FOREWORD **INTRODUCTION**

TRIS(2-ETHYLHEXYL)BENZENE-1,2,4-TRICARBOXYLATE

CAS N°: 3319-31-1

SIDS Initial Assessment Report

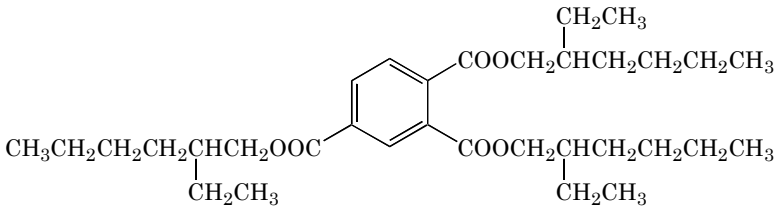
For

SIAM 14

Paris, France, 26-28 March 2002

1. Chemical Name:	Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
2. CAS Number:	3319-31-1
3. Sponsor Country:	Japan
4. Shared Partnership with:	
5. Roles/Responsibilities of the Partners:	
• Name of industry sponsor /consortium	Dr. Taku Kitamura, Dainippon Ink and Chemicals, Inc. E-mail: taku-kitamura@ma.dic.co.jp
• Process used	
6. Sponsorship History	
• How was the chemical or category brought into the OECD HPV Chemicals Programme ?	This substance is sponsored by Japan under the ICCA Initiative and is submitted for first discussion at SIAM 14.
7. Review Process Prior to the SIAM:	The industry consortium collected new data and prepared the updated IUCLID, and draft versions of the SIAR and SIAP. The Japanese government peer-reviewed the documents, audited selected studies. Testing: no testing (X) testing ( )
8. Quality check process:	
9. Date of Submission:	1 February 2002
10. Date of last Update:	
11. Comments:	The industry contact point is Dr. Taku Kitamura, Dainippon Ink and Chemicals , Inc. acting on behalf of the TOTM consortium (consortium members: Kao Corporation, Mitsubishi Gas Chemical Company, Inc., Asahi Denka Kogyo K.K.).

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	3319-31-1
Chemical Name	Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

In a single dose study of rats, 75 % of the orally administered chemical at 100 mg/kg bw was excreted in an unchanged form in the feces, 16 % as metabolites in the urine and 1.9 % was expired as CO_2.

The acute toxicity of the chemical is low because it showed no toxic signs at 2,000 mg/kg bw by oral route in rats [OECD TG 401] and at 2 mL/kg by dermal route in rabbits. During exposure by inhalation at 2600 mg/m^3, no death occurred in rats, but reddening patches in the lungs were observed after 14 days post exposure.. In an irritation-test for animals, the chemical was slightly irritating to the skin and the eyes. A sensitization test on guinea pigs showed no sensitization [OECD TG 406].

A feeding study with rats for 28 days showed a decrease of hemoglobin and an increase of leucocyte counts and serum cholesterol as well as an increased liver weight in the mid and high dose groups (0.67 and 2.0 %). Liver biochemistry revealed increases in palmitoyl CoA oxidation (increased in both sexes at 2.0% and males at all dose levels) and catalase activity (increased in males at 2.0%), suggesting the induction of peroxisome proliferation. Further analysis by an electron microscope indicated slight increased number of peroxisomes in hepatocytes at the high dose. It is generally accepted that the induction of peroxisome proliferation occurs specifically in rodents but much less in other species including humans. There were no dose-related histopathological changes in any treated groups. The NOAEL in this study was considered to be 0.2 % (184 mg/kg bw/day).

The OECD reproductive/developmental toxicity screening test [TG 421] for at least 46 days at doses of 100, 300 and 1,000 mg/kg/day demonstrated a decrease of spermatocytes and spermatids in testis in the 300 and 1000 mg/kg groups but not in the 100 mg/kg group.

Based on the testicular toxicity, the NOAEL for repeated dose toxicity is considered to be 100 mg/kg bw/day.

As for reproductive/developmental toxicity, the chemical showed no adverse effects on copulation, fertility, delivery and nursing of females nor on the viability, body weight and morphology of offspring in the above screening test [OECD TG 421]. However, the NOAEL for reproductive toxicity in males was considered to be 100 mg/kg bw/day because of the testicular toxicity described above. Both NOAELs for reproductive toxicity in females and developmental toxicity of offspring were considered to be 1,000 mg/kg bw/day.

The genotoxicity of this chemical was evaluated in many *in vitro* assay systems. It was neither mutagenic in bacteria [OECD TG 471 & 472] nor clastogenic in mammalian cells [Guidelines for Screening Mutagenicity Testing of

Chemicals (Japan)].

Environment

The Mackay level III fugacity Model was employed to estimate the environmental distribution of this chemical in air, water, soil and sediment. If released to air, this chemical will exist solely in the particulate phase in the ambient atmosphere. If released to soil, this chemical is not expected to be distributed to other compartments.

This chemical has to be considered as weakly toxic against aquatic organisms and is not biodegradable. This chemical has a high logPow value (5.94), the measured BCF is reported as less than 1 to 2.7 in carp for 6 weeks, but some uncertainty still remains regarding the bioaccumulation potential of this chemical. This result indicates that the bioavailability of this chemical is low. The toxicity results to aquatic plants (algae; *Selenastrum capricornutum*) were >100 mg/L for EC_{50} (72hr). The acute toxicity data in fish (medaka; *Oryzias latipes*) were >100 mg/L (96h, LC_{50}) and >75 mg/L (14d, LC_{50}). In *Daphnia magna*, the acute toxicity was >180mg/L (48hr: EC_{50}) and the chronic toxicity was >55.6 mg/L (21d, reproduction). All these data were obtained in supersaturated solution with the aid of solubilizer (HCO-40). The test solution was considered to be homogeneous. Another chronic toxicity data in *Daphnia magna* (NOEC >0.082mg/L) was reported (Procedure of ASTM and USEPA). Though this value is lower than the saturation point, the measured concentration data were less reliable.

Based on the description of the test results above, it can be concluded that Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate does not show any toxic effects at the limit of solubility towards those aquatic organisms, which were tested in the laboratory. Though it is difficult to determine a PNEC, this substance is not toxic at its water solubility (OECD TG105; 0.13 mg/L 25 C).

Exposure

This chemical is manufactured as a plasticizer for PVC.

The production volume in Japan is approximately 20,000 tonnes/year and there are 5 manufacturers in Japan. Estimated global production is 40,000-100,000 tonnes/year. This chemical is mainly used as a plasticizer for PVC electrical cable and wire.

Occupational exposure may occur through dermal contact and inhalation of mist. This chemical is produced in closed system and workers wear protective gloves and goggles during the operation, so actual exposure in the work place is considered to be low.

Since this chemical is difficult to extract from the polymeric matrix, consumer and environmental exposure are considered to be low.

NATURE OF FURTHER WORK RECOMMENDED

There is no recommendation for further work. The hazards of this chemical towards the environment and human health are considered to be low. Both occupational and consumer exposure are considered to be low.

FULL SIDS SUMMARY

CAS NO: 3319-31-1		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point		OECD TG 102	< - 50 °C (223 °K)
2.2	Boiling Point		Other (unknown)	283 °C (at 4 hPa)
2.3	Density		Other (unknown)	0.987-0.990 g/cm^3 at 20 °C
2.4	Vapour Pressure		OECD TG 104	< 2.8 x 10^{-4} hPa at 100 °C
2.5	Partition Coefficient (Log P_{ow})		OECD TG 107	5.94 at 25 °C
2.6A.	Water Solubility		OECD TG 105	0.13 mg/L at 25 °C
B.	Ph			None
	PKa			None
2.12	Oxidation: Reduction Potential			None
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation			None
3.1.2	Stability in Water		OECD TG 111	Stable at pH 4 at 50°C $T_{1/2}$=17.5 days at pH 7 at 25°C $T_{1/2}$=11.9 days at pH 9 at 25°C
3.2	Monitoring Data			None
3.3	Transport and Distribution		Calculated (Level III Fugacity Model)	(Release 100% to air) Air Water Soil Sediment 19.6% 4.7% 66.2% 9.5% (Release 100% to water) Air Water Soil Sediment 0.0% 32.7% 0.1% 67.2% (Release 100% to soil) Air Water Soil Sediment 0.0% 0.0% 100% 0.0% PEC_{local} = None
3.5	Biodegradation		OECD TG 302C	4.2 % after 28 days
3.7	Bioaccumulation		OECD TG 305C	BCF=1-2.7(Conc. 0.2 mg/L) BCF=0.1-0.23 (Conc. 2 mg/L)
ECOTOXICOLOGY				
4.1 A	Acute Toxicity to Fish	*Oryzias latipes*	OECD TG 203	LC_{50} (96 hr) > 100 mg/L
4.1 B	Prolonged Toxicity to Fish	*Oryzias latipes*	OECD TG 204	LC_{50} (14 day) > 75 mg/L NOEC(14 day) ≥ 75 mg/L LOEC(14 day) > 75 mg/L
4.2	Acute Toxicity to Aquatic Invertebrates (*Daphnia*)	*Daphnia magna*	OECD TG 20	EC_{50} (24 hr) > 180 mg/L EC_{50} (48 hr) > 180 mg/L NOEC ≥ 180 mg/L LOEC > 180 mg/L
4.3	Toxicity to Aquatic Plants e.g. *Algae*	*Selenastrum capricornutum* ATCC22662	OECD TG 201	EC_{50} (72 hr) > 100mg/L NOEC(72 hr) ≥ 100mg/L

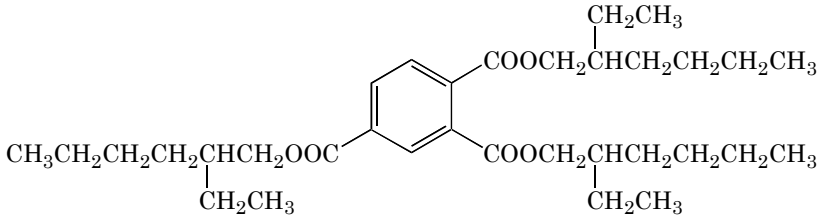
CAS NO: 3319-31-1		SPECIES	PROTOCOL	RESULTS
4.5.1	Chronic Toxicity to Fish			None
4.5.2	Chronic Toxicity to Aquatic Invertebrates (*Daphnia*)	*Daphnia magna*	OECD TG 211 Procedure of ASTM and USEPA	NOEC(21d,reproduction) =55.6mg/L EC_{50}(21d,reproduction)= 89.1mg/L LC_{50} (21d, parental) > 100 mg/L NOEC(21d)≥0.082mg/L
4.6.1	Toxicity to Soil Dwelling Organisms			None
4.6.2	Toxicity to Terrestrial Plants			None
4.6.3	Toxicity to Other Non- Mammalian Terrestrial Species (Including Birds)			None
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat	OECD TG 401	$LD_{50:}$ > 2,000 mg/kg (for both sexes)
5.1.2	Acute Inhalation Toxicity	Rat	Other	LD_0 > 2,600 mg/m^3
5.1.3	Acute Dermal Toxicity	Rabbit	Other	LD_0 > 2.0 mL/kg
5.2.1	Skin Irritation	Rabbit	Other	Slightly irritating
5.2.2	Eye Irritation	Rabbit	Other	Slightly irritating
5.3	Skin Sensitisation	Guinea pig	OECD TG 406	Not sensitizing
5.4	Repeated Dose Toxicity	Rat	OECD TG 421	NOAEL = 100 mg/kg bw/day
5.5	Genetic Toxicity *In Vitro*			
A.	Bacterial Test (Gene mutation)	*S.typhimurium, E. coli*	Japanese TG and OECD TG 471 & 472	Negative (With metabolic activation) Negative (Without metabolic activation)
B.	Non-Bacterial *In Vitro* Test (Chromosomal aberrations)	CHL/IU cells	Japanese TG	Negative (With metabolic activation) Negative (Without metabolic activation)
5.6	Genetic Toxicity *In Vivo*	Mouse	Other	Negative (dose level=ca.1,400mg/kg bw/day)
5.8	Toxicity to Reproduction	Rat	OECD TG 421	NOAEL = 100 mg/kg bw/day (male) NOAEL = 1,000 mg/ kg bw/day (female) NOAEL = 1,000 mg/ kg bw/day (offspring)
5.9	Developmental Toxicity/ Teratogenicity	Rat	OECD TG 421	NOAEL = 1,000 mg/ kg bw/day
5.11	Experience with Human Exposure			None

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 3319-31-1
IUPAC Name: Tris(2-ethylhexyl) benzene-1,2,4-tricarboxylate
Molecular Formula: $C_{33}H_{54}O_6$ (MW=546.79)
Structural Formula:



Molecular Weight: 546.79
Synonyms: TOTM
Tris(2-ethylhexyl) trimellitate
Benzene-1, 2, 4-tricarboxylic acid tris-(2-ethylhexyl) ester

1.2 Purity/Impurities/Additives

Purity: >98.5%

Impurity: Di(2-ethylhexyl) phthalate (DEHP) < 0.1%

Water

Additives: None

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Value	Protocol
Melting point	< -50 ℃	OECD TG 102
Boiling point	283 ℃ (4 hPa)	Unknown
Vapour pressure	<2.8 x 10^{-4} Pa (100 ℃)	OECD TG 104
Water solubility	0.13 mg/ L (25℃)	OECD TG 105
Partition coefficient n-octanol/water (log value)	5.94 (25 ℃)	OECD TG 107
Density	0.987 - 0.990 g/cm^3 (20 ℃)	Unknown

As the density of the substance is close to one, the substance can easily form stable emulsions in water. As shake-flask methods have been used to measure water solubility and Kow, it is possible that the water solubility of TOTM is overestimated and the Kow is underestimated.

2 GENERAL INFORMATION ON EXPOSURE

The production volume of TOTM in Japan is approximately 20,000 tonnes/year and there are five manufacturers in the country. Estimated global production is 40,000–100,000 tonnes/year. TOTM is generally produced in a closed system. TOTM is used in a wide range of flexible vinyl products. It is one of the important ingredients in such products as heat-resistant wire and cable, automotive parts (instrument panel skins, heat-resistant leathers etc.), heat-resistant hoses and tubes, and insulation tape. Among these, the most common use for TOTM is as a plasticizer for PVC electrical wire and cable, especially those for high temperature applications. TOTM is not a potential source of toxic emissions to the environment, except as a result of sampling or the maintenance of production facilities (see also results from aging and extraction test in section 2.2.2).

2.1 Environmental Exposure and Fate

Based upon the biodegradation measurement, TOTM is not readily biodegradable. TOTM achieved 4.2 percent of its theoretical BOD using an activated sludge inoculum during four weeks of incubation in a single screening study.

The Mackay levelIII fugacity model was employed to estimate the environmental distribution of TOTM in air, water, soil and sediment. The calculation results are shown in Table 2. If released into air, an estimated vapor pressure of less than 2.8 x 10^{-4} Pa at 100℃ indicates TOTM will exist solely in the particulate-phase in the ambient atmosphere. Particulate-phase TOTM is removed from the atmosphere by wet and dry deposition. If released into soil, TOTM is not expected to have mobility based upon the fugacity model calculation. Volatilization from soil surfaces is not expected to be an important environmental fate process based on the estimated vapor pressure of this substance. If released into water, TOTM is expected to adsorb into suspended solids and sediment based upon the fugacity model calculation. [Dainippon Ink and Chemicals, Inc. (2001)]

Table 2. Predicted Distribution of TOTM Using Fugacity level III (%)

Compartment	Release 100% into air	Release 100% into water	Release 100% into soil
Air	19.6	0.0	0.0
Water	4.7	32.7	0.0
Soil	66.2	0.1	100.0
Sediment	9.5	67.2	0.0

Conflicting results are available regarding hydrolysis. In one test no hydrolysis was observed at 100 °C at neutral pH over 4 days (Eastman Chemicals, 1982). In a second study, while no hydrolysis was observed at pH 4, hydrolysis was observed at pH 7 and 9. A half-live of 17.5 days at 25 °C and pH 7 and a half-live of 11.9 days at 25 °C and pH 9 was estimated (CERI, Japan, 1998). Hydrolysis products were not identified. There is currently no explanation for these conflicting results.

Measured BCF values of less than 1-2.7 in carp suggest that bioconcentration in aquatic organisms is low. It has to be noted though that, given the uncertainty regarding the water solubility and the

possibility of formation of stable emulsions, some uncertainty remains regarding the bioaccumulation potential of this substance.

2.2 Human Exposure

2.2.1 Occupational Exposure

Production of TOTM

TOTM is generally produced and used in a closed system, so occupational exposure is limited to sampling and the maintenance of production facilities. Moreover, the exposure time is very short. The major route of occupational exposure is inhalation and dermal. The atmospheric concentration was measured at two production sites in Japan. The monitoring data are shown in Table 3. The maximum exposure level is estimated according to working schedules, as follows. From Table 3, if a single worker (body weight: 70 kg, respiratory volume: 1.25 m^3/hour) is assigned to implement all daily operations without protection, the daily intake (EHE inh) is calculated as 1.77 x 10^{-3} mg/kg/day in the worst case. In contrast, the daily dermal dose (EHE der) for a single worker (surface area of exposed skin: 840 cm^2 for hands) is calculated as 2.47 mg/kg/day based on the calculation below, which uses the EASE model. In fact, workers wear protective gloves and goggles during operations, so actual exposure in the workplace is considered to be lower than these EHEs.

Table 3. Available Workplace Monitoring data for TOTM (EHE inh)

Occupation	Frequency Times/day	Duration Hr	Working hr/day	Max concentration mg/m^3	EHE inh mg/kg/day	Reference
Sampling	5	0.017	0.085	0.210	$3.19x10^{-4}$	JISHA, Japan (2001)
Analysis	5	0.067	0.335	0.053	$3.17x10^{-4}$	
Charge to drum	1	0.833	0.833	0.076	$1.13x10^{-3}$	
Total	11	-	1.253	-	$1.77x10^{-3}$	

EHE inh: Estimated Human Exposure for inhalation

Calculation: EHE der = (Cder * T * S * t) /W
EHE der: Estimated Human Exposure for dermal
Cder = 990 mg/cm^3 (Content in product contacted by worker)
T = 0.01 cm (Thickness of substance)
S = 840 cm^2 (Surface area of exposed skin) for hand
t = 0.0208 day/day (Exposure time per day ; 10 min/8Hr, [1day = 8Hr] assumed)
W = 70 Kg (body weight)

Industrial Use of TOTM

Exposure may occur on production lines in the plastics industry. Exposure may be expected in the following situations:

- Handling of TOTM (adding, blending, compounding)
- Processing of flexible PVC (extrusion, injection, calendaring, powder slush molding)
- Service and maintenance of equipments

However, most of the gas emitted from the hot plasticized PVC will be collected rapidly with the local exhaust and general ventilation. Accordingly, it is not expected that workers will be seriously exposed to this substance.

2.2.2 Consumer Exposure

Usually, TOTM is already blended into the compound as a plasticizer, so it is unlikely that downstream users or consumers of electric wire industry, etc., will be exposed to this substance. The following information assumes exposure to the compound:

The heat-aging data are shown in Table 4. The comparison data of weight loss show that TOTM is hard to volatilize.

Table 4. Heat Aging Test for Plasticizer

Plasticizer	DEHP	DINP	DIDP	TOTM
Heat Aging Test: 120℃x168hrs, thickness 1mm size:20x50mm				
Weight loss(%)	23.5	14.5	6.7	0.0

The extraction data are shown in Table 5. TOTM has good water resistance properties and detergent resistance properties.

Table 5. Extraction Test for Plasticizer

Plasticizer	DEHP	TOTM
Extraction Test(water): 80℃x168hrs (after drying 110℃x4hrs)		
Weight loss(%)	0.7	0.0
Detergent Resistance: 1%Sodium Laurylbenzensulfonate 70℃x168hrs (after drying 110℃x4hrs)		
Weight loss(%)	13.8	0.0

Based on the additional information above, consumer exposure to TOTM is unlikely to be significant.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics and Metabolism

Absorption and metabolism were studied for TOTM (14C-labeled on the 2-carbon atom of 2-ethylhexyl group) mixed with corn oil and administered by gavage in a single dose of 100 mg/kg of body weight in four male SD rats. Rats were placed in glass metabolism cages and urine, feces and expired air were collected for 144 hrs. About 75% of the dose was excreted unchanged in the feces, 16% in the urine as metabolites and 1.9% was expired as $^{14}CO_2$. Radioactivity was excreted in the feces as unchanged TOTM (85% of the fecal radioactivity), mono- and di(2-ethylhexyl) trimellitate (MOTM and DOTM, respectively,) and unidentified polar metabolites. Metabolites in the urine

were identified as MOTM and metabolites of 2-ethylhexanol. Less than 0.6% of the dose remained in whole tissues. Elimination of $^{14}CO_2$ was biphasic with half-lives of 4.3 and 31 hrs, and excretion of radioactivity in the urine was biphasic with half-lives of 3.4 hrs and 42 hrs. Based on remaining labeled ratio (less than 0.6% of dose) in whole tissues at 144 hours, it is considered that the accumulation of this chemical is negligible. [Eastman Kodak, 1984]

3.1.2 Acute Toxicity

Acute toxicity data are reported primarily for rats, mice and rabbits. 12 Acute toxicity test results with animals are available, oral(6), inhalation(1), IP(2) and dermal(3). A study (oral) conducted by Japan's MHW(1996); and two (oral and dermal) studies conducted by Nuodex Inc.(1981 and 1982c), were conducted using OECD TG and a similar method.

The data, which are informative and useful in evaluating acute toxicity, are listed in Table 6.

Table 6. Summary of the Effects of TOTM on Animals (Acute Toxicity)

Route	Animals	Values	Type	References
Oral	Rat	>2000 mg/kg	LD50	MHW, Japan (1996)
	Rat	>5000 mg/kg bw	LD0	Nuodex Inc.(1981)
Inhalation	Rat	>2600 mg/m^3	LC0	Nuodex Inc.(1982b)
Dermal	Rabbit	>2 ml/kg	LD0	Nuodex Inc(1982c)
	Rabbit	>1970 mg/kg bw	LD0	Tenneco Chemicals(1981))
I.P.	Rat	>3200 mg/kg bw	LD50	Eastman Kodak (1983)
	Mouse	>3200 mg/kg bw	LD50	Eastman Kodak (1983)

With regard to single dose oral toxicity, no macroscopic abnormalities that could be attributed to treatment with the test substance were seen on pathological examination. During exposure by inhalation at 2600 mg/m^3, no death occurred in rats but reddening patches in lungs were observed after 14 days post-exposure.

Accordingly, it can be concluded that the acute toxicity(Oral) of TOTM is LD_{50} >2000 mg/kg in rats.

3.1.3 Repeated Dose Toxicity

Among the eight available data, four were conducted according to GLP. Three studies were considered to be key studies.

The first study was the oral study by CMA(1985), which determined the subchronic toxicity of TOTM administered orally in the diet to groups of 5 male and 5 female Fischer 344 rats at levels of 0(0), 0.2(184), 0.67(650), 2.0(1826) % (mg/kg bw/day) for 28 days. There were no statistically significant differences in body weights between control and TOTM treated groups. There were significant differences between control and treated groups in hemoglobin concentration (lower in both sexes at 0.67 and 2.0% TOTM), leucocyte counts (higher in males at 0.67 and2.0%), absolute and relative liver weights (higher in both sexes at all levels except 0 and 0.2%), serum albumin (higher in both sexes at 0.67 and 2.0%), serum cholesterol levels (higher in males at 0.67 and 2.0%), serum urea (higher in males at 2.0%) and serum lipids (decreased in females at 2.0%). Liver biochemistry revealed statistically significant differences between treated and control groups as indicated by palmitoyl CoA oxidation (increased in both sexes at 2.0% and males at all dose levels), and catalase activity (increased in males at 2.0%), suggesting the induction of peroxisome

proliferation. Further analysis by an electron microscope indicated a slight increase in the number of peroxisome in hepatocytes at high doses. It is generally accepted that the induction of peroxisome proliferation occurs specifically in rodents, but much less frequently in other species, including humans. There were no dose-related histopathological changes in any of the treated groups. Accordingly, the NOAEL for repeated dose toxicity is considered to be 184 mg/kg for both sexes.

The second study was an oral study (for 28 days) by Japan's MHW (1996), in SD rats (five males, five females) conducted at doses of 0, 100, 300, and 1,000 mg/kg/day of TOTM. No test substance-related changes were noted in terms of clinical signs, such as body weight and food consumption, or in hematology, blood examination, urinalysis and pathological findings. Accordingly, the NOEL for repeat dose toxicity is considered to be 1,000 mg/kg/day for both sexes.

The third study was an OECD preliminary reproduction toxicity screening test by Japan's MHW(1998). Gavage study in SD rats conducted at doses of 100, 300 and 1,000 mg/kg/day (males: 46 days, females: from 14 days before mating to day 3 of lactation) of TOTM. Decreases in spermatocytes and spermatids in males were observed in the 300 and 1,000 mg/kg groups as a result of histopathological examination. No effects on the general appearance, body weight, food consumption, autopsy findings or weights of reproductive organs of either sex, or on the histopathlogical features of the ovary of females, were detected. Accordingly, the NOAEL is considered to be 100 mg/kg/day for males, and 1,000 mg/kg/day for females.

Four further studies were conducted using exposure by an unspecified route of injection and are unlikely to provide relevant and useful information.

There is no available information on human toxicity.

Conclusions

The NOAEL and the LOAEL for repeated oral toxicity are considered to be 100 and 300 mg/kg/day for rats, respectively.

3.1.4 Genotoxicity/Mutagenicity

There are five reports for Ames Tests. One (MHW, Japan: 1996) was conducted according to GLP, while the others were not. The study by the MHW is considered to be a key study.

TOTM has been investigated in *in vitro* tests. The substance did not induce gene mutation in bacterial systems (MHW, Japan: 1996) or chromosomal aberration in mammalian cultured cells (MHW, Japan: 1996), with or without an exogenous metabolic activation system. Among these studies, the MHW study was identified as key study because it was conducted and reported well.

Reverse gene mutation assays were conducted by OECD TG 471 and 472, using the plate incorporation method. TOTM was not mutagenic in *Salmonella typhimurium* TA100, TA1535, TA98, TA1537 and Escherichia coli WP2 uvrA at concentrations up to 5000 ug/plate, with or without an exogenous metabolic activation system (MHW, Japan: 1996).

The chromosomal aberration test by the Guidelines for Screening Mutagenicity Testing of Chemicals (Japan) was conducted in cultured Chinese hamster lung (CHL/IU) cells. Structural chromosomal aberrations and polyploidy were not induced up to a maximum concentration of 5.0 mg/mL with continuous treatment (without metabolic activation), or with short-term treatment (with or without an exogenous metabolic activation system) (MHW, Japan: 1996).

Result of all other tests (HGPRT assay, unscheduled DNA synthesis and dominant lethal assay for example) show that TOTM is not genetoxic.

Conclusions:

TOTM is considered to be not genotoxic with or without an exogenous metabolic activation system in *in vitro* bacterial and chromosomal aberration tests.

3.1.5 Carcinogenicity

One brief report states only that tests in mice, which have propensity to form pulmonary adenomas, were negative for TOTM, unlike tests using urethane (CMA, 1983). Although it is considered that these tests reveal the chemical is not carcinogenic, test results were invalid because no further detailed information is contained in the report.

3.1.6 Toxicity for Reproduction

An OECD reproductive/developmental toxicity screening test [TG 421] was performed. [MHW, Japan: 1998]. This study was identified to have been well conducted and reported.

A gavage study in SD rats was conducted at doses of 100, 300 and 1,000 mg/kg/day (male: 46 days, female: from 14 days before mating to day 3 of lactation) of TOTM.

