FOREWORD INTRODUCTION

P-TERT-BUTYL PHENOL

CAS N°: 98-54-4

COVER PAGE
SIDS Initial Assessment Report
for
10th SIAM

(Japan, March 15-17, 2000)

Chemical Name: p-tert-Butylphenol
CAS No: 98-54-4
Sponsor Country: Japan

National SIDS Contact Point in Sponsor Country: Mr. Kazuhide Ishikawa
Ministry of Foreign Affairs

HISTORY:

SIDS Dossier and Testing Plan were reviewed in SIDS Review Process, where the following SIDS Testing Plan was agreed:

no testing ( )
testing (X) Solubility in water
Chronic toxicity to daphnia
Combined repeat dose and reproductive toxicity test
Gene mutation
Chromosomal aberration test in vitro

Conclusions and Recommendations on Environment were agreed and a part of Human Health was discussed at SIAM 7 and SIAM 9.

Deadline for circulation: November 30, 1999
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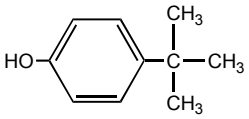
Previous circulation: December 31, 1997 and March 31, 1999
(To all National SIDS Contact Points and the OECD Secretariat)

SIDS INITIAL ASSESSMENT PROFILE

CAS NO.	98-54-4
CHEMICAL NAME	p-tert-Butylphenol
STRUCTURAL FORMULA	

RECOMMENDATIONS OF THE SPONSOR COUNTRY

The chemical is a candidate for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE RECOMMENDATIONS

Acute toxicity of p-t-butylphenol is low via any administration routes. This chemical is considered as an irritant to the skin, eyes and respiratory tract. The possibility of skin sensitization in humans still remains because of some positive results in human patch tests, despite negative results in animal experiments (OECD TG 406). The depigmentation was observed on the skin of various animals and humans exposed to this chemical. This change was likely induced by exposure to this chemical not only via direct contact but also via inhalation or ingestion route. In the OECD combined repeat dose and reproductive/developmental screening toxicity test (OECD TG 422) of rats by gavage at doses of 20, 60 and 200 mg/kg/day for 46 days, this chemical showed neither systemic toxicity nor reproductive toxicity even at the highest dose of 200 mg/kg/day. Although a noisy respiratory sound was induced in a few females at 200 mg/kg/day, it was considered due to irritation of the respiratory tract caused by this chemical. In a dose-finding study (14 days), this changed to respiratory difficulty, especially at 1,000 mg/kg/day. In other studies by the longer and higher exposure in diet (approx. 1 g/kg b.w./day, for 20 or 51 weeks), forestomach hyperplasia was induced. This chemical showed clear negative results in gene mutation tests. However, one chromosomal aberration study indicated structural chromosome aberration and polyploidy with metabolic activation in CHL/IU cells (OECD TG 473) although other studies in rat lymphocytes (OECD TG 473) and in rat liver epithelial-type cells resulted in negative. Therefore, the possibility of *in vivo* genotoxicity still remains. There was no sufficient carcinogenicity study and no evidence of carcinogenesis in manufacturing workers, however, a two-stage carcinogenicity study indicated this chemical has promoting activity of forestomach carcinogenesis (papilloma and squamous carcinoma) in rats treated with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). Furthermore, since the structural related chemical, BHA, (2(3)-tert-butyl-methoxylphenol) is a clear carcinogen, a carcinogenic potential of this chemical could not be ruled out.

p-t-Butylphenol is a stable solid and is classified as a readily biodegradable chemical (OECD TG 301). Bioaccumulation factors range from 34-120.

The lowest acute and chronic toxicity data were 48h EC_{50} (3.4 mg/l) of *Daphnia magna* and 21d NOEC (0.73 mg/l) of *Daphnia magna*, respectively. An assessment factor of 100 was chosen and applied to the chronic toxicity data (NOEC), because only two NOEC values (algae and *Daphnia*)

were available. Thus, PNEC of p-t-butylphenol is 7.3 x 10^{-3} mg/l in this report. (OECD classification categories for substances hazardous to the aquatic environment; Class: Acute II). p-t-butylphenol may have potential chronic toxicity to aquatic organisms, because NOEC of *Daphnia* is relatively low and the chemical has moderately bioaccumulative potential.

The production volume of this chemical was ca. 5,000 tonnes/year in 1993 in Japan. This chemical is used as an intermediate for phenol resins and polycarbonate resins. It is also used as a raw material for construction elements and floors in buildings. The potential environmental distribution of p-t-butylphenol obtained from a generic fugacity model (Mackey level III) shows that it will be mainly distributed to water. The main route of human exposure is inhalation with a limited numbers of workers potentially exposed during sampling and bag or tank filling operations.

IF FURTHER WORK IS RECOMMENDED, SUMMARISE ITS NATURE

Human Health

In *vivo* genotoxicity study such as *in vivo* micronucleus test is recommended because *in vitro* chromosomal aberration test indicates clear positive result and it is necessary to evaluate the *in vivo* genotoxicity potential.

