Unknown
Remarks:
Reference: Marhold: 1972

5.3 SKIN SENSITISATION

No data available

*5.4 REPEATED DOSE TOXICITY

(a)
Species/strain: Rats/ Cij;CD (SD)
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**

Route of Administration: Oral (by gavage)
Exposure period: Males; 42 days, Females; from 14 days before mating to day 3 of lactation
Frequency of treatment: Daily
Post exposure observation period: 1 day
Dose: 30, 100, 300 mg/kg/day
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**; Historical **[ ]**
NOAEL: < 30 mg/kg/day
LOAEL: 30 mg/kg/day
Results: No death occurred during the study. The mean body weight gains during week 1 of the 300 mg/kg males and 100 and 300 mg/kg females were significantly lower than those of the controls. Histopathological lesions included pigment deposit and extramedullary hematopoiesis in the liver and spleen, and congestion in the spleen in males and females that received 100 and 300 mg/kg. In males and females given 30 mg/kg, a slight increase in severity of pigmentation or extramedullary hematopoiesis in the spleen was noted.
Method: OECD Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test (OECD TG 422)
GLP: Yes **[X]**; No **[ ]**; ? **[ ]**
Test substance: purity: 99.0 %
Reference: MHW, Japan: 1995

(b)
Species/strain: Rat
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[ ]**; No data **[X]**
Route of Administration: Oral (gavage)
Exposure period: 30 and 90 days
Frequency of treatment: daily
Post exposure observation period: no data
Dose: 280 mg/kg b.w./day
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**; No other data
Concurrent no treatment **[ ]**; Concurrent vehicle **[ ]**; Historical **[ ]**
NOAEL: Not established
LOAEL: 280 mg/kg b.w./day
Results: Decreased body weight, increased relative spleen weight, anemia (reduced oxygenated hemoglobin content, erythrocytopenia) increased sulfonated hemoglobin content, appearance of Heinz-Ehrlich bodies, decreased SH-groups in the blood, disturbed vitamin C content (no further data available)
There are no histological data.
Method: Unknown
GLP: Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance: purity: Unknown
Reference: Vasilenko: 1977

*5.5 GENETIC TOXICITY IN VITRO

A. BACTERIAL TEST

(a)
Type: Bacterial reverse mutation assay
System of testing: *Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537, TA1538, G46, C3076, D3052, *Escherichia coli* WP2, WP2 uvr A
Concentration: up to 1000 µg/plate
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
S9: Aroclor1254-induced rat liver
Results: Negative
Cytotoxicity conc: Not reported
Precipitation conc: Not reported
Genotoxic effects:

	+	?	-
With metabolic activation:	**[ ]**	**[ ]**	**[X]**
Without metabolic activation:	**[ ]**	**[ ]**	**[X]**

Method: Other (Gradient plate test for bacterial mutation)
GLP: Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance: purity: Unknown
Remarks:
Reference: Thompson et al.: 1983

(b)
Type: Bacterial reverse mutation assay
System of testing: *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, *Escherichia coli* WP2, WP2uvrA
Concentration: up to 5000 µg/plate
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
Results: Negative
Cytotoxicity conc: Not observed
Precipitation conc: Not reported
Genotoxic effects:

	+	?	-
With metabolic activation:	**[ ]**	**[ ]**	**[X]**
Without metabolic activation:	**[ ]**	**[ ]**	**[X]**

Method: Guidelines for Screening Mutagenicity Testing of Chemicals (Japan) and OECD Guideline No. 471
GLP: Yes **[X]**; No **[ ]**; ? **[ ]**
Test substance: purity: 99.8 %
Remarks:
Reference: MHW, Japan: unpublished

(b)
Type: Bacterial reverse mutation assay
System of testing: *Salmonella typhimurium* TA102
Concentration: Up to 5000 µg/plate
Metabolic activation: With **[X]**; Without **[ ]**; With and Without **[ ]**; No data **[ ]**
S9: 10 % S9 mix from livers of Aroclor 1254-induced SD rat
Results: Negative
Cytotoxicity conc: Not reported
Precipitation conc: Not reported
Genotoxic effects:

	+	?	-
With metabolic activation:	**[ ]**	**[ ]**	**[X]**
Without metabolic activation:	**[ ]**	**[ ]**	**[ ]**

Method: Direct plate incorporation

GLP: Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance: purity: Unknown
Remarks:
Reference: Jung et al.: 1992

(c)
Type: Bacterial reverse mutation assay
System of testing: *Salmonella typhimurium* TA 98, TA 100
Concentration: No concentration data available
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
S9: Rat liver, induced with Aroclor 1254
Results: Negative
Cytotoxicity conc: No data
Precipitation conc: No data
Genotoxic effects:

	+	?	-
With metabolic activation:	**[ ]**	**[ ]**	**[X]**
Without metabolic activation:	**[ ]**	**[ ]**	**[X]**

Method: Other (Preincubation)
GLP: Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance: purity: Not specified (Purchased from Riedel. Checked through TLC)
Remarks: Negative in the presence of the co-mutagen Norharman
Reference: Gupta et al.: 1989

(d)
Type: Bacterial reverse mutation assay
System of testing: *Salmonella typhimurium* TA 98
Concentration: up to 200 µg/plate
Metabolic activation: With **[X]**; Without **[ ]**; With and Without **[ ]**; No data **[ ]**
S9: No data
Results: Negative
Cytotoxicity conc: No data
Precipitation conc: Not applicable
Genotoxic effects:

	+	?	-
With metabolic activation:	**[ ]**	**[ ]**	**[X]**
Without metabolic activation:	**[ ]**	**[ ]**	**[ ]**

Method: Other
GLP: Yes **[ ]** ; No **[ ]** ; ? **[X]**
Test substance: purity: Unknown
Remarks: Norharman absent/present in the test system
Reference: Sugimura et al.: 1982

(e)
Type: Bacterial reverse mutation assay
System of testing: *Salmonella typhimurium* TA 1538
Concentration: up to 100 µg/plate
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
S9: Rat liver, induced with Aroclor 1254
Results: Negative
Cytotoxicity conc: No data
Precipitation conc: Not applicable

		+	?	-
Genotoxic effects:				
	With metabolic activation:	**[ ]**	**[ ]**	**[X]**
	Without metabolic activation:	**[ ]**	**[ ]**	**[X]**

Method: Other (Direct plate incorporation)
GLP: Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance: purity: Unknown (Purchased from Aldrich chemical company Ltd.)
Remarks:
Reference: Garner and Nutman: 1977

(f)
Type: Bacterial reverse mutation assay
System of testing: *Salmonella typhimurium* TA 98, TA100
Concentration: 535.8 or 1071.6 µg/ml (5 or 10 mM)
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
S9: Male Fisher rat liver, induced with PCB (Kanechlor400)
Results: Negative
Cytotoxicity conc: No data
Precipitation conc: No data

		+	?	-
Genotoxic effects:				
	With metabolic activation:	**[ ]**	**[ ]**	**[X]**
	Without metabolic activation:	**[ ]**	**[ ]**	**[X]**

Method: Direct plate incorporation
GLP: Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance: Purity: Unknown
Remarks: No further data available
Reference: Nohmi et al.: 1984

(g)
Type: Bacterial reverse mutation assay
System of testing: *Salmonella typhimurium* TA 100, TA 1537, TA98
Concentration: No concentration data available
Metabolic activation: With **[X]**; Without **[ ]**; With and Without **[ ]**; No data **[ ]**
S9: Rat liver, induced with Aroclor 1254
Results: Negative
Cytotoxicity conc: No data
Precipitation conc: Not available

		+	?	-
Genotoxic effects:				
	With metabolic activation:	**[ ]**	**[ ]**	**[X]**
	Without metabolic activation:	**[ ]**	**[ ]**	**[ ]**

Method: Other
GLP: Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance: purity: Unknown
Remarks:
Reference: Zimmer et al.: 1980

(h)
Type: Bacterial reverse mutation assay
System of testing: *Salmonella typhimurium* TA98, TA100, TA1535, TA1537
Concentration: 321.5 µg/plate
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
S9: Rat liver, induced with Aroclor 1254

Results:	Negative
Cytotoxicity conc:	Negative at the test condition
Precipitation conc:	No precipitation at the test condition
Genotoxic effects:	+ ? -
	With metabolic activation: **[ ] [ ] [X]**
	Without metabolic activation: **[ ] [ ] [X]**
Method:	Other (Spot test)
GLP:	Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance:	purity: Unknown
Remarks:	
Reference:	Florin et al.: 1980

(i)

Type:	Bacterial reverse mutation assay
System of testing:	*Salmonella typhimurium* TA 98, TA 100
Concentration:	Up to 107 µg/plate
Metabolic activation:	With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
S9:	No data
Results:	Negative
Cytotoxicity conc:	No data
Precipitation conc:	No data
Genotoxic effects:	+ ? -
	With metabolic activation: **[ ] [ ] [X]**
	Without metabolic activation: **[ ] [ ] [X]**
Method:	
GLP:	Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance:	purity: Unknown
Remarks:	
Reference:	Mori et al.: 1980

(j)

Type:	Other (see remarks)
System of testing:	*Bacillus subtilis*
Concentration:	unknown
Metabolic activation:	With **[ ]**; Without **[ ]**; With and Without **[ ]**; No data **[X]**
S9:	No data
Results:	Negative
Cytotoxicity conc:	No data
Precipitation conc:	No data
Genotoxic effects:	No data + ? -
	With metabolic activation: **[ ] [ ] [ ]**
	Without metabolic activation: **[ ] [ ] [ ]**
Method:	No data
GLP:	Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance:	purity: Unknown
Remarks:	Assay for loss of transforming DNA activity 1070 mg m-toluidine/l was mixed with transforming DNA and incubated 60 minutes, mixed with competent cells and incubated 30 minutes, mixed with soft agar and poured onto the minimal agar plate, the number of transformants was counted after incubation for 2 days at 37 degree C.
Reference:	Nohmi et al.: 1984

B. NON-BACTERIAL IN VITRO TEST

(a)

Type:	Chromosomal aberration test
System of testing:	Chinese hamster CHU/IU cells
Concentration:	-S9 (continuous treatment): 0, 0.13, 0.26, 0.52 mg/ml -S9 (short-term treatment): 0, 0.3, 0.6, 1.1 mg/ml +S9 (short-term treatment): 0, 0.3, 0.6, 1.1 mg/ml
Metabolic activation:	With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]** S-9:Rat liver, induced with phenobarbital and 5,6-benzoflavone
Results:	
Cytotoxicity conc:	With metabolic activation: Not observed Without metabolic activation: Not observed
Precipitation conc:	Precipitant was not found.