Histopathological examination of the testes revealed decreases in spermatocytes and spermatids in males of the 300 and 1,000 mg/kg groups. No effects of TOTM were detected on general appearance, body weight, food consumption, autopsy findings, or weight of reproductive organs of either sex, or as a result of histopathological examination of the ovary. On the basis of' these findings, the NOELs of TOTM for repeat dose toxicity are considered to be 100 mg/kg/day for males, and 1,000 mg/kg/day for females.

Except for the effects in males observed on histopathological examination, no influence of this substance was detected regarding reproductive ability, organ weights or histopathological appearance of the ovaries, delivery or maternal behavior of dams. No effect of TOTM was detected on viability, general appearance, body weight or autopsy findings of offspring. Body weight gain of pups at 300 mg/kg bw/day was slightly low, but body weights of all pups at 100 and 1000 mg/kg bw/day were not statistically different form control. On the basis of these findings, the NOELs for reproductive / developmental toxicity were considered to be 100mg/kg bw/day for male rats, 1,000 mg/kg bw/day for female rats, and 1,000 mg/kg bw/day for offspring.

Conclusions

The NOELs for reproductive/developmental toxicity were considered to be 100 mg/kg/day for male rats, 1,000 mg/kg/day for female rats, and 1,000 mg/kg/day for offspring, respectively.

3.1.7 Others: Irritation and Sensitization

Six and three results are reported for skin and eye irritation tests, respectively. All these test results showed that TOTM is slightly irritating to the skin and eyes.

Sensitization tests on a guinea pig using OECD/TG 406 (Tenneco Chemicals, 1981) showed no sensitization.

3.2 Initial Assessment for Human Health

The acute toxicity of TOTM is considered to be LD_{50} >2000 mg/kg by oral route in rats and LD_0>2ml/kg by dermal route in rabbits. In the irritation test for animals, TOTM is slightly irritating to the skin and eyes. Sensitization test on guinea pig using OECD/TG 406 showed no sensitization.

The NOAEL and the LOAEL for repeated oral toxicity are considered to be 100 and 300 mg/kg/day for rats, respectively.

The NOELs for reproductive/developmental toxicity were considered to be 100 mg/kg/day for male rats, 1,000 mg/kg/day for female rats, and 1,000 mg/kg/day for offspring. TOTM is not genotoxic with or without an exogenous metabolic activation system in *in vitro* bacterial test and chromosomal aberration tests. .

TOTM produces the same spectrum of morphological and biochemical change in the rat livers as DEHP. TOTM, however, was much less potent in its action, with a dietary level of 2.0%, causing less peroxisome proliferation and peroxisome-associated enzyme induction than 0.67% DEHP. Also, the level of peroxisome induction in rats given TOTM is less than in those receiving a metabolically equivalent dose of 2-ethylhexanol. Furthermore, on a molar basis, effects were lower than with DEHP. No effects of MEHP, a metabolite of DEHP, were seen with TOTM. [The British Industrial Biological Research Association (1985), EPA OTS0510637 (1985), John R. Hodgson. (1987)]

In addition, studies have recently determined that rodents (rats) are susceptible to peroxisome proliferation. After all, these results suggest that the effect of DEHP on the liver is markedly different between rodents (rats) and other species (marmosets). [Yoshimasa Kurata, et al. (1998)] Therefore, DEHP was downgraded from Group 2B to Group 3 by the IARC Monographs Working Group. (February 2000). Group 3 “cannot be classified as to its carcinogenicity to humans”.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

TOTM has to be considered as weakly toxic against aquatic organisms. The effects were tested and results are summarized in Table 7.

Table 7. Summary of the Effects of TOTM on Aquatic Organisms

Organism	Test duration	Result (mg/L)	Reference
Algae			
Selenastrum capricornutum ATCC22662	72 hr	EC50 >100 NOEC≥100	EA, Japan
Invertebrates			
Daphnia magna	24 hr	EC50 > 180	EA, Japan
	48 hr	EC50 > 180 NOEC ≥180	
	48hr	EC50 >1	ICI 1990
	21 day	EC50 = 89.1 NOEC = 55.6	EA, Japan
	21day	NOEC≥0.082	CMA (1985)
Fish			
Oryzias latipes	96 hr	LC50 > 100	EA, Japan
	14 day	LC50 > 75 NOEC≥ 75	EA, Japan

As the lowest acute toxicity data, EC_{50} (>100 mg/L, 72 hr) of *Selenastrum capricornutum* ATCC22662 and EC_{50} (180 mg/L, 48 hr) of Daphnia magna were adopted. As the prolonged toxicity data of fish (Oryzias latipes), NOEC=75 mg/L (14 days) [EA Japan] was adopted. All these data in supersaturated solution, which was considered to be substantially homogeneous, were obtained with the aid of a solubilizer (HCO-40). Though the observed concentration data were less reliable, in one chronic toxicity data (Daphnia magna (21 days, Procedure of ASTM and USEPA; CMA 1985) NOEC ≥ 0.082 mg/L (highest concentration tested) was reported in a lower concentration than saturation point.

Based on the description of the test results above, it can be concluded that Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate does not show any toxic effects at the limit of solubility towards those aquatic organisms, which were tested in the laboratory. Though it is difficult to determine a PNEC, this substance is not toxic at its water solubility (OECD TG105; 0.13 mg/L 25 °C).

4.2 Terrestrial Effects

There is no available information.

4.3 Initial Assessment for the Environment

The Mackay levelⅢ fugacity model was employed to estimate the environmental distribution of TOTM in air, water, soil and sediment. If released into air, TOTM will exist solely in the particulate-phase in the ambient atmosphere. If released into soil, TOTM is not expected to have mobility. If released into water, TOTM is expected to adsorb to suspended solids and sediments. Although the chemical has large logPow value (5.94), measured BCF of values of less than 1 to 2.7 in carp suggest that bioconcentration in aquatic organisms is low.

As the lowest acute and chronic toxicity data, EC_{50} (>100 mg/L, 72 hr) of *Selenastrum capricornutum* ATCC22662 and NOEC (≥ 0.082 mg/L, 21 day) of *Daphnia magna* were adopted.

Based on the description of the test results above, it can be concluded that Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate does not show any toxic effects at the limit of solubility towards those aquatic organisms, which were tested in the laboratory. Though it is difficult to determine a PNEC, this substance is not toxic at its water solubility (OECD TG105; 0.13 mg/L 25 °C).

5 RECOMMENDATIONS

TOTM is currently of low priority for further work.

6 REFERENCES

Chemicals Evaluation and Research Institute, Japan Ministry of International Trade and Industry (1998)

Chemicals Inspection and Testing Institute Japan, Chemical Industry Ecology-Toxicology and Information Center (1992)

Chemicals Inspection and Testing Institute, Ministry of International Trade and Industry (1992)

Dainippon Ink and Chemicals, Inc. unpublished report (2001)

CMA. Tris(2-ethylhexyl) trimellitate: A voluntary testing program under Section 4 of TheToxic Substances Control Act. OTS 0510616. Doc. ID 408365005. Chemical Manufacturers Association, Washington DC, (1983).

CMA Doc ID 408565036 (1985)

Eastman Chemicals. Kodaflex TOTM. Product Literature. Coatings Chemicals Division, B-280, Kingsport (1982)

Eastman Kodak, *Absorption and metabolism of (hexyl-2-^{14} C) Tri-(2-ethylhexyl) trimellitate in the rat* (1984)

Environmental Agency of Japan (1999a), *Ecotoxicity testing report*, Test No.NMMP/E09/1080

Environmental Agency of Japan (1999b), *Ecotoxicity testing report,* Test No.NMMP/E09/2080

Environmental Agency of Japan (1999c), *Ecotoxicity testing report,* Test No.NMMP/E09/3080

Environmental Agency of Japan (1999d), *Ecotoxicity testing report,* Test No.NMMP/E09/4080

Environmental Agency of Japan (1999d), *Ecotoxicity testing report,* Test No.NMMP/E09/5080

EPA Document No. 40-8565037, Fiche No. OTS0510637

John R. Hodgson, *Results of peroxisome induction studies on tri(2-ethylhexyl)trimellitate and 2-ethylhexanol*, Toxic.Ind. Hlth, Vol.3, No.2, 1987

Thomas W. Lapp, Charles E Mumma Joseph Chaszar, Midwest Reserch Institute, *A Survey of Plasticizers: Epoxies, Linear Polyesters and Trimellitates Chemical Technology and Economics in Environmental Perspective*, Task Ⅳ, Environmental Protection Agency (Nov. 1981)

Ministry of Health and Welfare, Japan (1996), *Toxicity Testing Report*, Vol. 4, 695-720

Ministry of Health and Welfare, Japan (1998), *Toxicity Testing Report,* Vol. 6, 569-578

MITI Japan (1992), *Green Card of "biodegradation and bioaccumulation data of existing*

Chemicals based on the CSCL Japan"

Nuodex Inc., *Acute dermal toxicity test of Tenneco Chemicals, Inc. compound Nuoplaz 6959 in rabbits. Doc ID878214467* (1982a)

Nuodex Inc., *Acute inhalation toxicity test in sprague-dawley rats using compound Nuoplaz 6959 Doc ID878214466* (1982b)

Nuodex Inc., *Acute oral toxicity – Rats Doc ID878214469* (1981)

The British Industrial biological Research Association, *A 28-day Toxicity Study with TOTM in the Rat with Cover Letter Dated 111885* (1985)

Yoshimasa Kurata, *Subchronic Toxicity of Di(2-ethylhexyl)phthalate in Common Marmosets: Lack of Hepatic Peroxisome Proliferation, Testicular Atrophy, or Pancreatic Acinar Cell Hyperplasia,* Toxicological Sciences 42, 49-56 (1998)

SIDS DOSSIER
ON THE HPV CHEMICAL

Tris(2-ethylhexyl) benzene-1,2,4-tricarboxylate

CAS No. 3319-31-1

Sponsor Country: Japan

Date: Jan. 28, 2002

1.01 SUBSTANCE INFORMATION

A. CAS Number 3319-31-1

B. Name Tris(2-ethylhexyl) benzene-1,2,4-tricarboxylate

C. OECD Name 1,2,4-Benzenetricarboxylic acid, tris(2-ethylhexyl) ester

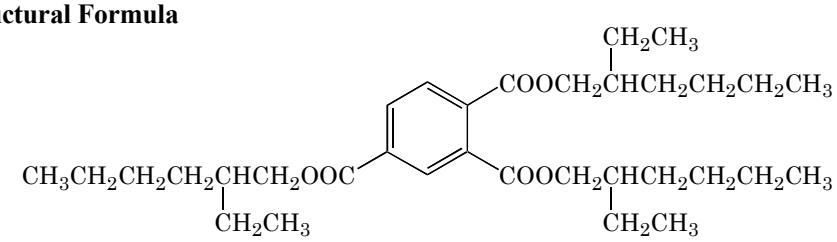
D. CAS Descriptor

Not applicable in this case.

E. EINECS-Number 222-020-0

F. Molecular Formula $C_{33}H_{54}O_6$

G. Structural Formula



H. Substance Group

Not applicable in this case

7 I. SUBSTANCE REMARK

None

J. Molecular Weight 546.79

1.0.2 OECD INFORMATION

A. Sponsor Country: JAPAN

B. Lead Organisation:

Name of Lead Organisation:	DAINIPPON INK & CHEMICALS, INC
Contact person:	Dr. T. KITAMURA
Address:	DIC Building, 7-20, Nihonbashi 3-chome, Chuo-ku
Town:	Tokyo
Country:	JAPAN
Tel:	81-3-5203-7753
Fax:	81-3-3278-0253

C. Name of responder

Name:	The same as Contact person
Address:	The same as Contact person

1.1 GENERAL SUBSTANCE INFORMATION

A. Type of Substance

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

B. Physical State *(at 20°C and 1.013 hPa)*

gaseous **[ ]**; liquid **[X]**; solid **[ ]**

C. Purity

More than 98.5 %

1.2 SYNONYMS

Tris(2-ethylhexyl) trimellitate
Benzene-1,2,4-tricarboxylic acid tris-(2-ethyl-hexyl) ester
1,2,4-Benzene tricarboxylic acid, tris(2-ethylhexyl) ester
Tri-2-ethylhexyl trimellitate
TOTM
Trioctyl trimellitate

1.3 IMPURITIES

Di (2-ethylhexyl) phthalate < 0.1%
Water

1.4 ADDITIVES

None

1.5 QUANTITY

Remarks: There are 5 companies in Japan. (Approximately 20,000 tonnes/year)
40,000 -- 100,000 tonnes in the world
Reference:

1.6 LABELLING AND CLASSIFICATION

None

1.7 USE PATTERN

A. General

Type of Use:	**Category: Non dispersive**
Main industrial use	Plasticizer for PVC electrical cable and wire for higher temperature specifications.

Reference:

B. Uses in Consumer Products

None

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUE

(a) Type of limit : TLV (US)
Limit value : 5 mg/m^3
Source : IUCLID (Keyser & Mackay Amsterdam)

(b) Type of limit : other: no occupational exposure limit
Limit value :
Source : IUCLID (Alusuisse Italia Spa S. Giovanni Valdarno(AR))

1.9 SOURCES OF EXPOSURE

(a) Remark : TOTM is manufactured in a closed reaction vessel. The product is used as a plasticizer for polymers and its use results in inclusion into a polymer
m

Source : IUCLID (FMC Corporation Manchester)

(b) Remark : A potential for exposure would be during the manufacture and initial downstream processing of TOTM all such operations conducted by specialist chemical companies to which detailed advice on safe handling is provided.
The other area of potential human exposure is TOTM containing PVC used in medicinal applications. Any plasticizer used in a blood bag for instance, may be extracted to some extent by blood. The steady state blood concentration of TOTM in patients dialysing for at least 2 years was found to be about 2 micrograms per millilitre (approx. 4 times less than equivalent levels of DOP which is more commonly used in this application.

Source : IUCLID (International Speciality Chemicals Ltd. Southampton)

1.10 ADDITIONAL REMARKS

None

2.1 MELTING POINT

(a) Preferred result

Value : < -50°C
Sublimation :
Method : OECD TG 102
GLP : Yes **[X]** No **[ ]** ? **[ ]**
Year : 1998
Remark :
Test substance : Tokyo Kasei Kogyo Co., Ltd. Purity: 98.5%
Source : Chemicals Evaluation and Reseach Institute (Japan)
Ministry of International Trade and Industry (1998)

(b) Value : -38 °C
Decomposition : Yes **[ ]** No **[X]** ? **[ ]**
Sublimation : Yes **[ ]** No **[X]** ? **[ ]**
Method :
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remark :
Reference : Midwest Research Institute
Environmental Protection Agency (Nov. 1981) (47)

(c) Value : -35°C
Sublimation : Yes **[ ]** No **[ ]** ? **[X]**
Method : other : see remarks
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remark : No information on method provided.
Source : IUCLID (21), (35), (37)

(d) Value : -30°C
Sublimation :
Method : other : see remarks
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remark : No information on method provided.
Source : IUCLID (2)

2.2 BOILING POINT

(a) Preferred result

Value : 283 °C
Pressure : at 4 hPa
Decomposition : Yes **[ ]** No **[X]** ? **[ ]**
Method :
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remark :
Reference : Midwest Research Institute
Environmental Protection Agency (Nov. 1981) (47)

(b) Value : 414°C
Pressure : at 1013 hPa
Decomposition :
Method :
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remark : No information on method provided.

Source : The Sigma-Aldrich Library of Regulatory and Safety Data Ministry of International Trade and Industry (1998)

(c) Value : 260° C
Pressure : at 8 hPa
Decomposition :
Method : other : see remarks
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remark : No information on method provided.
Source : IUCLID (68)

(d) Value : 221° C
Pressure : at .2 hPa
Decomposition :
Method : other : see remarks
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remark : No information on method provided.
Source : IUCLID (2)

(e) Value : 278 - 284°C
Pressure : at 4 hPa
Decomposition :
Method : other : see remarks
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remark : No information on method provided.
Source : IUCLID (21), (35), (37)

(f) Value : ca. 282° C
Pressure : at 4 hPa
Source : IUCLID (Alusuisse Italia Spa S. Giovanni Valdarno(AR))

2.3 DENSITY (relative density)

(a) Preferred result
Type : Bulk density **[ ]**; Density **[X]**; Relative Density **[ ]**
Value : 0.987 – 0.990 g/cm^3
Temperature : 20 °C
Method :
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remark :
Reference : Midwest Research Institute Environmental Protection Agency (Nov. 1981) (47)

(b) Type : Bulk density **[ ]**; Density **[X]**; Relative Density **[ ]**
Value : 0.9888 g/cm^3
Temperature : 20 °C
Method :
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Test substance : Tokyo Kasei Kogyo Co., Ltd. Purity: 98.5%
Remark :
Source : Tokyo Kasei Kogyo Co., Ltd. Ministry of International Trade and Industry (1998)

(c) Type : Bulk density **[ ]**; Density **[X]**; Relative Density **[ ]**
Value : 0.985 g/cm^3

Temperature : 20 °C
Method : other : see remarks
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remark : No information on method provided.
Source : IUCLID (2)

(d) Type : Bulk density **[ ]**; Density **[X]**; Relative Density **[ ]**
Value : 0.99 g/cm^3
Method : other : see remarks
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remark : No information on method provided.
Source : IUCLID (21), (35), (37), (68)

(e) Type : Bulk density **[ ]**; Density **[X]**; Relative Density **[ ]**
Value : 0.989 - 0.992 g/cm^3
Temperature : 20 °C
Method : other
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Source : IUCLID (Alusuisse Italia Spa S. Giovanni Valdarno(AR))

2.4 VAPOUR PRESSURE

(a) Preferred result
Value : < 2.8 x 10^{-4} Pa
Temperature : 100 °C
Decomposition :
Method : OECD TG 104
GLP : Yes **[X]** No **[ ]** ? **[ ]**
Year : 1998
Remark :
Test substance : Tokyo Kasei Kogyo Co., Ltd. Purity: 98.5%
Source : Chemicals Evaluation and Reseach Institute, Japan
Ministry of International Trade and Industry (1998)

(b) Value : 0.27 – 6.7 hPa
Temperature : 250 - 260 °C
Method : calculated **[ ]**; measured **[X]**
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remarks :
Reference : Midwest Research Institute
Environmental Protection Agency (Nov. 1981) (47)

(c) Value : 8 hPa
Temperature : 260 °C
Decomposition :
Method : other (calculated): see remarks
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remark : No information on method provided.
Source : IUCLID (21), (69)

(d) Value : 1.3 hPa
Temperature : 260 °C
Method other (calculated): see remarks
GLP : Yes **[ ]** No **[ ]** ? **[X]**

Remark : No information on method provided.
Source : IUCLID (27)

(e) Value : 0.056 hPa
Temperature : 20 °C
Decomposition :
Method : other (calculated): see remarks
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remark : No information on method provided.
Source : IUCLID (2)

(f) Value : < 0.13 hPa
Temperature : 25 °C
Source : IUCLID (Alusuisse Italia Spa S. Giovanni Valdarno(AR))

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

(a) Preferred result
Log Pow : 5.94
Temperature : 25 °C
Method : OECD TG "Partition Coefficient (n-octanol / water) : 107, (Shake Flask Method)" (1995)
Year : 1998
GLP : Yes **[X]** No **[ ]** ? **[ ]**
Test substance : Tokyo Kasei Kogyo Co., Ltd. Purity: 98.5%
Remark :
Source : Chemicals Evaluation and Reseach Institute, Japan
Ministry of International Trade and Industry (1998)

(b) Log Pow : 4.35
Temperature : 25 °C
Method : other (measured): see remarks
Year : 1984
GLP : Yes **[X]** No **[ ]** ? **[ ]**
Remark : The study was conducted following the methods outlined in the ABC protocol # A-8003 (revised 6 August, 1984) for CMA Environmental Effects Testing Program with TOTM. 0.4% solutions of TOTM (supplied by CMA) were prepared in n-octanol and 40 ml portions were shaken for 24 hours with 400 ml water. After a 48 hour settling period, aliquots from both phases were drawn to analyse their TOTM concentrations using GC or HPLC.
Source : IUCLID (11)

2.6 WATER SOLUBILITY

A. Solubility

(a) Preferred result
Value : 0.13 mg/L
Temperature : 25 °C
Description : Miscible **[ ]**; Of very high solubility **[ ]**;
Of high solubility **[ ]**; Soluble **[ ]**; Slightly soluble **[ ]**;
Of low solubility **[ ]**; Of very low solubility **[X]**; Not soluble **[ ]**
Method : OECD TG 105
Year : 1998

GLP : Yes **[X]** No **[ ]** ? **[ ]**
Test substance : Tokyo Kasei Kogyo Co., Ltd. Purity: 98.5%
Remark :
Source : Chemicals Evaluation and Reseach Institute, Japan
Ministry of International Trade and Industry (1998)

(b) Value : 0.00039 mg/L
Temperature : 25 °C
Description : Miscible **[ ]**; Of very high solubility **[ ]**;
Of high solubility **[ ]**; Soluble **[ ]**; Slightly soluble **[ ]**;
Of low solubility **[ ]**; Of very low solubility **[X]**; Not soluble **[ ]**
Method : other : see remarks
Year : 1983
GLP : Yes **[X]** No **[ ]** ? **[ ]**
Remark : The method was based on a procedure entitled 'Measurement of tris(2-ethylhexyl) trimellitate', #A-8303, revised May 26, 1983.
Source : IUCLID (14)
Test condition : The test used deionised water.

(c) Value : 0.1 g/L
Temperature : 25 °C
Description : Miscible **[ ]**; Of very high solubility **[ ]**;
Of high solubility **[ ]**; Soluble **[ ]**; Slightly soluble **[ ]**;
Of low solubility **[ ]**; Of very low solubility **[X]**; Not soluble **[ ]**
Method :
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remarks :
Reference : Midwest Research Institute
Environmental Protection Agency (Nov. 1981) (47)

(d) Value : < 1 mg/L
Temperature : 20 °C
Description : Miscible **[ ]**; Of very high solubility **[ ]**;
Of high solubility **[ ]**; Soluble **[ ]**; Slightly soluble **[ ]**;
Of low solubility **[ ]**; Of very low solubility **[X]**; Not soluble **[ ]**
Method : other: see remarks
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remark : No information on method provided.
Source : IUCLID (3)

(e) Value : 0.034 - 0.179 mg/L
Temperature : 8 °C
Description : Miscible **[ ]**; Of very high solubility **[ ]**;
Of high solubility **[ ]**; Soluble **[ ]**; Slightly soluble **[ ]**;
Of low solubility **[ ]**; Of very low solubility **[X]**; Not soluble **[ ]**
Method : other : see remarks
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remark : No information on method provided.
Source : IUCLID (10)
Test condition : The test used aged well water.

B. pH Value, pKa Value

No data available

.

2.7 FLASH POINT *(liquids)*

(a) Preferred result
Value : 254 - 263 °C
Type of test : Closed cup **[ ]**; Open cup **[X]**; Other **[ ]**
Method :
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remarks :
Reference : Midwest Research Institute
Environmental Protection Agency (Nov. 1981) (47)

(b) Value : 271 ° C
Type : Closed cup **[ ]**; Open cup **[X]**; Other **[ ]**
Method : other : see remarks
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remark : The method used was the Pensky Martens open cup. No further details on method are provided.
Source : IUCLID (2)

(c) Value : ca. 227 ° C
Type : Closed cup **[ ]**; Open cup **[ ]**; Other **[X]**
Method : other : see remarks
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remark : The method used was that of ASTN D-92. No further details on method are provided.
Source : IUCLID (10), (59)

(d) Value : ca. 260 ° C
Type : Closed cup **[ ]**; Open cup **[X]**; Other **[ ]**
Method : other : see remarks
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remark : No information on method provided.
Source : IUCLID (41), (51)

(e) Value : > 225 ° C
Type : Closed cup **[ ]**; Open cup **[X]**; Other **[ ]**
Method : other
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Source : IUCLID (Alusuisse Italia Spa S. Giovanni Valdarno(AR))

2.8 AUTO FLAMMABILITY

None

2.9 FLAMMABILITY

Results : Extremely flammable **[ ]**; Extremely flammable - liquefied gas **[ ]**; Highly Flammable **[ ]**; Flammable **[X]**; Non flammable **[ ]**; Spontaneously flammable in air **[ ]**; Contact with water liberates highly flammable gases **[ ]**; Other **[ ]**
Method :
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remarks :
Reference : Midwest Research Institute
Environmental Protection Agency (Nov. 1981) (47)

2.10 EXPLOSIVE PROPERTIES

No data

2.11 OXIDISING PROPERTIES

No data

2.12 OXIDATION: REDUCTION POTENTIAL

No data

2.13 ADDITIONAL DATA

(a)
Remark : STABILITY: TOTM is chemically stable at high temperatures.
Source : IUCLID (2), (22), (36)

(b) Remark : THERMAL DECOMPOSITION: Combustion generates oxides of carbon and thermal decomposition may produce acrid fumes.
Source : IUCLID (2)

(c) Remark: VAPOUR DENSITY: 18 (air=1)
Source : IUCLID (2)

(d) Remark: VISCOSITY: 300 cP (20°C) 9.8 cP (100°C)
Source : IUCLID (2)

(e) Remark: COEFFICIENT OF CUBICAL EXPANSION: 0.0007 (per °C at 20°C).
Source : IUCLID (2)

(f) Remark: TOTM is incompatible with strong acids and alkalis.
Source : IUCLID (2)

3.1 STABILITY

3.1.1 PHOTODEGRADATION

Type	:	other: general comments
Light source	:	
Light spect.	:	
Rel. intensity	:	
Deg. Product	:	
Method	:	other (calculated): see remarks for general comment
GLP	:	Yes **[ ]** No **[ ]** ? **[X]**
Remark	:	General statements suggest that in an aquatic environment photolysis of TOTM would probably be slow, due to low solubility and the tendency to sorb onto humic matter (Dynamac, 1982; Spangler, 1983).
Source	:	IUCLID (21), (36), (61)

3.1.2 STABILITY IN WATER

(a) Preferred result

Type	:	abiotic
t1/2 pH4	:	No hydrolysis at 50°C in 5 days
t1/2 pH7	:	17.5 days at 25°C
t1/2 pH9	:	11.9 days at 25°C
Method	:	OECD TG 111
Year	:	1998
GLP	:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance	:	Tokyo Kasei Kougyou Co.Ltd. Purity: 98.5%
Remark	:	
Source	:	Chemicals Evaluation and Reseach Institute, Japan Ministry of International Trade and Industry (1998)

(b)

Type	:	abiotic
t1/2 pH4	:	
t1/2 pH7	:	
t1/2 pH9	:	
Degradation	:	0 % after 96 hour(s) at pH and 100 °C
Deg. Product	:	
Method	:	other: no further data, see remarks for general comments
GLP	:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance	:	no data
Remark	:	TOTM does not hydrolyse in water at neutral pH (Eastman Chemicals, 1982b). There is no detectable hydrolysis when boiled in water for 96 hours (Eastman Chemicals, 1982a). TOTM would be expected to persist in aquatic environments, especially in sediments (EPA, 1982). Hydrolysis would probably be slow, forming 2-ethylhexanol (BP, 1991a), and would be reduced by sorption onto sediments and low solubility (Dynamac, 1982).
Source	:	IUCLID (2), (21), (22), (23), (35)

3.1.3 STABILITY IN SOIL

Type	:	other: general comments
Radiolabel	:	
Concentration	:	
Soil temp.	:	

Soil humidity :
Soil classif. :
Year :
Deg. Product :
Method : other: see remarks for general comments
Year :
GLP :
Test substance :
Remark : Low water solubility and a high octanol/water partition coefficient would indicate strong absorption to sediments and soils (EPA, 1982), minimizing any degradative processes (Dynamac, 1982). Significant portions of sediments and soils would be expected to be anaerobic; degradation of TOTM under anaerobic conditions would probably be a slow process (EPA, 1982). TOTM would not be expected to be particularly mobile in soil and leaching from soil would be slow (Dynamac, 1982; McCall, 1979).
Source : IUCLID (21), (35), (46)

3.2 MONITORING DATA (ENVIRONMENTAL)

No data available

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

3.3.1 TRANSPORT

(a) Type : adsorption
Media : water - soil
Air (level I) :
Water (level I) :
Soil (level I) :
Biota (level II / III) :
Soil (level II / III) :
Method : other: see remarks for general comments
Remark : Leaching of TOTM from soil to water and ovement between sediment and water are both expected to be slow, limited by the relatively high octanol / water partition coefficient, low water solubility and the consequent sorption onto soil, sediment and humic matter (Dynamac, 1982 and EPA, 1982).
Source : IUCLID (21), (35)

(b) Type : desorption
Media : soil - air
Air (level I) :
Water (level I) :
Soil (level I) :
Biota (level II / III) :
Soil (level II / III) :
Method : other: see remarks for general comments
Remark : The atmosphere is not expected to play a direct role in the fate of TOTM (Dynamac, 1982).
Source : IUCLID (21)

3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

(a) Preferred result

Media : Air-biota **[ ]**; Air-biota-sediment-soil-water **[X]**; Soil-biota **[ ]**; Water-air **[ ]**; Water-biota **[ ]**; Water-soil **[ ]**; Other **[ ]**

Method : Fugacity level I **[ ]**; Fugacity level II **[ ]**; Fugacity level III **[X]**; Fugacity level IV **[ ]**; Other(calculation) **[ ]**; Other(measurement) **[ ]**

Results : Predicted distribution of TOTM using Fugacity level III (%)

Compartment	*Release 100% to air*	*Release 100% to water*	*Release 100% to soil*
Air	19.6	0.0	0.0
Water	4.7	32.7	0.0
Soil	66.2	0.1	100.0
Sediment	9.5	67.2	0.0

Remark : Refer to Appendix 1.