FULL SIDS SUMMARY

CAS NO: 98-54-4		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point		Other (unknown)	99.3 °C
2.2	Boiling Point		Other (unknown)	237 °C (at 1,013 hPa)
2.3	Density		Other (unknown)	0.92 g/m^3 at 110 °C
2.4	Vapour Pressure		Other (unknown)	1.3 x 10^2 Pa at 60 °C
2.5	Partition Coefficient (Log Pow)		OECD TG 107	3.29 at 25 °C
2.6 A.	Water Solubility		OECD TG 105	610 mg/l at 25 °C
B.	pH			
	pKa		OECD TG 112	10.16 at 25 °C
2.12	Oxidation: Reduction Potential			
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation			None
3.1.2	Stability in Water		OECD TG 111	Stable at pH 4, 7and 9
3.2	Monitoring Data			In air = In surface water = not detected In soil/sediment = not detected In biota =
3.3	Transport and Distribution		Calculated (Fugacity, Mackey Level III type)	Release: 100% to water In Air 0.2 % In Water 95.3 % In Sediment 4.4 % In Soil 0.2 %
			(local exposure)	PEC_{local} = 2.7 x 10^{-4} mg/l
3.5	Biodegradation		OECD TG 301C	readily biodegradable
3.7	Bioaccumulation		Other (Static test)	34 - 120
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	*Oryzias latipes*	OECD TG 203	LC_{50} (24 hr) = 5.1 mg/l, LC_{50} (48 hr) =5.1 mg/l, LC_{50} (72 hr) = 5.1mg/l, LC_{50} (96 hr) = 5.1 mg/l
4.2	Acute Toxicity to Aquatic Invertebrates *Daphnia*	*Daphnia magna*	OECD TG 202	EC_{50} (24 hr) = 7.3 mg/l, EC_{50} (48 hr) = 3.4 mg/l,
4.3	Toxicity to Aquatic Plants e.g. Algae	Selenastrum *capricornum* ATCC2262	OECD TG 201	EC_{50} (72 hr) = 22.7 mg/l NOEC = 9.53 mg/l
4.5.2	Chronic Toxicity to Aquatic Invertebrates (*Daphnia*)	*Daphnia magna*	OECD TG 202	EC_{50}s (21 d) = 2.0mg/l (Reproduction) NOEC = 0.73mg/l (Reproduction)

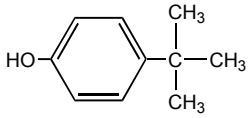
4.6.1	Toxicity to Soil Dwelling Organisms			None
4.6.2	Toxicity to Terrestrial Plants			None
4.6.3	Toxicity to Other Non-Mammalian Terrestrial Species (Including Birds)			None
	TOXICOLOGY			
5.1.1	Acute Oral Toxicity	Rat	OECD TG 401	LD_{50} = 4,000 mg/kg
5.1.2	Acute Inhalation Toxicity	Rat	Other (unknown)	No lethal effects in saturated air
5.1.3	Acute Dermal Toxicity	Rabbit	Other (unknown)	LD_{50} = 2,318 mg/kg
5.2.1	Skin Irritation	Rabbit	Other (unknown)	Irritating
5.2.2	Eye Irritation	Rabbit	Other (unknown)	Irritating
5.3	Skin Sensitisation	Guinea pig	OECD TG 406	Not sensitising
5.4	Repeated Dose Toxicity	Rat	OECD TG 422	NOAEL = 200 mg/kg/day
5.5	Genetic Toxicity In Vitro			
A.	Bacterial Test (Gene mutation)	S.typhimurium E. coli	Japanese TG and OECD TG 471 & 472	- (With metabolic activation) - (Without metabolic activation)
B.	Non-Bacterial In Vitro Test (Chromosomal aberrations)	CHL cells	Japanese TG and OECD TG 473	+ (With metabolic activation) + (Without metabolic activation)
5.6	Genetic Toxicity In Vivo			None
5.7	Carcinogenicity	Rat	Two stage test	Promoting forestomach tumor
5.8	Toxicity to Reproduction	Rat	OECD TG 422	NOAEL = 200 mg/kg/day
5.9	Developmental Toxicity/ Teratogenicity			None
5.11	Experience with Human Exposure			Depigmentation on skin

SIDS INITIAL ASSESSMENT REPORT

p-tert-Butylphenol (CAS No. 98-54-4)

1. IDENTITY

- OECD Name: p-tert-Butyl phenol
- Synonym: 4-tert-Butylphenol; Butylphen; 1-hydroxy-4-tert-butylbenzene; p-t-butylyphenol; Dimethylethyl)phenol; Phenol, 4-(1,1-dimethylethyl)-
- CAS Number: 98-54-4
- Empirical Formula: $C_{10}H_{14}O$
- Structure:



- Degree of Purity: 99.9%
- Major Impurity: none
- Essential Additives: none
- Physical-chemical properties
  - Melting Point: 99.3 °C
  - Vapour pressure: 1.3 x 10^2 Pa at 70 °C
  - Water solubility: 610 mg/l
  - Log Pow: 3.29

2. GENERAL INFORMATION ON EXPOSURE

2.1 Production and import

The production volume of p-t-butylphenol in Japan is 5,000 tonnes/year in 1993. According to ECDIN database, the production volume of USA is 11,000 tonnes/year in 1993. According to IUCLID database, maximum production volume is 10,000 tonnes/year. Less than 5000 tonnes/year are produced in France. Less than 1000 tonnes/year are sold to be used either as a chemical intermediate for the production of vulcanization agents or as for the production of phenolic resins.

2.2 Use pattern

All of p-t-butylphenol produced in Japan is used as intermediate for resins, and no consumer uses are reported. Most of the produced quantities are used on-site by the producer for the production of phenolic resins in France.

2.3 Other information

None

3. ENVIRONMENT

3.1 Environmental Exposure

3.1.1 General Discussion

p-t-Butylphenol is stable abiotically (OECD 111) and readily biodegradable (OECD 301C: 98 % after 28 d) in water. Photodegradation is expected because p-t-butylphenol has an absorption band at UV region.

p-t-Butylphenol is moderately bioaccumulative (BCF = 120), and log Pow is 3.29 at 25 °C.

The potential environmental distribution of p-t-butyl phenol obtained from a generic fugacity model (Mackay level III) is shown in Table 1. Parameters used for this model are shown as Annex to this report. The results show that, if p-t-butyl phenol is released into water or soil, it is unlikely to be distributed into other compartment. If p-t-butyl phenol is released into air, it is likely to be transported to other compartment.

Table 1. Environmental distribution of p-t-butyl phenol
Using a generic fugacity model Mackey level III).

Compartment	Release 100% to air	Release 100% to water	Release 100% to soil
Air	39.7 %	0.2 %	0.0 %
Water	23.3 %	95.3 %	0.4 %
Soil	35.9 %	0.2 %	99.6 %
Sediment	1.1 %	4.4 %	0.0 %

As this chemical is used in a closed system and is not used for consumer products, its release to environments may occur only from the production site.

In Japanese environmental survey, p-t-butylphenol was not detected from surface water and bottom sediments in 1977. Detection limits in this survey were 0.0005 mg/l and 0.03 mg/kg, respectively.

3.1.2 Predicted Environmental Concentration

As p-t-butyl phenol is produced under the well controlled closed system, the amount of release of this chemical to air is negligibly small. The waste of p-t-butyl phenol treated at the centralized wastewater treatment plant of the factory itself transferred into a centralized wastewater treatment plant and then released into the bay. Therefore, Predicted Environmental Concentration (PEC) will be calculated only for the water environment.

a. Local exposure

According to the report from a Japanese manufacturer, 12,000 kg/year (estimated) of p-t-butyl phenol is discharged into a centralized wastewater treatment plant (CWTP). Wastewater treated in CWTP is released with 4.4×10^{10} l/year of effluent into the bay along the coast near from the manufactory. Removal rate of this chemical by the CWTP is estimated to be negligible. Local Predicted Environmental Concentration (PEC_{local}) is calculated to be 2.7×10^{-4} mg/l, employing the following formula and dilution factor of 1,000.

$$\frac{\text{Amount of release } (1.2 \times 10^{10} \text{ mg/y})}{\text{Volume of effluent } (4.4 \times 10^{10} \text{ l/y}) \times \text{Dilution Factor } (1{,}000)}$$

According to a German exposure information, German proposed to integrate a generic exposure scenario using following parameters.

Production volume:	10,000 tonnes/year (maximum production volume given in IUCLID)
Emission factor:	1 % (production and processing at the same site)
Number of production days:	300 days/year
Elimination in stp:	91 % (according to the Simpletreat)
Flow-rate of receiving river:	60 m^3/s (according to the TGD)

With this data, a PEC_{local} of about 5.8 x 10^{-3} mg/l can be calculated.

b. Regional exposure

No data are available.

3.2 Effects on the Environments

Acute and chronic toxicity data of p-t-butylphenol to aquatic organisms are summarized in Table 1. As the lowest acute and chronic toxicity data, 48h EC_{50} of *Daphnia magna* (3.4 mg/l) and 21d NOEC (reproduction) of *Daphnia magna* (0.73 mg/l) were selected, respectively. An assessment factor of 100 was chosen and applied to the chronic toxicity data to determine PNEC (according to the OECD Provisional Guidance for Initial Assessment of Aquatic Effects), because only two NOEC values (algae and *Daphnia*) were available.

From the lowest chronic toxicity value 0.73 mg/l (21 d NOEC of *Daphnia*) and the assessment factor 100 : PNEC = 0.73/ 100 = 0.0073 mg/l

Table 1. Acute and chronic toxicity data of p-tert-Butylphenol to aquatic organisms at different trophic levels.