Genotoxic effects:	clastogenicity			polyploidy		
	+	?	-	+	?	-
without metabolic activation:	**[ ]**	**[ ]**	**[X]**	**[ ]**	**[ ]**	**[X]**
with metabolic activation:	**[ ]**	**[ ]**	**[X]**	**[ ]**	**[ ]**	**[X]**

Method:	Guidelines for Screening Mutagenicity Testing of Chemicals (Japan)
GLP:	Yes **[X]**; No **[ ]**; ? **[ ]**
Test substance:	purity: 99.0 %
Remarks:	Positive controls: -S9, Mitomycin C +S9, Cyclophosphamide
Reference:	MHW, Japan: 1995

(b)

Type:	Unscheduled DNA synthesis
System of testing:	Rat liver hepatocyte
Concentration:	0.5-1,000 nmol/ml
Metabolic activation:	With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
S9:	No data
Results:	Negative
Cytotoxicity conc:	Not observed
Precipitation conc:	No data

Genotoxic effects:	+	?	-
With metabolic activation:	**[ ]**	**[ ]**	**[X]**
Without metabolic activation:	**[ ]**	**[ ]**	**[X]**

Method:	Unknown
GLP:	Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance:	purity: Unknown
Remarks:	
Reference:	Thompson et al.: 1983

***5.6 GENETIC TOXICITY IN VIVO**

(a)

Type:	Sister chromatid exchange assay
Species/strain:	Mouse
Sex:	Female **[ ]**; Male **[ ]**; Male/Female **[ ]**; No data **[X]**
Route of Administration:	i.p.
Exposure period:	once

Doses: 10, 50, 100 and 200 mg/kg b.w.
Results:
Effect on mitotic index or P/N ratio: Unknown
Genotoxic effects: + ? -
[ ] [ ] [X]
Method: Unknown
GLP: Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance: purity: Unknown
Remarks:
Reference: Gorecka-Turska et al.: 1983

(b)
Type: Sister chromatid exchange assay
Species/strain: Mouse
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[ ]**; No data **[X]**
Route of Administration: i.p.
Exposure period: single application
Doses: No data
Results:
Effect on mitotic index or P/N ratio: Unknown
Genotoxic effects: + ? -
[ ] [ ] [X]
Method: Unknown
GLP: Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance: purity: Unknown
Remarks:
Reference: Vasil'eva et al.: 1985

(c)
Type: Inhibition of DNA-synthesis
Species/strain: Mouse
Sex: Female **[ ]**; Male **[X]**; Male/Female **[ ]**; No data **[ ]**
Route of Administration: oral unspecified
Exposure period: single application
Doses: 200 mg/kg b.w.
Results: no inhibition of testicular DNA-synthesis
Effect on mitotic index or P/N ratio: No data
Genotoxic effects: + ? -
[ ] [ ] [X]
Method: Unknown
GLP: Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance: purity: Unknown
Remarks:
Reference: Seiler: 1977

(d)
Type: Inhibition of DNA-synthesis
Species/strain: Mouse

Sex: Female **[ ]**; Male **[ ]**; Male/Female **[ ]**; No data **[X]**
Route of Administration: i.p.
Exposure period:
Doses: 2 - 300 mg/kg b.w.
Results: No inhibition of DNA-synthesis was found
Effect on mitotic index or P/N ratio:
Genotoxic effects: + ? -
[ ] [ ] [X]
Method: Unknown
GLP: Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance: purity: Unknown
Remarks: 3 mice per dose-level and control group were examined. Autoradiographs of nuclei of renal tubular and liver epithelium were examined by visual silver-grain counting.
Reference: Amlacher and Rudolph: 1983, Amlacher: 1981

5.8 CARCINOGENICITY

(a)
Species/strain: Rat/Charles River CD (SD)
Sex: Female **[ ]**; Male **[X]**; Male/Female **[ ]**; No data **[ ]**
Route of Administration: Oral feed
Exposure period: 18 months
Frequency of treatment: Daily
Post exposure observation period: Up to approximately 6 months
Doses: 3 M: 8000 (400 mg/kg b.w./day), 16000; 15 M: 4000, 8000 ppm in diet
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[X]**; Concurrent vehicle **[ ]**; Historical **[ ]**
Results: 8000 and 16000 ppm in diet for 3 months led to a reduced body weight gain (10 % and more) or death, therefore after 3 months the dosages were reduced to 4000 and 8000 ppm diet for the remaining 15 months. No tumors were observed.
Method: Other [According to the method described in Russfield, A.U. et al. (1975) Toxicol. Appl. Pharmacol., 31, 47-54]
GLP: Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance: m-toluidine-HCl, purity: 97-99% (Aldrich)
Remarks: Dosages (calculation is based on 50 g diet per kg b.w. and day): 3 months: 400 and 800 mg/kg b.w./day; further 15 months: 200 and 400 mg/kg b.w./day; 25 male rats per group; histological examination was done on lungs, liver, spleen, kidney, adrenal, heart, bladder, stomach, intestine, reproductive organs and pituitaries.
Reference: Weisburger et al.: 1978

(b)
Species/strain: Mouse /CD-1
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**
Route of Administration: Oral feed
Exposure period: 18 months
Frequency of treatment: Daily

Post exposure observation period: 13 weeks
Doses: Male; 5 M: 16000, 32000 (4800 mg/kg b.w./day) ppm in diet
13 M: 4000, 8000 ppm in diet
Female; 5 M: 16000, 32000; 13 M: 8000, 16000 ppm in diet
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[X]**; Concurrent vehicle **[ ]**; Historical **[ ]**
Results: 16000 and 32000 mg/kg diet for 5 months led to a reduced body weight gain (10 % and more) or death, therefore after 5 months the dosages were reduced for the remaining 13 months: males 4000 and 8000 mg/kg diet, females 8000 and 16000 mg/kg diet. No tumors were observed except liver tumors– male mice (4 out of 16 examined) at 4000 mg/kg diet; simultaneous control 1/18, pooled control 7/99.
Method: Other [According to the method described in Russfield, A.U. et al. (1975) Toxicol. Appl. Pharmacol., 31, 47-54]
GLP: Yes **[ ]**; No **[ ]**; ? **[X]**
Test substance: m-toluidine-HCl, purity: 97-99 % (Aldrich)
Remarks: Dosages 5 months: 16000 and 32000 ppm: 2400 and 4800 mg/kg b.w./day; 13 months: males 4000 and 8000 ppm: 600 and 1200 mg/kg b.w./day, females 8000 and 16000 ppm: 1200 and 2400 mg/kg b.w./day; 25 male and female mice per group; histological examination was done on lungs, liver, spleen, kidney, adrenal, heart, bladder, stomach, intestine and reproductive organs.
Reference: Weisburger, et al.: 1978

*5.8 TOXICITY TO REPRODUCTION

(a)
Type: Fertility **[ ]**; One-generation study **[X]**; Two-generation study **[ ]**; Other **[ ]**
Species/strain: Rats/ Cij;CD (Sprague-Dawley)
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**
Route of Administration: Oral (gavage)
Exposure period: Male: 42 days
Female: from 14 days before mating to day 3 of lactation
Frequency of treatment: Daily
Post exposure observation period: 1 day
Premating exposure period: male: 14 days, female: 14 days
Duration of the test: Male; 43 days, Female; for 41-53 days
Doses: 0 (Vehicle), 30, 100, 300 mg/kg/day
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**; Corn oil
Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**; Historical **[ ]**
NOAEL: 30 mg/kg/day
Results: No compound-related adverse effects were detected with regard to the mating performances of any of the dosed rats. However, two of ten pregnant females receiving 100 mg/kg and all the eleven receiving 300 mg/kg showed total implantation losses in utero. In two of eleven pregnant females receiving 30 mg/kg and three of ten receiving 100 mg/kg, all pups or more than half number of pups died due to the lack of the nursing activity of dams. No significant differences in the pup weights and incidence of morphological

abnormalities of pups were apparent in the groups given 100 mg/kg or less when compared to the controls.

Method: OECD Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test (OECD TG 422)
GLP: Yes **[X]**; No **[ ]**; ? **[ ]**
Test substance: purity: 99.0%
Reference: MHW, Japan: 1995

*5.9 DEVELOPMENTAL TOXICITY/ TERATOGENICITY

(a)
Species/strain: Rats/ Cij;CD (Sprague-Dawley)
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**
Route of Administration: Oral (gavage)
Duration of the test: Male; 43 days, Female; for 41-53 days
Exposure period: Male: 42 days
Female: from 14 days before mating to day 3 of lactation
Frequency of treatment: Daily
Doses: 0 (Vehicle), 30, 100, 300 mg/kg/day
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**; Historical **[ ]**
NOAEL for maternal Toxicity: < 30 mg/kg/day
NOAEL for developmental toxicity: 100 mg/kg/day
Results: No compound-related adverse effects were detected with regard to the mating performances of any of the dosed rats. However, two of ten pregnant females receiving 100 mg/kg and all the eleven receiving 300 mg/kg showed total implantation losses in utero. In two of eleven pregnant females receiving 30 mg/kg and three of ten receiving 100 mg/kg, all pups or more than half number of pups died due to the lack of the nursing activity of dams. No significant differences in the pup weights and incidence of morphological abnormalities of pups were apparent in the groups given 100 mg/kg or less when compared to the controls.
Method: OECD Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test (OECD TG 422)
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: purity: 99.0%
Remarks:
Reference: MHW, Japan: 1995

5.10 OTHER RELEVANT INFORMATION

A. Specific toxicities

(a)
Type: Methemoglobin induction in rat
Results: Methemoglobin concentrations up to 36.4 % were detected in the blood of rats after a single oral application (200 mg/kg b.w.; stomach tube) of m-toluidine. Concentrations up to 40% were detected after dermal exposure (2.5-12.5 mg/ml) for 2-6 h (no further details available).