Reference : Dainippon Ink and Chemicals, Inc. unpublished report.(2001)

(b) Media : Air-biota **[ ]**; Air-biota-sediment-soil-water **[ ]**; Soil-biota **[ ]**; Water-air **[ ]**; Water-biota **[ ]**;Water-soil **[X]**; Other**[ ]**

Method : Fugacity level I **[ ]**; Fugacity level II **[ ]**; Fugacity level III **[ ]**; Fugacity level IV **[ ]**; Other(calculation) **[X]**; Other(measurement)**[ ]** see remarks for general comments

Remark : TOTM is apparently readily extracted from PVC by oils and soapy water (Bell Labs, 1982) and could leach form landfills. TOTM would be predicted, based on its properties, to partition to the terrestrial rather than the aquatic or atmospheric components, showing persistence particularly in sediments and soils (Dynamac, 1982; EPA, 1982,1983; McCall et al. 1979).

Source : IUCLID (1), (21), (35), (36), (46)

3.4 IDENTIFICATION OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE

Remark : From the very sparse data and comments identified, aerobic degradation would seem likely to be more important than anaerobic biodegradation in the breakdown of TOTM.

Source : IUCLID (International Speciality Chemicals Ltd. Hythe FMC Corporation Manchester)

3.5 BIODEGRADATION

(a) Preferred result

Type : Aerobic

Inoculum : activated sludge

Concentration : 30mg/L related to test substance

Contact time :

Degradation : 4.2 % after 28 day

Result :

Deg. Product :

Method : OECD TG 302C "Inherent Biodegradability: Modified MITI Test(II)"

Year : 1977

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

Remark :

	Source	:	Chemicals Inspection and Testing Institute (1992) Ministry of International Trade and Industry (48)
(b)	Type	:	Aerobic
	Inoculum	:	activated sludge
	Concentration	:	100mg/L related to test substance
	Contact time	:	
	Degradation	:	3.4 % after 28 day
	Result	:	
	Deg. Product	:	
	Method	:	OECD TG 301C "Ready Biodegradability: Modified MITI Test (I)"
	Year	:	1990
	GLP	:	Yes **[X]** No **[ ]** ? **[ ]**
	Test substance	:	
	Remark	:	Chemical Oxygen Demand (COD) 2.37 g/g Biological Oxygen Demand (BOD 5 Day) 0.06 g/g Biological Oxygen Demand (BOD 28 Day) 0.08 g/g Dissolved Organic Carbon Removal (DOC Removal) (OECD TG 301C)>95%
	Source	:	IUCLID (44)
(c)	Type	:	Aerobic
	Inoculum	:	domestic sewage
	Concentration	:	0.26 mg/L related to DOC (Dissolved Organic Carbon)
	Contact time	:	
	Degradation	:	68 % after 28 day
	Result	:	inherently biodegradable
	Deg. Product	:	
	Method	:	other: see remarks
	Year	:	
	GLP	:	Yes **[X]** No **[ ]** ? **[ ]**
	Test substance	:	other TS
	Remark	:	A 28-day shake-flask method was conducted, using 14C-labelled TOTM, due to problems of sorption and low solubility. The inoculum contained raw domestic sewage and soil (CMA, 1986).
	Source	:	IUCLID (15), (49), (65)
	Test substance	:	TOTM (Nuoplaz 6959). The purity is not stated in this report, however two reports would indicate that Nuoplaz TOTM and Nuoplaz 6979 are identical, with a purity of 98.95% (Tenneco Chemicals, 1981a; Nuodex Inc. 1981a).
(d)	Contact time	:	
	Degradation	:	14 %
	Result	:	
	Deg. Product	:	
	Method	:	other: CEC test
	Year	:	
	GLP	:	Yes **[ ]** No **[ ]** ? **[X]**
	Test substance	:	
	Source	:	IUCLID (42)
(e)	Deg. Product	:	
	Method	:	other: see remarks for general comments
	Year	:	
	GLP	:	Yes **[ ]** No **[ ]** ? **[X]**

Test substance :
Remark : Anaerobic biodegradation of TOTM would be expected to be slow, proceeding at a rate similar to that for DEHP, which takes longer than 30 days (no further details) (EPA, 1982). TOTM was biodegraded in an (aerobic) activated sludge plant (no further details presented) (Dynamac, 1982; EPA, 1982) and would be expected to biodegrade in a suitably acclimated treatment plant (BP, 1991).
Source : IUCLID (2), (21), (35)

3.6 BOD_5, COD OR RATIO BOD_5/COD

No data

3.7 BIOACCUMULATION

(a) Preferred result
Results : BCF(42days) < 1 - 2.7 (conc: 0.2 mg/L)
< 0.1 - 0.23 (conc: 2 mg/L)
Method : OECD TG 305C "Degree of Bioconcentration in Fish
Year : 1978
GLP : Yes **[ ]** No **[X]** ? **[ ]**
Remark : Species: *Cyprinus carpio*
Exposure Priod : 42days
Source : Chemicals Inspection and Testing Institute (1992)
Ministry of International Trade and Industry (48)

(b) Elimination :
Method : Other:see remarks for general comments
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remark : TOTM has been predicted to have a high potential for bioaccumulation due to the high octanol / water partition coefficient and structural similarity to the dialkyl phthalates (EPA, 1982).
Bioaccumulation may be limited by metabolism and excretion and in short-term tests, by slow-uptake (Dynamac, 1982).
Dialkyl phthalates in general have high bioconcentration factors (BCF). BCF values of 107,000 and log BCF values of 2-4 have been quoted (BUA, 1989; EPA, 1982; Howard, 1986).
Source : IUCLID (5), (21), (35), (40)

4.1 ACUTE / PROLONGED TOXICITY TO FISH

A. ACUTE

(a) Preferred result
Type of test : static **[ ]**; semi-static **[X]**; flow-through **[ ]**; other *(e.g. field test)* **[ ]**
open-system **[ ]**; closed-system **[ ]**
Species : *Oryzias latipes*
Exposure period: 96 hours
Results : LC_{50} (96h) > 100 mg/L
Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**
Method : OECD TG 203
GLP : Yes **[X]** No **[ ]** ? **[ ]**
Test substance : Tokyo Kasei Kogyo Co., Ltd. Purity: more than 95%
Remarks : Groups of 10 *Oryzias latipes* were exposed to the nominal concentration of 100 mg/L, solubilizer control (hydrogenated caster oil = HCO-40) and laboratory water control at 23.5-24.1℃. A change of water was every 24hrs. Measured concentration was 101-103% of nominal concentration.
Reference : The test was performed by the Toray Research Center, Japan Environment Agency of Japan (1998) (32)

(b) Type : static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other *(e.g. field test)* **[ ]**
open-system **[ ]**; closed-system **[ ]**
Species : Salmo gairdneri (Fish, estuary, fresh water)
Exposure period: 96 hours
Analytical monitoring: no
NOEC : > 1 mg/L
LC50 : > 1 mg/L
Method : other
Year : 1990
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Test substance :
Remark : In common with other substances of low solubility, the aquatic toxicity was measured using a test concentration at the limit of solubility. No toxicity was observed at this level.
Source : IUCLID (43)

B. PROLONGED

Type of test : static **[ ]**; semi-static **[ ]**; flow-through **[X]**; other *(e.g. field test)* **[ ]**
open-system **[ ]**; closed-system **[ ]**
Species : *Oryzias latipes*
Exposure period: 14 days
Results : LC_{50} (14day) > 75mg/L
NOEC (14day) > 75mg/L
LOEC (14day) > 75mg/L
Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**
Method : OECD TG 204 (1984)
GLP : Yes **[X]** No **[ ]** ? **[ ]**
Test substance : Tokyo Kasei Kogyo Co., Ltd. Purity: more than 95%
Remarks : Groups of 10 *Oryzias latipes* were exposed to the nominal concentration of 18.8, 37.5, 75.0 mg/L, solubilizer control (hydrogenated caster oil = HCO-40) and laboratory water control at 23.5-24.1℃. Measured concentration

was 80.0 -95.2 % of nominal concentration.
Reference : The test was performed by the Toray Research Center, Japan Environment Agency of Japan (1998) (33)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

A. Daphnia

(a) Preferred result
Type of test : static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other *(e.g. field test)* **[ ]**; open-system **[ ]**; closed-system **[ ]**
Species : *Daphnia magna*
Exposure period: 48 hours
Results : EC_{50} (24h) > 180 mg/L
EC_{50} (48h) > 180 mg/L
NOEC >180 mg/L
LOEC >180 mg/L
Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**
Method : OECD TG 202
GLP : Yes **[X]** No **[ ]** ? **[ ]**
Test substance : Tokyo Kasei Kogyo Co., Ltd. Purity: more than 95%
Remarks : 20 *daphnids* (4 replicates by 5 organisms) were exposed to the nominal concentrations of 17.1, 30.9, 55.6, 100.0 and 180.0 mg/L, solubilizer control (hydrogenated caster oil=HCO-40) and laboratory water control at 19.9-20.2℃. Measured concentrations were 90.1-99.6 % of nominal concentration throughout the test period. Nominal concentration of 180.0 mg/L was the maximum under which the observations of the symptoms derived from each concentration could be practicable because of cloudiness of the tested waters.
Reference : The test was performed by the Toray Research Center, Japan Environment Agency of Japan (1998) (30)

(b) Type :
Species : *Daphnia magna* (Crustacea)
Exposure period: 48 hour
Analytical monitoring: no
NOEC : > 1 mg/L
EC50 : > 1 mg/L
Method : other
Year : 1990
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Test substance :
Remark : In common with other substances of low solubility, the aquatic toxicity was measured using a test concentration at the limit of solubility. No toxicity was observed at this level.
Source : IUCLID (44)

4.3 TOXICITY TO AQUATIC PLANTS, *e.g. algae*

Species : *Selenastrum capricornutum* ATCC 22662
Endpoint : Biomass **[ ]**; Growth rate **[X]**; Other **[ ]**
Exposure period: 72 hours
Results : Growth EC_{50} (72h) >100 mg/L
NOEC > 100 mg/L
Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**

Method : OECD TG 201
GLP : Yes **[X]** No **[ ]** ? **[ ]**
Test substance : Tokyo Kasei Kogyo Co., Ltd. Purity: more than 95%
Remarks : Cultivation with shaking test. The EC_{50} value for growth rate was calculated based on 1 concentration(100mg/L). Hydrogenated caster oil (=HCO-40) was used as solubilizer.
Reference : The test was performed by the Toray Research Center, Japan Environment Agency of Japan (1998) (29)

4.4 TOXICITY TO BACTERIA

No data available

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) Preferred result
Type of test : static **[ ]**; semi-static **[X]**; flow-through **[ ]**; other *(e.g. field test)* **[ ]**; open-system **[ ]**; closed-system **[ ]**
Species : *Daphnia magna*
Endpoint : Mortality **[X]**; Reproduction rate **[X]**; Other **[ ]**
Exposure period: 21 days
Results : LC_{50} (21days)>100.0 mg/L
EC_{50} (21day) = 89.1 mg/L (Logit Method)
NOEC = 55.6 mg/L (Dunnet method)
LOEC > 100.0 mg/L
Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**
Method : OECD TG 211 (1997)
GLP : Yes **[X]** No **[ ]** ? **[ ]**
Test substance : Tokyo Kasei Kogyo Co., Ltd. Purity: more than 95%
Remark : 10 daphnids were exposed to 2 nominal concentrations (55.6 and.100 mg/L), solubilizer control (hydrogenated caster oil=HCO-40) and laboratory water control at 19.9 - 20.8℃. Measured concentrations were 94.7 - 101.3 % of the nominal concentrations throughout the 21 days test period.
Reference : The test was performed by the Toray Research Center, Japan Environment Agency of Japan (1998) (31)

(b) Species : *Daphnia magna* (Crustacea)
Endpoint : mortality
Exposure period: 21 days
Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**
NOEC : > 82 ug/l
Method : other: see remark
Year : 1984
GLP : Yes **[X]** No **[ ]** ? **[ ]**
Test substance : other TS
Remark : The study was conducted following procedures outlined in ABC Protocol No. 7901, approved 7 October 1984. The procedures follow those of the American Society for Testing and Materials and the U.S. Environmental Protection Agency.

Result	:	No significant effects were seen on survival, mean adult length or mean young/adult reproduction day.
Source	:	CMA (10)
Test condition	:	This dynamic flow-through chronic toxicity study was conducted at 20°C (+/- 2°C). Measured exposure concentrations, up to 101 ug/l (mean concentration 82 ug/l), were lower than nominal concentrations. The solubility of TOTM in the test water (aged well water) was stated to be 34-179 ug/l.
Test substance	:	TOTM (Nuoplaz 6959), 98.95% purity.

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 data available

4.8 BIOTRANSFORMATION AND KINETICS

No data available

4.9 ADDITIONAL REMARKS

No data available

5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

(a) Preferred result
Type : LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain : Rats (crj:CD(SD))
Value : > 2,000mg/kg for both sexes
Discriminating dose: N/A
Method : OECD TG 401 (1981)
GLP : Yes **[X]** No **[ ]** ? **[ ]**
Test substance : Daihachi Kagaku Kogyo Co., Ltd. Purity >99.0 %
Remarks : Loosening erring of the stool attributable to the treatment with corn oil (vehicle) was observed for 3 hours from the administration for both sexes in the groups given 0 and 2,000mg/kg. However no deaths occurred of either male or female animals. The test substance did not cause any changes in body weight. No macroscopic abnormalities that could be attributed to treatment with the test substance was seen on pathological examination.
Reference : The test was performed by the Biosafety Research Center, Foods, Drugs and Pesticides (An-Pyo Center), Japan
Ministry of Health & Welfare, Japan (49)

(b) Type : LD_0 **[X]**; LD_{100} **[ ]**; LD_{50} **[ ]**; LDL_0 **[ ]**; Other **[ ]**
Species : Rat
Strain : SD
Sex : male & female
Number of animals: 5 for both sexes
Vehicle :
Value : > 5000 mg/kg bw
Method : other: see remarks
Year : 1981
GLP : Yes **[X]** No **[ ]** ? **[ ]**
Test substance : Nouplez TOTM. Purity 98.95%
Remark : The test method was similar to that described in section 1500.3 Federal Hazardous Substances Act Regulations, 16 CFR, p 114, and apparently similar to OECD TG 401 and Directive 84/449/EEC, B.1. Five rats of each sex were observed for 14 days following gavage administration of 5 g/kg bw. No deaths, or behavioural or gross pathological effects were seen.
Source : Bioserch Incorporated.
Environmental Protection Agency (55)

(c) Type : LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species : Rat
Strain :
Sex :
Number of animals:
Vehicle :
Value : > 3200 mg/kg bw
Method : other: see remarks
Year :
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remark : No information on method is given in this brief data sheet.
Source : IUCLID (28)

Test substance : Kodaflex TOTM, purity not specified.

(d) Type : LD_0 **[X]**; LD_{100} **[ ]**; LD_{50} **[ ]**; LDL_0 **[ ]**; Other **[ ]**
Species : Rat
Strain :
Vehicle :
Method : other: Two rats/sex were administered the test material once orally at a dosage level of 10 mg/kg and observed for signs of toxicity for 14 days.
Year : 1984
GLP : Yes **[ ]** No **[X]** ? **[ ]**
Test substance :
Remark : Results: No rats died during the course of the study. The only sign of toxicity was piloerection in the two males at one and two hours postdose.
Source : IUCLID (62)

(e) Type : LD_0 **[X]**; LD_{100} **[ ]**; LD_{50} **[ ]**; LDL_0 **[ ]**; Other **[ ]**
Species : Rat
Strain :
Vehicle :
Value : 9850 mg/kg bw
Method : other: see remarks
Year :
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remark : Two rats of each sex were given 10 ml/kg by gavage (approximately 9.85 g/kg bw). There were no gross abnormalities on autopsy at 14 weeks. Piloerection occurred in males 2-3 hours after administration. No deaths were recorded.
Source : IUCLID (6)
Test substance : Reomol OTM, purity not specified.

(f) Type : LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species : mouse
Strain :
Sex :
Number of animals:
Vehicle :
Value : > 3200 mg/kg bw
Method : other: see remarks
Year :
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remark : No information on method is given in this brief data sheet.
Source : IUCLID (28)
Test substance : Kodaflex TOTM, purity not specified.

(g) Type : LD_0 **[X]**; LD_{100} **[ ]**; LD_{50} **[ ]**; LDL_0 **[ ]**; Other **[ ]**
Species : mouse
Strain :
Sex :
Number of animals:
Vehicle :
Value : > 60000 mg/kg bw
Method : other: see remarks
Year :
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Test substance : no data

Remark : No information on method is presented in the translation of this Russian paper (Timofievskaya, 1981). A citation of this study reports no deaths but sluggishness at 60 g/kg bw (Dynamac, 1982). A dose (apparently by gavage) of 3 g/kg bw was said to be the limiting acute gastric dose, "based on changes in kidney function". No further details were presented.
Source : IUCLID (21), (68)

(h) Type : LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species : other
Strain :
Sex :
Number of animals:
Vehicle :
Value : > 10000 mg/kg bw
Source : IUCLID(Alusuisse Italia Spa S. Giovanni Valdarno(AR))

5.1.2 ACUTE INHALATION TOXICITY

Type : LC_0 **[X]**; LC_{100} **[ ]**; LC_{50} **[ ]**; LCL_0 **[ ]**; Other **[ ]**
Species/Strain : Rats (crj:CD(SD))
Sex : Male & Female
Number of animals: 5 for both sexes
Vehicle :
Exposure time : 4 hour
Value : 2,600 mg/m^3
Method : other: see remarks
Year : 1982
GLP : Yes **[X]** No **[ ]** ? **[ ]**
Test substance : Nuoplaz 6959. Pirity 98.95%
Remarks : A 0.5 m^3 stainless steel inhalation chamber was used during this study. The 4-hour exposure time interval included the chamber build-up time but not the chamber exhaust phase. After the exposure, all animals were observed daily for 14 days for clinical sign of toxicity.
Source : Midwest Research Institute (1982)
Environmental Protection Agency (53)

5.1.3 ACUTE DERMAL TOXICITY

(a) Type : LD_0 **[X]**; LD_{100} **[ ]**; LD_{50} **[ ]**; LDL_0 **[ ]**; Other **[ ]**
Species : Rabbit
Strain :
Sex : Male & Female
Number of animals: 5 of both sexes
Vehicle :
Value : > 2.0 mL/kg
Method : other: see remarks
Year : 1981
GLP : Yes **[X]** No **[ ]** ? **[ ]**
Remark : This study was designes in accordance with the procedure set forth in the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).
A dosage of 2.0 mL/kg was applied to the exposure area (approximately 10% of the body surface area) of 3 male and female rabbits. The other two male and two female rabbits served as control animals. A 2x2-inch gauze pad was placed on the exposure area to prevent seepage of the compound

from the area. Each rabbit was then wrapped with a rubber dam. After 24 hour of exposure, the rubber dam and gauze pad was removed and the exposure area was wiped to remove any remaining test material. The rabbits were observed for a total of 14 days; no toxic signs were noted.

Source : Midwest Research Institute.
Environmental Protection Agency (54)
Test substance : Nuoplaz 6959, 98.95% purity.

(b) Type : LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species : rabbit
Strain :
Sex :
Number of animals:
Vehicle :
Value : > 1970 mg/kg bw
Method : other: see remarks
Year :
GLP : Yes **[X]** No **[ ]** ? **[ ]**
Remark : The method used was similar to OECD TG 402 limit test (1981) except that only 3 male and 3 female animals were used. Covered contact for 24 hours with abraded skin exposed 10% of the body surface area. Observation for 14 days was followed by gross necropsy. No overt toxicity or gross pathological effects were seen on examination at 14 days.
Source : IUCLID (66)
Test substance : Nuoplaz 6959, 98.95% purity.

(c) Type : LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species : guinea pig
Strain :
Sex :
Number of animals:
Vehicle :
Value : > 19700 mg/kg bw
Method : other: see remarks
Year :
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Test substance : no data
Remark : No further details presented in this brief review.
Source : IUCLID (28)

5.1.4 ACUTE TOXICITY, OTHER ROUTES OF ADMINISTRATION

(a) Type : LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species : rat
Strain :
Sex :
Number of animals:
Vehicle :
Route of admin.: i.p.
Exposure time :
Value : > 3200 mg/kg bw
Method : other: see remarks
Year :
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remark : No information on method provided.

Source : IUCLID (27)
Test substance : Kodaflex TOTM, purity unspecified.

(b) Type : LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species : mouse
Strain :
Sex :
Number of animals:
Vehicle :
Route of admin.: i.p.
Exposure time :
Value : > 3200 mg/kg bw
Method : other: see remarks
Year :
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remark : No details on method provided.
Source : IUCLID (27)
Test substance : Kodaflex TOTM, purity unspecified.

5.2 CORROSIVENESS/IRRITATION

5.2.1 SKIN IRRITATION/CORROSION

(a) Species : Rabbit
Concentration : 0.5 mL
Exposure :
Exposure time : 24 hr
Number of animals: 6
PDII :
Result : slightly irritating
EC classification:
Method : other: see remarks
Year : 1981
GLP : Yes **[X]** No **[ ]** ? **[ ]**
Remark : The test method was similar to Section 1500.41. Federal Hazardous Substances Act Regulations - 16 CFR. 0.5 ml of the neat material was held in covered contact with the abraded and unabraded skin of 6 rabbits, for 24 hours, and examined on removal of the patch and again 48 hours later (Tenneco Chemicals, 1981c). The primary irritation score of 1.04 would be equivalent to a classification (<2) of mildly irritant (Draize, 1944). This report concluded that TOTM was not a primary skin irritant in rabbits. It is not possible to assign a classification according to Directive 67/548/EEC.
Source : Biosearch Incorporated.
Environmental Protection Agency (56)
Test substance : Nuoplaz TOTM, 98.95% purity.

(b) Species : rabbit
Concentration :
Exposure :
Exposure time :
Number of animals:
PDII :
Result : slightly irritating
EC classification: not irritating

Method : OECD TG 404 "Acute Dermal Irritation/Corrosion"
Year : 1984
GLP : Yes **[ ]** No **[X]** ? **[ ]**
Test substance :
Remark : Methods: Two rabbits/sex were patched with 0.5 ml of the test material as supplied to one test site each along the midline of the back under a 4cm square gauze pad. This was covered with aluminum foil and secured with surgical tape, thus producing an occlusive patch. After 4 hours the dressing was removed and the compound residue rinsed from the site. Sites were scored for edema and erythema 30-60 minutes after removal of the dressing, and again at 24, 48 and 72 hours and 7 days.
Results : Slight erythema was seen in all rabbits 30-60 minutes after removal of the occlusive patch. Only one rabbit was affected at 72 hours and no abnormalities were observed at 7 days.
Source : IUCLID (64)

(c) Species : rabbit
Concentration :
Exposure :
Exposure time :
Number of animals:
PDII :
Result : slightly irritating
EC classification: not irritating
Method : OECD TG 404 "Acute Dermal Irritation/Corrosion"
Year : 1981
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remark : Slight, barely perceptible, erythema occurred in all (4) rabbits at 30-60 minutes and one at up to 72 hours. No erythema was evident at 7 days and there was no oedema at any time. TOTM was not irritating according to the classification of Directive 67/548/EEC (Commission, 1993).
Source : IUCLID (7), (17)
Test substance : Reomol OTM (TOTM), purity unspecified.

(d) Species : guinea pig
Concentration : 0.5 mL
Exposure :
Exposure time : 24 hr
Number of animals: 10
PDII :
Result : not irritating
EC classification:
Method : other: see remarks
Year : 1981
GLP : Yes **[X]** No **[ ]** ? **[ ]**
Remark : Following the modified Buehler method, 10 repeated 24-hour covered applications of 0.5 ml neat TOTM were made to 10 male guinea-pigs, each followed by 24-hour rest periods before scoring.
No erythema or oedema was recorded at any time. It is not possible to assign a classification according to Directive 67/548/EEC.
Source : Biosearch Incorporated.
Environmental Protection Agency. (58)
Test substance : Nuoplaz TOTM, 98.95% purity.

(e) Species : guinea pig

Concentration :
Exposure :
Exposure time : 24 hr
Number of animals:
PDII :
Result : slightly irritating
EC classification:
Method : other: see remarks
Year :
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Remark : Covered contact for 24 hours with neat TOTM, no further infomation on method provided. This brief summary notes slight irritation. It is not possible to assign a classification according to Directive 67/548/EEC.
Source : IUCLID (27), (28)
Test substance : Described as TOTM(Eastman Kodak, 1983b) and Kodaflex TOTM (Eastman Kodak, 1983a).

(f) Species : mouse
Concentration :
Exposure :
Exposure time :
Number of animals:
PDII :
Result : slightly irritating
EC classification:
Method : other: see remarks
Year :
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Test substance : no data
Remark : Repeated 4 hour applications were made to the tail. No further details are provided. Treatment resulted in "injection" of the vessels and reddening of the skin. It is not possible to assign a classification according to Directive 67/548/EEC.
Source : IUCLID (68)

5.2.2 EYE IRRITATION/CORROSION

(a) Species : rabbit
Concentration : 0.1mL
Dose : Single
Exposure Time: 1, 2, 3, 4, 7 days
Comment :
Number of animals: 6
Result : slightly irritating
EC classification :
Method : other: see remarks
Year : 1981
GLP : Yes **[X]** No **[ ]** ? **[ ]**
Remark : The method used was similar to section 1500.42. Federal Hazardous Substances Act Regulations - 16 CFR. The neat material (0.1 ml) was instilled into one eye of each of 6 adult New Zealand White rabbits. Treated eyes were examined at 1, 2, 3, 4 and 7 days (Nuodex Inc, 1981c). An average ocular irritation score of 2.3 (out of a maximum of 110) on day 1, and 1.7 on day 2, would be equivalent to minimal irritation (Kobel & Gfeller, 1985). This report concluded that TOTM was not a primary

ocular irritant. It is not possible to assign a classification according to Directive 67/548/EEC.
Source : Bioserch Incorporated.
Environmental Protection Agency (57)
Test substance : Nuoplaz TOTM, 98.96% purity (see Section 3.5).