Species	Endpoint		Conc. (mg/l)	Notes
Selenastrum capricornutum (algae)	Bms	72h EC_{50}	22.7	a, 1)
		72h NOEC	9.53	c, 1)
Tetrahymena pyriformis (protozoa)	Pgr	60h IC_{50}	18.4	a, 2)
Daphnia magna (water flea)	Imm	24h EC_{50}	7.3	a, 1)
		48h EC_{50}	6.7	a, 1)
	Rep	21d NOEC	0.73	c, 1), C
Daphnia magna	Imm	48h EC_{50}	3.4	a, 3), A
Crangon septemspinosa (shrimp)	Mor	96h LC_{50}	1.9	a, 4)
Oryzias latipes (fish)	Mor	24h LC_{50}	5.1	a, 1)
		48h LC_{50}	5.1	a, 1)
		72h LC_{50}	5.1	a, 1)

		96h LC_{50}	5.1	a, 1)
Pimephales promelas	Mor	24h LC_{50}	6.2	a, 5)
(fathead minnow)		48h LC_{50}	5.7	a, 5)
		72h LC_{50}	5.3	a, 5)
		96h LC_{50}	5.1	a, 5)

Notes: Bms; growth measured by biomass change, Pgr; population growth, Imm; immobilization, Rep; reproduction. 1)- 5); reference number, A, C; the lowest values of the acute (a) or chronic (c) toxicity data among algae, cladocera (water flea) and fishes.

References; 1) Environmental Agency of Japan (1996), 2) Schultz, T.W. and Riggin, G.W. (1985), 3) Kuhn, R., Pattard, M., Penak, K. and Winter, A. (1989), 4) McLeese, D.W., Zitoko, V., and Peterson, M.R. (1979), 5) Holcombe, G.W., Phipps, G.L., Knuth, M.L. and Felhaber, T. (1984)

3.2.2 Effects on other organisms

No data for terrestrial organisms are available.

3.2.3 Other effects

No data are available.

3.3 Initial Assessment for the Environment

p-t-Butylphenol is readily biodegradable, but have moderately high BCF (34-120) and log Pow (3.29). The lowest acute and chronic toxicity values were 3.4 mg/l (48h EC_{50} of *Daphnia*) and 0.73 mg/l (21 d NOEC of *Daphnia*), respectively. Thus, this chemical may have potential chronic toxicity to aquatic organisms.

PNEC of p-t-butylphenol for aquatic organisms was calculated as 0.0073 mg/l. PEC from Japanese local exposure scenario was 2.7×10^{-4} mg/l. Thus,

$$PEC_{local}/PNEC = 2.7 \times 10^{-4}/0.0073 = 3.7 \times 10^{-2} < 1$$

PEC from German local exposure scenario was 5.8×10^{-3} mg/l. Thus,

$$PEC_{local}/PNEC = 5.8 \times 10^{-3}/0.0073 = 0.79 < 1$$

4. HUMAN HEALTH

4.1 Human Exposure

4.1.1 Occupational exposure

p-t-Butylphenol is produced in a closed system. It is used as an intermediate for resins, modifiers for polymers and stabilizers for polymers. Occupational exposures in production sites are expected in sampling and bag or tank filling operations. Inhalation is considered to be the main route and the dermal exposure may occur during sampling operations.

Inhalation exposure

The exposure levels were measured in two production facilities. Air samples were collected at 20-40 cm away from the worker's face, using silica gel tube method and analysed by HPLC with UVD. The workers wear respiratory protecting equipment and protective gloves during sampling, bag filling, and coupling and decoupling operations for tank loading. The bag filling operation was done semi-automatically except bag handling in the building which has a local exhaust ventilation system. Other operations were done in open space. Durations and frequencies of sampling, bag filling and tank loading were 1 minutes, 6 times/day, 8.5 hours, 20 times/month and 40 minutes, 7 times/month.

The average exposure levels were:

Sampling	7.3 mg/m^3	(max: 32.3,	min: <0.1;	9 samples)
Bag filling	0.1 mg/m^3	(max: 0.2,	min: <0.1;	10 samples)
Tank loading	0.3 mg/m^3	(max: 0.3,	min: 0.2;	2 samples)

If a single worker is assigned to implement all above daily operation without protective equipment, the daily intake is calculated as 0.087 mg/kg/day, based on the average atmosphere concentration.

Dermal exposure

p-t-Butylphenol is solid at normal temperature and dermal absorption during bag filling work is presumed to be low. During sampling operation, workers could be exposed to liquid p-t-butylphenol, and dermal exposure is estimated to be 0 – 0.1 mg/cm^2/day by EASE model as wide dispersive, direct handling but incidental.

Assuming that one of the worker's hand contacts with this chemical during every sampling work, and he clean his hands after each sampling work because of irritating property, total intake is calculated to be 0.005 mg/kg/day. Considering that the temperature of this chemical at the sampling site is 115 °C, direct handling without protective gloves is impossible, so actual intake is less than the estimation.