Remarks:
Reference: Senczuk and Rucinska: 1984a

(b)
Type: Methemoglobin induction in rat
Results: An application of 700 mg m-toluidine/kg b.w. led to an increase of methemoglobin from 1.3 % up to 32.6 % in the blood of rats.
Remarks:
Reference: Vasilenko et al.: 1977

(c)
Type: Methemoglobin induction in cat
Results: An intravenous injection of 0.25 mmol (= 26.79 mg) m-toluidine-HCl/kg b.w. increased the methemoglobin content in the blood of cats. The maximum was reached after 4 hours; and the mean maximum ratio of methemoglobin was 60.2 %.
Remarks:
Reference: McClean et al.: 1967
McClean et al.: 1969

(d)
Type: Methemoglobin induction in dog
Results: 6 hours after a single intravenous administration of 0.77 mmol (= 111.1 mg) m-toluidine-HCl/kg b.w. to dogs the concentration of methemoglobin was ca. 56 %.
Remarks:
Reference: Kiese: 1963

(e)
Type: Methemoglobin binding in rat
Results: 0.6 mmol (= 64.3 mg)/kg b.w. m-toluidine was orally (gavage) administered to female rats. After 24 h a covalent binding of m-toluidine to hemoglobin was found. The hemoglobin binding index was determined as 4.9 mmol m-toluidine/mol hemoglobin/ dose (mmol/kg b.w.).
Remarks:
Reference: Birner and Neumann: 1988

(f)
Type: Methemoglobin induction in cat
Results: Intraperitoneal injection of m-toluidine (1-80 mg/kg b.w. in corn oil) led to an increase of methemoglobin in the blood of cats. The effect was dose-dependent, but doses above 30 mg/kg b.w. did not cause any further increase of the methemoglobin level. A dose of 2 mg/kg b.w. caused a formation of Heinz-Ehrlich bodies in 10 % of the erythrocytes; and a dose of 80 mg/kg b.w. generated Heinz-Ehrlich bodies in up to 70 % of the erythrocytes. At high methemoglobin concentrations the cats showed an increased pulmonary respiration; and higher dosages of m-toluidine led to a loss of muscle tone with dilated pupil, somnolence, vomiting, incontinence and often severe salivation.

Remarks:
Reference: Reiter and Leusser: 1952

(g)
Type: *In vitro* cell proliferation
Results: Incubation of Ascites sarcoma BP8 cells with 1 mM (= 107.16 mg/l) m-toluidine for 48 h did not inhibit the cell growth.
Remarks:
Reference: Curvall et al.: 1984

(h)
Type: *In vitro* teratogenicity
Results: Incubation of embryo chicken trachea with 5 mM (= 535 mg/l) m-toluidine in ethanol did not inhibit the ciliary activity within 60 minutes.
Remarks:
Reference: Curvall et al.: 1984
Petterson et al.: 1982

(i)
Type: Enzyme induction
Results: Significantly ($p < 0.05$) enhanced glutathione S-transferase activity was found in the liver. The NADPH-cytochrome c reductase activity was significantly ($p < 0.05$) decreased in the kidney. The enzyme activities in the lungs were within the normal range. The cytochrome P-450 and cytochrome b5 contents in liver and kidney were not influenced by m-toluidine.
Remarks:
Reference: Gnojkowski et al.: 1984

B. Toxicodynamics, toxicokinetics

(a)
Type: Skin absorption
Results: m-Toluidine was detected in the blood plasma of rats after dermal application (tail). The plasma levels correlated with the dose level.
Remarks:
Reference: Senczuk et al.: 1984

(b)
Type: Metabolism
Results: 30 min after a single intravenous administration of 0.77 mmol (= 111.1 mg) m-toluidine-HCl/kg b.w. to dogs a maximum concentration of 3.5 µg m-nitrosotoluene/ml blood was reached. 5 hours after the injection the concentration of m-nitrosotoluene was still ca. 1 µg/ml blood.
Remarks:
Reference: Kiese: 1963

(c)
Type: Metabolism *in vitro*

Results: *In vitro*, the p-hydroxylation of m-toluidine by rabbit liver microsomes was measured with a specific activity of 0.43 nmol/ min and mg microsomal protein.
Remarks:
Reference: Ichikawa et al.: 1969

(d)
Type: Mechanism for metabolism
Results: The microsomal oxidation of m-toluidine was described as follows (no further information available): with atmospheric oxygen to the corresponding primary hydroxylamine or to the corresponding nitroso compound with water to the corresponding p-hydroxy- or o-hydroxyamine
Remarks:
Reference: Beckett and Belanger: 1976
Schreiber: 1974

(e)
Type: Metabolism and Excretion
Results: After a single oral administration of 500 mg m-toluidine to rats, only 2.5 % of the unchanged compound was recovered from the urine for 24 hrs and two metabolites, 2-amino-4-methylphenol and 4-amino-2-methylphenol were identified after hydrolysis of the urine extract.
Remarks:
Reference: Cheever et al.: 1980

(f)
Type: Excretion
Results: m-Toluidine was detected in the urine of rats after a single oral application (stomach tube) of 20, 100 or 200 mg/kg b.w. High correlation between levels administered and eliminated, was observed (no further details available).
Remarks:
Reference: Senczuk and Rucinska: 1984b

* 5.11 EXPERIENCE WITH HUMAN EXPOSURE

A. Cigarette related effect

(a)
Results: m-Toluidine was detected in the urine (0.3-7.7 µg/24 h) of 2 of 11 smokers and 4 of 9 nonsmokers.
Remarks:
Reference: El-Bayoumy et al.: 1986

(b)
Results: The mainstream smoke of one US 85 mm cigarette without filter tip contained 13.0 - 19.0 ng m-toluidine per cigarette.
Remarks:
Reference: Patrianakos and Hoffmann: 1979

(c)
Results: m-Toluidine was detected in the blood of smokers (approx. 1050 pg/g hemoglobin) and nonsmokers (approx. 1140 pg/g hemoglobin) in Turin. In Boston m-toluidine was detected in the blood of smokers (approx. 810 pg/g hemoglobin) and nonsmokers (approx. 990 pg/g hemoglobin).
Remarks:
Reference: Skipper et al.: 1988

(d)
Results: m-Toluidine was detected as hemoglobin adduct in the blood of smokers (blond tobacco: 1097 pg/g hemoglobin; black tobacco 11401 pg/g hemoglobin) and nonsmokers (1141 pg/g hemoglobin) in Turin.
Remarks:
Reference: Bryant, M.S. et al.: 1988

(e)
Results: Hemoglobin examination showed no evidence for different concentration of m-toluidine in the blood of smokers (approx. 490 pg/g hemoglobin) and nonsmokers (approx. 680 pg/g hemoglobin).
Remarks:
Reference: Stillwell et al.: 1987

B. Other effects

(a)
Results: An exposure of 40 ppm (176 mg/m^3) in the air for 60 minutes produced severe intoxication in persons (no further details available).
Remarks:
Reference: Goldblatt: 1955

(b)
Results: Incubation of human diploid embryonic lung fibroblasts with 25 mM (= 2679 mg/l) m-toluidine for 30 minutes did not damage the membrane.
Remarks:
Reference: Curvall et al.: 1984
Thelestam et al.: 1980

7. REFERENCES

All-Union Institute of Scientific and Tech. Information (Moscow, USSR) #4035-77.

Amlacher, E. and C. Rudolph (1981) Arch. Geschwulstforschung, 51(7), 605-610.

Amlacher, E. and C. Rudolph (1983) Acta histochemica Suppl.-Band XXVII, 155-162.

Beckett, H.A. and P.M. Belanger (1976) Biochem. Pharmacol., 25, 211-214.

Birner, G. and H.G. Neumann (1988) Arch. Toxicol. 62, 110-115.

Bryant, M.S. et al. (1988) Proc. Natl. Acad. Sci. USA 85, 9788-9791.

Cheever, K.L. et al. (1980) Toxicol. Appl. Pharmacol., 56, 361-369.

Citroni, M. (1951) Archivo Italiano di Scienze Farmacologiche, 1, 284-291.

Curvall, M. et al. (1984) Cell Biol. Toxicol., 1, 173-193.

Deneer J. W. et al. (1988) Ecotoxicol. Environ. Safety, 15, 72-77

Dieke, S.H. et al. (1947) J. Pharmakol. Exper. Ther., 90, 260-270.

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)

ECDIN database (1994)

El-Bayoumy, K. et al. (1986) Cancer Res., 46, 6064-6067.

Estimation Method", McGraw Hill Book Co.

Florin, I. et al. (1980) Toxicology, 15, 219-232.

Garner, R.C. and Nutman, C.A. (1977) Mutat. Res., 44, 9-19.

Gnojkowski, J. et al. (1984) Toxicology, 32, 335-342.

Goldblatt, M.W. (1955) Brit. J. Industr. Med., 12, 1-20.

Gorecka-Turska, D. et al. (1983) Bromat. Chem. Toksykol., XVI 1, 37-42.

Gupta, R.L. et al. (1989) Toxicol. Lett., 48, 75-81.

Hermens, J. et al., (1984) Aqua. Toxicol., 5, 315-322.

Ichikawa, Y. et al. (1969) Biochim. Biophys. Acta, 171, 32-46.

Jung, R. et al. (1992) Mutation Research, 278, 265-270.

Kiese, M. (1963) Naunyn Schmiedeberg’s Arch. exp. Path. Und Pharmak., 244, 387-404.

Lange's Handbook of Chemistry (11th edition)

Lyman, W.J, W. F. Reehl and D. H. Rosenblatt (1981) "Handbook of Chemical Property

Marhold, J.V. (1972) Institut Pro Vychovu Vedoucicen Pracovniku Chemickeho Prumyclu, Praha, Czechoslovakia, p. 66.

Marhold, J. (1986) Prehled Prumyslove Toxikol. Org. Latky, 459-460.

McClean, S. et al. (1967) J. Pharm. Pharmacol., 19, 146-154.

McClean, S. et al. (1969) J. Pharm. Pharmacol., 21, 441-450.

Ministry of Health and Welfare: Japan (1995) *Toxicity Testing Reports of Environmental Chemicals*, 2, 79-102.

Ministry of Health and Welfare: Japan, unpublished

MITI, Japan (1998): Unpublished data

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)

Mori, Y. et al. (1980) Carcinogenesis, 1, 121-127.

National Technical Information Service, Springfield, VA22161, Formerly U.S. Clearinghouse for Scientific and Technical Information, AD691-490.

Nohmi, T. et al. (1984) Mutat. Res., 136, 159-168.

Petterson, B. et al. (1980) Toxicology, 18, 1-15.

Petterson, B. et al. (1982) Toxicology, 23, 41-55.

Patrianakos, C. and D. Hoffmann, (1979) J. Anal. Toxicol., 3, 150-154.

Reiter, M. and K. Leusser (1952) Arch. exper. Path. u. Pharmakol., 214, 158-164.

Schreiber, E.C. (1974) J. Pharm. Sci., 63, 1177-1190.

Seiler, J.P. (1977) Mutat. Res., 46, 305-310.

Senczuk, W. et al. (1984) Bromat. Chem. Toksykol., 17, 109-111.

Senczuk, W. and H. Rucinska (1984b) Bromat. Chem. Toksykol., 17, 57-62.