(b) Species : rabbit
Concentration : 0.1 mL
Dose : single
Exposure Time:
Comment :
Number of animals:
Result : slightly irritating
EC classification: not irritating
Method : OECD TG 405 "Acute Eye Irritation/Corrosion"
Year : 1984
GLP : Yes **[ ]** No **[X]** ? **[ ]**
Test substance :
Remark : Methods: Two rabbits/sex were administered 0.1 ml of the test material into the conjunctival sac of the left eye. Eyelids were then held closed for 1 second. The rabbits were examined using a direct ophthalmoscope, at 1, 24, 48 and 72 hours after application of the test compound.
Results : Injection of the conjunctival vessels was seen in all rabbits at 1 and 24 hours after dosing. After 72 hours two of the rabbits had reversed. No abnormalities were seen at 72 hours postdose.
Source : IUCLID (68)

(c) Species : rabbit
Concentration :
Dose :
Exposure Time :
Comment :
Number of animals:
Result : slightly irritating
EC classification:
Method : other: see remarks
Year :
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Test substance : no data
Remark : A single drop (approx. 0.05 ml) instilled into the conjunctival sac caused slight and transient irritation which cleared at 24 hours (Eastman Kodak, 1983a, 1983b). No further details are provided in these brief summaries, probably of the same study. It is not possible to assign a classification according to Directive 67/548/EEC.
Source : IUCLID (27), (28)

5.3 SKIN SENSITISATION

(a) Type : Buehler Test
Species : guinea pig
Number of animals:
Vehicle :
Result : not sensitizing
Classification : not sensitizing
Method : OECD TG 406 "Skin Sensitization"

Year : 1981
GLP : Yes **[X]** No **[ ]** ? **[ ]**
Test substance : other TS
Remark : The reference cited for this method is the same as that cited for the Buehler test in OECD TG 406, 1981. 24 hour covered contact with 0.5 ml neat TOTM was repeated on alternate days for 10 applications. A similar challenge application was made after a 2 week rest period.
No sensitization was seen in any of the 10 animals tested. TOTM did not induce sensitization according to the classification of Directive 67/548/EEC (Commission, 1993).
Source : IUCLID (17), (67)
Test substance : Nuoplaz TOTM, 98.95% purity.

(b) Type : no data
Species : guinea pig
Number of animals:
Vehicle :
Result : not sensitizing
Classification :
Method : other: see remarks
Year :
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Test substance : no data
Remark : Described in one reference (Eastman Kodak, 1983a) as a standard sensitization test. Apparently TOTM was applied neat. No further details are provided in these three brief reports, probably of a single study.
Source : IUCLID (18), (27), (28)

5.4 REPEATED DOSE TOXICITY

(a) Preferred result
Species : rat
Sex : male/female
Strain : Fischer 344
Route of admin.: oral feed
Exposure period: 28 days
Frequency of treatment : daily
Post obs. period: none
Doses : 0(0), 0.2(184), 0.67(650), 2(1826) % (mg/kg bw/day)
Control group : yes, concurrent no treatment
NOAEL : 184 mg/kg bw
LOAEL : 650 mg/kg bw
Method : other: see remarks
Year : 1985
GLP : Yes **[X]** No **[ ]** ? **[ ]**
Test substance : Purity 98.2 % (GC/FID), 97.9 % (HPLC)
Remark : Groups of 5 males and 5 females were fed diets containing the specified levels of TOTM. Body weight and food intake were monitored throughout and preserved tissues from the control and top dose groups were examined histologically. Liver samples from all groups were examined microscopically and with biochemical analyses.
Result : Rats of both sexes receiving 0.67% in the diet had slightly increased liver weights and increased activities of certain liver enzymes (including palmitoyl CoA and carnitine acetyl transferase). Blood effects including reduced erythrocytes and increased leucocytes, and raised cholesterol

levels occurred in treated rats of both sexes at 0.67%. Palmitoyl CoA acitvity was increased in male rats at the lowest dose (0.2%). Slight peroxisome proliferation was seen in rats receiving the top dose (2%).
Source : The British Industrial Biological Research Association Chemical Manufacture Association. (9)

(b) Species/strain : Rats (Crj:CD(SD))
Sex : Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**
Route of Administration: Oral feed.
Exposure period: Males & Females, 28 days
Frequency of treatment: Daily
Post exposure observation period: 15 days
Dose : 0, 100, 300, 1,000 mg/kg/day (5 males, 5 females)
Control group : Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[X]**; Concurrent vehicle **[ ]**; Historical **[ ]**
NOEL : Males & Females, 1,000 mg/kg/day
Results : No test substance related changes were noted in terms of clinical signs, body weights food consumption and haematology, blood chemical examination, urinalysis, and pathological findings.
The NOEL for repeat dose toxicity is considered to be 1,000 mg/kg/day for both sexes.
Method : Guidelines for 28-day Repeated Dose Toxicity Testing of Chemicals (Japan)
GLP : Yes **[X]** No **[ ]** ? **[ ]**
Test substance : Commercial, purity: more than 99.0 %
Reference : The test was performed by the Biosafety Research Center, Foods, Drugs and Pesticides (An-Pyo Center), Japan.
Ministry of Health & Welfare, Japan (49)

(c) Species : rat
Sex : male
Strain : Fischer 344
Route of admin.: gavage
Exposure period: 28 days
Frequency of treatment : 5 days/wk, 4 wk
Post obs. period: none
Doses : 0(5), 1000(5) mg/kg bw/day
Control group : yes, concurrent vehicle (corn oil)
LOAEL : 1000 mg/kg bw
Method : other: see remarks
Year : 1981
GLP : Yes **[X]** No **[ ]** ? **[ ]**
Remark : Full necropsies and retention of liver, kidney, brain, spleen and testis followed sacrifice. No microscopic studies were reported. The biological significance of the liver effect is not clear from this study.
Result : There was no overt indication of toxicity and no significant effect on body or liver weights in treated animals compared to controls. A slight (non-significant) increase in liver and relative liver weights occurred in treated animals. Blood triglyceride levels were significantly lower than controls.
Source : Bioserch Incorporated.
Environmental Protection Agency. (52)
Test substance **:** Nuoplaz TOTM and Nuoplaz 6959, 98.95% purity.

(d) Species : rat
Sex : male/female

Strain : Fischer 344
Route of admin.: gavage
Exposure period: 21 days
Frequency of treatment : daily
Post obs. period: none
Doses : 0(10), 200(10), 700(10), 2000(10) mg/kw bw/day
Control group : yes, concurrent vehicle
LOAEL : 200 mg/kg bw
Method : other: see remarks
Year :
GLP : Yes **[X]** No **[ ]** ? **[ ]**
Test substance : no data
Remark : The groups of 5 males and 5 females were monitored for food intake and body weight throughout. On sacrifice, blood samples were taken and liver, kidney and testis were weighed and taken for histological examination.
Result : Relative liver weights were significantly increased in female rats at all dose levels (a non dose-related increase) compared to controls. Males in the top dose group (the only group examined) showed a slight increase in hepatic peroxisomes compared to controls. Various hepatic enzyme activities (palmitoyl-CoA and lauric acid 12-hydroxylase) were increased in males at 200 mg/kg bw and in females at 2000 mg/kg bw.
Source : IUCLID (8), (39)

(e) Species : rat
Sex : male
Strain : no data
Route of admin.: i.p.
Exposure period: 7 days
Frequency of treatment : daily
Post obs. period: none
Doses : 0(6), ca. 985(6) mg/kg bw/day
Control group : yes
Control group : yes
NOAEL : 985 mg/kg bw
Method : other: see remarks
Year :
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Test substance : other TS
Remark : An unspecified strain of albino rat was tested. The test group received injections of 1 ml sample and the controls 1 ml normal saline. Animals were sacrificed 16 hours after the final treatment. Examinations were limited to liver enzyme activity. The NOEL value is clearly restricted by study limitations.
Result : There were no significant changes in the activity of the enzymes aminopyrine-N-demethylase, aryl hydrocarbon hydroxylase, glutathione-S-transferase or glutathione. No overt signs of toxicity or effects on body or liver weight were seen.
Source : IUCLID (60)
Test substance : Hatcol 200, >99% purity.

(f) Species : rat
Sex : no data
Strain : no data
Route of admin.: other: see remarks
Exposure period: 14 days

Frequency of treatment : daily
Post obs. period: no data
Doses : 14, 42 mg/kg bw/day
Control group : yes
LOAEL : 42 mg/kg bw
Method : other: see remarks
Year :
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Test substance : no data
Remark : TOTM was injected into the rats although the exact method of injection was unspecified. Group numbers, the extent of examinations and raw data were not presented in this very brief review. The LOEL is clearly limited by the restrictions of the study and its report.
Result : Relative spleen and liver weights were increased, in the top dose group, compared to controls. Microscopic examination of these tissues indicated noncaseous granulomata and vacuoles containing TOTM. There were no deaths and "all other organ systems" were reported to be normal.
Source : IUCLID (18)

(g) Species : mouse
Sex : no data
Strain : no data
Route of admin.: other: see remarks
Exposure period: 14 day
Frequency of treatment : daily
Post obs. period: no data
Doses : 14, 42 mg/kg bw/day
Control group : no data specified
NOAEL : 42 mg/kg bw
Method : other: see remarks
Year :
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Test substance : no data
Remark : TOTM was injected into mice although the exact method of injection was not reported. Group numbers, the extent of examinations and raw data were not presented in this brief review. The NOEL is clearly limited by the restrictions of the study and its report.
Result : No effects on morbidity or mortality were reported in this very brief report.
Source : IUCLID (18)

(h) Species : dog
Sex : no data
Strain : no data
Route of admin.: other
Exposure period: 14 days
Frequency of treatment : daily
Post obs. period: no data
Doses : (apparently) 14, 42 mg/kg bw/day
Control group : no data specified
NOAEL : 42 mg/kg bw
Method : other: see remarks
Year :
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Test substance : no data

Remark : TOTM was injected (exact route of injection unspecified) into an unstated number of animals. No details on the extent of examination were reported in this very brief review. The NOEL is clearly limited by the lack of data in this report.
Result : No abnormalities were reported to the cardiovascular system or on gross examination.
Source : IUCLID (18)

5.5 GENETIC TOXICITY IN VITRO

A. BACTERIAL TEST

(a) Type : Bacterial reverse mutation assay (Ames test)
System of testing: Species/strain: *S.typhimurium* TA100, TA1535, TA98, TA1537 and *Eschrichia coli* WP2 UVY A
Concentration : -S9mix,0,313-5000ug/plate(TA100,TA1535,TA98,TA1537,WP2)
+S9mix,0,313-5000ug/plate(TA100,TA1535,TA98,TA1537,WP2)
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
Results :
Cytotoxicity conc: With metabolic activation: None within 5000ug/plate for TA100, TA1535 TA98, TA1537, WP2
Without metabolic activation: None within 5000ug/plate for TA100, TA1535, TA98, TA1537, WP2.
Precipitation conc: not stated
Genotoxic effects:

	TA100	TA1535	TA98	TA1537	WP2
With metabolic activation:	-	-	-	-	-
Without metabolic activation:	-	-	-	-	-

Method : Guideline for Screening Mutagenicity Testing of Chemicals (Japan) and OECD TG 471 and 472.
GLP : Yes **[X]** No **[ ]** ? **[ ]**
Test substance : Commercial, purity: more than 99.0%
Remarks : procedure: Plate incorporation method
Plates/test: 3
No. Replicates: 2
Solvent: Acetone
This chemical did not induce gene mutations in the *S.typhimurium* and *E coli* strains with and without S-9 mix. Toxicity was not at 5000ug/plate in the five strains in either the without S9 mix or the with S9 mix cases.
Reference : The tests were performed by the Hatano Research Institute, Food and Drug Safety Center, Japan.
Ministry of Health & Welfare, Japan (49)

(b) Type : Ames test
System of testing: Salmonella typhimurium (TA 97, 98, 100, 1535)
Concentration : 0, 100, 333, 1000, 3333, 10000 ug/plate
Cycotoxic conc.:
Metabolic activation: with and without
Result : negative
Method : other: see remarks
Year :
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Test substance : no data

Remark : The pre-incubation assay was as described in Haworth et al, 1983 but with some modifications. TOTM (0.05 ml), Salmonella culture (0.10 ml) and S9 mix or buffer were incubated at 37°C without shaking for 20 minutes. S9 from Arochlor 1254-induced male Sprague-Dawley rats and male Syrian hamsters was used at 10% and 30%. Histidine-independent colonies were counted after incubation for 2 days at 37°C. Doses were tested in triplicate and experiments repeated 1 week following the initial trial. Concurrent solvent and positive controls were run with each trial (Zeiger et al. 1988). There was no evidence of any genotoxic activity.
Source : IUCLID (38), (70)

(c) Type : Ames test
System of testing: Salmonella typhimurium (TA 98, 100)
Concentration : no data
Cycotoxic conc.:
Metabolic activation: with and without
Result : negative
Method : other: see remarks
Year :
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Test substance : no data
Remark : No further details are presented in this very brief report.
Source : IUCLID (18)

(d) Type : Bacterial gene mutation assay
System of testing: Salmonella typhimurium (strains not specified)
Concentration : up to 1 mg/plate
Cycotoxic conc.:
Metabolic activation: no data
Result : negative
Method : other: see remarks
Year :
GLP : Yes **[ ]** No **[ ]** ? **[X]**
Test substance : no data
Remark : The method is described in a very brief summary only as plate incorporation; SOP P-002. Tests up to 1 mg/plate were negative in all strains (unspecified).
Source : IUCLID (34)

B. NON-BACTERIAL IN VITRO TEST

(a) Type : Cytogenetics Assay
System of testing: Species/strain: Chinese Hamster 1mg(CHL/IU) cells
Concentration : Incubated with 0, 0.005, 1.3, 2.5,5.0 mg/ml
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
Results :
Cytotoxicity conc: With metabolic activation: None within 5.0 mg/ml
Without metabolic activation: None within 5.0mg/ml
Precipitation conc: not stated
Genotoxic effects:

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

Method : Guidelines for Screening Mutagenicity Testing of Chemicals (Japan)
GLP : Yes **[X]** No **[ ]** ? **[ ]**

Test substance : Commercial, purity: more than 99.0 %
Remarks : Solvent Acetone
Plates/test: 2
This chemical did not induce structural chromosomal aberrations or polyploidy under the conditions of this experiment.
Reference : The test was performed by the Hatano Reseach Institute, Food and Drug Safety Center, Japan.
Ministry of Health & Welfare, Japan (49)

(b) Type : HGPRT assay
System of testing: Chinese hamster ovary
Concentration : 5 - 200 nl/ml (6 concentrations)
Cycotoxic conc.:
Metabolic activation: with and without
Result : negative
Method : other: see remarks
Year :
GLP : Yes **[X]** No **[ ]** ? **[ ]**
Test substance : other TS
Remark : Preliminary cytotoxicity tests (±S9) used ten concentrations of 5-5000 nl/ml (in ethanol), in an F12 culture medium containing 5 or 10% heat-inactivated foetal bovine serum. TOTM was insoluble under the study conditions at 100 nl/ml. Six treatment concentrations (5-200 nl/ml) were selected for the mutation assay. Mutant frequencies were, in the main, comparable to the concurrent vehicle controls and within the range of variation of negative controls, and showed no dose-related increase. Under conditions of non-activation one culture (50 nl/ml) achieved 99% confidence level of having elevated mutant frequencies over vehicle controls, a result not repeated in the duplicate culture and considered to represent a statistical failure. In the activated assays both 200 nl/ml cultures had statistically elevated mutant frequencies. A repeated trial did not confirm this response. The evaluation stated that TOTM was non-mutagenic.
Source : IUCLID (12)
Test substance : Nuoplaz 6959 (Nuodex Inc., New Jersey), 98.95% purity (see remarks in Section 3.5).

(c) Type : Unscheduled DNA synthesis
System of testing: primary rat hepatocytes
Concentration : 250 - 5000 nl/ml
Cycotoxic conc.:
Metabolic activation: without
Result : negative
Method : other: see remarks
Year :
GLP : Yes **[X]** No **[ ]** ? **[ ]**
Test substance : no data
Remark : The stability in cell numbers and normal morphological appearance indicated the hepatocyte cultures were in good metabolic condition. No significant change in the nuclear labelling of cultured cells, and no dose-related response was observed. Positive controls had greatly increased nuclear labelling, exceeding all three criteria used to indicate UDS.
Source : IUCLID (13)

5.6 GENETIC TOXICITY IN VIVO

Type	:	Dominant lethal assay
Species	:	mouse
Sex	:	male
Strain	:	Swiss
Route of admin.	:	other: see remarks
Exposure period:		no data
Doses	:	ca. 1400 mg/kg bw (possibly per day)
Result	:	
Method	:	other: see remarks
Year	:	
GLP	:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance	:	no data
Remark	:	Guaranteed fertile males were treated by an unspecified route. This very brief account gives no further details.
Result	:	TOTM was not mutagenic when compared with the positive control (METEPA, probably tris(1-(2-methyl)aziridinyl)phosphine oxide); results with METEPA confirmed the validity of the system.
Source	:	IUCLID (16)

5.7 CARCINOGENICITY

Species	:	mouse
Sex	:	no data
Strain	:	Strain A
Route of admin.	:	other: see remarks
Exposure period:		no data
Frequency of treatment	:	no data
Post. obs. period:		no data
Doses	:	ca. 1400 mg/kg bw (possibly per day)
Result	:	
Control group	:	no data specified
Method	:	other: see remarks
Year	:	
GLP	:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance	:	no data
Remark	:	This brief report states only that tests in mice, with a propensity to form pulmonary adenomas, were negative for TOTM, unlike those using urethane. No further details were presented.
Source	:	IUCLID (16)

5.8 TOXICITY TO REPRODUCTION

Type	:	Fertility **[ ]**; One-generation study **[ ]**;Two-generation study **[ ]**; Other **[X]**
Species/strain	:	Rat/Crj: CD (SD)
Sex	:	Female **[ ]**;Male **[ ]**;Male/Female **[X]**; No data **[ ]**
Route of Administration:		Oral (gavage)
Exposure piriod	:	(male) 46days (female) from 14days before mating to day 3 of lactation
Post exposure period:		None
Terminal kill	:	(male) 47days (female) day 4 of lactation

Doses : 0(vehicle), 100,300,1000 mg/kg/day
Control group : Yes **[X]**; No **[ ]**; No data **[ ]**
Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**; Historical **[ ]**
NOEL parental : 100 mg/kg/day (male)
1,000 mg/kg/day (female)
NOEL Offspring: 1,000 mg/kg/day
Results : <*F1 Male*> Histopathological examination of the tests, domonstrated decrease of spermatocytes and spermatids of the 300 and 1000 mg/kg groups. No effects of TOTM on general appearance, body weight, food consumption, autopsyfindings, weight of the reproductive organs. On the basis of these findings, the NOELs of TOTM for repeat dose toxicity are considered to be 100 mg/kg/day for males.
<*F1 Female*> No effects of TOTM on general appearance, body weight, food consumption, autopsyfindings, weight of the reproductive organs. On the basis of these findings, the NOELs of TOTM for repeat dose toxicity are considered to be 1,000 mg/kg/day for females.
<*Offspring*> No influence of TOTM was detected regarding reproductive ability, organ weights or histopathological features of the ovary, delivery or maternal behavior of dams. No effects of TOTM were detected on viability, general appearance, body weights or autopsy findings for offspring. On the basis of these findings, the NOELs of TOTM for reproductive / developmental toxicity are considered to be 1000 mg/kg/day for offspring.
Method : OECD Preliminary reproductive toxicity screening test.
GLP : Yes**[X]**; No**[ ]**; ?**[ ]**
Test substance : Daihachi Kagaku Kogyo (Ltd.) purity 99.0%
Reference : The tests were performed by the Safety Reserch Institute for Chemical Compounds Co., Ltd., Japan
Ministry of Health & Welfare, Japan (50)

5.9 DEVELOPMENTAL TOXICITY/ TERATOGENICITY

No data available

5.10 OTHER RELEVANT INFORMATION

A. Specific toxicities

No data available

B. Toxicodynamics, toxicokinetics

(a) Type : Distribution
Remark : TOTM given intravenously accumulated in the liver (72%), lungs and spleen in rats within 24 hours. Biliary excretion, the main elimination route, was slow indicating a potential for accumulation in these target organs.
Source : IUCLID (45)

(b) Type : Metabolism
Remark : Absorption and metabolism were studied for TOTM mixed with corn oil and administered by gavage in a single dose of 100 mg/kg of body weight in 4 male SD rats. Rats were placed in glass methabolism cages and urine, feces and expired air were collected for 144 hrs(6 days), and at 144 hours, tissues and carcasses were collected for subsequent analysis. About 75% of the dose was excreted unchanged in the feces, 16% in the urine as metabolites and 1.9% was expired as $^{14}CO_2$. Radioactivity was excreted in the feces as

unchanged TOTM (85% of the fecal radioactivity), mono- and di(2-ethylhexyl) trimellitate (MOTM and DOTM, respectively), and as unidentified polar metabolites. Metabolites in the urine were identified as MOTM and metabolites of 2-ethylhexanol. Less than 0.6% of the dose remained in whole tissues. Elimination kinetics were estimated from breath and urinary excretion data. The absorption profile as reflected by excretion of $^{14}CO_2$ was complex and appeared to involve two rate controlling processes. Elimination of $^{14}CO_2$ was biphasic with half-lives of 4.3 and 31 hrs, and excretion of radioactivity in the urine was biphasic with half-lives of 3.4 hrs and 42 hrs. These studies show that TOTM was hydrolyzed to a limited extent in the gastrointestinal tract and was largely excreted unchanged in the feces.

Source : Eastman Kodak Company (1984) (24), (25)

(c) Type : Metabolism
Remark : Studies using a rat gut homogenate confirmed the very limited hydrolysis of TOTM.
Source : IUCLID (26)

(d) Type : Metabolism
Remark : Hydrolysis to the parent acid (trimellitic acid) may occur on ingestion (no further details).
Source : IUCLID (2)

5.11 EXPERIENCE WITH HUMAN EXPOSURE

(a) Remark : High concentrations of mist or vapour may cause irritation to the eyes, nose, throat and upper respiratory tract. Slight irritation to the skin or eyes may occur from contact with the liquid. Prolonged and repeated skin contact may cause defatting, making the skin more susceptible to damage by other substances. Significant absorption through the skin is unlikely.
Source : IUCLID (2)

(b) Remark : Inhalation or the vapour or mist may affect respiratory function.
Source : IUCLID (21), (69)

(c) Remark : Ingestion of TOTM may cause irritation of the throat, mouth and digestive tract and cause gastrointestinal effects including irritation, following hydrolysis to trimellitic acid.
Source : IUCLID (2)

(d) Remark : Mist and fumes from hot processing may cause irritation (presumably to mucous membranes), nausea and vomiting. (It is not clear from this note what thermal changes might occur.)
Source : IUCLID (10), (59)

(1) Bell Labs. Unpublished data provided by Paul Warren, 1982 (cited in Dynamac, 1982).

(2) BP Hythe. Material Safety Data Sheet, Bisoflex TOT (STAB),000266/001, BP Hythe Chemicals Ltd, Southampton, Hants, 1991.

(3) BP. Data provided directly from International Speciality Chemicals Ltd, Hythe, Southampton, Hants, 1991b.

(4) BUA. GDCh-Advisory Committee on Existing Chemicals of Environmental Relevance. VCH, New York, 1989.

(5) Chemicals Inspection and Testing Institute Japan. Chemical Industry Ecology-Toxicology and Information Center. ISBN 4-89074-101-1 (1992)

(6) Ciba-Geigy. (Reomol OTM) Acute oral median lethal dose (LD50) in rats with cover letter dated 010987. OTS 0513265. Doc ID 86870000080. Ciba-Geigy Pharmaceuticals, Stamford Lodge, Cheshire, 1984a.

(7) Ciba-Geigy. (Reomol OTM) Primary dermal irritation test in Californian rabbits. OTS 0513266. Doc ID 86870000081, Ciba-Geigy Pharmaceuticals, Stamford Lodge, Cheshire, 1984b.

(8) CMA. A 21-day gavage study of 2-ethylhexanol and tris(2-ethylhexyl) trimellitate to rats: effects on the liver and liver lipids. Chemical Manufacturers Association, Washington, D.C., 1987.

(9) CMA. A 28-day toxicity study with tris(2-ethylhexyl) trimellitate in the rat. OTS 408565037. Chemical Manufacturers Association, Washington D.C., 1985d.

(10) CMA. Chronic toxicity of tris(2-ethylhexyl) trimellitate to Daphnia magna under flow -through conditions. OTS 0510636. Doc ID 408565036. Chemical Manufacturers Association. 1985c.

(11) CMA. Determination of octanol/water partition coefficient of TOTM (supplementary study) with cover letter dated 012186. OTS 0510638. Doc ID 408665042. Chemical ManufacturersAssociation, 1985a.

(12) CMA. Evaluation of tris(2-ethylhexyl) trimellitate in the CHO/HGPRT forward mutation assay. Final Report. OTS 0510642. Doc. ID 408565041. Chemical Manufacturers Association, 1985f.

(13) CMA. Evaluation of tris(2-ethylhexyl) trimellitate in the rat primary hepatocyte unscheduled DNA synthesis assay. Final Report. OTS 0510641. Doc ID 408565039. LBI Project No.20991. Chemical Manufacturers Association, 1985e.

(14) CMA. Method validation for tris(2-ethylhexyl) trimellitate analysis in aquatic test water, deionised water and octanol, and solubility in deionised water. OTS 0510634. Doc ID408565047. Chemical Manufacturers Association. 1985b.

(15) CMA. Shake flask degradation of 14C-tris(2-ethylhexyl) trimellitate with cover letter dated 031786. Report No. OTS0510640. Chemical Manufacturers Assoc., 1986.

(16) CMA. Tris(2-ethylhexyl) trimellitate: A voluntary testing program under Section 4 of The Toxic Substances Control Act. OTS 0510616. Doc. ID 408365005. Chemical Manufacturers Association, Washington DC, 1983.

(17) Commission. Annexes I, II, III and IV to the Commission Directive 91/21/EEC adapting to technical progress for the 18th time Council Directve 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labeling of dangerous substances. Off. J. Eur. Commun. 36, L110A, 1-86, 1993.

(18) DHSS. Summary for Basis of Approval BB-NDA 80-77/04. Department of Health and Human Services, FDA, Bethesda, Maryland, 1981.

(19) Di Vincenzo G.D. et al. Bacterial mutagenicity testing of urine from rats dosed with 2-ethylhexanol derived plasticizers. OTS 206391 8(d). Eastman Kodak Co., Rochester, N.Y., 1984.

(20) Di Vincenzo G.D. et al. Bacterial mutagenicity testing of urine from rats dosed with 2-ethylhexanol derived plasticizers. Toxicology 34, 247-259, 1985.

(21) Dynamac. Working Draft Information Review: Tris(2-ethylhexyl) trimellitate (revised), IR-301. Dynamac Corp., Rockville, Maryland, 1982.

(22) Eastman Chemicals. Kodaflex TOTM. Product literature. Coatings Chemicals Division, B-280, Kingsport, 1982b (citedin EPA, 1983).