The risk through skin might be very low because the workers always use protective equipment.

4.1.2 Consumer exposure

In Germany, p-t-butylphenol is not directly used as the consumer products but it is used as the raw material for consumer uses, such as Cerement CE 49 (with concentration of 1 to $\leq$ 1.5%) and Epoxy FC (with concentration of 15-25%) as cover materials for constructions in buildings. Cerement CE 49 is used as plating material for constructional articles and Epoxy FC as floor plating materials. Based on their use pattern, it is considered that the consumer exposure is presumably low.

In Japan and France, no direct consumer uses of p-t-butylphenol could be identified.

4.1.3 Indirect exposure via environment

As p-t-butylphenol is not readily biodegradable and moderately bioaccumulative, the exposure to the general population via the environment would be possible through drinking water processed from surface water and through fish which may accumulate this chemical.

Based on the physical chemical properties of this chemical (e.g. relatively high water solubility to the PEC calculated in Section 3.1.2), a significant removal during the processing is not expected.

Therefore, the concentration in drinking water is estimated to be equal to PEC, as the worst case. The daily intake is calculated as 1.9 x 10^{-4} mg/kg/day (2 l/day, 60 kg b.w.).

Using the maximum bioconcentration factor of 120 obtained from IUCLID database, the concentration of this chemical in fish can be calculated as follows:

$$PEC_{fish} = 120 \times (5.8 \times 10^{-3} \text{ mg/l}) = 7.0 \times 10^{-4} \text{ mg/g-wet}$$

As a daily intake of fish in Japan is estimated to be 90 g for 60 kg body weight person, a daily intake of this chemical will be 1.0 x 10^{-3} mg/kg/day.

In case of France, at the production site, where most of the production volume is further processed, all liquid effluents are incinerated. Therefore, there are no releases to surface water.

4.2 Effects on Human Health

a) Motion of action of the chemical, toxicokinetics and metabolism

Metabolism

^{14}C-labelled p-t-butylphenol was given intravenously to male Wistar rats at a single dose of 1.2 - 10.4 mg/kg b.w. and, bile and urine were collected for 4 hours, subsequently. 65 - 71 % and 17 - 21 % of the applied dose were excreted as glucuronide conjugate and sulfate conjugate, respectively (total recovery of radioactivity: 91 - 93 %). The study on incubation of isolated hepatocytes with 3.6 - 120.2 µg/ml at 37 °C for 1 hour supported the above results concerning the ratio of conjugates and dose-dependency. (Koster *et al.*: 1981)

[U-^{14}C] p-t-butylphenol was also given intravenously to rats at a dose of 18 mg/kg b.w. Urine and bile were collected during 24 hours. 1.5 ± 0.2 µmol was excreted as sulfate in the urine, while no significant amounts were found in the biliary excretes. Incubation of 112.65 mg [U-^{14}C] p-t-butylphenol with rat liver cytosol at 37 °C for 1 hour yielded 65.5 +/- 11.8 nmol/min/mg protein-1 of sulfated test substance. (Nanbo: 1991)

Distribution and excretion

^{14}C-labelled p-t-butylphenol (147 µg/kg/day) in Keltrol solution was administered to male Wistar rats by gavage daily for 3 days. Urine and feces were collected daily. 26.7 % and 72.9 % of the applied dose was eliminated via feces and urine, respectively. Distribution in tissues and organs was as follows: retention in abdominal adipose tissue: not detectable (< 0.01 %/g), liver: 0.02 %, lung: not detectable (< 0.01 %), carcass: 0.1 % (data in percent of the applied doses). (Freitag *et al.*: 1982)

There were some human data on excretion of this chemical, in which urine samples from workers handling p-t-butylphenol in the factory were examined.

Urine samples of workers engaged in packing of p-t-butylphenol (bagging, weighing and sealing of the bags) were collected for 24 hours after the start of each shift. Mean level in urine was 4.20 µg/ml at day shift and 6.12 µg/ml at night shift. In contrast to the urine samples, no free p-t-butylphenol could be detected in sweat collected from the back of workers immediately after bathing. (Kosaka *et al.*: 1989)

In another data, workers in the factory with semi-automatization were examined. Non-detectable amounts to traces were found in the urine of plant operators and 1.55 - 3.34 μg/ml were found in urine of 3 product packers (time averages). The biological half-life of p-t-butylphenol in urine taken from these 3 examinees was calculated to be 4 h on average. (Ikeda *et al.*: 1978)

Based on these data, it was considered that p-t-butylphenol was rapidly excreted mostly as conjugates to urine.

b) Acute toxicity

[SIDS data] Oral LD_{50} for p-t-butylphenol was 4,000 mg/kg b.w. for rats (OECD TG 401) (Huels-Bericht: 1985a). In inhalation study, no lethal effects were observed in rats exposed for 8 hours to an atmosphere saturated with this chemical at 20 degree C (BASF AG: 1971). Dermal LD_{50} for this chemical was 2,318 mg/kg b.w. for rabbits (Smyth *et al*.: 1969).