Senczuk, W. and H. Rucinska (1984a) Bromat. Chem. Toksykol., 17, 241-243.

Skipper, P.L. et al. (1988) Carcinogenic and Mutagenic responses to Aromatic Amines and Nitroarenes, 65-71.

Stillwell, W.G. et al. (1987) Biomed. Environ. Mass. Spec., 14, 221-227.

Sugimura, T. et al. (1982) Adv. Exp. Med. Biol., 136, 1011-1025.

Thelestam, M. et al. (1980) Toxicology, 15, 203-217.

Thompson, C.Z. et al. (1983) Environ. Mutag., 5, 803-811.

Trenel, J. and Kuehn,R. (1982) Bewertung wassergefaehrdender Stoffe im Hinblick auf Lagerung, Umschlag und Transport und Untersuchung zur Abklaerung substanz- und bewertungsmethodenspezifischer Grenzfaelle bei der Bewertung wassergefaehrdender Stoffe, UFOPLAN des Bundesministers des Innern im Auftrag des Umweltbundesamtes, Juli 1982

Vasilenko, N.M. et al. (1977) Deposited Doc. ISS Viniti, 4035-4077.

Vasilenko, N.M. et al. (1981) Gig. Tr. Prof. Zabol., 25(8), 50.

Vasil'eva, L.N. et al. (1985) Gig. Tr. Prof. Zabol., 16-19.

VINIT* Vsesoyuznyl Institut Nauchnoi i Tekhnicheskoi Informatsii (VINITI)

Weisburger, E.K. et al. (1978) J. Environ. Pathol. Toxicol., 2, 325-356.

Zimmer D, et al. (1980) Mutat. Res., 77, 317-326.

PROPOSED ROBUST SUMMARY for m-toluidine

PHYSICAL/CHEMICAL ELEMENTS

MELTING POINT

TEST SUBSTANCE

- m-Toluidine (CAS No 108-44-1)
- Remarks: Source:

METHOD

- Method/guideline: Unknown
- GLP: Unknown
- Year: Unknown
- Remarks: None

RESULTS

- Melting point value: - 31.2 °C
- Decomposition: No
- Sublimation: No
- Remarks: None

CONCLUSIONS

Melting point is - 31.2 °C.

DATA QUALITY

- Reliabilities: Key study
- Remarks:

REFERENCES (Free Text)

Encyclopedia Chimica, Kyoritu Shuppan, Japan (1963)

OTHER

- Last changed:
- Order number for sorting
- Remarks:

BOILING POINT

TEST SUBSTANCE

- M-Toluidine (CAS No 108-44-1)
- Remarks: Source:

METHOD

- Method: Unknown
- GLP: Unknown
- Year: Unknown
- Remarks: None

RESULTS

- Boiling point value: 203.3 °C
- Pressure:
- Pressure unit:
- Decomposition: No
- Remarks:

CONCLUSIONS

Boiling point is 203.3 °C.

DATA QUALITY

- Reliabilities: Key study
- Remarks:

REFERENCES (Free Text)

Encyclopedia Chimica, Kyoritu Shuppan, Japan (1963)

OTHER

- Last changed:
- Order number for sorting
- Remarks:

VAPOR PRESSURE

TEST SUBSTANCE

- m-Toluidine (CAS: 108-44-1)
- Remarks: source: Tokyo Kasei Kogyo Co., LTD., - Purity: >98%, kept at 5 °C until use. The structure was identified by Infrared red spectroscopy.

METHOD

- Method: OECD TG104 (Gas saturation method)
- GLP: yes
- Year: 1994
- Remarks: Vapour pressure was measured in triplicate at 30, 40 and 50 °C. The vapour pressure at 25 °C was calculated by extrapolating the linear regression equation between the logarithm of vapour pressure and the reciprocal of temperature

RESULTS

- Vapour Pressure value: 14, 19 and 20 Pa at 30 °C, 26, 34 and 25 Pa at 40 °C, 27, 33 and 16 Pa at 50 °C and 17 Pa at 25 °C (extrapolated value).
- Decomposition: no
- Remarks:

CONCLUSIONS

- The vapour pressure at 25 °C is 17 Pa.

DATA QUALITY

- Reliabilities: reliable without restrictions, Key study
- Remarks: Well conducted study, carried out by Chemicals Inspection & Testing Institute, Japan

REFERENCES (Free Text)

MITI, Japan

OTHER

- Last changed
- Order number for sorting
- Remarks:

PARTITION COEFFICIENT

TEST SUBSTANCE
- m-Toluidine (CAS: 108-44-1)
- Remarks: source: Tokyo Kasei Kogyo Co., LTD., - Purity: >98%, kept at 5 °C until use. The structure was identified by Infrared red, mass and nmr spectroscopies.

METHOD
- Method: OECD TG 107 (Flask shake method)
- GLP: yes
- Year: 1992
- Remarks: After partition equilibrium of the test substance was established between n-octanol and water at three volume ratios, the concentrations of the test substance of both phases were determined with HPLC.

RESULTS
- Log P_{ow} 1.53
- Temperature: 25°C
- Remarks:
  Concentration in n-octanol and water phases under three conditions (mg/L):

Condition	Run 1		Run 2	
	Water phase	Octanol phase	Water phase	Octanol phase
1	19.9	791.0	19.3	784.7
2	12.4	403.9	13.2	436.4
3	7.90	230.5	8.12	232.3

CONCLUSIONS
- Log P_{ow} is 1.53.

DATA QUALITY
- Reliabilities: reliable without restrictions, Key study
- Remarks: Well conducted study, carried out by Chemicals Inspection & Testing Institute, Japan

REFERENCES (Free Text)

OTHER
- Last changed
- Order number for sorting
- Remarks:

WATER SOLUBILITY

TEST SUBSTANCE

- m-Toluidine (CAS: 108-44-1)
- Remarks: source: Tokyo Kasei Kogyo Co., LTD., - Purity: >98%, kept at 5 °C until use. The structure was identified by Infrared red spectroscopy.

METHOD

- Method: OECD TG 105 (Flask method)
- GLP: yes
- Year: 1994
- Remarks: 0.8 g of the test substance was added in duplicate to 40 ml of water in glass vessel. The vessel was tightly stopped and then shook at 30 °C for 17 hours and then equilibrated for 24 hours at 25 °C with occasional shaking. After the aqueous phase was filtrated, the concentration of the test substance in the filtrate was determined with HPLC.

RESULTS

- Value: 10 g/L at 25 °C
- Description of solubility: Soluble
- pH value:
- pKa value: 4.66 at 25 °C
- Remarks:

CONCLUSIONS

- Water solubility is 10 g/L

DATA QUALITY

- Reliabilities: reliable with restrictions, Key study
- Remarks: Well conducted study, carried out by Chemicals Inspection & Testing Institute, Japan

REFERENCES (Free Text)

MITI, Japan

OTHER

- Last changed
- Order number for sorting
- Remarks:

STABILITY IN WATER

TEST SUBSTANCE
- m-Toluidine (CAS: 108-44-1)
- Remarks: source: Tokyo Kasei Kogyo Co., LTD., - Purity: >98%, kept at 5 °C until use. The structure was identified by Infrared red spectroscopy.

METHOD
- Method/guideline: OECD TG 111
- Type: Hydrolysis as a function of pH
- GLP: yes
- Year: 1994
- Remarks: The preliminary test was performed at 1000 mg/L and at 50 °C for 5 days in each buffer of pH 4.0, 7.0 and 9.0. The kinetics of the hydrolysis was studied at 1000 mg/L and at 60, 70 and 80 °C in the buffer of pH 4.0, at which the test substance was unstable in the preliminary test. The first-order rate constants of the hydrolysis at three temperatures were calculated by lease squares method. The rate constant of hydrolysis at 25°C was calculated by extrapolating the linear regression equation between the logarithm of the rate constant and reciprocal of temperature. The half-life time of hydrolysis was calculated from the rate constant. All tests were performed in duplicate. The concentration was determined with HPLC.

RESULTS
- Nominal concentration: 1000mg/L
- Measured value:
- Degradation % at pH 4.0, 7.0 and 9.0 at 50°C after 5 days in the preliminary test: 86.6 and 86.7 % at pH 4.0, 98.6 and 99.2 % at pH 7.0, 102.4 and 101.8 % at pH 9.0
- Half-life ($t_{1/2}$) in days at pH 4.0 at 60, 70, 80 and 25 °C: 8.92 at 60 °C, 3.68 at 70 °C, 3.11 at 80 °C and 72.1 at 25 °C (extrapolated value)
- Breakdown products: not studied
- Remarks: The variation in the concentration of the test substance with time at pH 4.0 satisfactorily obeyed the first-order kinetics at all temperature

CONCLUSIONS
- m-Toluidine is stable (half-life time >1 year) at pH 7.0 and 9.0, but it is hydrolysed with the half-life time of 72.1 days at pH 4.0.

DATA QUALITY
- Reliabilities: reliable without restrictions, Key study
- Remarks: Well conducted study, carried out by Chemicals Inspection & Testing Institute, Japan

REFERENCES (Free Text)

OTHER
- Last changed
- Order number for sorting
- Remarks:

TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS (FUGACITY)

TEST SUBSTANCE

- m-Toluidine (CAS: 108-44-1)
- Remarks:.

METHOD

- Test (test type) Calculation
- Method: Fugacity level III
- Year: 1994
- Remarks:

RESULTS

- Media: air, water, soil and sediment
- Estimated Distribution and Media Concentration under three emission scenarios:

Compartment	Release 100% to air	Release 100% to water	Release 100% to soil
Air	18.06%	0.15%	0.56%
Water	30.95%	99.15%	28.01%
Soil	50.91%	0.43%	71.35%
Sediment	0.08%	0.27%	0.08%

- Remarks:

CONCLUSIONS

- Remarks: If m-Toluidine is released mainly to water, it is unlikely to distribute into other compartments. But, if it is released mainly to air, it is likely to be transported both to water and soil.

DATA QUALITY

- Reliabilities: reliable without restrictions, Key study
- Remarks:

REFERENCES (Free Text)

MITI, Japan

OTHER

- Last changed
- Order number for sorting
- Remarks:

BIODEGRADATION

TEST SUBSTANCE
- m-Toluidine (CAS: 108-44-1)
- Remarks: source: Tokyo Kasei Kogyo Co., LTD., - Purity: >98%, kept at 5 °C until use. The structure was identified by Infrared red, mass and nmr spectroscopies.