(23) Eastman Chemicals. Technical Datasheet No. L-167c, 1982a (cited in Dynamac, 1982).

(24) Eastman Kodak. Absorption and metabolism of (hexyl-2-14C) tri-(2-ethylhexyl) trimellitate in the rat. OTS 42040. Doc. ID 408465031, 1984a.

(25) Eastman Kodak. Absorption and metabolism of (hexyl-2-14C)tri-(2-ethylhexyl) trimellitate in the rat. OTS 84003A. Doc. ID 878214717, 1983b.

(26) Eastman Kodak. The in vitro hydrolysis of selected plasticizers by rat gut homogenates. OTS 0510633. Doc ID408465046, 1984c.

(27) Eastman Kodak. Toxicity and health hazard summary. Unpublished data. OTS 84003A. Doc ID 878214436. Eastman Kodak Co., Rochester, N.Y., 1983a.

(28) Eastman Kodak. Toxicity summary tris(2-ethylhexyl) trimellitate. Unpublished report. OTS 0206572. Doc ID878214437. Eastman Kodak Co., Rochester, N.Y., 1983b.

(29) Environmental Agency of Japan (1999a), Ecotoxicity testing report, Test No. NMMP/E09/1080

(30) Environmental Agency of Japan (1999b), Ecotoxicity testing report, Test No. NMMP/E09/2080

(31) Environmental Agency of Japan (1999c), Ecotoxicity testing report, Test No. NMMP/E09/3080

(32) Environmental Agency of Japan (1999d), Ecotoxicity testing report, Test No. NMMP/E09/4080

(33) Environmental Agency of Japan (1999d), Ecotoxicity testing report, Test No. NMMP/E09/5080

(34) EPA. Bacterial Mutagenicity Test Results. Environmental Protection Agency. OTS 84003A. Doc ID 878211440, 1980.

(35) EPA. Eleventh report of the Interagency Testing Committee to the administrator; receipt of report and request for comments regarding priority list of chemicals. Fed. Reg. 47, 54626-54642. Environmental Protection Agency, 1982.

(36) EPA. Tris(2-ethylhexyl) trimellitate; response to Interagency Testing Committee. Environmental Protection Agency. Fed. Reg. 48, 51842-51845, 1983

(37) Hawley G.G. The Condensed Chemical Dictionary, 9th edition, 1977 (cited in Dynamac, 1982).

(38) Haworth S. et al. Salmonella mutagenicity results for 250 chemicals. Environ. Mutagen.5(Suppl.1) 3-142, 1983.

(39) Hodgson J.R. Results of peroxisome induction studies on tri(2-ethylhexyl) trimellitate and 2-ethylhexanol. Toxic.ind. Hlth, 3, 49-61, 1987.

(40) Howard P.H. Fate and Exposure Data for Organic Chemicals. Vol 1. Lewis Publ., Chelsea, Michigan, 1986.

(41) HSDB. Hazardous Substances Databank. U.S. National Library of Medicine. SilverPlatter, Chem-Bank, 1994.

(42) ICI Chemicals & Polymers Limited (1990), Internal Company Data.

(43) ICI Group Environmental Laboratory (1989). Report Number BLS/B/0746.

(44) ICI Group Environmental Laboratory (1990), Letter report 15th Aug 1990.

(45) Martis L et al. Tissue distribution and excretion of tris(2-triethylhexyl) trimellitate in rats. J. Toxicol. envir. Hlth, 20, 357-366, 1987.

(46) McCall P.J. Fourth ASTM Symposium on Aquatic Toxicology, Chicago. ASTM, Philadelphia, Pennsylvania, 1979 (cited in Dynamac, 1982).

(47) Midwest Research Institute; Thomas W. Lapp, Charles E Mumma Joseph Chaszar: A Survey of Plasticizers : Epoxies, Linear Polyesters and Trimellitates Chemical Technology and Economics in Environmental Perspective, Task □, Environmental Protection Agency (Nov. 1981)

(48) MITI Japan (1992) Green Card of "biodegradation and bioaccumulation data of existing Chemicals based on the CSCL Japan"

(49) Ministry of Health and Welfare, Japan (1996) Toxicity Testing Report, Vol. 4, 695-720

(50) Ministry of Health and Welfare, Japan (1998) Toxicity Testing Report Vol. 6, 569-578

(51) NFPA. Fire Protection Guide on Hazardous Materials. 7th edition. Boston, Mass., 1978 (cited in HSDB, 1994).

(52) Nuodex Inc. 28-day Hepatotoxicity study in rats. Doc ID 878214468, OTS 0206575 (8d), 1981a.

(53) Nuodex Inc. Acute inhalation toxicity test in sprague-dawley rats using compound Nuoplaz 6959 Doc ID878214466 OTS 0206575. (1982)

(54) Nuodex Inc. Acute dermal toxicity test of Tenneco Chemicals Inc. compound Nouplaz 6959 in rabbits. Doc ID 878214467 OTS 0206575 (1983)

(55) Nuodex Inc. Acute oral toxicity - rats. Doc. ID 878214469, OTS 0206575 8(d), (1981)

(56) Nuodex Inc. Primary skin irritation-Rabbits Doc. ID 878214470, OTS 0206575 (1981)

(57) Nuodex Inc. Primary eye irritation-Rabbits Doc. ID 878214471, OTS 0206575 (1983)

(58) Nuodex Inc. Guinea pig contact dermal irritation/sensitization-Modified Buehler Method Doc. ID 878214472, OTS 0206574 (1983)

(59) Nuodex Inc. Nuodex Material Safety Data Sheet, 12 January, 1983 (included in CMA, 1985c).

(60) Rathinam K. et al. Hepatic studies of intraperitoneally administered tris(2-ethylhexyl) trimellitate (TOTM) and di(2-ethylhexyl) phthalate in rats. J. appl. Toxicol. 10, 39-40, 1990.

(61) Spangler W.J. Capital Systems Inc. and Dynamac Corp. Final technical support document. TOTM. US EPA Contract No. 68-01-6530, 1983 (cited in EPA, 1983).

(62) Swallow, J. J., Acute Oral Median Lethal Dose (LD50) in Rats, Study No. 84R004, Ciba-Geigy P & A Co., July 11, 1984.

(63) Swallow, J. J., Eye Irritation Test in Californian Rabbits, Study No 84L004, Ciba-Geigy P & A Co., June 16, 1984.

(64) Swallow, J. J., Primary Dermal Irritation Test in Californian Rabbits, Study Report No 84L004, Ciba-Geigy P & A Company, 6/19/84.

(65) Tenneco Chemicals. 28-day hepatotoxicity study in rats conducted for Tenneco Chemicals, incorporated with samples Nuoplaz 6959, Nuoplaz DOP. OTS 0510621. Doc ID 878220032, 1981a.

(66) Tenneco Chemicals. Acute dermal toxicity test of Tenneco Chemicals, Inc. (TCI) compound

(67) Tenneco Chemicals. Guinea-pig contact dermal irritation/sensitization - modified Buehler method. Doc ID 878230175, OTS 206574, 1981d.

(68) Timofievskaya L.A. Toxicity and danger of some plasticisers. Gig. Sanit. 46, 87-89, 1981. (translation)

(69) Union Camp. Unpublished information provided by J.M. Ralston, Union Camp to M. Greif, TSCA Interagency Testing Committee, 21 July 1982 (cited in Dynamac, 1982).

(70) Zeiger E. et al. Salmonella mutagenicity tests: IV Results from the testing of 300 chemicals. Envir. molec. Mutagen. 11(Suppl.12), 1-158, 1988.

Parameters used in caluculation of distribution by Mackay level III fugacity model.

Physico-chemical Parameter for TOTM

molecular weight		546.79	Measured
melting point [°C]		-50	Measured
vapor pressure [Pa]		2.80E-04	Estimated
water solubility [g/m^3]		0.13	Measured
log Kow		5.94	Measured
half life [h]	in air	12	Estimated
	in water	288	Estimated
	in soil	288	Estimated
	in sediment	864	Estimated

Temp. [°C] 25

Environmental Parameter

		volume [m^3]	depth [m]	area [m^2]	organic carbon [-]	lipid content [-]	density [kg/m^3]	residence time [h]
bulk air	air	1.0E+13					1.2	100
	particles	2.0E+03						
	total	1.0E+13	1000	1E+10				
bulk water	water	2.0E+10					1000	1000
	particles	1.0E+06			0.04		1500	
	Fish	2.0E+05				0.05	1000	
	Total	2.0E+10	10	2E+09				
bulk soil	Air	3.2E+08					1.2	
	Water	4.8E+08					1000	
	Solid	8.0E+08			0.04		2400	
	Total	1.6E+09	0.2	8E+09				
bulk sediment	Water	8.0E+07					1000	
	Solid	2.0E+07			0.06		2400	50000
	Total	1.0E+08	0.05	2E+09				

Intermedia Transport Parameter (m/h)

air side air-water MTC	5	soil air boundary layer MTC	5
water side air water MTC	0.05	sediment-water MTC	1E-04
rain rate	1E-04	sediment deposition	5E-07
aerosol deposition	6E-10	sediment resuspension	2E-07
soil air phase diffusion MTC	0.02	soil water runoff	5E-05
soil water phase diffusion MTC	1E-05	Soil solid runoff	1E-08

Theoretical Distribution of TOTM

scenario 1

	emission rate [kg/h]	conc. [g/m^3]	amount [kg]	percent [%]	transfomation rate [kg/h]	
					reaction	advection
air	1,000	1.3.E-07	1.3.E+04	19.6	7.5.E+02	1.3.E+02
water	0	1.6.E-05	3.1.E+03	4.7	7.6.E+00	3.1.E+00
soil	0	2.5.E-03	4.4.E+04	66.2	1.1.E+02	
sediment		1.3.E-02	6.3.E+03	9.5	5.1.E+00	1.3.E-01
		total amount	6.7.E+04			

scenario 2

	emission rate [kg/h]	conc. [g/m^3]	amount [kg]	Percent [%]	transfomation rate [kg/h]	
					reaction	advection
air	0	1.8.E-09	1.8.E+02	0.0	1.0.E+01	1.8.E+00
water	1000	9.7.E-04	1.9.E+05	32.7	4.7.E+02	1.9.E+02
soil	0	3.4.E-05	6.2.E+02	0.1	1.5.E+00	
sediment		7.9.E-01	3.9.E+05	67.2	3.2.E+02	7.9.E+00
		total amount	5.9.E+05			

scenario 3

	emission rate [kg/h]	conc. [g/m^3]	amount [kg]	Percent [%]	transfomation rate [kg/h]	
					Reaction	Advection
air	0	7.0.E-13	7.0.E-02	0.0	4.1.E-03	7.0.E-04
water	0	5.2.E-08	1.0.E+01	0.0	2.5.E-02	1.0.E-02
soil	1000	2.3.E-02	4.2.E+05	100.0	1.0.E+03	
sediment		4.2.E-05	2.1.E+01	0.0	1.7.E-02	4.2.E-04
		total amount	4.2.E+05			

scenario 4

	emission rate [kg/h]	conc. [g/m^3]	amount [kg]	Percent [%]	transfomation rate [kg/h]	
					reaction	Advection
air	600	7.8.E-08	7.8.E+03	3.0	4.5.E+02	7.8.E+01
water	300	3.0.E-04	6.0.E+04	23.5	1.5.E+02	6.0.E+01
soil	100	3.8.E-03	6.8.E+04	26.6	1.6.E+02	
sediment		2.4.E+01	1.2.E+05	46.9	9.8.E+01	2.4.E+00
		total amount	2.6.E+05			

ROBUST STUDY SUMMARIES
for
Tris (2-ethylhexyl)benzene-1,2,4-tricarboxylate

CAS No. 3319-31-1

Sponsor Country: Japan

DATE: Aug 24, 2001

PHYSICAL/CHEMICAL ELEMENTS

MELTING POINT

TEST SUBSTANCE

- **Identity:**Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
- **Remarks:** Source: Tokyo Kasei Kogyo Co., Ltd. Lot No. AX01, Purity: 98.5%

METHOD

- **Method/guideline:** OECD TG 102
- **GLP:** Yes
- **Year:** 1998
- **Remarks:** Not stated.

RESULTS

- **Melting point value:** <-50 °C (223 K)
- **Decomposition:** Not stated.
- **Sublimation:** Not stated.
- **Remarks:** Not stated.

CONCLUSIONS

Melting point is <-50°C (223 K).

DATA QUALITY

- **Reliabilities:** Key study
- **Remarks:** Well conducted study, carried out by Chemicals Evaluation and Research Institute (Kurume, Japan).

REFERENCES

Ministry of International Trade and Industry (1998)

GENERAL REMARKS

BOILING POINT (a)

TEST SUBSTANCE

- **Identity:** Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
- **Remarks:** Source: Unavailable.

METHOD

- **Method:** Not specified.
- **GLP:** Not stated.
- **Year:** Not stated.
- **Remarks:** Not stated.

RESULTS

- **Boiling point value:** 283°C
- **Pressure:** 4
- **Pressure unit:** hPa
- **Decomposition:** Not stated.
- **Remarks:** Not stated.

CONCLUSIONS

Boiling point is 283°C at 4 hPa.

DATA QUALITY

- **Reliabilities:** Key study
- **Remarks:** Not stated.

REFERENCES

Midwest Research Institute; Thomas W. Lapp, Charles E Mumma Joseph Chaszar: A Survey of Plasticizers: Epoxies, Linear Polyesters and Trimellitates Chemical Technology and Economics in Environmental Perspective, Task □, Environmental Protection Agency (Nov. 1981)

GENERAL REMARKS

BOILING POINT (b)

TEST SUBSTANCE

- **Identity:** Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
- **Remarks:** Source: Unavailable.

METHOD

- **Method:** Not specified.
- **GLP:** Not stated.
- **Year:** Not stated.
- **Remarks:** Not stated.

RESULTS

- **Boiling point value:** 414°C (687K)
- **Pressure:** 1,013
- **Pressure unit:** hPa
- **Decomposition:** Not stated.
- **Remarks:** Not stated.

CONCLUSIONS

Boiling point is 414°C at 1,013hPa.

DATA QUALITY

- **Reliabilities:** Key study
- **Remarks:** The Sigma-Aldrich Library of Regulatory and Safety Data.

REFERENCES

Ministry of International Trade and Industry (1998)

GENERAL REMARKS

DENSITY

TEST SUBSTANCE

- **Identity:** Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
- **Remarks:** Source: Unavailable.

METHOD

- **Method:** Not specified.
- **GLP:** Not stated.
- **Year:** Not stated.
- **Remarks:** Not stated.

RESULTS

- **Density:** 0.987 – 0.990 g/cm^3
- **Temperature:** 20°C
- **Remarks:** Not stated.

CONCLUSIONS

Density is 0.987-0.990 g/cm^3 at 20°C.

DATA QUALITY

- **Reliabilities:** Key study
- **Remarks:** Not stated.

REFERENCES

Midwest Research Institute; Thomas W. Lapp, Charles E Mumma Joseph Chaszar: A Survey of Plasticizers: Epoxies, Linear Polyesters and Trimellitates Chemical Technology and Economics in Environmental Perspective, Task □, Environmental Protection Agency (Nov. 1981)

GENERAL REMARKS

VAPOR PRESSURE (a)

TEST SUBSTANCE

- **Identity:** Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
- **Remarks:** Source: Tokyo Kasei Kogyo Co., Ltd. Lot No. AX01, Purity: 98.5%

METHOD

- **Method/guideline:** OECD TG 104
- **GLP:** Yes
- **Year:** 1998
- **Remarks:** Not stated.

RESULTS

- **Vapour pressure value:** $< 2.8 \times 10^{-4}$ Pa
- **Temperature:** 100°C
- **Decomposition:** Not stated.
- **Remarks:** Not stated.

CONCLUSIONS

Vapour pressure is $< 2.8 \times 10^{-4}$ Pa at 100°C.

DATA QUALITY

- **Reliabilities:** Key study
- **Remarks:** Well conducted study, carried out by Chemicals Evaluation and Research Institute (Kurume, Japan).

REFERENCES

Ministry of International Trade and Industry (1998)

GENERAL REMARKS

VAPOR PRESSURE (b)

TEST SUBSTANCE

- **Identity:** Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
- **Remarks:** Source: Unavailable.

METHOD

- **Method/guideline:** Not stated
- **GLP:** Not stated
- **Year:** Not stated
- **Remarks:** Not stated.

RESULTS

- **Vapour Pressure value:** 0.27 – 6.7 hPa
- **Temperature:** 250 – 260 °C
- **Decomposition:** Not stated.
- **Remarks:** Not stated.

CONCLUSIONS

Vapour pressure is 0.27- 6.7 hPa at 250 – 260 °C.

DATA QUALITY

- **Reliabilities:** Key study
- **Remarks:** Not stated.

REFERENCES

Midwest Research Institute; Thomas W. Lapp, Charles E Mumma Joseph Chaszar: A Survey of Plasticizers: Epoxies, Linear Polyesters and Trimellitates Chemical Technology and Economics in Environmental Perspective, Task □, Environmental Protection Agency (Nov. 1981)

GENERAL REMARKS

PARTITION COEFFICIENT

TEST SUBSTANCE

- **Identity:** Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
- **Remarks:** Source: Tokyo Kasei Kogyo Co., Ltd. Lot No. AX01, Purity: 98.5%

METHOD

- **Method/guideline:** OECD TG 107 (Shake Flask Method, 1995)
- **GLP:** Yes
- **Year:** 1998
- **Remarks:** Not stated.

RESULTS

- **Log P_{ow} :** 5.94
- **Temperature:** 25°C ±1°C
- **Remarks:** Test condition: Test was conducted in duplicate under the following three conditions. Test chemical was analyzed by HPLC.

Test condition	**Condition-1**	**Condition-2**	**Condition-3**
1-Octanol saturated with water	10 mL	20 mL	40 mL
Water saturated with 1-octanol	240 mL	230 mL	210 mL
Test chemical in 1-octanol saturated with water (52.2 mg)	10 mL	10 mL	10 mL

Test results	**Log Pow**		
	a	**b**	**Mean**
Condition-1	5.99	5.99	
Condition-2	5.95	5.87	5.94
Condition-3	5.92	5.93	

CONCLUSIONS log P_{ow} is 5.94.

DATA QUALITY

- **Reliabilities:** Key study
- **Remarks:** Well conducted study, carried out by Chemicals Evaluation and Research Institute (Kurume, Japan).

REFERENCES

Ministry of International Trade and Industry (1998)

GENERAL REMARKS

WATER SOLUBILITY

TEST SUBSTANCE

- **Identity:** Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
- **Remarks:** Source: Tokyo Kasei Kogyo Co., Ltd. Lot No. AX01, Purity: 98.5%

METHOD

- **Method:** OECD TG 105 (flask method).
- **GLP:** Yes
- **Year:** 1998.
- **Remarks:** Not stated.

RESULTS

- **Value:** 0.13 mg/L at 25 °C±1°C
- **Description of solubility:** Of very low solubility
- **pH value:** No dissociation group.
- **pKa value:** There is no pertinent functional group.
- **Remarks:** Not stated.

CONCLUSIONS

This chemical is very low solubility in water.

DATA QUALITY

- **Reliabilities:** Key study
- **Remarks:** Well conducted study, carried out by Chemicals Evaluation and Research Institute (Kurume, Japan).

REFERENCES

Ministry of International Trade and Industry (1998)

GENERAL REMARKS

ENVIRONMENTAL FATE AND PATHWAYS ELEMENTS

STABILITY IN WATER

TEST SUBSTANCE

- **Identity:** Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
- **Remarks:** Source: Tokyo Kasei Kogyo Co., Ltd. Lot No. AX01, Purity: 98.5%

METHOD

- **Method/guideline:** OECD TG 111
- **Type :** Hydrolysis as a function of pH
- **GLP:** Yes
- **Year:** 1998
- **Remarks:** No hydrolysis of test chemical was observed at pH 4 at 50°C±1°C for 5 days. Hydrolysis rates at pH 7 were determined at 60, 70 and 80 °C, and at pH 9 at 50, 60, and 70°C . They were extrapolated to 25 °C using Arrhenius relationship. Half life at 25 °C was calculated from the rate constant.

RESULTS

- **Nominal:** ca. 0.2 mg/L
- **Measured value:** Not stated.
- **Degradation:** No hydrolysis occurred in 5 days, at 50 °C pH 4. At pH 7 and pH 9, test chemicals were hydrolysed at all temperatures studied.
- **Half-life ($t_{(1/2)}$):**

	Rate Constant (hr^{-1})	Half-life(day)
pH 7	1.65×10^{-3}	17.5
pH 9	2.44×10^{-3}	11.9

- **Breakdown products:** Not stated.
- **Remarks:** Not stated.

CONCLUSIONS

This chemical is stable in aqueous water at pH 4 under the condition studied, but it is hydrolysed at pH 7 and pH 9 at 25 °C with half-life of 17.5 and 11.9 days.

DATA QUALITY

- **Reliabilities:** Key study
- **Remarks:** Well conducted study, carried out by Chemicals Evaluation and Research Institute (Kurume, Japan).

REFERENCES

Ministry of International Trade and Industry (1998)

GENERAL REMARKS

TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS (FUGACITY)

TEST SUBSTANCE

- **Identity:** Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
- **Remarks:** Source: Not applicable.

METHOD

- **Test:** Calculation
- **Method:** Fugacity level III
- **Year:** 2001
- **Remarks:** The parameters used are shown in Appendix.

RESULTS

- **Media :**
- **Estimated distribution under three emission scenarios :**

Compartment	Release100 % to air	Release 100 % to water	Release 100 % to soil
Air	19.6 %	0.0 %	0.0 %
Water	4.7 %	32.7 %	0.0 %
Soil	66.2 %	0.1 %	100.0 %
Sediment	9.5 %	67.2 %	0.0 %

- **Remarks:**

CONCLUSIONS

If this chemical is released into water, the majority of this chemical is expected to stay in sediment, but if it is released into air or soil, this chemical is expected to stay in soil.

DATA QUALITY

- **Reliabilities:** Key study.
- **Remarks:** Not stated.

REFERENCES

Dainippon Ink and Chemicals, Incorporated (2001), unpublished report.

GENERAL REMARKS

BIODEGRADATION

TEST SUBSTANCE

- **Identity:** Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
- **Remarks:** Source: Unavailable

METHOD

- **Method:** OECD TG 302C "Inherent Biodegradability: Modified MITI Test(II)"
- **Test Type:** Aerobic
- **GLP:** No
- **Year:** 1977
- **Contact time:** 28 days
- **Inoculum:** The supernatant (500ml) of activated sewage sludge obtained from ten sampling sites and 5 liters of supernatant removed from a previously established culture are transferred to a culture vessel. The pH of the culture mixture was adjusted to 7.0±1.0 and constantly aerated. Thirty minutes after stopping aeration, discard about 1/3 of the whole volume of the supernatant, and add an equal volume of 0.1% synthetic sewage and the aeration re-started. Repeat this procedure once a day.
- **Remarks:** During the aeration, appearance of supernatant and the formation of activated sewage was observed. The sludge was found to form a clear supernatant on settling and formed cloudy flocs when on aeration. Operating temperature, pH and a dissolved oxygen concentration were recorded. The protozoa of sludge were observed under an optical microscope.
  *Incubation apparatus: Respirometry(Closed bottle) Ohkura Electric Co.
  *CO_2 absorbent: Soda lime No.1 (Wako pure chemicals Inc.)
  *Stirrer : Magnetic stirrer
  *Temperature : 25±1
  *Concentration of test chemical: 30mg/L, 100mg/L
  *Reference substance: Aniline

RESULTS

- **Degradation:**
- **Results:** 4.2% after 28days
- **Kinetic:** The percentage degradation in term of oxygen consumption was calculated as follows:
  % degradation = (BOD-B)/TOD x 100
  BOD: Biological Oxygen Demand of the test material
  B : Oxygen consumption in basal culture medium to which incoculum is added (control)
  TOD: Theoretical oxygen demand to completely oxidize the test material
- **Breakdown products:** Not stated.
- **Remarks:** At the end of incubation, measure the residual dissolved organic carbon and test material concentration. The reference substance, aniline, attained more than 40% and 60% degradation after 7 and 14days confirming the suitability of the inoculum and culture conditions.

CONCLUSIONS

This chemical is low biodegradable.

DATA QUALITY

- **Reliabilities:** Key study
- **Remarks:** Well conducted study, carried out by Chemical Inspection and Testing Institute.

REFERENCES

Biodegradation and Bioaccumulation Data of Existing Chemicals Based on the CSCL Japan.(1992), Ministry of International Trade and Industry.

GENERAL REMARKS

BIOACCUMULATION

TEST SUBSTANCE

- **Identity:** Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
- **Remarks:** Source: Unavailable

METHOD

- **Method:** OECD TG 305C
- **Species:** *Cyprinus Carpio* (Obtained from Nakajima hatchery in Kumamoto, Japan)
- **GLP:** No
- **Year:** 1978
- **Exposure Period:** 42 days
- **Remarks:** Test fish: Acclimated for ca. 8 weeks before testing at 25±2. Fish with ca.10cm in length and ca.30g in weight were selected at random. Lipid content was 2-6%.
  Test condition Concentrations: 0.2 and 2 mg/L, solubilizer controlled. Type of test: flow-through (200-800mL/min), 100L glass tank. Dissolved oxygen concentration: 6-8mg/L Temperature: 25±2 Water chemistry was tested in the control and two concentrations every 2 times in a week. Test was conducted in duplicate every 2 weeks for two concentrations. (The control was done before and after testing.)

RESULTS

- **Results:** BCF=1-2.7 (concentration: 0.2mg/L)
  BCF=0.1-0.23(concentration: 2mg/L)
- **Kinetic:** BCF=C1/C2
  C1: Concentration of this chemical in Fish
  C2: Concentration of this chemical in water
- **Breakdown products:** Not stated.

CONCLUSIONS

This chemical has a low bioaccumulation potential.

DATA QUALITY

- **Reliabilities:** Key study
- **Remarks:** Well conducted study, carried out by Chemical Inspection and Testing Institute

REFERENCES

Biodegradation and Bioaccumulation Data of Existing Chemicals Based on the CSCL Japan.(1992), Ministry of International Trade and Industry

GENERAL REMARKS

ECOTOXICITY ELEMENTS

ACUTE TOXICITY TO FISH

TEST SUBSTANCE

- **Identity:** Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
- **Remarks:** Source: Tokyo Kasei Kogyo Co., Ltd. Lot No. AX01, Purity: >95.0%

METHOD

- **Method:** OECD TG 203
- **Type:** Semi-static
- **GLP :** Yes
- **Year :** 1998
- **Species/Strain/Supplier:** *Oryzias latipes*(Medaka): Obtained from commercial domestic
- hatcheries.
- **Analytical monitoring:** Yes.
  Test solutions were measured by HPLC before and after 24 hours exposure period.
  Test solutions were replaced every 24 hours to new ones.
- **Exposure period (h):** 96
- **Statistical methods:** Not applicable because of no mortality.
- **Remarks:**

Test fish: Acclimated for more than 12 days before testing; any groups showing no mortality for 7 days before test started. Fish with 22.1 mm (18.3~23.8 mm) in length were selected at random. Average body weight of fish was 0.1462 g (n=10).