There were other studies on acute oral toxicity. In one study, LD_{50} was 5,360 mg/kg b.w. and 3,620 mg/kg b.w. for male and female rats, respectively. Sluggishness, unsteady gait, prostration, unkempt appearance, and nasal discharge were observed as the principal signs of toxicity. Signs of toxicity subsided in survivors at 3 to 7 days after dosing. Deaths were induced from 2 hours to 5 days after dosing. In rats died during the study, there were mottling of the lungs and livers as the principal macroscopic lesions in female but no significant gross lesions in male. (Klonne *et al*.: 1988)

There was another inhalation toxicity study. Rats were exposed for 4 hours to this chemical as dust aerosol of 5,600 mg/cm^3 with additional vapour component of 30 mg/cm^3. Within one to two days following exposure, 1/5 rat of each sex died, which showed dark red of purple discoloration of the lungs and/or kidneys but not survivors. Clinical signs observed on the day of exposure and up to 7 days postexposure included signs of mucosal irritation (perinasal, perioral, and periocular encrustation) and signs of respiratory distress (audible respiration, gasping, and a deceased respiration rate). (Klonne *et al*.: 1988)

In another dermal study using rabbits, application of this chemical at 2,000, 8,000, 16,000 mg/kg induced severe skin irritation but not death, and the sign of toxicity was only prostration in one female at 12,000 mg/kg (Klonne *et al*.: 1988). This conflict with Smyth's report may be due to the difference in vehicle.

The intraperitoneal LD_{50} value was 225 mg/kg and 78.46 mg/kg for rats and mice, respectively (BASF AG: 1971, Biagi *et al*.: 1975).

c) Irritation

Skin irritation

There were many data on skin irritation, which showed that p-t-butylphenol was mildly to highly irritating and corrosive to the skin.

Standard Draize tests were performed in rabbits. Administration onto the skin at dose of 500 mg for 4 hours and 24 hours induced moderate irritation. (Klonne *et al.*: 1988, *Prehled Prumyslove Toxikologie*: 1986) In one study, no signs of skin irritation in majority of rabbits (4/6). However, in another rabbit, minor, transient erythema and desquamation was evident. The remaining rabbit exhibited slight edema, dermal necrosis, scab formation, and desquamation. The skin appeared to be normal on post-exposure day 17.

In IUCLID database, there were three data on skin irritation in rabbits other than the above. Uncovered application of 0.01 ml on the rabbit belly induced irritation and the injury grade was described as 6 of 10. (Smyth et al.: 1969) In the irritation tests conducted according to OECD Guideline, irritation was induced, but the severity was not described. (Huels-Bericht: 1985b) Corrosion was induced in BASF test, but the severity was not also described. (BASF: 1971) There were no details of these tests.

Recent studies also show this chemical is irritating to skin (The Dow Chemical Company: 1997a, b).

In depigmentation tests, irritation was also induced. 0.1 ml solution (p-t-butylphenol in various solvents) was applied daily to 9 cm^2 of the shaved skin of black guinea pigs for up to three weeks. (Gellin *et al*.: 1970) As a result, 5 mg and 10 mg in acetone (5 % and 10 %) induced mild irritation and strong irritation (erythema and edema extending beyond area of application), respectively. 10 mg in dimethylsulfoxide (10 %) and 10 mg in propylene glycol (10 %) induced moderate irritation. 1 mg caused no irritation in any vehicle. 0.1 ml aliquot (from 0.01 M to 1.0 M for liquid solvents and from 0.1 % to 10 % for solid ointment bases) was applied to black guinea pigs on the dorsal epilated surface, and the unepilated skin of ears and nipples. p-t-Butylphenol induced severe irritation (eschar formation) to the skin of the back and moderate irritation (erythema and edema beyond area of application) to the skin of ear. (Gellin et al.: 1979)

Eye irritation

It was reported that this chemical was highly irritating and corrosive to eyes in four experiments. Two standard Draize tests were performed in rabbits. Application to eyes at dose of 10 mg or 80 mg/24 hours induced severe corneal injury, iritis, and severe conjunctival irritation. This effect was severe and moderate to severe at 80 mg and 10 mg, respectively. At 10 mg, the severity of this effect decreased with time. (Klonne *et al*.: 1988) In another data, high irritation was induced by administration at dose of 50 μg/24 hours. (Prehled Prumyslove Toxikologie: 1986)

In IUCLID database, there were two data on eye irritation in rabbits other than the above. Application of excess of 1 % solution in water or propylene glycol to the centre of the cornea resulted in injury grade 9 of 10 after 18 - 24 hours (not classifiable according to current day standards). (Smyth *et al*.: 1969) Corrosion was induced in BASF test, but the severity was not described. (BASF: 1971) There were no details of these tests.