METHOD
- Method/guideline: OECD TG 301C
- Test Type: aerobic
- GLP: yes
- Year: 1992
- Contact time: 28 days
- Inoculum: activated sludge cultivated for OECD TG 301C
- Remarks: 30 mg of the test substance or aniline (reference substance) and 9mg as MLSS of the activated sludge were added to 300 mL of test medium. The test and reference solutions were cultivated in BOD meter together with the inoculum blank and abiotic control ones at 25°C for 28 days, during which the oxygen consumption was continuously measured. After termination of the test, the total organic carbon concentration (TOC) of the test solution and the residual amount of the test substance were determined with TOC meter and HPLC, respectively. The biodegradability was calculated from the oxygen consumption, TOC and the residual amount.

RESULTS
- Degradation % after 28 days: 0, 1 and 0 % from BOD
  3, 0 and 4 % from TOC
  5, 1 and 3 % from HPLC
- Results: not ready biodegradable
- Kinetic: Biodegradability of reference substance from BOD: 58 % after 7 days, 70 % after 14 days and 70 % after 28 days
- Breakdown products: no
- Remarks:

CONCLUSIONS
- This chemical is not ready biodegradable

DATA QUALITY
- Reliabilities: reliable without restrictions, Key study
- Remarks: Well conducted study, carried out by Chemicals Inspection & Testing Institute, Japan

REFERENCES (Free Text)
MITI, Japan

OTHER
- Last changed
- Order number for sorting
- Remarks:

ECOTOXICITY ELEMENTS

ACUTE TOXICITY TO FISH

TEST SUBSTANCE

• Identity: m-Toluidine
=> Remarks: Source: Wako Pure Chemical Industries - purity > 99 % (Lot. WDQ8839)

METHOD

• **Method/guideline followed (experimental/calculated):** OECD Test Guideline 203 (1981)
• **Type (test type):** semi-static, 96 hours mortality
• **GLP (Y/N):** No
• **Year (study performed):** 1993
• **Species/Strain/Supplier:** *Oryzias latipes* (Medaka), obtained from commercial hatcheries
• **Analytical monitoring:** Not described
• **Exposure period (h):** 96 hours
• **Statistical methods:** Probit method

=> Remarks field for Test Conditions. Detail and discuss any significant protocol deviations, and detail differences from the guideline followed including the following as appropriate:

– Test fish (Age/length/weight, loading, pretreatment): Acclimated for several days before testing; any groups showing > 5 % mortality during 7 days were not used for testing
– Test conditions, e.g.
· Details of test (static, semi-static, flow-through): Semi-static, open-system
· Dilution water source: Distilled water (Purifies tap water)
· Dilution water chemistry (hardness, alkalinity, pH, DOC, TSS, salinity): Not described
· Stock and test solution and how they are prepared:
· Concentrations dosing rate, flow-through rate, in what medium: Concentrations of 10, 18, 32, 56, 100, 180 and 320 mg/L were tested
· Vehicle/solvent and concentrations: Final concentration of 500 mg/L DMSO:HCO-40 (9:1) was used.
· Stability of the test chemical solutions: Not described
· Exposure vessel type (e.g., size, headspace, sealed, aeration, lighting, # per treatment): Not described
· Number of replicates, fish per replicate: 10 fish were used at each concentration.
· Water chemistry in test (O_2, pH) in the control and one concentration where effects were observed: DO and pH were measured daily; pH 7.0 - 7.9, DO = 5.4 - 8.1 mg/L
· Test temperature range: 21 - 23 °C
– Method of calculating mean measured concentrations (i.e. arithmetic mean, geometric mean, etc.): Not described

RESULTS

• **Nominal concentrations (as mg/L):** 10, 18, 32, 56, 100, 180 and 320
• **Measured concentrations (as mg/L):** Not described

• **Unit (results expressed in what unit):** mg/L
• **Element value:** LC_{50} at 96 hours = 34 mg/L based on nominal concentrations
• **Statistical results, as appropriate:** Not described

=> Remarks field for Results. Discuss if the effect concentration is greater than materials solubility. Describe additional information that may be needed to adequately assess data for reliability and use, including the following, if available:

– Biological observations: Not described
– Table showing cumulative mortality:

Test substances Concentration (mg/L)	Cumulative mortality of each exposure (%)			
	24 hours	48 hours	72 hours	96 hours
0	0	0	0	0
10	0	0	0	0
18	0	0	10	20
32	0	0	20	20
56	0	20	40	50
100	0	50	90	100
180	10	80	100	100
320	100	100	100	100

– Lowest test substance concentration causing 100 % mortality: at 56 mg/L (96 hours)
– Mortality of controls: 0% during exposure period
– Abnormal responses: Not described
– Reference substances (if used) – results: LC_{50} (96 hours) = 0.32 mg/L for sodium pentachlorophenol

CONCLUSIONS
=> Remarks field with the ability to identify source of comment, i.e. author and/or submitter

DATA QUALITY
• Reliabilities: Klimisch Code: 2 = Reliable with restrictions

=> Remarks field for Data Reliability

REFERENCES (Free Text)
Environment Agency Japan (1994): Investigation on the Ecotoxicological effects of OECD High Volume Chemicals (Phase 3): p. 167 - 208.

OTHER
• Last changed (administrative field for updating)
• Order number for sorting (administrative field)
=> Remarks field for General Remarks (Use for any other comments necessary for clarification.)

ACUTE TOXICITY TO AQUATIC INVERTEBRATES (E.G., DAPHNIA)

TEST SUBSTANCE

• Identity: m-Toluidine

=> Remarks: Not described

METHOD

• **Method/guideline:** The concept NEN reports 6501 or 6502 (Dutch Standard Organization (1980) and Canton et al. (1975))
• **Test type:** Static, 48 hours mortality test
• **GLP (Y/N):** Not described
• **Year (study performed):** Not described
• **Analytical procedures:** Only the lowest and highest tested concentrations were measured by gas chromatography method.
• **Species/Strain:** *Daphnia magna*
• **Test details:** Not described
• **Statistical methods:** Not described

=>Remarks field for Test Conditions. Detail and discuss any significant protocol deviations and detail differences from the guideline followed including the following as appropriate:

– Test organisms:
· source, supplier, any pretreatment, breeding method: Not described
· Age at study initiation: < 1 day
· Control group: Not described

– Test conditions
· Stock solutions preparation and stability:
· Test temperature range: 18 - 20
· Exposure vessel type: The test volume was 1 liter
· Dilution water source: Dutch Standard Water (DSW)
· Dilution water chemistry: Not described
· Lighting: Not described
· Water chemistry in test: Hardness = ca 1 mmol/L

– Element (unit) basis: 50 % mortality
–Test design: Number of replicates = 2; individuals per replicate = 25 (mortality); the common factor: 3.2
– Method of calculating mean measured concentrations: Described “be averaged” only
– Exposure period: 48 hours
– Analytical monitoring:

RESULTS

• **Nominal concentrations:** Although the common factor was 3.2, nominal concentration was not described
• **Measured concentrations:** Not described
• **Unit [results expressed in what unit]:** mg/L
• LC_{50} (48 hours, mortality) 0.73; calculated based on the corrected values by measure concentrations.
• **Statistical results, as appropriate:** Not described

=> Remarks field for Results.

– Biological observations
· Number mortality as compared to the number exposed: Not described
· Concentration response with 95 % confidence limits: Not described
· Cumulative mortality: Not described
· Was control response satisfactory: Unknown

CONCLUSIONS

=> Remarks field with the ability to identify source of comment, i.e. author and/or submitter
The tests were conducted to produce for the joint effects on mortality and on reproduction against *Daphnia magna* on 14 toxicants and these mixtures. Experimental design and testing methods were not described well, but LC50 was calculated using corrected values. (comments by submitter).

DATA QUALITY

• **Reliabilities:** Klimisch Code: 2 = Reliable with restrictions

=> Remarks field for Data Reliability

REFERENCES (Free Text)

J. Hermens, H. Canton, N. Steyger and R. wegman (1984): Joint effects of a mixture of 14 chemicals on mortality and inhibition of reproduction of *Daphnia magna*, Aquatic Toxicology, (5): 315 - 322.

OTHER

• Last changed (administrative field for updating)
• Order number for sorting (administrative field)

⇨ Remarks field for General Remarks (Use for any other comments necessary for clarification.)

TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

TEST SUBSTANCE

• Identity: m-Toluidine

=> Remarks: Source: Wako Pure Chemical Industries - purity > 99 % (Lot. WDQ8839)

METHOD

• **Method/guideline followed (experimental/calculated):** OECD Test Guideline 201 (1984)

• **Test type (static/other):** Static, closed-system

• **GLP (Y/N):** No

• **Year (study performed):** Not described (1992 - 1993)

• **Species/strain # and source:** *Selenastrum capricornutum*, ATCC22662

• **Element basis:** The area under growth curve

• **Exposure period:** 72 hours

• **Analytical monitoring:** No

• **Statistical methods:** Probit method

=> Remarks field for Test Conditions. Detail and discuss any significant protocol deviations and detail differences from the guideline followed including the following as appropriate:

– Test organisms
  · Laboratory culture
  · Method of cultivation
  · Controls
– Test Conditions
  · Test temperature range: 23 - 25 °C
  · Growth/test medium: OECD medium
  · Shaking: Occasional shaking
  · Dilution water source: Not described
  · Exposure vessel type: 100 mL-medium in a 300 mL-Erlenmeyer flask with a silicon cap which allow ventilation
  · Water chemistry in test (pH) in at least one replicate of each concentration (at start and end of the test): Not described
  · Stock solutions preparation: DMSO was used as a solvent (Final concentration: 61.2 - 648 mg/L)
  · Light levels and quality during exposure: 4000 - 7000 lux, continuous
–Test design:
  · Number of replicates: 3 parallel runs for each nominal concentration
  · Concentrations: 6.8, 12.4, 22.2, 40 and 72 mg/L
  · Initial cell number in cells/ml: 1.0×10^4
– Method of calculating mean measured concentrations (i.e. arithmetic mean, geometric mean, etc.): Not described

RESULTS

• **Nominal concentrations in mg/L:** 6.8, 12.4, 22.2, 40 and 72

• **Measured concentrations in mg/L:** Not described
• **Unit [results expressed in what unit]:** mg/L
• EbC_{50} = 17.7 mg/L (72 hours)
• NOEC < 6.8 mg/L
• **Was control response satisfactory:** Yes (Cell density increased 82 times after 72 hours compared to the density at the start of test.)
• **Statistical results, as appropriate:** Not described

=> Remarks field for Results. Discuss if effect concentration is not less than materials solubility. Describe additional information that may be needed to adequately assess data for reliability and use including the following:
– Biological observations
· Cell density at each flask at each measuring point: Not described
· Cell concentration at each flask on each measuring point:

Test substance concentration (mg/L)	Cell concentration of each exposure (10^4 cells/mL)			
	0 hour	24 hours	48 hours	96 hours
0	1.2	3.8	34.0	98.4
6.8	1.2	3.7	22.8	69.2
12.4	1.2	5.0	19.3	59.7
22.2	1.2	3.3	14.5	58.5
40	1.2	3.0	12.8	31.0
72	1.2	3.0	4.5	4.0

· Growth curves: Logarithmic growth until end of the test

CONCLUSIONS
=> Remarks field with the ability to identify source of comment, i.e. author and/or submitter

DATA QUALITY
• Reliabilities: Klimisch Code: 2 = Reliable with restrictions

=> Remarks field for Data Reliability

REFERENCES (Free Text)
Environment Agency Japan (1994): Investigation on the Ecotoxicological effects of OECD High Volume Chemicals (Phase 3): p. 1 - 64.