Test conditions: Details of test: Semi-static (water changed every 24 hours)
Dilution water source: Tap water after dechlorinated by passing through activated carbon.
Dilution water chemistry: Hardness: 25 mg/L as $CaCO_3$; pH: 6.7
Stock and test solution and how they are prepared: Pipette or pour the appropriate amount of the solution (0.3 wt% of test chemical with solubilizer hydrogenated caster oil HCO-40 3000mg/L) into the test waters.
Concentrations dosing rate, flow-through rate, in what medium:
Concentrations of 0, 100 mg/L and dispersant control were tested.
Vehicle/solvent and concentrations: Hydrogenated caster oil HCO-40, 100 mg/L
Stability of the test chemical solutions: Stable, measured concentration was 101-103%.
Exposure vessel type: 10 fish per group in 3L glass beaker without aeration under room light.
Number of replicates, fish per replicate: One replicate was done.
Water chemistry in test (O_2, pH) in the control and all concentration where effects were observed: Dissolved oxygen readings and pH values were taken daily during 96 h exposure period.
Dissolved oxygen concentration: 5.0~9.2 mg/L.
pH values: 6.7~6.8.
Test temperature range: Water temperature at 23.5~24.1°C.
Method of calculating mean measured concentrations: Geometric mean.

RESULTS

- **Nominal concentrations :** 0, 100 (mg/L)

- **Measured concentrations :** <1, 103 (0hr), <1, 102 (24hr)
- **Unit :** mg/L.
- **Element value:** LC_{50} at 96 hours >100.0 mg/L based on nominal concentrations.
- **Statistical results as appropriate:** Not applied.
- **Remarks:**
  Biological observations: Not described.
  Table showing cumulative mortality:

Percent mortality of *Oryzias latipes* exposed to the test chemical

Nominal concentration (mg/L)	Cumulative number of dead fish (% mortality)			
	24 hour	48 hour	72 hour	96 hour
Control	0(0)	0(0)	0(0)	1(10)
Dispersant Control	0(0)	0(0)	0(0)	0(0)
100	0(0)	1(10)	1(10)	1(10)

Lowest test substance concentration causing 100% mortality:
Not obtained under the test conditions studied.
Mortality of controls: 1 fish was dead at 96h.
Abnormal responses: At 24 hr, one fish showed abnormal breathing behaviour at 100mg/L.
Reference substances: Copper(II)sulfate pentahydrate. LC_{50} at 96h was 0.43 mg/L.
Any observations, such as precipitation that might cause a difference between measured and nominal values: It became clouded in 100mg/L concentration, but not precipitation.

CONCLUSIONS

LC50 (96h) > 100mg/L for fish.

DATA QUALITY

- **Reliabilities:** Klimisch Code: 1=reliable without restrictions.
- **Remarks field for Data Reliability:**
  Experimental design and analytical procedure were well documented.
  Carried out by Toray Research Center (Japan).

REFERENCES

Environment Agency of Japan (1998).

GENERAL REMARKS

PROLONGED TOXICITY TO FISH

TEST SUBSTANCE

- **Identity:** Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
- **Remarks:** Source: Tokyo Kasei Kogyo Co., Ltd. Lot No. AX01, Purity: >95.0%

METHOD

- **Method:** OECD TG 204
- **Type:** Flow-through.
- **GLP:** Yes
- **Year :** 1998
- **Species/Strain/Supplier:** *Oryzias latipes* (Medaka): Obtained from commercial domestic hatcheries.
- **Analytical monitoring:** Yes. Test solutions were measured by HPLC before and after 7, 14days exposure period.
- **Exposure period:** 14 day.
- **Statistical methods:** Binomial method (TOXDAT MULTI-METHOD PROGRAM, USEPA) Dunnet method was used for LC_{50} and for fish body weight difference, respectively.

TEST CONDITIONS:

Test fish: Acclimated for more than 12 days before testing; any groups showing 2.9% mortality for 7 days before test started. Fish with 20.0 mm (18.5~21.6 mm) in length were selected at random. Average body weight of fish was 0.1484g (0.1182~0.2014g)(n=10). Fish were starved for 24 hours before the test started.

Test conditions: Details of test: Flow-through.

Dilution water source: Tap water after dechlorinated by passing through activated carbon.

Dilution water chemistry: Hardness: 15.3mg/L as $CaCO_3$; pH: 7.0

Stock and test solution and how they are prepared: The working solution (4.8wt% of test chemical with solibilizer HCO-40 controlled) was prepared with the dilution water. The test solution was supplied continuously by mixing the working solution and the dilution water with the help of a mechanically operated quantitative water-pump.

Concentrations dosing rate, flow-through rate, in what medium: Nominal concentrations of 0, 18.8, 37.5 and 75.0 mg/L and Dispersant control were tested.

Vehicle/solvent and concentrations: Hydrogenated caster oil HCO-40, Max. 75.0 mg/L

Stability of the test chemical solutions: It became clouded in high concentration, but not precipitation.

Exposure vessel type: 10 fish per group in 3L glass beaker without aeration under room light.

Number of replicates, fish per replicate: One replicate was done.

Water chemistry in test (O_2, pH) in the control and one concentration where effects were observed: Dissolved oxygen readings and pH values were taken every 3 days during the exposure period.

Dissolved oxygen concentration: 6.6~7.7 mg/L.

pH values: 6.9~7.2.

Test temperature range: Water temperature at 23.5~24.1°C (24±2°C).

Method of calculating mean measured: Geometric mean.

RESULTS

- **Nominal concentrations :** 0, 18.8, 37.5, 75.0 (mg/L) and dispersant control
- **Measured concentrations :**

Measured concentration of the test chemical during a 14-day exposure of orange killifish (*Oryzias latipes*) under flow-through test conditions

Nominal concentration (mg/L) Measured concentration (mg/L) (percent of nominal)

	0 day	7 day	14 day	Mean
Control	< 1.0	< 1.0	< 1.0	--
Dispersant Control	< 1.0	< 1.0	< 1.0	--
18.8	17.7(94.1)	15.8(84.0)	15.5(82.4)	16.3(86.9)
37.5	35.7(95.2)	33.2(88.5)	30.0(80.0)	33.3(87.9)
75.0	70.6(94.1)	68.8(91.7)	71.2(94.9)	70.2(93.6)

- **Unit :** mg/L
- **Element value:**

LC_{50} (7 days) > 75.0mg/L (nominal concentration)
LC_{50} (14 days) > 75.0mg/L (nominal concentration)
NOEC (14 days) > 75.0 mg/L (nominal concentration)

- **Statistical results, as appropriate:**

The mean body weight of fish exposed to all concentration of the test chemical was not significantly different from controls during the test period (alfa=0.05, Dunnet).

- **Remarks:** Biological observations: Not described.

Cumulative mortality:

Percent mortality of *Oryzias latipes* exposed to the test chemical under flow-through test conditions

Nominal conc. (mg/L)	Cumulative number of dead fish (% mortality) (days)														
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Control	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(10)	1(10)	1(10)
Disp. Cont.	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
18.8	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
37.5	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
75.0	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)

Fish weight:

Nominal conc. (mg/L)	Fish weight (g)										
	No.1	**No.2**	**No. 3**	**No.4**	**No.5**	**No.6**	**No.7**	**No.8**	**No.9**	**No.10**	**Ave.**
Control	0.1879	0.2526	0.1273	0.2239	0.1139	0.1434	0.1708	0.1789	0.1558	-a	0.1727
Disp. Cont.	0.2205	0.1827	0.1192	0.1884	0.1438	0.1823	0.1563	0.2120	0.1635	0.1580	0.1727
18.8	0.1731	0.1513	0.1593	0.1472	0.2150	0.1548	0.1547	0.1306	0.2104	0.1020	0.1598
37.5	0.1264	0.1495	0.1872	0.1237	0.2055	0.1396	0.1805	0.2101	0.1577	0.1303	0.1611
75.0	0.1746	0.1848	0.1804	0.1625	0.1494	0.1633	0.2103	0.1454	0.1600	0.1818	0.1713

-a : No measurement was made because the Orange Killifish was dead.

Lowest test substance concentration causing 100% mortality: >75.0 mg/mL (nominal).
Mortality of controls:10 % mortality observed during the test period (12 through 14 days
Food intake: Fish was fed with TetraMin® fish food (2% of fish body weight).
Abnormal responses: No abnormal response showed through 14 days.
Reference substances (if used) – results: Copper (II) sulfate pentahydrate. LC_{50} at 96h was 0.30 mg/L.
Any observations, such as precipitation that might cause a difference between measured and nominal values: It became clouded high concentration, but not precipitation.

CONCLUSIONS

LC_{50} (7 days) > 75.0mg/L (nominal concentration)
LC_{50} (14 days) > 75.0mg/L (nominal concentration)
NOEC (14 days) > 75.0 mg/L (nominal concentration)

DATA QUALITY

- **Reliabilities:** Klimisch Code: 1=reliable without restrictions.
- **Remarks field for Data Reliability:**
  Experimental design and analytical procedure were well documented.
  Carried out by Toray Research Center (Japan).

REFERENCES

Environment Agency of Japan (1998).

GENERAL REMARKS

ACUTE TOXICITY TO AQUATIC INVERTEBRATES (e.g., *Daphnia*)

TEST SUBSTANCE

- **Identity:** Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
- **Remarks:** Source: Tokyo Kasei Kogyo Co., Ltd. Lot No. AX01, Purity: >95.0%

METHOD

- **Method:** OECD TG 202
- **Type:** Static
- **GLP :**Yes
- **Year :**1998
- **Species/Strain/Supplier:** *Daphnia magna*
- **Analytical monitoring:** Yes. Test solutions were measured by HPLC before and after 48 hours exposure period.
- **Exposure period (h):** 48
- **Statistical methods:** Not applicable.

TEST CONDITIONS

Test organisms: Source, supplier, any pre-treatment, breeding method: Supplied by NIES (Japan).
Age at study initiation: Juveniles within 24h old.
Control group: Yes.
Test conditions: Stock solutions preparation and stability: No solvent used. Test chemical was diluted to 1800mg/L(with solubilizer HCO-40 1000mg/L controlled) with diluting water (Elendt M4) before use.
Test temperature range: 19.9-20.2 °C (average temperature 20°C).
Exposure vessel type: 100mL test solution in a 100 mL glass beaker; 4 beakers per treatment
Dilution water source: Elendt M4(OECD guideline No.211 Annex 2)
Dilution water chemistry: Hardness: 228mg/L as $CaCO_3$
Lighting: room light 16h:8h light-darkness cycle
Water chemistry in test: DO= 8.0-8.6mg/L; pH=7.3-7.8.
Feeding: none
Test design: Number of replicates=20
Concentrations: 0, 17.1, 30.9, 55.6, 100 and 180 mg/L, because 48h-EiC_{50} for parent Daphnia (Acute immobilization test) was >1000mg/L. Dispersant control was also tested.
Method of calculating mean measured concentrations: Geometric mean.
Exposure period: 48 h
Analytical monitoring: By HPLC analysis. 95.1-99.6% of the nominal concentration at preparation; 90.1-97.7% after 48hr.

RESULTS

- **Nominal concentrations :** 17.1, 30.9, 55.6, 100.0, 180.0 (mg/L) (Solubilizer controlled)
- **Measured concentrations :**

Measure Concentrations of test chemicals during a 48hr.

Nominal Concentration (mg/L)	Measured concentration(mg/L)			Percent of nominal	
	0hr	48hr	Mean	0hr	48hr

Control	< 1.0	< 1.0	-	-	-
Disp.Cont.	< 1.0	< 1.0	-	-	-
17.1	16.3	15.4	15.8	95.3	90.1
30.9	29.4	28.5	28.9	95.1	92.2
55.6	53.0	52.1	52.5	95.3	93.7
100.0	98.4	96.3	97.3	98.4	96.3
180.0	179.2	175.8	177.5	99.6	97.7

- **Unit :** mg/L.
- **Element value:** EC_{50} at 24 hours >180.0 mg/L
  EC_{50} at 48 hours >180.0 mg/L
  NOEC > 180.0 mg/L
  LOEC > 180.0 mg/L
- **Statistical results as appropriate:** Not applied.
- **Remarks**

Biological observations: Not described.

Table showing mortality or immobility:

Mortality or immobility of *Daphnia magna* to the test chemical

Nominal concentration (mg/L)	**Cumulative number of dead or immobilizes *Daphnia* (Percent Mortality or Immobility)**	
	24 hour	**48 hour**
Control	0(0)	0(0)
Dispersant Control	0(0)	1(5)
17.1	0(0)	1(5)
30.9	0(0)	0(0)
55.6	0(0)	0(0)
100.0	0(0)	0(0)
180.0	0(0)	0(0)

Lowest test substance concentration causing 100% mortality:
Not obtained under the test conditions studied.
Mortality of controls: No mortality observed during test period.
Abnormal responses: No abnormal responses observed during test period.
Reference substances Potassium dichromate EC_{50} at 48h was 0.87 mg/L.
Any observations, such as precipitation that might cause a difference between measured and nominal values: It became clouded in high concentration, but not precipitation.

CONCLUSIONS

EC_{50} (48h) > 180mg/L and NOEC (48h) > 180mg/L for *Daphnia magna*.

DATA QUALITY

- **Reliabilities:** Klimisch Code: 1=reliable without restrictions.
- **Remarks field for Data Reliability:**
  Experimental design and analytical procedure were well documented.
  Carried out by Toray Research Center (Japan).

REFERENCES

Environment Agency of Japan (1998).

GENERAL REMARKS

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

TEST SUBSTANCE

- **Identity:** Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
- **Remarks:**Source: Tokyo Kasei Kogyo Co., Ltd. Lot No. AX01, Purity: >95.0%

METHOD

- **Method/guideline followed :** OECD TG 201
- **Test type :** Static.
- **GLP :** Yes
- **Year :** 1998
- **Species/strain # and source:** *Selenastrum capricornutum* ATCC22662 (purchased from ATCC)
- **Element basis:** Area under the growth curve.
- **Exposure period:** 72 h.
- **Analytical monitoring:** Yes, measured by HPLC at start and end of the test (72hr).
- **Statistical methods:** Bartlett test for homogeneity in variances and One-way Anova (EcoTox-Statistics Ver.1.0 beta-edition R1.4) were used for EC_{50}, LC_{50} and NOEC determination (p=0.05).

TEST CONDITIONS :

Test organisms: Laboratory culture: OECD medium
Method of cultivation: Shaking at 100rpm
Controls: OECD medium. EC_{50} of potassium dichromate was 0.41 mg/L.
Test Conditions: Test temperature range: 23±2 °C
Growth/test medium: OECD medium.
Shaking: 100 rpm
Dilution water source: OECD medium.
Exposure vessel type: 100 mL OECD medium in a 300 mL Erlenmeyer flask with a silicon cap which allows ventilation.
Water chemistry in test (pH) in at least one replicate of each concentration (at start and end of the test): pH=7.3-7.4 at start and 8.3-8.8 at end of the test (72h)
Stock solutions preparation: No stock solution was prepared. Test chemical was diluted to 100mg/L (solubilizer, HCO-40 100mg/L) with OECD medium and sterilised with filter before use.
Light levels and quality during exposure: 4,756-4,822 lux, continuous illumination.
Test design : Number of replicates: Triplicate
Concentrations: 0, 100 mg/L and dispersant control were tested.
Initial cell number in cells/mL: $1x10^4$
Method of calculating mean measured concentrations: Geometric mean.

RESULTS

- **Nominal concentrations :**
  0, 100 (mg/L) and dispersant control.
- **Measured concentrations :**
  At start of the test (0 hr), <1.0, 80.6, <1.0(mg/L)
  At end of the test (72 hr), <1.0, 68.7, <1.0 (mg/L)
- **Unit :** mg/L
- **Results:**(calculated based on nominal concentrations)

(1) Growth inhibition (comparison of area under growth curve)

EC_{50} (0-72 h) > 100 mg/L

NOEC (0-72 h)> 100 mg/L

(2) Growth inhibition (comparison of growth rates)

EC_{50} (24-48) > 100 mg/L

EC_{50} (24-72) > 100 mg/L

NOEC (24-72) > 100 mg/L

- **Was control response satisfactory:**

  Yes: Mean cell density increased to $2.70x10^6$ cells/mL (270-fold increase) after 72 hr for control. Mean cell density increased to $2.75x10^6$ cells/mL (275-fold increase) after 72 hr for Dispersant control.

- **Statistical results as appropriate:**

  Significant difference in the growth curve was not observed between values at 100 mg/L and in each control.

- **Remarks**

Biological observations

Cell density at each flask at each measuring point:

Nominal Concentration (mg/L)	**Cell Density ($x10^4$ cells/mL)**			
	0 hr	**24 hr**	**48 hr**	**72 hr**
Control	1.0 ± 0.00	6.5 ± 0.50	50.5 ± 3.48	270.5 ± 23.50
Dspersant Control	1.0 ± 0.00	9.3 ± 1.66	57.5 ± 9.39	275.2 ± 17.22
100	1.0 ± 0.00	16.1 ± 7.82	65.1 ± 12.82	283.3 ± 7.98

(Each value represents the mean of three sample counts.)

Growth curves: Logarithmic growth until end of the test (72 h).

Percent biomass/growth rate inhibition per concentration: Not described.

Observations: Test group(100mg/L) showed normal and similar growth to that of control (283 fold increase after 72 hr).

CONCLUSIONS

(1)Growth inhibition(comparison of area under growth curve)	EC_{50} (0-72 h) > 100 mg/L NOEC (0-72 h) > 100 mg/L
(2)Growth inhibition (comparison of growth rates)	EC_{50} (24-48) > 100 mg/L EC_{50} (24-72) > 100 mg/L NOEC (24-72) > 100 mg/L

DATA QUALITY

- **Reliabilities:** Klimisch Code: 1=reliable without restrictions.
- **Remarks field for Data Reliability:**

Experimental design and analytical procedure were well documented.

Carried out by Toray Research Center (Japan).

REFERENCES

Environment Agency of Japan (1998).

GENERAL REMARKS

CHRONIC TOXICITY TO AQUATIC INVERTEBRATES (e.g., *DAPHNIA*) (1)

TEST SUBSTANCE

- **Identity:** Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
- **Remarks:**Source: Nuoplaz 6965

METHOD

- **Method:** ASTM and USEPA
- **Test type:** Flow-through condition
- **GLP:** Yes
- **Year:** 1984
- **Analytical procedures:** Yes. Measured by GLC, on 0,4,7,14,21day)
- **Species/Strain:** *Daphnia magna*
- **Test details:** Dynamic flow-through
- **Statistical methods:** ANOVA, 2WANOVA, arcsin transformation and Fisher's protected Least Significant Difference (LSD)

TEST CONDITIONS

Test organisms: Source; in house culture
Age at study initiation: Juveniles within 24h old.
Control group: Yes (control and solvent control).
Test conditions: Dilution Solvent for Concentrated stock standards : Acetone (1.049mg/mL)
A proportional diluter system was used for the intermittent introduction of test material and dilution water into the test chambers.
Test temperature range: 18-22 °C (average temperature 20°C).
Well water was delivered to the chambers as a minimum rate of 2.0mL/min.
Exposure vessel type: 900mL test solution in a 1000 mL glass beaker; 4 beakers per treatment.
Dilution water chemistry: Hardness and other characteristics are reported.
Dilution water pH in test: pH=8.3-8.4.
Lighting: 37-74 footcandles , 16h:8h light-darkness cycle
Feeding: Algae (Selenastrum capricornutum) three times a day
Supplemented with a trout chow suspension at least twice a week
Element (unit) basis: Mean cumulative numbers of juveniles produced per adult (reproduction)
Growth (length) of parental Daphnia
Long-term survival
Test design: Number of replicates=4; individuals per replicate=10;
Method of calculating mean measured concentrations: Geometric mean.
Exposure period: 21 d
Analytical monitoring: By GLC analysis. 33-101% of the nominal concentration at Preparation

RESULTS

- **Nominal concentrations:** 0, 0.0074, 0.012, 0.027, 0.048, 0.100 mg/L
- **Measured concentrations:**

Measured concentration of test chemical during 21-day exposure

Nominal concentration (mg/L)	Measured concentration (day, mg/L) 0	4	7	14	21	mean
Control	ND	ND	ND	ND	ND	ND
Solvent Cont.	ND	ND	ND	ND	ND	ND

0.0074	0.00328	0.00366	0.00558	0.00246	0.00482	0.0040
0.012	0.00748	0.00626	0.00843	0.00478	0.00747	0.0069
0.027	0.0172	0.0150	0.0204	0.0110	0.0157	0.0159
0.048	0.0305	0.0252	0.0371	0.0176	0.0348	0.029
0.100	0.0824	0.0766	0.0870	0.0630	0.1011	0.082

Cumulative Number of Dead Parental *Daphnia*.

Nominal conc.	**Days**									
(mg/L)	**0**	**3**	**5**	**7**	**10**	**12**	**14**	**17**	**19**	**21**
Control	0	0	0	0	0	0	0	1	1	2
Solvent Cont.	0	0	0	0	0	1	1	2	3	4
0.0074	0	0	0	0	0	1	1	1	1	1
0.012	0	0	0	0	0	0	0	0	0	0
0.027	0	0	0	0	0	0	0	0	0	0
0.048	0	0	0	0	1	1	1	1	1	1
0.100	0	0	0	0	0	0	0	0	0	0

Mean Growth data of Parental *Daphnia* (21-d)

Nominal conc. (mg/L)	**Replicate A**	**Replicate B**	**Replicate C**	**Replicate D**
Control	58.6 (n=9)	58.4 (n=9)	58.8 (n=10)	58.5 (n=10)
Solvent Cont.	59.1 (n=7)	59.0 (n=10)	59.0 (n=9)	59.3 (n=10)
0.0074	59.5 (n=10)	58.5 (n=10)	60.1 (n=9)	59.5 (n=10)
0.012	59.1 (n=10)	59.4(n=10)	59.5 (n=10)	59.8 (n=10)
0.027	59.8 (n=10)	58.4 (n=10)	59.9 (n=10)	60.3 (n=10)
0.048	59.6 (n=10)	59.6 (n-10)	59.7 (n=9)	58.6 (n=10)
0.100	58.7 (n=10)	60.0 (n=10)	58.8 (n=10)	59.0 (n=10)

Mean numbers of instar produced during 21-d.

Nominal conc.	**Days**									
(mg/L)	**0**	**3**	**5**	**7**	**10**	**12**	**14**	**17**	**19**	**21**
Control	-	-	-	-	109	196	317	86	179	170
Solvent Cont.	-	-	-	16	164	178		240	75	156
0.0074	-	-	-	3	141	202	302	261	75	274
0.012	-	-	-	3.5	122	206	373	221	96	265
0.027	-	-	-	8.3	150	189	317	218	138	313
0.048	-	-	-	-	113	203	242	120	233	214
0.100	-	-	-	5.3	135	186	223	180	93	269

- **Statistical results as appropriate:**

Calculated LC_{50} Value for Parental *Daphnia:* LC_{50}(21day) >0.082(mg/L)
Calculated EC_{50} value for Inhibition of Reproduction: EC_{50}(21day) > 0.082(mg/L)

- **Remarks:**

Biological observations
Cumulative numbers of dead parental *Daphnia*: Control: 2 (mortality: 5%)
Solv. Cont: 4 (mortality: 10%)
0.0074 mg/L: 1 (mortality: 2.5%)
0.012 mg/L: 0 (mortality: 0%)
0.027 mg/L: 0 (mortality: 0%)
0.048 mg/L: 1 (mortality: 2.5%)
0.100 mg/L : 0 (mortality: 0%)

Time of the first production of juveniles: Control : 7-10d
Solvent control: 5-7d
0.0074 mg/L: 5-7d
0.012 mg/L: 5-7d

0.027 mg/L: 5-7d
0.048 mg/L: 7-10d
0.100 mg/L : 5-7d

Mean cumulative numbers of juveniles produced per adult alive for 21days:
Control : 112.7
Solvent control: 168.5
0.0074mg/L: 119.6
0.012 mg/L: 139.3
0.027 mg/L: 133.3
0.048 mg/L: 116.0
0.100 mg/L 112.9
Was control response satisfactory: Yes.

CONCLUSIONS

·NOEC (21-d, reproduction) : 0.082 mg/L
·LOEC (21-d, reproduction) : >0.082 mg/L
·EC50 (21-d, reproduction) : >0.082 mg/L
·LC50 for parental *Daphnia* (21-d) :>0.082 mg/L

DATA QUALITY

- **Reliabilities:**
- **Remarks field for Data Reliability:**
  Experimental design and analytical procedure were well documented.
  Carried out by Analytical Biochemistry Laboratories, Inc.,

REFERENCES

CMA Doc. I.D. 40-8565036 (1985).

GENERAL REMARKS

CHRONIC TOXICITY TO AQUATIC INVERTEBRATES (e.g., *DAPHNIA*) (2)

TEST SUBSTANCE

- **Identity:** Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
- **Remarks:** Source: Tokyo Kasei Kogyo Co., Ltd. Lot No. AX01, Purity: >95.0%

METHOD

- **Method:** OECD TG 211 (revised edition of No.202).
- **Test type:** Semi-static.
- **GLP:** Yes
- **Year:** 1998
- **Analytical procedures:** Yes. Measured by HPLC 2-3 times a week (before and after the replacement of the test water.)
- **Species/Strain:** *Daphnia magna*
- **Test details:** Semi-static (water renewal: 3 times a week), open-system.
- **Statistical methods:** Eco-Statics (Version 1.0 beta-edition R1.4)

TEST CONDITIONS

Test organisms: Source, supplier, any pre-treatment, breeding method: Supplied by NIES (Japan).
Age at study initiation: Juveniles within 24h old.
Control group: Yes.
Test conditions: Stock solutions preparation and stability: No solvent used. Test chemical was diluted to 1.0wt.% (with solubilizer HCO-40 1.0wt.% controlled) with diluting water (Elendt M4) before use. Solubilizer concentration was controlled 100mg/L with working solution (HCO-40 1.0wt.%).
Test temperature range: 19.9-20.8 °C (average temperature 20°C).
Exposure vessel type: 80mL test solution in a 100 mL glass beaker; 10 beakers per treatment
Dilution water source: Elendt M4(OECD guideline No.211 Annex 2)
Dilution water chemistry: Hardness: 251mg/L as $CaCO_3$
Lighting: <1,200 lx, 16h:8h light-darkness cycle
Water chemistry in test: DO= 7.0-9.2mg/L; pH=7.4-7.9.
Feeding: *Chlorella regularis*, 0.1-0.2 mgC/day/individual
Element (unit) basis: Mean cumulative numbers of juveniles produced per adult (reproduction)
Test design: Number of replicates=10; individuals per replicate=10;
Concentrations: 0, 55.6, and 100 mg/L, because 48h-EiC_{50} for parent Daphnia (Acute immobilization test) was >180mg/L. Dispersant control was also tested.
Method of calculating mean measured concentrations: Geometric mean.
Exposure period: 21 d
Analytical monitoring: By HPLC analysis. 99.7-101.3% of the nominal concentration at preparation; 94.7-99.3% just before the renewal of the test water (after 2 days exposure).

RESULTS

- **Nominal concentrations:** 0, 55.6, 100 mg/L
- **Measured concentrations:** Time-weighted measured concentrations of test chemical during a 21-day exposure were 54.8 and 98.7 mg/L.

Measured concentration of test chemical during 21-day exposure

Nominal concentration	Measured concentration (day, mg/L)					
(mg/L)	0(new)	2 (old)	7(new)	9(old)	16(new)	19(old)
Control	< 1.0	< 1.0	< 1.0	< 1.0	< 1.0	< 1.0
Disp.Cont.	< 1.0	<1.0	< 1.0	< 1.0	< 1.0	< 1.0
55.6	56.3	54.4	55.4	53.9	56.3	52.6
100	100.4	99.3	100.0	98.5	99.8	95.2

new: freshly prepared test solutions.
old: test solution after 2 days exposure.

- **Unit :** mg/L
  - · NOEC (21-d, reproduction) : 55.6 mg/L,
  - · LOEC (21-d, reproduction) : >100 mg/L,
  - · EC50 (21-d, reproduction) : 89.1 mg/L ;
  - · LC50 for parental *Daphnia* (21-d) : >100 mg/L; calculated based on nominal concentrations.