Respiratory irritation

In rat acute inhalation study, mucosal irritation (perinasal, perioral, and periocular encrustation) and respiratory distress (audible respiration, gasping, and a deceased respiration rate) was observed, following exposure to p-t-butylphenol as dust aerosol of 5,600 mg/m^3 with additional vapour component of 30 mg/m^3. (Klonne *et al*.: 1988) In addition, the noisy respiratory sound, which seems to relate to irritation of the respiratory tract, was observed in repeated dose gavage study (MHW, Japan: 1996).

Based on the above information, p-t-butylphenol is considered as irritating to the skin, eyes and respiratory tract, although this chemical is not listed in IUCLID labelling and classification.

d) Sensitization

The maximisation test in guinea pigs was performed according OECD TG 406. Intracutaneous injections of 0.5 % p-t-butylphenol and topical application with 10 % p-t-butylphenol after one week were conducted to the bare skin of shoulder region in guinea pigs. 2 weeks after these

inductions, the challenge treatment with 1 % p-t-butylphenol was conducted onto the clipped right flank of the animals. Any skin reactions were not observed 48 and 72 hours after challenge treatment. (Hüls Infracor GmbH: 1998)

White female guinea pigs were painted daily on the bare skin behind their ears with an application of 30 % p-t-butylphenol for three weeks, followed by a two weeks rest and an application with 1 % p-t-butylphenol (Malten: 1967). 14 of 20 animals were sensitized with p-t-butylphenol. However, this study was not conducted by fully accepted protocol.

There are many data of human Patch test in the IUCLID database.

One data reported that in a routine test series of the North American Contact Dermatitis Group in 1974/75, 1,900 patients with contact dermatitis revealed 1.9 % positive reactions and the test series in 1975/76 with 900 – 2,000 contact dermatitis patients revealed 1.1 % positive reactions to 2 % of p-t-butylphenol. (Rudner: 1977)

In another data (Romaguera and Grimalt: 1981), all of 8 workers with leukoderma showed positive results. They were working in two factories (Derfesa and Givaudan) where they were handling with p-t-butylphenol and showed leukoderma on the hands and forearms, sometimes wrists, neck and neckline. The four patients from Derfesa showed an achromic response to the patch test between 8 and 15 days later. The workers from Givaudan were positive after 48 and 96 hours.

Ten shoemakers with eczema due to occupational exposure to p-t-butylphenol containing glues were patch-tested for sensitization in 1957. Positive reactions to the glue, its ingredients formaldehyde-p-t-butylphenol resin (50 % in ethyl acetate; three patients: 75 % in ethyl acetate) and p-t-butylphenol (50 % in ethyl acetate) were observed in all patients. After 24 hours, reaction in the p-t-butylphenol test was erythema, edema or papules, and some patients showed a few vesicles. After 48 hours, all patients showed these symptoms. (Malten: 1958, 1977)

Other three data showed no sensitizing of p-t-butylphenol to human, but these data are not reliable, because of a few men examined. (Bruze *et al*.: 1985, Budde & Stary: 1988, Hausen & Jung: 1985)

In a chemical industry worker with a history of work-related breathlessness, a bronchial provocation test with p-t-butylphenol elicited a dual asthmatic reaction. But there was no other information. (Brugnami *et al.*: 1982)

Although clear result of no skin sensitization in guinea pig maximisation test was given, the possibility of skin sensitization in human can not be ruled out because of some positive results in human Patch tests.

e) Repeated dose toxicity

[SIDS data] Oral toxicity study of p-t-butylphenol was performed in SD (Crj: CD) rats by an OECD combined repeat dose and reproductive/developmental toxicity screening test (OECD TG 422). Administration was conducted at doses of 0 (vehicle), 20, 60, 200 mg/kg/day by gavage for 44 days in males and from 14 days before mating to day 3 of lactation in females. (MHW, Japan: 1996)

No treatment related changes were observed except noisy respiratory sound in a few females of the 200 mg/kg. This change seems to be resulted from the irritation of this chemical to the respiratory tract, which was likely exposed to this chemical inavoidably and accidentally by gavage

administration. Therefore, the highest dose of 200 mg/kg/day is considered NOAEL for systemic toxicity.

The dose finding study (14 days) for the above combined study showed also noisy respiratory sound at 250, 500 and 1,000 mg/kg/day and some animals died by the respiratory difficulty at 1,000 mg/kg/day (MHW, Japan: Unpublished). However, there were no systemic toxic signs up to 1,000 mg/kg/day. Because of incomplete study such as no histopathological examination, this study was not applied to concern of NOAEL.

There are two feeding studies which commonly indicate the higher incidence of hyperplasia in forestomach by the longer exposure.