OTHER
• Last changed (administrative field for updating)
• Order number for sorting (administrative field)

=> Remarks field for General Remarks (Use for any other comments necessary for clarification.)

CHRONIC TOXICITY TO AQUATIC INVERTEBRATES (E.G., DAPHNIA)

TEST SUBSTANCE

• Identity: m-Toluidine

=> Remarks: Source: Wako Pure Chemical Industries - purity > 99 % (Lot. WDQ8839)

METHOD

• **Method/guideline:** OECD Test Guideline 202 (1984)

• **Test type:** 21 days reproduction test

• **GLP (Y/N):** No

• **Year (study performed):** 1992 - 1993

• **Analytical procedures:** Not described

• **Species/Strain:** *Daphnia magna*

• **Test details:** Semi-static (water renewal: 48 hours), open-system

• **Statistical methods:** Probit method

=> Remarks field for Test Conditions. Detail and discuss any significant protocol deviations and detail differences from the guideline followed including the following as appropriate:

– Test organisms:

· source, supplier, any pretreatment, breeding method: supplied from National Institute for Environmental Science

· Age at study initiation: < 24 hours old

· Control group: 0.010, 0.032, 0.10, 0.32 and 1.0 mg/L

– Test conditions

· Stock solutions preparation and stability: Stock solution was prepared with DMSO: HCO-40 = 9:1 (Final concentration: 200 mg/L).

· Test temperature range: 21 - 23 °C

· Exposure vessel type: 400 mL-test solution in a 500 mL-glass beaker; 4 beakers per treatment

· Dilution water source: Reconstituted water

· Dilution water chemistry: hardness = 64 mg/L; pH 7.8; Ca/Mg ratio = 8.2; Na/K ratio = 6.4; alkalinity = 26.5 mg/L

· Lighting: 16:8 hours; light-darkness cycle

· Water chemistry in test: DO and pH were measured when the test solution was exchanged. The results of the measurement were not described.

· Feeding: Green algae, Daily

– Element (unit) basis: Reproduction

–Test design: 40 Daphnia (4 replicates: 10 organisms per replicate) were exposed to 5 nominal concentrations (0.010, 0.032, 0.10, 0.32 and 1.0 mg/L).

– Method of calculating mean measured concentrations (i.e. arithmetic mean, geometric mean, etc.): Not described

– Exposure period: 21 days

– Analytical monitoring: Not described

RESULTS

• **Nominal concentrations:** 0.010, 0.032, 0.10, 0.32 and 1.0 mg/L

• **Measured concentrations:** Not described

• **Unit [results expressed in what unit]:** mg/L

• **Reproduction** EC_{50} (14 days, reproduction) = 0.029 mg/L

EC_{50} (21 days, reproduction) = 0.026 mg/L

EC_{50} for parental *Daphnia* (7 days) = 0.11 mg/L

EC_{50} for parental *Daphnia* (14 days) = 0.11 mg/L

EC_{50} for parental *Daphnia* (21 days) = 0.08 mg/L

LOEC (21 days reproduction) = 0.032 mg/L

NOEC (21 days, reproduction) = 0.010 mg/L

• **Statistical results, as appropriate:** Not described

=> Remarks field for Results. Discuss if element effect concentration is not less than materials solubility. Describe additional information that may be needed to adequately assess data for reliability and use including the following as appropriate:

– Biological observations

• Time of the first production of young (d): 8 - 15 days

• Mean cumulative numbers of young produced per adult:

Chemical Concentration (mg/L)	Mean cumulative numbers of young produced per adult	
	14 days	21 days
0	12.4	31.9
0.010	13.4	28.3
0.032	5.9	15.8
0.10	0.08	0.0
0.32	0	0

• Was control response satisfactory: Yes

CONCLUSIONS

=> Remarks field with the ability to identify source of comment, i.e. author and/or submitter

DATA QUALITY

• **Reliabilities:** Klimisch Code: 2 = Reliable with restrictions

=> Remarks field for Data Reliability

REFERENCES (Free Text)

Environment Agency Japan (1994): Investigation on the Ecotoxicological effects of OECD High Volume Chemicals (Phase 3): p. 65 - 164.

OTHER

• Last changed (administrative field for updating)

• Order number for sorting (administrative field)

=> Remarks field for General Remarks (Use for any other comments necessary for clarification.)

HEALTH ELEMENTS

REPEATED DOSE TOXICITY

TEST SUBSTANCE

- m-Toluidine (CAS No. 108-44-1)

Remarks: Source: Nippon Kayaku Co., ltd., Lot No. 102011, Purity: 99.0%, Kept cool and dark until use

METHOD

- **Method/guideline:** OECD TG 422
- **Test type:** OECD Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test
- **GLP:** Yes
- **Year:** 1992
- **Species:** Rat
- **Strain:** Crj;CD (SD)
- **Route of administration:** oral (by gavage)
- **Doses/concentration levels:** 0, 30, 100, 300 mg/kg/day (in corn oil)
- **Sex:** Male & Female
- **Exposure period:** Males; for 42 days
  Females; from 14 days before mating to day 3 of lactation
- **Frequency of treatment:** Once daily
- **Control group and treatment:** Concurrent vehicle
- **Post exposure observation period:** 1 day
- **Duration of test:** Male; for 43 days
  Female; for 41-53 days
- **Statistical methods:** Dunnett's or Scheffe's test for continuous data and Chi square test for quantal data

Remarks Field For Test Conditions

- **Test Subjects:**

- ***Age at study initiation*:** 7 weeks old for males and females
- ***Weight at study initiation*:** 267.2-361.7 g for males, 200.1-247.2 g for females
- ***No. of animals per sex per dose*:** 13 per sex per dose group

- **Study Design:**

  - ***Vehicle*:** Corn oil
  - ***Satellite groups and reasons they were added*:** none
  - ***Clinical observations performed and frequency*:**
    General condition was observed once a day, body wt. and food/water consumption were determined once a week.
    Hematology, biochemistry and urinalysis for males only at time of necropsy after 42 days of chemical exposure.
  - ***Organs examined at necropsy:***
    organ weight: thymus, liver, kidney, testes, epididymis
    microscopic: for all the animals in control and 300 mg/kg: thymus, liver, kidney, testes, epididymis, brain, heart, spleen, adrenal and any organs which have gross pathological changes at necropsy. For the animals in 30 and 100 mg/kg: any organs, which are shown to have histopathological changes at the higher dose.

RESULTS

- **NOAEL**

  Male: less than 30 mg/kg/day, Female: less than 30 mg/kg/day

- **LOAEL**

  Male: 30 mg/kg/day (suspected hemolytic anemia with methemoglobinemia)
  Female: 30 mg/kg/day (suspected hemolytic anemia with methemoglobinemia)

Remarks Field For Results.

- ***Body weight:*** The mean body weight gains during week 1 of the 300 mg/kg males and of the 100 and 300 mg/kg females were significantly lower than those of the controls.
- ***Food/water consumption:*** The mean food consumption of the 300 mg/kg males and females was significantly reduced at week 1.
- ***Clinical signs*** *(description, severity, time of onset and duration)**:***
  Males/Females: Compound-related clinical signs included brownish urine and increased salivation in males and females receiving 100 mg/kg or more. Low locomotor activity and pale extremities were other notable findings in male and female rats given 300 mg/kg.
- ***Haematology*:**
  Males: Values for erythrocyte counts, hemoglobin concentration and hematocrit decreased, and the mean corpuscular volume increased in the 100 and 300 mg/kg. Significant increases in the mean corpuscular hemoglobin and decreases in the mean corpuscular hemoglobin concentration and platelet counts were also noted in males given the 300 mg/kg dose.

Dose level (mg/kg/day)	0	30	100	300
No. of animals	13	13	13	13
Count (10^4/mm^3, Mean ± SD)				
erythrocyte (10^4/mm^3, Mean ± SD)	768 ± 76	772 ± 31	626 ± 37**	391 ± 30**
platelet (10^4/mm^3, Mean ± SD)	104.1 ± 8.3	108.7 ± 9.4	108.5 ± 7.3	91.7± 8.7**
Hemoglobin (g/dl, ± SD)	14.5 ± 1.1	13.7 ± 0.4	13.3 ±0.4**	11.3 ± 0.8**
Hematocrit (%, Mean ± SD)	40.1 ± 4.8	39.9 ± 1.3	38.3 ± 1.2*	35.8 ± 1.6**
MCV(μ^3, Mean ± SD)	52.1 ± 2.0	51.7 ± 1.6	61.3 ± 2.5**	91.9 ± 4.2**
MCH (pg, Mean ± SD)	19.0 ± 1.2	17.8 ± 0.5	21.2 ± 0.8	28.8 ± 1.0**
MCHC (%, Mean ± SD)	36.5 ± 3.3	34.5 ± 0.5	34.6 ± 0.7	31.4 ± 1.2**

* $p < 0.05$, ** $p < 0.01$

- ***Biochem:***

  Males: The A/G ratio, and serum bilirubin, potassium and chloride levels in the 100 and 300 mg/kg significantly increased with dose. Other differences in the 300 mg/kg males included significant decreases in serum glucose and total cholesterol levels, and increases in albumin, phosphorus and GOT levels.