Cumulative Number of Dead Parental *Daphnia*.

Nominal conc.	Days																				
(mg/L)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Disp.Cont.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
55.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2	2	2	2

Mean cumulative numbers of juveniles produced per adult during 21-d.

Nominal conc.	Days																				
(mg/L)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Control	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.8	2.2	7.1	7.7	8.2	19.6	20.4	23.2	43.8	48.0	61.6	83.0	88.0	88.7
Disp.Cont.	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.3	8.2	8.2	8.7	29.2	31.9	33.0	55.8	61.5	64.8	72.0	73.8	73.8
55.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	1.0	2.0	2.7	5.1	9.3	13.6	26.6	34.4	43.9	51.4	66.2	74.3	79.9
100	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.6	2.6	3.6	7.8	9.3	11.0	15.1	17.5	20.3	30.3	33.0	33.0

Cumulative Number of Juveniles produced per Adult Alive for 21–d.

	Nominal Concentration(mg/L)			
Vessel No.	Cont.	Disp.Cont.	55.6	100.0
1	74	74	68	37
2	57	71	70	25
3	126	92	65	-
4	127	78	96	-
5	90	73	89	36
6	84	70	116	29
7	71	76	78	35
8	94	84	93	28
9	78	75	87	34
10	86	45	37	40
Mean (S.D)	88.7(22.524)	73.8(12.072)	79.9(21.533)	33.0(5.127)
Inhibition rate(%)		0.832	0.901	0.372
Significant difference		*1		**

-:were not calculated because the parental *Daphnia* was dead during a 21-days testing period.
1*:Indicates a significant difference by Dunnet multiple comparison procedure, Two-sides test.
**:Indicates a significant difference (alpha=0.01) from the control.

- **Statistical results as appropriate:**
  Calculated LC_{50} Value for Parental *Daphnia:* LC_{50}(21day) >100(mg/L)
  Calculated EC_{50} value for Inhibition of Reproduction: EC_{50}(21day) = 89.1(mg/L)
  (Statistical method: Logit)

- **Remarks:**
  Biological observations
  Cumulative numbers of dead parental *Daphnia*: Control: 0 (mortality: 0%),

Disp.Cont.: 0(mortality: 0%)
55.6 mg/L: 0(mortality: 0%)
100 mg/L: 2 (mortality: 20%)
Time of the first production of juveniles: 8-13d for control
8-12d for dispersant control
8-13d for 55.6 mg/L
10-14d for 100 mg/L
Mean cumulative numbers of juveniles produced per adult alive for 21days:
Control: 88.7, Dispersant control: 73.8
55.6 mg/L: 79.9, 100 mg/L: 33.0
Was control response satisfactory: Yes. Mean cumulative numbers of juveniles produced per adult was 88.7 and 73.8 > 60.

CONCLUSIONS

NOEC (21-d, reproduction) : 55.6 mg/L,
LOEC (21-d, reproduction) : >100 mg/L,
EC50 (21-d, reproduction) : 89.1 mg/L ;
LC50 for parental *Daphnia* (21-d) : >100 mg/L; calculated based on nominal concentrations.

DATA QUALITY

- **Reliabilities:** Klimisch Code: 1=reliable without restrictions.
- **Remarks field for Data Reliability:**
  Experimental design and analytical procedure were well documented.
  Carried out by Toray Research Center (Japan).

REFERENCES

Environment Agency of Japan (1998).

GENERAL REMARKS

HEALTH ELEMENTS

ACUTE ORAL TOXICITY

TEST SUBSTANCE

- **Identity:** Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
- **Remarks:** Source: Daihachi Kagaku Kogyo Co., Ltd. Lot. No. N-60601, Purity: >99.0%
  Kept at room temperature in a dark place until use. Stability of mixture of dose was confirmed for 7 days under 4C.

METHOD

- **Method:** OECD TG 401
- **Test type:** Single Dose Oral Toxicity Test
- **GLP:** Yes
- **Year:** 1996
- **Species:** Rat
- **Strain:** Crj: CD(SD)
- **Route of administration:** Oral (by single-dose gavage)
- **Doses/concentration levels:** 0(vehicle) and 2,000 mg/kg
- **Sex:** Male & Female
- **Vehicle:** Corn oil
- **Post exposure observation period:** Two weeks.
- **Statistical methods:** Not applicable because of no fatality.

TEST CONDITIONS

Test Subjects: *Age at study initiation*: 6 weeks old for both sexes.
Weight at study initiation: 149-163 g for male.
126-140 g for female
No. of animals per sex per dose: 5 per sex per dose group

Study Design: *Vehicle*: Corn oil. 40.0w/v% for 2000 mg/kg.
Satellite groups and reasons they were added: None
Clinical observations performed and frequency:
Each rat was weighed immediately prior to treatment, 7 and 14 days after post-treatment observation period. The rats were observed each hour to 6hr, after that, 2 times for one day during this time for signs of toxicity.

RESULTS

- **LD_{50}:** Male : > 2,000 mg/kg
  Female : > 2,000 mg/kg

Body weight: The test substance did not cause any changes in body weight.
No detailed body weight data available.
Food/water consumption: No detailed data available.
Clinical signs: Loosening erring of the stool attributable to the treatment with corn oil was

observed for 3 hours from the administration for both sexes in the groups given 0 and 2000 mg/kg. However, no deaths occurred of either male or female animals.

***Haematology*:** Not done.
Biochem: Not done.
Ophthalmologic findings: Not examined.
Mortality and time to death: No deaths were recorded in treated and control group.
Gross pathology incidence and severity: No macroscopic abnormalities that could be attributes to treatment with the test substance were seen on pathological examination.
Organ weight changes: Not done.
Histopathology *(incidence and severity)**:*** Not done.

CONCLUSIONS

LD_{50} was established at > 2,000 mg/kg for both sexes.

DATA QUALITY

- **Reliabilities:** Klimisch Code: 1=reliable without restrictions.
- **Remarks field for Data Reliability:**
  Well conducted study, carried out by the Biosafety Research Center, Food, Drugs and Pesticides (An-pyo Center), Japan

REFERENCES

Toxicity Testing Reports of Environmental Chemicals, vol.4(1996), Ministry of Health & Welfare, Japan.

GENERAL REMARKS

ACUTE INHALATION TOXICITY

TEST SUBSTANCE

- **Identity:** Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
- **Remarks:** Source: Nouplaz 6959, Batch No. 39049, Purity: 98.95%

METHOD

- **Method:** Not specified
- **GLP:** Yes
- **Year:** 1982
- **Species:** Rat
- **Strain:** Crj: CD(SD)
- **Doses/concentration levels:** 2,600 mg/m^3
- **Sex:** Male & Female
- **Post exposure observation period:** Two weeks.
- **Statistical methods:** Not applicable because of no fatality.

TEST CONDITIONS

Test Subjects: ***Age at study initiation*****:** Not stated.
Weight at study initiation**:** 210-275 g for both sexes.
No. of animals per sex per dose**:** 5 per sex per dose group

Study Design: ***Inhalation Chamber:*** A 0.5m^3 stainless steel inhalation chamber was used. (Youg and Bertke, Cincinnati, Ohio)
The test compound atmosphere was generated directly into the chamber by means of Jet Nebulizer Mechanism. Chamber concentrations were monitored by a filter paper/gravimetric technique approximately every 30 min during the exposure period.
The HEPA filtered chamber air-flow was maintained between 10 to 20 air changes per hour during the exposure period with the chamber under slightly negative pressure.
The temperature in the chamber was maintained at 69-75 degree F with relative humidity of 30-50%
Satellite groups and reasons they were added**:** None
Clinical observations performed and frequency**:**
After the exposure, all animals were observed daily for 14 days for clinical signs of toxicity. Body weights were recorded prior to exposure and weekly thereafter. All animals were subjected to necropsy at termination of the study.

RESULTS

- LD_0**:** Male : > 2,600 mg/m^3
  Female : > 2,600 mg/m^3

Body weight: The test substance did not cause any changes in body weight.

Mean body weight(g) of rats exposed to this chemical

Males	**Initial weight**	**265.1(8.40)**
	First week	**297.8(14.02)**
	Second week	**329.7(15.27)**
Females	**Initial weight**	**213.9(2.66)**

First week	**223.2(3.96)**	
Second week	**238.1(4.82)**	**Mean(S.D.)**

Food/water consumption: No detailed data available.
Clinical signs : All animals (male and female) had matted, drenched coats for the first 2 days, otherwise no visible signs.
***Haematology*:** Not done.
Biochem: Not done.
Ophthalmologic findings: Not examined.
Mortality and time to death: No deaths were recorded.
Organ weight changes: Not done.
General necropsy observations: All males and 3/5 females exhibited reddening patches on lungs.

CONCLUSIONS

LD_0 was 2,600 mg/m^3 for both sexes.

DATA QUALITY

- **Reliabilities:** Klimisch Code: 1=reliable without restrictions.
- **Remarks field for Data Reliability:**
  Well conducted study, carried out by Midwest Research Institute.

REFERENCES

Nuodex Inc. Acute inhalation toxicity test in Sprague-Dawley rats using compound Nouplaz 6959, Environmental Protection Agency (1983)

GENERAL REMARKS

ACUTE DERMAL TOXICITY

TEST SUBSTANCE

- **Identity:** Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
- **Remarks:**Source: Nouplaz 6959, Batch No. 39049, Purity: 98.95%

METHOD

- **Method:** Procedure set forth in the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)
- **GLP:** Yes
- **Year:** 1981
- **Species:** Rabbits
- **Strain:** New Zealand albino white rabbits
- **Doses/concentration levels:** 2.0 mL/kg
- **Sex:** Male & Female
- **Post exposure observation period:** Two weeks.
- **Statistical methods:** Not applicable because of no fatality.

TEST CONDITIONS

Test Subjects: ***Age at study initiation*:** Not stated.
***Weight at study initiation*:** 2.3-3.2 kg for both sexes.
***No. of animals per sex per dose*:** 3 per sex per dose group and 2 per sex for control.

Study Design: ***Procedure:*** 24 hours prior to treatment the hair on the back of each rabbit was clipped so as to expose approximately 10% of the body surface area. Before dosing, epidermal abrasions were made longitudinally over the exposure area. The abrasions were sufficiently deep to penetrate the stratum corneum but not so deep as to cause bleeding.
A dosage was applied to the exposure area. A 2 x 2-inch gauze pad was placed on the exposure area to prevent seepage of the compound from the area. Each animal was then wrapped with a rubber dam. After 24 hour of exposure, the rubber dam and gauze pad were removed, and the exposure area was wiped to remove any remaining test material.
***Satellite groups and reasons they were added*:** None
***Clinical observations performed and frequency*:**
After the exposure, all animals were observed daily for 14 days for clinical signs of toxicity. A gross necropsy was performed on all animals at the end of the 14 day observation period.

RESULTS

- **LD_0:** Male : > 2.0 mL/kg
  Female :> 2.0 mL/kg

Body weight: The test substance did not cause any changes in body weight.

Individual Animal Body Weights

	Sex	Body weight (kg)		
Control		day 1	day 7	day 14
	male	3.2	3.4	3.6
		3.2	3.4	3.6

	female	2.7	3.0	3.1
		2.9	3.1	3.3
2.0 mL/kg	male	2.3	2.3	2.5
		2.4	2.4	2.5
		2.3	2.2	2.4
	female	2.3	2.5	2.7
		2.4	2.6	2.7
		2.4	2.5	2.6

Food/water consumption: No detailed data available.
Clinical signs : No toxic sign.
***Haematology*:** Not done.
Biochem: Not done.
Ophthalmologic findings: Not examined.
Mortality and time to death: No deaths were recorded.
Organ weight changes: Not done.
Gross Pathology: Nothing noted.

CONCLUSIONS

LD_{50} was 2.0 mL/kg for both sexes.

DATA QUALITY

- **Reliabilities:** Klimisch Code: 1=reliable without restrictions.
- **Remarks field for Data Reliability:**
  Well conducted study, carried out by Midwest Research Institute.

REFERENCES

Nuodex Inc. Acute dermal toxicity test of Tenneco Chemicals Inc. compound Nouplaz 6959 in rabbit. Environmental Protection Agency (1981)

GENERAL REMARKS

SKIN IRRITATION

TEST SUBSTANCE

- **Identity:** Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
- **Remarks:** Source: Nouplaz TOTM(Tenneco Chemicals, Inc.)
  Purity: 98.95%

METHOD

- **Method:** The test method was similar to Section 1500.41.Federal Hazardous Substances Act Regulations - 16 CFR.
- **GLP:** Yes
- **Year:** 1981
- **Species:** Rabbits
- **Strain:** New Zealand albino white rabbits
- **Doses/concentration levels:** 0.5 mL
- **Sex:**
- **Post exposure observation period:** 24, 72 hours after patch application
- **Statistical methods:** Not applicable because of no fatality.

TEST CONDITIONS

Husbandry Conditions : Temperature - 70 ± 2 degree F
Relative Humidity - 45% ± 5%
Light - 12 hour light/dark cycle
Diet - Wayne 15% Rabbit Ration and tap water are provided ad libitum. Based on our current knowledge no contaminants are known to be in this diet or water that might be expected to interfere with the objectives of the study.
Caging - Stainless steel with elevated wire mesh flooring 1 rabbit/cage
Bedding - Techbord
Shepherd Products Company
Kalamazoo, Michigan 49005

Test method : A 0.5 mL portion of material was applied to an abraded and an intact akin site on the same rabbit. Gauze patches were then placed over the treated areas and an impervious material was wrapped snugly around the trunks of the animals to hold the patches in place. The wrapping was removed at the end of the twenty-four hour period and the treated areas were examined. Readings were also made after seventy-two hours. The Draize method of scoring was employed.

Evaluation : Draize Scale For Scoring Reactions

Erythema and Eschar Formation	Value
No erythema	0
Very slight erythema(barely perceptible)	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4

Oedema Formation	Value
No oedema	0
Very slight oedema(barely perceptible)	1
Slight oedema(edges of area well defined by definite raising)	2
Moderate edema (raised approximately 1 millimetre)	3

Severe edema (raised more than 1 millimetre and extending beyond the area of exposure) ····· 4

RESULTS

- **Primary Irritation Score : 4.16/4 =1.04**

Erythema and Eschar Formation	Reading (Hours)	Rabbit Number 1	2	3	4	5	6	Average
Intact skin	24	2	1	2	1	2	1	1.50
Intact skin	72	0	0	1	0	0	0	0.17
Abraded skin	24	2	1	2	1	2	1	1.50
Abraded skin	72	0	0	1	1	0	0	0.33
						Subtotal		3.50
Oedema Formation								
Intact skin	24	1	0	0	0	1	0	0.33
Intact skin	72	0	0	0	0	0	0	0.00
Abraded skin	24	1	0	0	0	1	0	0.33
Abraded skin	72	0	0	0	0	0	0	0.00
						Subtotal		0.66
						Total		4.16

CONCLUSIONS

Slightly irritating
This report concluded that TOTM was not a primary skin irritant in rabbit.
It is not possible to assign a classification.

DATA QUALITY

- **Reliabilities:** Klimisch Code: 1 = reliable without restrictions.
- **Remarks field for Data Reliability:**
  Well conducted study, carried out by Biosearch Inc.

REFERENCES

Nuodex Inc. Primary Skin Irritation - Rabbits. OTS 2065758. Doc ID 878214470,1981

GENERAL REMARKS

EYE IRRITATION

TEST SUBSTANCE

- **Identity** : Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
- **Remarks** : Source: Nouplaz TOTM(Tenneco Chemicals, Inc.)
  Purity: 98.95%

METHOD

- **Method** : The test method was similar to Section 1500.42. Federal Hazardous Substances Act Regulations - 16 CFR.
- **GLP** : Yes
- **Year** : 1981
- **Species** : Rabbits
- **Strain** : New Zealand albino white rabbits
- **Numbers of animals** : 6
- **Doses/concentration levels** : 0.1 mL
- **Sex** :
- **Post exposure observation period**
  : 1, 2, 3, 4, 7 days
- **Statistical methods** : Not applicable because of no fatality

TEST CONDITIONS

Husbandry Conditions : Temperature - 70 ± 2 degree F
Relative Humidity - 45% ± 5%
Light - 12 hour light/dark cycle
Diet - Wayne 15% Rabbit Ration and tap water are provided ad libitum. Based on our current knowledge no contaminants are known to be in this diet or water that might be expected to interfere with the objectives of the study.
Caging - Stainless steel with elevated wire mesh flooring 1 rabbit/cage
Bedding - Techbord
Shepherd Products Company
Kalamazoo, Michigan 49005

Test method : 0.1 mL of the experimental material was instilled into the right eyes of the test animals while the other eyes remained untreated to severe as controls. The treated eyes were examined at one, two, three, four and seven days following instillation of the test materials into the eyes.

Evaluation : Interpretation of the results was made in accordance with the Draize Scale of Scoring Ocular Lesions.

Scale of Scoring Ocular Lesions

	Value range
(1) CORNEA	
A. Opacity - Degree of Density(area most dense taken for reading)	0 - 4
B. Area of Cornea Involved	1 - 4
Score equals A x B x 5 (Total Maximum = 80)	
(2) IRIS	
A. Values	0 - 2
Score equals A x 5 (Total Maximum = 10)	
(3) CONJUNCTIVAE	
A. Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)	0 - 3
B. Chemosis	0 - 4

C. Discharge····· 0 - 3
Score equals (A+B+C) x 2 (Total Maximum =20)

RESULTS

- Average Ocular Irritation Score : 2.3(1 day), 1.7(2day), 0(3,4,7day)
- Remarks:

Rabbit number	Tissue		Reading 1 day	2 day	3 day	4 day	7day
1	(1) Cornea total		0	0	0	0	0
	(2) Iris total		0	0	0	0	0
	(3) Conjunctivae total		2	2	0	0	0
	Total Ocular Irritation Score	2	2	0	0	0	
2	(1) Cornea total		0	0	0	0	0
	(2) Iris total		0	0	0	0	0
	(3) Conjunctivae total		4	2	0	0	0
	Total Ocular Irritation Score	4	2	0	0	0	
3	(1) Cornea total		0	0	0	0	0
	(2) Iris total		0	0	0	0	0
	(3) Conjunctivae total		2	2	0	0	0
	Total Ocular Irritation Score	2	2	0	0	0	
4	(1) Cornea total		0	0	0	0	0
	(2) Iris total		0	0	0	0	0
	(3) Conjunctivae total		2	2	0	0	0
	Total Ocular Irritation Score	2	2	0	0	0	
5	(1) Cornea total		0	0	0	0	0
	(2) Iris total		0	0	0	0	0
	(3) Conjunctivae total		2	2	0	0	0
	Total Ocular Irritation Score	2	2	0	0	0	
6	(1) Cornea total		0	0	0	0	0
	(2) Iris total		0	0	0	0	0
	(3) Conjunctivae total		2	0	0	0	0
	Total Ocular Irritation Score	2	0	0	0	0	
	Average Ocular Irritation Score		2.3	1.7	0.0	0.0	0.0

CONCLUSIONS

Slightly irritating
This report concluded that TOTM was not a primary skin irritant in rabbit.
It is not possible to assign a classification.

DATA QUALITY

- **Reliabilities** **:** Klimisch Code: 1=reliable without restrictions.
- **Remarks field for Data Reliability**
  : Well conducted study, carried out by Biosearch Inc

REFERENCES

Nuodex Inc. Primary Eye Irritation - Rabbits. OTS 2065758. Doc ID 878214471,1983

GENERAL REMARKS

SENSITIZATION

TEST SUBSTANCE

- **Identity** : Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
- **Remarks** : Source: Nouplaz TOTM(Tenneco Chemicals, Inc.)
  Purity: 98.95%

METHOD

- **Method** : Buehler test
- **GLP** : Yes
- **Year** : 1981
- **Species** : Guinea pig
- **Strain** : Albino guinea pig
- **Numbers of animals** : 10
- **Doses/concentration levels** : 0.5 mL
- **Sex** : Male
- **Post exposure observation period**
  : 10 application
- **Statistical methods** : Not applicable because of no fatality

TEST CONDITIONS

Husbandry Conditions : Temperature - 70 ± 2 degree F
Relative Humidity - 45% ± 5%
Light - 12 hour light/dark cycle
Diet - Charless River Guinea Pig Furmula and tap water are provided ad libitum. Based on our current knowledge no contaminants were known to be in this diet or water that might be expected to interfere with the objectives of the study.
Caging - Stainless steel with elevated wire mesh flooring 5 guinea pigs/cage
Bedding - Deotized Animal Cage Board(DACB)
Shepherd Products Company
Kalamazoo, Michigan 49005

Test method : A 0.5 mL portion of material was applied to the intact akin test site on the guinea pigs. A gauze patch was placed over the treated area and an impervious material was wrapped snugly around the trunks of the animals to hold the patches in place. After a 24 hour contact period the patch was removed and the animals were allowed to rest for one day. Following this rest period another application was applied to the same skin site using a fresh sample. After the tenth application the animals were rested for a two week period. At the termination of the rest period a challenge application was put on skin sites differing from the original test sites. The challenge application remained on for 24 hours. The sites were examined for reaction using the Draize method of scoring to grade reactions.

Evaluation : Draize Scale For Scoring Reactions

Erythema and Eschar Formation	Value
No erythema	0
Very slight erythema(barely perceptible)	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4

Oedema Formation	Value
No oedema	0
Very slight oedema(barely perceptible)	1
Slight oedema(edges of area well defined by definite raising)	2
Moderate oedema (raised approximately 1 millimetre)	3
Severe oedema (raised more than 1 millimetre and extending beyond the area of exposure)	4

RESULTS

- No sensitization
- Remarks:

		Reading After Application number										Challenge	
Guinea pig No.		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**24 hours**	**48 hours**
1	**Erythema**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
	Oedema	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
2	**Erythema**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
	Oedema	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
3	**Erythema**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
	Oedema	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
4	**Erythema**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
	Oedema	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
5	**Erythema**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
	Oedema	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
6	**Erythema**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
	Oedema	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
7	**Erythema**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
	Oedema	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
8	**Erythema**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
	Oedema	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
9	**Erythema**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
	Oedema	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
10	**Erythema**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
	Oedema	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**

CONCLUSIONS

No sensitization

DATA QUALITY

- **Reliabilities** **:** Klimisch Code: 1=reliable without restrictions.
- **Remarks field for Data Reliability**
  : Well conducted study, carried out by Biosearch Inc.

REFERENCES

Nuodex Inc. Guinea Pig Contact Dermal Irritatiom/Sensitization-Modified Buehler Method OTS 206574. Doc ID 878214475, 1981

GENERAL REMARKS

REPEATED DOSE TOXICITY (a)

TEST SUBSTANCE

- **Identity** : Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
- **Remarks** : Source: Nuoplaz 6959
  Purity: 98.2% (GC/FID) 97.9% (HPLC)
  Impurities were detected at level than 0.1-0.5%, one being di(2-ethylhexyl) phthalate (DEHP).

METHOD

- **Method** : BIBRA Standard Operating Procedures
- **Test type** : Repeat Dose Toxicity
- **GLP** : Yes
- **Year** : 1984
- **Species** : Rat
- **Strain** : Fischer 344
- **Route of administration** : Oral
- **Doses/concentration levels** : 0(0), 0.2(184), 0.67(650) and 2(1826) % (mg/kg bw/day)
- **Vehicle** : Rodent diet
- **Sex** : Male & Female
- **Exposure period** : 28 days
- **Frequency of treatment** : Once daily
- **Control group and treatment**
  : Dietary level 0% and reference compound DEHP 0.67%.
- **Post exposure observation period**
  : None
- **Duration of test** : Males and females; for 28 days
- **Statistical methods** : The control and TOTM treated groups were subject to analysis of variance, and if this was significant the treated groups were compared with the controls using the Least Significant Difference test. The controls and DEHP groups were compared using a two-tailed pooled student t test with Welch's correction. In all cased a probability level of $P<0.05$ was taken to indicate statistical significance.

TEST CONDITIONS

Test Subjects : ***Age at study initiation*:** 48-51 days old for males and females.
***Weight at study initiation*:** 137-154g for male.
111-132g for female.
***No. of animals per sex per dose*:** 5 Rats per sex per dose group

Study Design : ***Vehicle*:** Diet
***Satellite groups and reasons they were added*:** None
***Clinical observations performed and frequency*:**
Body wt. was recorded immediately prior to the first exposure and again for each animal 1, 3, 7, 10, 14, 17, 21, 24, 27th days.
Twice each day the animals were observed in their cages for variations in behaviour or condition, and once weekly a more detailed examination was made at the time of a weighing.
Food intakes were measured over the period day –3 to 0 and continuos intakes were measured at twice-weekly intervals until the day preceding autopsy. The intakes of test article or reference compound for each animal were calculated twice weekly

using the analysed dietary concentrations of TOTM or DEHP, and the individual valued for bodyweight and food intake.

Haematologic parameters were evaluated for each animal. On the day preceding the start of the autopsies a sample of blood was collected from a caudal vein of each animal.

Autopsy: At the end of the 28th day treatment period the rats were deprived of food overnight, with water available. On the day of autopsy each animal was weighted and then killed. The blood was used to provide serum for clinical chemistry. During the autopsy any abnormalities of the external condition and of the thoracic or abdominal viscera were noted.

Organs: The weight of the following organs was recorded: adrenal glands, lungs, brain, ovaries, heart, spleen, kidneys, testes, liver and thyroids.

Serum chemistry was performed for each animal. Serum separated from the blood taken prior to autopsy was analyzed.

Liver biochemistry was performed for each animal. Homogenized liver tissues were measured for protein, cyanide-insensitive palmitoyl-CoA, carnitine acetyltranferase and catalase.

Histopathology was made for haematoxylin and eosin stained sections from paraffin embedded samples, of all the preserved tissues.

Transmission electron microscopy: Two thin slices of liver, one from the left lobe, the other from the median lobe, were fixed for analysis. (The remainder of the liver was used for biochemical analysis.)

RESULTS

- **NOAEL** 184 mg/kg bw/day
- **LOAEL** 650 mg/kg bw/day

Body weight **:** No statistically significant differences of bodyweight between the control and TOTM treated groups of either sex. There was a trend for the male rats from all the TOTM treated groups to be lighter than the controls (92 to 97% of control). In the females, this trend was only evident in the 2.0% TOTM group (94% of control).

Food/water consumption **:** Female rats fed 2.0% TOTM consumed significantly less diet than the controls during first seven days of treatment after which their intakes increased but remained lower than those of the controls. In the males there were no statistically significant differences between the control and TOTM fed groups during the treatment period.

Haematology **:** In both sexes haemoglobin concentration of the rats given diet containing 0.67 or 2.0% TOTM were statistically significantly lower than the control (94 to 97% of control). In the males there was a small lowering of erythrocyte count in all groups given TOTM (96 to 97% of control) but this was not reproduced in the females. Both sexes given the two higher dietary concentrations of TOTM had higher leucocyte counts than the control (118 to 123% of control), but the differences were statistically significant only in the males. These male groups also had lower proportions of the leucocytes as eosinophils and monocytes (42 to 67 and 26 to 37%, respectively). Significantly lower values for haemotocrit and mean cell volume were limited to females given the two lower dose levels of TOTM (91 to 95 and 96 to 97% , respectively).

Organ weights **:** In both sexes the liver weights, and liver weights relative to bodyweight, were increased in the TOTM (114 to 135% of control) treated animals compared to the controls. These differences were small and not statistically significant in the 0.2% TOTM group. In the males fed TOTM the higher values for brain weights relative to body weight, in the absence of any significant differences in the recorded weight probably reflect the lower bodyweights in the groups concerned. In the females there were statistically significant higher lung weights in the rats fed 0.2 or 0.67% TOTM when compared to the controls. In the case of the TOTM treated animals this difference was not dose related and not statistically significant when expressed relative to

bodyweight.