Dose level (mg/kg/day)	0	30	100	300
No. of animals	13	13	13	13
A/G ratio (-, Mean ± SD)	1.03 ±0.13	1.03 ±0.08	1.20 ±0.15**	1.56 ±0.12**
GOT (IU/l, Mean ± SD)	59 ± 22	53 ±9	64 ± 16	75 ± 5**
Total bilirubin (mg/dl, Mean ± SD)	0.07 ± 0.02	0.08 ± 0.02	0.14 ± 0.04**	0.35 ± 0.05**
Na (mEq/l, Mean ± SD)	140.7 ± 2.0	141.4 ± 1.3	143.2 ± 1.1**	143.4 ± 0.8**
Cl (mEq/l, Mean ± SD)	104.3 ± 1.5	105.1 ± 1.4	105.7 ± 1.5*	106.6 ± 1.2**
Total cholesterol (mg/dl, Mean ± SD)	59 ±15	52 ± 5	50 ± 6	44 ± 7
Glucose (mg/dl, Mean ± SD)	189 ± 21	178 ± 15	183 ± 17	152 ± 12**
Phosphorus (mg/dl, Mean ± SD)	5.1 ±0.4	4.9 ±0.4	4.8 ± 0.5	5.6 ± 0.5**
Albumin (g/dl, Mean ± SD)	2.9 ± 0.4	2.9 ± 0.2	3.1 ± 0.3	3.4 ± 0.1**

* $p < 0.05$, ** $p < 0.01$

- ***Ophthalmologic findings:*** not examined
- ***Mortality and time to death:*** No deaths occurred during the study.
- ***Gross pathology incidence and severity:*** Dark colored liver and kidneys are observed in many of the animals in groups given 100 mg/kg and over. Dark colored and swelling spleen were noted in these groups and some in 300 mg/kg group were associated with unclear follicle.
- ***Organ weight changes:***

  Male: increase in kidney weight at 300 mg/kg (relative) ($p<0.05$)

	Males	
Dose level (mg/kg/day)	**0**	**300**
Body weight (g, Mean ± SD)	511.2 ± 60.4	467.6 ± 42.2
Absolute weight		
Kidney (g, Mean ± SD)	3.05 ± 0.22	3.09 ± 0.30
Relative weight		
Kidney (g%, Mean ± SD)	0.60 ± 0.06	0.66 ± 0.07*

* $p < 0.05$

Histopathology *(incidence and severity)**:***

<u>Male</u>:

Liver: Increased deposit of pigment, extramedullary hematopoiesis and swelling of hepatocytes in centrilobular zone at 100 mg/kg and 300 mg/kg

Dose level (mg/kg/day)	degree*	0	30	100	300
No. of animals		13	13	13	13
deposit of pigment	-	13	13	0	0
in Kupffer cell	±	0	0	9	0
	+	0	0	4	13
extramedullary	-	13	13	0	0
hematopoiesis	±	0	0	9	0
	+	0	0	4	13
swelling of hepatocyte	-	13	13	4	1
in centrilobular zone	±	0	0	9	12

*degree: - negative, ± very slight, + slight, ++ moderate, +++ marked

Spleen: Increased deposit of pigment and extramedullary hematopoiesis at 30 mg/kg or more Increased congestion at 100 mg/kg and 300 mg/kg

Dose level (mg/kg/day)	degree*	0	30	100	300
No. of animals		13	13	13	13
deposit of pigment	-	0	0	0	0
	±	10	0	0	0
	+	3	13	13	0
	++	0	0	0	13
extaramedullary hematopoiesis	-	4	0	0	0
	±	7	4	0	0
	+	2	9	13	0
	++	0	0	0	13
congestion	-	13	12	0	0
	±	0	1	0	0
	+	0	0	3	6
	++	0	0	10	7

*degree: - negative, ± very slight, + slight, ++ moderate, +++ marked

Kidney: Increased deposit of pigment at 300 mg/kg and eosinophilic droplets in the renal tubular epithelium at 100 mg/kg and 300 mg/kg

Dose level (mg/kg/day)	degree*	0	30	100	300
No. of animals		13	13	13	13
deposit of pigment	-	13	13	13	0
in tubular epithelium	+	0	0	0	2
	++	0	0	0	11
eosinophlic droplet	-	7	4	2	0
of tubular epithelium	±	5	9	4	0
	+	1	0	7	1
	++	0	0	0	12

*degree: - negative, ± very slight, + slight, ++ moderate, +++ marked

Urinary bladder: Increased focal hyperplasia of epithelium at 300 mg/kg

Dose level (mg/kg/day)	degree*	0	30	100	300
No. of animals		13	13	13	13
focal hyperplasia of epithelium	-	13	13	13	11
	±	0	0	0	2
infiltration of lymphocyte	-	12	12	13	9
	±	1	1	0	4

*degree: - negative, ± very slight, + slight, ++ moderate, +++ marked

Female:

Liver: Increased deposit of pigment and extramedullary hematopoiesis at 100 mg/kg or more and swelling of hepatocytes in centrilobular zone at 300 mg/kg

Dose level (mg/kg/day)	degree*	0	30	100	300
No. of animals		13	12	13	13
deposit of pigment	-	13	12	0	0
in Kupffer cell	±	0	0	5	0
	+	0	0	8	9
	++	0	0	0	4
extramedullary	-	13	11	0	0
hematopoiesis	±	0	1	5	0
	+	0	0	8	9
	++	0	0	0	4
swelling of hepatocyte	-	13	12	13	0
in centrilobular zone	±	0	0	0	13

*degree: - negative,± very slight,+ slight, ++ moderate, +++ marked

Spleen: Increased deposit of pigment and extramedullary hematopoiesis at 30 mg/kg or more Increased congestion at 100 mg/kg and 300 mg/kg

Dose level (mg/kg/day)	degree*	0	30	100	300
No. of animals		13	12	13	13
deposit of pigment	-	0	0	0	0
	±	3	0	0	0
	+	10	10	10	1
	++	0	2	3	12
extaramedullary hematopoiesis	-	2	0	0	0

	±	1	0	0	0
	+	10	5	2	0
	++	0	7	11	8
	+++	0	0	0	5
congestion	-	12	11	0	0
	±	1	1	0	1
	+	0	0	8	7
	++	0	0	5	5

*degree: - negative,± very slight,+ slight, ++ moderate, +++ marked

Kidney: Increased deposit of pigment at 300 mg/kg and regenerated tubule in medulla- at 100 mg/kg or more

Dose level (mg/kg/day)	**degree***	**0**	**30**	**100**	**300**
No. of animals		13	12	13	13
deposit of pigment	-	13	12	13	0
in tubular epithelium	±	0	0	0	0
	+	0	0	0	0
	++	0	0	0	13
regenerated tubule	-	13	11	11	2
in medulla	±	0	1	0	4
	+	0	0	2	6
	++	0	0	0	1

*degree: - negative,± very slight,+ slight, ++ moderate, +++ marked

CONCLUSIONS

The critical effect of m-toluidine is a hemolytic anemia, supported by reduction of erythrocyte counts and hemoglobin concentration, and histological changes such as pigment deposit and extramedullary hematopoiesis in liver and spleen. Other major change is renal tubular epithelium lesions accompanied with pigment deposit. As there is suggestive evidence of hemolytic anemia at the lowest dose of 30 mg/kg, probably caused by methemoglobin formation, NOAEL is not established.

DATA QUALITY

- **Reliabilities:** Valid without restriction

Remarks field for Data Reliability

Well conducted study, carried out by the Hatano Research Institute, Food and Drug Safety Center (Japan).

REFERENCES (Free Text)

Ministry of Health and Welfare: Japan (1995), Toxicity Testing Reports of Environmental Chemicals 2, 79-102

GENERAL REMARKS

.

TOXICITY TO REPRODUCTION/DEVELOPMENT

TEST SUBSTANCE

- m-Toluidine (CAS No. 108-44-1)

Remarks: Source: Nippon Kayaku Co., ltd., Lot No. 102011, Purity: 99.0 %, Kept cool and dark until use

METHOD

- **Method/guideline:** OECD TG 422
- **Test type:** OECD Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test
- **GLP:** Yes
- **Year:** 1992
- **Species:** Rat
- **Strain:** Crj;CD (SD)
- **Route of administration:** oral (by gavage)
- **Doses/concentration levels:** 0, 30, 100, 300 mg/kg/day (in corn oil)
- **Sex:** Male & Female
- **Exposure period:** Male; for 42 days
  Female; from 2 weeks prior to mating to day 3 postpartum throughout mating and pregnancy
- **Frequency of treatment:** Once daily
- **Control group and treatment:** Concurrent vehicle
- **Post exposure observation period:** 1 day
- **Duration of test:** Male: for 43 days
  Female: for 41-53 days
- **Statistical methods:** Dunnett's or Scheffe's test for continuous data and Chi square test for quantal data

Remarks Field For Test Conditions

- **Test Subjects:**
  - ***Age at study initiation*:** 7 weeks old for males and females
  - ***Weight at study initiation*:** 267.2-361.7 g for males, 200.1-247.2 g for females
  - ***No. of animals per sex per dose*:** 13 per sex per dose group

- **Study Design:**
  The animals were sacrificed on the day 4 of lactation for females. Females with no delivery were killed on the day 25 of pregnancy.
  - ***Vehicle*:** Corn oil
  - ***Satellite groups and reasons they were added*:** none
  - ***Mating procedures*:** Male/female per cage; 1/1, length of cohabitation; at the most 4 days, until proof of pregnancy (formation of vaginal closing or sperm detection in vagina)
  - ***Clinical observations performed and frequency*:**
    Parent: General appearance once a day
    Foetus: General appearance once a day after birth
    Hematology, biochemistry and urinalysis for males only at time of necropsy after 42

days of chemical exposure

- ***Organs examined at necropsy*:**
  Parent: organ weight: liver, kidney, thymus, testes, epididymis
  microscopic: all animals in control, 300 mg/kg group and unfertilised animals in other groups: brain, thymus, heart, liver, kidney, adrenal, spleen, urinary bladder, testes, epididymis, ovary
  Foetal: full macroscopic examinations on all of pups
- ***Parameters assessed during study*:**
  Body wt. (once a week), food/water consumption (once a week), No. of pairs with successful copulation, copulation index (No. of pairs with successful copulation/No. of pairs mated x 100), pairing days until copulation, No. of pregnant females, fertility index = (No. of pregnant animals/No. of pairs with successful copulation x 100), No. of corpora lutea, No. of implantation sites, implantation index (No. of implantation sites/No. of corpora lutea x 100), No. of living pregnant females, No. of pregnant females with parturition, gestation length, No. of pregnant females with live pups on day 0, gestation index (No. of females with live pups/No. of living pregnant females x 100), No. of pregnant females with live pups on day 4, delivery index (No. of pups born/No. of implantation sites x 100), No. of pups alive on day 0 of lactation, live birth index (No. of live pups on day 0/No. of pups born x 100), sex ratio (Total No. of male pups/Total No. of femle pups), No. of pups alive on day 4 of lactation, viability index (No. of live pups on day 4/No. of live pups on day 0 x 100), body wt. of live pups (on day 0 and 4)

RESULTS

- **NOAEL and LOAEL for reproductive toxicity**
  NOAEL: 30 mg/kg/day
  LOAEL: 100 mg/kg/day

- **NOAEL and LOAEL for developmental toxicity**
  NOAEL: 100 mg/kg/day
  LOAEL: greater than 100 mg/kg/day

- **Actual dose received by dose level by sex if available:**
  0, 30, 100, 300 mg/kg/day for both sexes

- **Reproductive/developmental data**
  Two of ten pregnant females receiving 100 mg/kg and all the eleven receiving 300 mg/kg showed total implantation losses in utero. Two of eleven pregnant females receiving 30 mg/kg and three of ten receiving 100 mg/kg showed that all pups or more than half number of pups died due to the lack of the nursing activity of dams. No significant differences in the pup viability, pup weights and incidence of morphological abnormalities of pups were apparent in the groups given 100 mg/kg or less when compared to the controls.

Dose level (mg/kg/day)	**0**	**30**	**100**	**300**
No. of pairs mated	13	13	13	13
No. of pregnant females	11	11	10	11
No. of pregnant females with pups alive	11	11	8	0
Gestation index	100.0	100.0	80.0	0.0**
Gestation length in days (Mean ± SD)	22.8 ± 0.4(11)	22.6 ±0.5(11)	22.4 ± 0.5(8)	a)
Number of corpora lutea (Mean ± SD)	14.7 ±4.5(11)	78.1 ±22.2(11)	76.6 ± 27.3(10)	75.7 ± 20.9(11)
No. of implantation sites (Mean ± SD)	14.7 ± 4.5(11)	14.6 ± 4.2(11)	14.3 ± 5.5(10)	14.3 ± 3.4(11)
Implantation index	72.7 ±26.7(11)	78.1 ± 22.2(11)	76.6 ± 27.3(10)	75.7 ± 20.9(11)
Day 0 of lactation				
No. of pups born (Mean ± SD)	12.6 ± 3.6(11)	13.2 ±4.2(11)	10.8 ± 7.2(10)	0.0 ± 0.0**(11)

Delivery index		87.6 ±10.4(11)	89.3 ± 8.0(11)	68.1 ± 41.1(10)	0.0 ± 0.0**(11)
Number of pups alive (Mean ± SD)		11.4 ±3.4(11)	11.1 ± 3.6(11)	9.0 ± 6.3(8)	
Birth index		80.8 ±19.0(11)	77.1 ± 16.1(11)	58.1 ± 35.1(8)	
Live birth index		91.4 ±15.1(11)	86.9 ± 18.0(11)	70.7 ±36.2(7)	
Sex ratio (Mean ± SD)		57.2 ± 14.7(11)	53.1 ±17.4(11)	48.6 ± 14.3(7)	
Day 4 of lactation					
Number of pups alive (Mean ± SD)		11.2 ± 3.3(11)	9.4 ±4.9(11)	8.3 ± 6.3(7)	
Viability index		98.6 ±3.1(11)	82.6 ± 32.6(11)	75.3 ± 38.7(7)	
Body weight of live pups (grams) (Mean ± SD)					
on day 0	Males	7.1 ± 0.8	6.6 ± 1.2	6.0 ± 0.5	
	Females	6.4 ± 0.5	6.1 ± 1.0	5.5 ± 0.6	
on day 4	Males	11.2± 2.6	10.4 ± 3.3	8.9 ±1.5	
	Females	10.5 ± 2.2	10.0 ± 3.0	8.5 ± 1.6	

Parenthesis indicates the number of litters evaluated.
** : Significant difference from control, $p < 0.01$
a) All litters showed total implantation loss

Remarks Field For Results.

- ***Mortality and day of death*:** No deaths occurred during the study.
- ***Body weight**:* The mean body weight gains during week 1 of the 300 mg/kg males and of the 100 and 300 mg/kg females were significantly lower than those of the controls.
- ***Food/water consumption:*** The mean food consumption of the 300 mg/kg males and females was significantly reduced at week 1.
- ***Grossly visible abnormalities, external, soft tissue and skeletal abnormalities*:** no statistically significant effects

CONCLUSIONS

m-Toluidine induced implantation losses in rats at 100 and 300 mg/kg by gavage. Any developmental toxicity including teratogenicity was not observed. The NOAEL for reproductive and developmental toxicity is considered to be 30 mg/kg/day and 100 mg/kg/day, respectively.

DATA QUALITY

- **Reliabilities:** Valid without restriction

Remarks field for Data Reliability
Well conducted study, carried out by the Hatano Research Institute, Food and Drug Safety Center (Japan).

REFERENCES (Free Text)

Ministry of Health and Welfare: Japan, (1995) Toxicity Testing Reports of Environmental Chemicals 2, 79-102

GENERAL REMARKS

This study was conducted to examine both repeated dose toxicity and reproductive/developmental toxicity as an OECD screening combined study. Therefore, estrous cycle length and pattern, anogenital distances and sperm examination were not performed because the test was conducted by the TG adopted in 1990.

GENETIC TOXICITY IN VITRO (BACTERIAL TEST)

TEST SUBSTANCE

- m-Toluidine (CAS No. 108-44-1)

Remarks: Aldrich or Eastman, Purity: Not specified

METHOD

- **Method/guideline**: Other [Gradient plate test (McMahon, et al., 1979, Cancer Reserch, 39, 682-693)]
- **Test type**: Reverse mutation assay
- **GLP***:* Unknown
- **Year**: 1983
- **Species/Strain:** *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538 G46, C3076, D3052, *Escherichia coli* WP2, WP2 uvrA
- **Metabolic activation:** With and without Aroclor1254 induced-rat liver S-9
- **Statistical methods**: No statistic analysis

Remarks Field For Test Conditions

- **Study Design:**
  - ***Concentration*:** Up to 1,000 μg/plate
  - ***Number of replicates*:** 1
  - ***Plates/test*:** 4
  - ***Procedure*:** No data
  - ***Solvent*:** Agar
  - ***Positive controls*:** Streptozotocin, 2-acetylaminofluorene

RESULTS

- **Cytotoxic concentration:**

  Not reported.

- **Genotoxic effects:**

	+	?	-
With metabolic activation:	**[ ]**	**[ ]**	**[X]**
Without metabolic activation:	**[ ]**	**[ ]**	**[X]**

Remarks Field For Results.

CONCLUSIONS

Bacterial gene mutation is negative with and without metabolic activation.

DATA QUALITY

- **Reliabilities:** Valid with restriction because of no information on GLP

Remarks field for Data Reliability

Well conducted study, carried out by The Lilly Research Laboratories

REFERENCES (Free Text)

Christina Z. Thompson, Leo E. Hill, Janet K. Epp and Gregory S. Probst (1983) The Induction of Bacterial Mutation and Hepatocyte Unscheduled DNA Synthesis by Monosubstituted Anilines, Environmental Mutagenesis **5**, 803-811

GENERAL REMARKS

GENETIC TOXICITY IN VITRO (NON-BACTERIAL IN VITRO TEST)

TEST SUBSTANCE

- m-Toluidine (CAS No. 108-44-1)

Remarks: Source: Nippon Kayaku Co., ltd., Lot No. 102011, Purity: 99.0 %, Kept cool and dark until use

METHOD

- **Method/guideline**: Guidelines for Screening Mutagenicity Testing of Chemicals (Japan)
- **Test type**: Chromosomal aberration test
- **GLP***:* Yes
- **Year**: 1992
- **Species/Strain:** CHL/IU cell
- **Metabolic activation:** With and without S9 from rat liver, induced with phenobarbital and 5,6-benzoflavone
- **Statistical methods**: Fisher's exact analysis

Remarks Field For Test Conditions

- **Study Design:**

  For continuous treatment, cells were treated for 24 or 48 hrs without S9. For short-term treatment, cells were treated for 6 hrs with and without S9 and cultivated with fresh media for 18 hrs.

  · ***Concentration*****:** -S9 (continuous treatment): 0, 0.13, 0.26, 0.52 mg/ml
  -S9 (short-term treatment): 0, 0.3, 0.6, 1.1 mg/ml
  +S9 (short-term treatment): 0, 0.3, 0.6, 1.1 mg/ml
  · ***Plates/test*****:** 2
  · ***Solvent*****:** DMSO
  · ***Positive controls*****:** - S9, Mitomycin C
  + S9, Cyclophosphamide

RESULTS

- **Cytotoxic concentration:**

  Toxicity was not observed up to 1.1 mg/ml in continuous and short-term treatment with or without S9 mix.

- **Genotoxic effects:**

	clastogenicity			polyploidy		
	+	?	-	+	?	-
– With metabolic activation:	**[ ]**	**[ ]**	**[X]**	**[ ]**	**[ ]**	**[X]**
– Without metabolic activation:	**[ ]**	**[ ]**	**[X]**	**[ ]**	**[ ]**	**[X]**

Remarks Field For Results.

Structural chromosomal aberrations and polyploidy were not induced up to the highest concentration of 0.52 mg/ml on continuous treatment, and 1.1 mg/ml on short-term treatment with and without an exogenous metabolic activation system. Polyploidy was significantly increased as 1.25 % on continuous treatment and 0.88 % on short-term treatment with and without an exogenous metabolic activation system. However as these values remain within historical control as well as a criteria of significance (5 %), the result was concluded as negative.

POLYPLOID (%)

	Short term (exposure 6hr)			Continuous (exposure 48hr)	
	Conc. (mg/ml)	+S9	-S9	Conc. (mg/ml)	-S9
Control	0	0.13	0.38	0	0.38
Solvent	0	0.13	0.13	0	0.25
m-toluidine	0.3	0	0.13	0.13	0.13
m-toluidine	0.6	0.13	0.13	0.26	0.38
m-toluidine	1.1	0.88*	0.88*	0.52	1.25*

* Significantly different from solvent control at $p < 0.05$

CONCLUSIONS

Chromosomal aberration in CHL/IU cells is negative with and without metabolic activation.

DATA QUALITY

- **Reliabilities:** Valid without restriction

Remarks field for Data Reliability

Well conducted study, carried out by the Hatano Research Institute, Food and drug Safety Center (Japan).

REFERENCES (Free Text)

Ministry of Health and Welfare: Japan, (1995) Toxicity Testing Reports of Environmental Chemicals **5**, 475-498

GENERAL REMARKS