Serum analyses

: Analysis of serum from the males and females showed statistically significantly increased levels of albumin in the groups given 0.67 or 2.0% TOTM (104 to 108% of control). In the males there were statistically significantly higher cholesterol levels in the 0.67 and 2.0% TOTM groups (115 to 125% of control). Concentration of serum urea was statistically significantly increased in the male 2.0% TOTM group to the control value (115%). In the females there was also an isolated statistically significantly lower value for lipid concentration in the 0.2% TOTM group (83% of control).

Liver Biochemistry

: TOTM treatment did not influence to a statistically significant degree the concentration of hepatic protein. After TOTM treatment PCoA activity was statistically significantly higher than controls in both sexes at the highest dose and in the males at the lower two doses (133 to 237% of control). In the groups given TOTM only the highest dose level males had statistically significant increases of catalase level (165% of control). Both sexes given 0.67 or 2.0% TOTM had statistically significantly increased carnitine acetyltransferase activity with little difference between the two sexes (262 to 1002% of control).

Histopathology

: No abnormalities were detected in the majority of the animals. The only lesions occurring with any frequency were focal interstitial pneumonitis and nephrocalcinosis in the females. The observations were not firmly dose related. The pneumonitis was of limited extent, often only a single focus. Two female rats fed 2.0% TOTM showed reductions in cytoplasmic basophilia in the liver although it was only marginal.

Transmission Electron Microscopy

: In the hepatocytes from the control rats the peroxisomes varied in size from small to moderately large. They had uniformly electron dense contents and some possessed a lattice core. They were ubiquitously distributed throughout the cytoplasm. Feeding diet containing 2.0% TOTM produced a slight increase in the numbers of peroxisomes which varied between cells. No difference was seen between the centrilobular and periportal areas.

CONCLUSIONS

The NOAEL for repeated dose toxicity is considered to be 184 mg/kg/day (0.2%) and the LOAEL is considered 650 mg/kg/day (0.67%) for both sexes.

DATA QUALITY

- **Reliabilities** **:** Klimisch Code: 1=reliable without restrictions.
- **Remarks field for Data Reliability**
  : Well conducted study, carried out by the British Industrial Biological Research Associations

REFERENCES

Chemical Manufacturers Association, Project No. 3.0496. Report No. 0496/1/85, CMA Reference. TM-3.0-BT-BIB

GENERAL REMARKS

REPEATED DOSE TOXICITY (b)

TEST SUBSTANCE

- **Identity** : Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
- **Remarks** : Source: Daihachi Kagaku Kogyo Co., Ltd. Lot. No. N-60601
  Purity: >99.0% Kept at room temperature in a dark place until use.

METHOD

- **Method** : Guidelines for 28-day Repeated Dose Toxicity Testing of Chemicals (Japan)
- **Test type** : Repeat Dose Toxicity
- **GLP** : Yes
- **Year** : 1996
- **Species** : Rat
- **Strain** : Crj:CD(SD)
- **Route of administration** : Oral
- **Doses/concentration levels** : 0(vehicle), 100, 300 and 1,000 mg/kg/day
- **Vehicle** : Corn oil
- **Sex** : Male & Female
- **Exposure period** : 28 days
- **Frequency of treatment** : Once daily
- **Control group and treatment**
  : Vehicle (corn oil)
- **Post exposure observation period**
  : 2 weeks for 0 and 1,000 mg/kg/day dose.
- **Duration of test** : Males and females; for 28 days
- **Statistical methods** : Bartlett's test, Dunnett's test or Kruskal-Wallis test depending on whether or not the data were nonhomogeneous or homogeneous. Fisher's test for the pathological result. Jonckheere's test for the correlation of dosage

TEST CONDITIONS

Test Subjects : ***Age at study initiation*:** 6 weeks old for males and females.
***Weight at study initiation*:** 130-151g for male.
110-121g for female.
***No. of animals per sex per dose*:** 5 Rats per sex per dose group

Study Design : ***Vehicle*:** Corn oil
***Satellite groups and reasons they were added*:** None
***Clinical observations performed and frequency*:**
Body weights were recorded immediately prior to the first exposure and again for each animal every week.
Haematologic parameters were evaluated for each animal. Blood samples for the haematologic determinations were taken from abdominal artery in rats after 16 hr fast.
Clinical chemistry analyses were performed on serum samples from each animal.
Urinalyses were performed for each rat. Urine samples were collected from each rat on the day prior to scheduled termination.
***Organ weights*:** brain, liver, kidneys, spleen, adrenals, testes (male) and ovaries (females) for each animal.
***Histopathology*:** heart, liver, kidneys, spleen, adrenals and femoral bone marrow from rats of the control and high dosed groups, and kidneys from all dosage male.

RESULTS

- **NOAEL** Male: >1,000 mg/kg/day
  Female: >1,000 mg/kg/day

Body weight **:** The mean body weight of treatment groups of rats for males and females had no significant differences from the controls during the course of the study.

Food/water consumption
: There was no significant difference between control and treatment groups throughout treatment and recovery periods for both sexes.

Clinical signs **:** No abnormality was detected during the study.

Haematology **:**

at the end of dosing

Males and females
: No dose-related significant changes were observed. In the examination of blood coagulating system, prothrombin time for males was slightly prolonged, but they were considered within the physiological fluctuation. For females, no significant changes in all test items.

after recovering period

Males **:** Haemoglobin was slightly increased for males at 1000mg/kg group, but they were considered within the physiological fluctuation. In the examination of blood coagulation system, no significant changes were observed in all test items.

Females **:** No significant change in all tests.

Biochemistry**:**

at the end of dosing

Males **:** No dose-related significant adverse treatment-related effect in clinical chemistry.

Females **:** At 300, and 1,000 mg/kg dosing, chlorine contents were low.

after recovering period

Males **:** At 1,000 mg/kg dosing, potassium contents were slightly high.

Females **:** At 1,000 mg/kg dosing, GOT were slightly high. But both changes were considered to be no meaning, because at the end of treatment these changes were not recognised.

Urinalysis**:**

at the end of dosing

Males and Female
: At 1,000 mg/kg dosing, some of rats (both sexes), amounts of urinary increased, but the mean urinary specific gravity values in the 1,000 mg/kg dosing group was not significant change from control group.

after recovering period

Males and Females
: No dose-related significant change in all tests.

Mortality and time to death
: No deaths prior to scheduled termination.

Organ weight changes**:**

at the end of dosing

Male **:** No dose-related change in all tested organs.

Female **:** Relative liver weight were slightly increased at 100 mg/kg dosing, but no dose-related change. Other organs, no significant change.

after recovering period**:**

Males **:** At 1,000 mg/kg dosing, relative kidney weight were slightly low.

Female **:** At 1,000 mg/kg dosing, absolute and relative adrenal weight were slightly high. But both changes were considered no related to dosing and recovering of this chemical.

Gross pathlogy and histopathlogy:

at the end of dosing

Males **:** Coloured patch/zone of lungs were observed 1 of 100 mg/kg, 2 of 300 mg/kg and 3 animals of 1,000 mg/kg dosing group. Also hypertrophy of the kidney, hypertrophy of parathyroid, and etc. were observed. Amounts of eosinophilic body in the kidney were slightly increased in dosing group. But all these changes were considered no related the dosing and recovering of this chemical, because the degree and rate of changes were same of all the group included control.

Females **:** Red patch/zone of thymus dilated lumen of the uterus and etc. were observed. But all these changes were considered no related the dosing and recovering of this chemical, because the degree and rate of changes were same of all the group included control.

after recovering period:

Males and Females

: No dose-related significant change in all tests.

CONCLUSIONS

No test substance related changes were noted in terms of clinical signs, body weight, food consumption, and haematology, blood chemical examination, urinalysis, and pathological findings. The NOEL for repeated dose toxicity is considered to be 1,000 mg/kg/day for both sexes.

DATA QUALITY

- **Reliabilities** **:** Klimisch Code: 1=reliable without restrictions.
- **Remarks field for Data Reliability**
  : Well conducted study , carried out by the Biosafety Research Center, Food, Drugs and Pesticides (An-pyo Center), Japan

REFERENCES

Toxicity Testing Reports of Environmental Chemicals, vol.4(1996), Ministry of Health & Welfare, Japan

GENERAL REMARKS

TOXICITY TO REPRODUCTION

TEST SUBSTANCE

- **Identity:** Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
- **Remarks:** Source: Daihachi Kagaku Kogyo Co., Ltd. Lot. No. N-80301
  Purity: >99.0% Kept at room temperature in a dark place until use.

METHOD

- **Method:** OECD Preliminary reproductive toxicity screening test
- **Test type:** Preliminary reproduction toxicity screening test.
- **GLP:** Yes
- **Year:** 1998
- **Species:** Rat
- **Strain:** Crj;CD (SD)
- **Route of administration:** Oral (by gavage)
- **Doses/concentration levels:** 0(vehicle), 100, 300, 1,000 mg/kg/day
- **Vehicle:** Corn oil
- **Sex:** Male & Female
- **Administration period:** Male; for 46 days from 2 weeks prior to mating
  Female; from 2 weeks prior to mating to day 3 of lactation
- **Frequency of treatment:** Once daily.
- **Control group and treatment:** Vehicle (corn oil)
- **Post exposure observation period:** None.
- **Terminal kill:** Male: day 47
  Female: day 4 of lactation
- **Statistical methods:** Chi square test for 1 grade positive data and Fisher's test for another.
  Bartlett's test or Kruskal-Wallis' test for 2 or more grade positive data.
  And used Dunnett's test or Mann-Whitney's U-test for examination.

TEST CONDITIONS

- **Test Subjects:** ***Age at study initiation*****:** 10 week old for both sexes.
  Weight at study initiation**:** 373-435 g for males, 217-257 g for females
  No. of animals per sex per dose**:** 12 per sex per dose group

- **Study Design:** The animals were sacrificed on the day 4 of lactation for females.
  Males and females with no mated were killed 1 day after the mating period. Females with no delivery killed 26th day of gestation period.
  Vehicle**:** Corn oil
  Satellite groups and reasons they were added**:** None
  Mating procedures**:** Male/female per cage; 1/1, length of cohabitation; with in the limit of 14 days until proof of pregnancy (formation sperm detection in vagina) was observed.
  Clinical observations performed and frequency**:**
  Parent: General appearance once a day
  Foetus: General appearance once a day after birth
  Organs examined at necropsy**:**
  Parent: Males and females: Gross pathlogy of all organs were tested.
  Males: Organ weight: Testis and epididymis of all animals.
  Female: Organ weight: Ovary of all animals.
  Count: Implantation sites and corpus luteum of ovary of all animals.

Microscopic: Males: Testis and epididymis. Count of sertoli sells, spermatocytes, round spermatids and elongate spermatids in seminiferous tubules of 5animals of all dosing groups.(Stage I-VI, VII-VIII, IX-XI, XII-XIV of spermatozoon formative cycle.)
Females: Ovary
Pup: Gross pathlogy of all organs were tested. Dead pups and abnormal organs were tested histopathogy.

***Parameters assessed during study*:**
Body weight. Males: Prior to the first dosing and 2, 5, 7, 10, 14 day. After that once a week, the day sacrificed. Females: Prior to the first dosing and 2, 5, 7, 10, 14 day. During gestation period, 0, 1,3, 5, 7, 10, 17 and 20 day. During lactation period, 0, 1, and 4. During cohabitation period, the same day with male. Pups: Day 0 and 4
Food/water consumption. The same day when body wt. determined, except lactation period and the day sacrificed for males, also, 0 day of gestation and lactation for female.
No. of pairs with successful copulation, copulation index (No. of pairs with successful copulation/No. of pairs mated) x 100, duration of mating, 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 pups born, delivery index (No. of pups born/No. of implantation sates)x 100, No. of love pups born, live birth index (No. of love pups born/No. of pups born) x 100, sex ratio of pups, No. of dead pups born, gestation length, gestation index (No. of females with live pops delivered/ No. of pregnant females) x 100, nursing index (No. of females nursing live pups/No. of females with normal delivery) x 100, No. of live pups on day 4, viability index (No. of live pups on day 4/No. of live pups born) x 100,

RESULTS

Repeat dose toxicity: NOEL 100 mg/kg/day for males
1,000 mg/kg/day for female
Reproductive and developmental toxicity: NOEL 100 mg/kg/day for males
1,000 mg/kg/day for female
1,000 mg/kg/day for offspring

Mortality and day of death : None.
Body weight : No statistical significant difference from controls.
Food/water consumption: No statistical significant difference from controls.
Reproductive data: No statistical significant difference from controls.
Pups data : Body weight and weight gain of 300 mg/kg dosing group for both sexes were slightly low. But all pups of 100 and 1000 mg/kg dosing group were not statistical significant difference from controls.
At the other tests, no statistical significant difference from controls.
Grossly visible abnormalities, external, soft tissue and skeletal abnormalities :
For males:
Slightly decrease of spermatocytes and spermatids: 2 animals of 300 mg/kg dosing group. 11 of 1000 mg/kg dosing group.
Moderate decrease of spermatocytes and spermatids: 1 of 1000 mg/kg/dosing group. At this animal, a few multinucleate giant cell were appeared and slightly vacuolization of sertoli sells were observed. Also, at the epididymis, moderate amount of cell debris moderate decrease of spermatids and slightly granuloma of spermatic were observed.
For the control group, atrophy of seminiferous tubule were observed 2 animals. At these animals, slightly amount of cell debris were observed. one of these animals, slight decrease of spermatids was also observed.
Number of cells in seminiferous tubules:
Group 1(Stage I-VI): Low value of spermatids at 300 mg/kg dosing group.
Low values of spermatocytes and spermatids at 1000 mg/kg dosing group.

Group 2(Stage VII-VIII): Low values of round spermatids and ratio of sertoli cells at 1000 mg/kg.
Group 3(stage IX-XI): Low values of elongate spermatids and ratio of sertoli cells at 1000 mg/kg.
Group 4(stage XII-XIV) : Low values of spermatocytes, elongate spermatids, and ratio of sertoli cells at 1000 mg/kg dosing group.

For females:
Cyst of corpus luteum of ovary was observed 2 animals of 300 mg/kg dosing group.
No abnormal ovary observed at the female of 100 mg/kg dosing without successful copulation, females of control and 100 mg/kg dosing without pregnant.

Histopathological finding in rats

		dose (mg/kg)			
Items		**0**	**100**	**300**	**1,000**
No. of male animals examined		12	12	12	12
Organ: Findings					
	Grade				
Testis:					
Decrease, spermatocyte and spermatid	**Total**	0	0	2	12**
	+	0	0	2	11
	++	0	0	0	1
Multinuclear giant cell, seminiferous tubule	+	0	0	0	1
Vacuolozation, Sertoli cell	+	0	0	0	1
Atrophy, seminiferous tubule	+	2	0	0	0
Epididymis:					
Cell debris, lumen	**Total**	2	0	0	1
	+	2	0	0	0
	++	0	0	0	1
Decrease, sperm	**Total**	1	0	0	1
	+	1	0	0	0
	++	0	0	0	1
Granuloma, spermatic	+	0	0	0	1
No. of female animals examined		12	12	12	12
Ovary:					
Cyst, corpus luteum	<+>	0	0	2	0

Values are no, of animals with finding.
Grade: +=slight, ++=moderate change and <+>=detected
Significantly different from 0 mg/kg group: **:p<0.01.

Number of cells in seminiferous tubules of male rats.

	dose (mg/kg)			
Items	**0**	**100**	**300**	**1,000**
No. of animals examined	5	5	5	5
Group 1 (Stage I-VI)				
No. of Sertoli cells	20.12(3.18)	19.08(1.49)	18.52(1.45)	18.08(1.45)
Spermatogonia				
No.	16.80(5.65)	20.52(2.58)	18.48(3.17)	15.76(2.61)
ratio [a)]	0.85(0.29)	1.08(0.19)	1.01(0.21)	0.87(0.11)
Spermatocytes				
No.	50.80(7.44)	51.80(4.84)	42.64(2.63)	40.84(5.63)*
ratio	2.53(0.13)	2.72(0.26)	2.37(0.24)	2.25(0.16)
Round spermatids				
No.	138.36(17.20)	128.00(8.89)	117.68(5.59)*	112.60(3.11)**
ratio	6.91(0.35)	6.75(0.84)	6.39(0.70)	6.26(0.48)
Elongate spermatids				

No.	130.00(21.71)	132.32(11.17)	103.28(12.34)*	95.36(8.44)**
ratio	6.53(1.15)	6.98(0.88)	5.62(0.90)	5.30(0.69)
Group 2 (Stage VII-VIII)				
No. of Sertoli cells	16.96(2.63)	17.04(2.17)	16.64(2.73)	16.52(2.23)
Spermatogonia				
No.	2.92(1.06)	2.40(0.93)	2.04(0.68)	2.60(1.10)
ratio	0.18(0.09)	0.14(0.05)	0.12(0.03)	0.16(0.06)
Spermatocytes				
No.	91.68(10.37)	94.68(6.55)	84.44(6.99)	82.32(6.70)
ratio	5.45 (0.56)	5.60(0.51)	5.16(0.79)	5.03(0.54)
Round spermatids				
No.	142.08(13.39)	131.64(13.72)	123.96(8.23)	118.76(8.28)*
ratio	8.45(0.62)	7.75(0.39)	7.66(1.66)	7.25(0.62)*
Elongate spermatids				
No.	129.24(17.37)	128.32(16.88)	114.72(9.80)	105.65(13.47)
ratio	7.78(1.54)	7.56(0.72)	7.09(1.62)	6.46(1.05)
Group 3 (Stage VII-VIII)				
No. of Sertoli cells	19.28(1.92)	20.52(1.55)	19.20(1.58)	19.32(2.18)
Spermatogonia				
No.	4.52(1.32)	4.20(1.50)	4.92(1.63)	3.32(1.02)
ratio	0.23(0.05)	0.21(0.08)	0.26(0.11)	0.18(0.05)
Spermatocytes				
No.	102.52(10.83)	99.08(8.42)	97.56(4.50)	89.04(9.00)
ratio	5.34(0.56)	4.85(0.50)	5.10(0.36)	4.62(0.32)
Elongate spermatids				
No.	145.24(11.01)	130.64(9.90))	131.68(19.71)	119.24(15.90*
ratio	7.56(0.61)	6.37(0.23)	6.88(1.04)	6.21(0.83)*
Group 4 (Stage VII-VIII)				
No. of Sertoli cells	19.16(2.81)	20.92(1.73)	18.64(1.72)	16.72(0.92)
Spermatogonia				
No.	4.04(0.89)	3.72(0.72)	3.64(0.48)	3.64(0.71)
ratio	0.21(0.05)	0.18(0.03)	0.20(0.02)	0.22(0.05)
Spermatocytes				
No.	109.80(13.15)	110.36(9.22)	99.44(4.54)	88.76(4.33)**
ratio	5.76 (0.29)	5.28(0.12)	5.36(0.34)	5.32(0.46)
Elongate spermatids				
No.	159.76(15.91)	150.28(18.99)	137.08(17.70)	105.16(18.34)**
ratio	8.39(0.63)	7.19(0.71)	7.35(0.62)	6.33(1.31)**

Values are expressed as Mean(S.D.)
Significantly different from 0 mg/kg group; * $p<0.05$, ** $p<0.01$
a): (No. of spermatogenic cells/no. of sertoli cells in a seminiferous tubule)

Influence on reproductive performances of rats

	dose (mg/kg)			
Items	**0**	**100**	**300**	**1,000**
No. of male animals examined	12	12	12	12
No. of pairs with successful copulation	12	12	12	12
Duration of mating (day, Mean, (SD))	2.1(1.2)	2.3(1.3)	2.7(1.2)	2.7(1.1)
Copulation index(%)*	100.0	91.7	100.0	100.0
No. of pregnant animals	11	10	12	12
Fertility index(%)**	91.7	90.9	100.0	100.0

*(No.of pairs with successful copulation/no.of pairs mated) x 100
**(No. of pregnant animals/no.of pairs with successful copulation) x 100

Influence on developmental performances of rats

	dose (mg/kg)			
Items	**0**	**100**	**300**	**1,000**
No. of male animals examined	12	12	12	12
No. of corpora lutea	16.8(1.5)	17.3(1.3)	17.0(2.3)	17.9(2.2)
No. of implantation sites	15.5(1.7)	16.6(1.3)	16.0(2.0)	16.3(2.3)
Implantation index(%) [a)]	92.5(7.2)	96.2(6.6)	94.5(8.4)	91.3(8.8)
No. of pups born(%)	13.7(3.1)	15.0(1.7)	15.0(1.8)	15.1(2.7)
Delivery index(%) [b)]	87.6(15.4)	90.3(6.8)	94.1(7.2)	92.2(9.6)
Live pups born				
No.	13.3(2.9)	14.7(2.0)	14.9(2.0)	15.0(2.7)
Live birth index(%) [c)]	97.1(5.6)	97.8(3.6)	99.2(2.6)	99.4(2.1)
Sex ratio(M/F)	1.09(0.69)	1.05(0.50)	1.17(0.75)	0.76(0.44)
Dead pups born				
No.	0.5(0.9)	0.3(0.5)	0.1(0.3)	0.1(0.3)
Gestation length(day)	22.7(0.5)	22.7(0.5)	22.5(0.5)	11.6(0.5)
Gestation index(%) [d)]	100.0	100.0	100.0	100.0
Nursing index(%) [e)]	100.0	100.0	100.0	100.0
Live pups on day 4				
No.	13.2(2.8)	14.6(2.1)	14.4(2.9)	14.5(2.9)
Viability index(%) [f)]	99.5(1.8)	99.3(2.3)	95.6(11.5)	96.7(6.7)
Body weight of pups(g)				
Male Day 0	7.32(0.77)	7.13(0.52)	6.69(0.55)	6.87(0.84)
Day 4	11.71(1.76)	11.09(0.93)	10.23(0.98)*	10.60(1.47)
Day 0-4, gain(g)	4.39(1.04)	3.96(0.53)	3.54(0.77)*	3.73(0.80)
Body weight gain(%) [g)]	59.41(8.87)	55.54(6.16)	53.19(11.91)	54.39(9.50)
Female Day 0	6.93(0.83)	6.63(0.64)	6.33(0.58)	6.58(0.62)
Day 4	11.08(1.71)	10.28(1.01)	9.84(1.01)*	10.03(1.46)
Day 0-4, gain(g)	4.16(1.00)	3.65(0.56)	3.14(0.79)*	3.46(0.96)
Body weight gain(%)	59.63(10.42)	55.24(8.07)	49.95(13.09)	52.17(11.10)

Values are expressed as Mean (S.D.)
Significantly difference from 0 mg/kg group ; p□0.05
a): (No. of implantation sites/no. of corpora lutea) x 100
b): (No. of pups born/no. of implantation sites) x 100
c): (No. of live pups born/no. of pups born) x 100
d): (No. of females with live pups delivered/ no. of pregnant remales) x 100
e): (No. of females nursing live pups/no. of females with normal delivery) x 100
f): (No. of live pups on day 4/ no. of live pups born) x 100
g): (Body weight gain/body weight on day 0) x 100

CONCLUSIONS

Repeat dose toxicity

Histopathological examination of the testes, demonstrated decrease of spermatocytes and spermatids in males of the 300 and 1000 mg/kg group. No effects of this chemical on general appearance, body weight, food consumption, autopsy findings, weights of the reproductive organs of both sexes, or histopathlogical features of the ovary were detected.

The NOELs are considered to be 100 mg/kg/day for males, and 1,000 mg/kg/day for females.

Reproductive and developmental toxicity

Except for the effects in males observed on histopathological examination, no influence of this chemical was detected regarding reproductive ability, organ weight or histopathological feature of the ovary, delivery or maternal behaviour of dams. No effects of this chemical were detected on viability, general appearance, body weights or autopsy findings for offspring.

The NOELs are considered to be 100 mg/kg/day for males, 1,000 mg/kg/day for females, and 1,000

mg/kg/day for offspring.

DATA QUALITY

- **Reliabilities:** Klimisch Code: 1=reliable without restrictions.
- **Remarks field for Data Reliability:**
  Well conducted study , carried out by the Safety Research Institute for Chemical Compounds Co., Ltd.(Japan)

REFERENCES

Toxicity Testing Reports of Environmental Chemicals, vol.6(1998), Ministry of Health & Welfare, Japan

GENERAL REMARKS

GENETIC TOXICITY IN VITRO (BACTERIAL TEST)

TEST SUBSTANCE

- **Identity:** Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
- **Remarks:** Source: Daihachi Kagaku Kogyo Co., Ltd. Lot. No. N-60601
  Purity: >99.0% Kept at room temperature in a dark place until use.

METHOD

- **Method**: Guideline for Screening Mutagenicity Testing of Chemicals (Japan) and OECD TG 471 and 472
- **Test type**: Reverse mutation assay
- **GLP***:* Yes
- **Year:** 1996
- **Species/Strain:** *Salmonella typhimurium* TA100, TA1535, TA98, TA1537
  Escherichia coli WP2 *uvr*A
- **Positive controls:** -S9 mix, 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide (TA100, WP2, TA98)
  Sodium azide (TA1535)
  9-Aminoacridine (TA 1537)
  +S9 mix, 20Aminoanthracene (five strains)
- **S9:** Rat liver, induced with phenobarbital and 5,6-benzoflavone
- **Statistical methods**: No statistical analysis was done.

TEST CONDITIONS

- **Study Design:**
  ***Concentration*:** -S9: 0, 313, 625, 1,250, 2,500, 5,000 ug/plate (five strains)
  +S9: 0, 313, 625, 1,250, 2,500, 5,000 ug/plate (five strains)
  ***Number of replicates*:** 2
  ***Plates/test*:** 3
  ***Procedure*:** Plate incorporation method
  ***Solvent*:** Acetone

RESULTS

- **Cytotoxic concentration:**
  Toxicity was not observed up to 5,000 ug/plate in five strains with and without metabolic activation (S9 mix).
- **Genotoxic effects:**

	+	?	-
With metabolic activation:	[ ]	[ ]	[x]
Without metabolic activation:	[ ]	[ ]	[x]

CONCLUSIONS

Bacterial gene mutation is negative with and without metabolic activation.

DATA QUALITY

- **Reliabilities:** Valid without restriction.
- **Remarks field for Data Reliability**
  Well conducted study, carried out by Hatano Research Institute, Food and Drug Safety Center

(Hadano, Japan).

REFERENCES

Toxicity Testing Reports of Environmental Chemicals, vol.4(1996), Ministry of Health & Welfare, Japan

GENERAL REMARKS

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

TEST SUBSTANCE

- **Identity:** Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
- **Remarks:** Source: Daihachi Kagaku Kogyo Co., Ltd. Lot. No. N-60601
  Purity: >99.0% Kept at room temperature in a dark place until use

METHOD

- **Method**: Guideline for Screening Toxicity Testing of Chemicals (Japan)
- **Test type**: Chromosomal aberration test
- **GLP***:* Yes
- **Year**: 1996
- **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

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, 1.3, 2.5, 5.0 mg/mL
  -S9 (short-term treatment): 0, 1.3, 2.5, 5.0 mg/mL
  +S9 (short-term treatment): 0, 1.3, 2.5, 5.0 mg/mL
  Plates/test**:** 2
  Solvent**:** Acetone
  Positive controls**:** Mitomycin C for continuous treatment
  Cyclophosphamide for short-term treatment

RESULTS

- **Cytotoxic concentration:**
  Toxicity was not observed up to 5.0 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]

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 Hatano Research Institute, Food and Drug Safety Center

(Hadano, Japan).

REFERENCES

Toxicity Testing Reports of Environmental Chemicals, vol.4(1996), Ministry of Health & Welfare, Japan

GENERAL REMARKS