Male Syrian Golden hamsters were given at 15 g/kg diet (approx. 1.25 g/kg b.w./day) for 20 weeks (Hirose *et al*.: 1986). Hyperplasia observed in the forestomach was mild (< 0.1 mm; 15/15 and 7/15 in treated and control group, respectively), moderate (0.1 - 0.5 mm; 12/15 and 1/15) and severe (> 0.5 mm; 11/15 and 0/15). Another category of changes was papillomatous lesions (7/15 and 0/15).

Fischer 344 male rats were given at 15 g/kg diet (approx. 1.07 g/kg b.w./day) for 51 weeks (Hirose *et al*.: 1988) in a part of two-stage carcinogenicity study. Histological changes observed in the forestomach were hyperplasia (14/15, 0/10 for treated and control rats, respectively), but no papilloma and carcinoma was found. Furthermore no tumors were observed in the other organs examined such as the esophagus and intestines.

Based on the above information, NOAEL of this chemical for systemic toxicity for 46 days exposure is considered to be 200 mg/kg/day and the longer and higher exposure induces forestomach hyperplasia.

f) Reproductive/developmental toxicity

[SIDS data] Oral toxicity study of p-t-butylphenol was performed in SD (Crj: CD) rats by an OECD combined repeat dose and reproductive/developmental toxicity screening test (OECD TG 422). Administration was conducted by gavage at doses of 0 (vehicle), 20, 60, 200 mg/kg/day from 14 days before mating to 14 days after mating in males and from 14 days before mating to day 3 of lactation in females. (MHW, Japan: 1996)

There were no treatment related toxic effects on pregnant and lactating females or their offspring. NOAEL for reproductive/developmental toxicity is the highest dose of 200 mg/kg/day.

g) Genetic toxicity

Bacterial test

p-t-Butylphenol did not induce gene mutation in *S. Typhimurium* TA100, TA98, TA1535, TA1537 and *E. coli* WP2 *uvrA* with and without exogenous metabolic activation system. (MHW, Japan: 1996)

Other studies also indicate this chemical did not induce gene mutation in *S. Typhimurium* TA100, TA98, TA1535, TA1537, TA1538, *E. coli* WP2, WP2*uvrA*, WP2*uvrA*$^{-}$ and *S. cerevisiae* DJ1 with and without exogenous metabolic activation system. (Safepharm Laboratories Ltd.: 1992a, Dean et al.: 1985)

No bacterial test *in vitro*

p-t-Butylphenol induced structural chromosome aberration in CHL/IU cells with exogenous metabolic activation by short term treatment in 6.5-12.0 % of cells at all concentrations studied (OECD TG 473). This chemical also induced polyploidy with and without exogenous metabolic activation system. The high incidences of polyploidy cell were observed after 48 hr continuous treatment even though this chemical showed approximately 20% cytotoxicity (= 80 % cell growth of control culture) at the two high concentrations. Based on these results, there is no doubt to conclude that p-t-butylphenol induces both structural and numerical chromosome aberrations *in vitro*. (MHW, Japan: 1996)

Two other chromosomal aberration tests were conducted. In one study, this chemical induced neither clastogenicity nor polyploidy in rat lymphocytes by 20 or 30 hours treatment with and without exogenous metabolic activation (OECD TG 473). (Safepharm Laboratories Ltd.: 1992b) In another study, this chemical did not induce chromosomal aberration in rat liver epithelial-type cells by 24 hours treatment without exogenous metabolic activation at the higher concentrations than the above studies. As for polyploidy, it is not mentioned. (Dean *et al*.: 1985)

This chemical was not mutagenic to L5178Y mouse lymphoma cells at the thymidine kinase TK +/- locus with and without exogenous metabolic activation. (Safepharm Laboratories Ltd.: 1992c)

Genetic toxicity *in vivo*
There was no available data for evaluation.

In summary, p-t-butylphenol showed clear negative results in several gene mutation tests but one chromosomal aberration study indicated structural chromosome aberration and polyploidy with metabolic activation in CHL/IU cells in spite of negative results in rat lymphocytes and rat liver epithelial-type cells. Therefore, the possibility of *in vivo* genotoxicity should be considered.

h) Carcinogenecity

There was no sufficient carcinogenicity study but a two-stage promoting study was conducted.

N-Methyl-N'-nitro-N-nitrosoguanidine (MNNG) was used as an initiator. Male Fischer rats were administered with or without MNNG at a dose of 150 mg/kg b.w. by stomach tube. After a week, rats were given diet containing 15 g/kg p-t-butylphenol (calculated dose: 1.07 g/kg b.w.) or basal diet for 51 weeks. (Hirose *et al*.: 1988)

Without MNNG, histological change observed in the forestomach was hyperplasia (14/15, 0/10 for treated and control) but papilloma (1/14, 1/15), carcinoma *in situ* (0/15, 0/15) and squamous cell carcinoma (0/15, 0/10) were no changes. No tumors were observed in the other organs examined such as the esophagus and intestines.

With MNNG, grossly, small papillary or polypoid tumours were found in the forestomach of control rats, while very large single or multiple tumor masses occupied the forestomach in treated rats. Histological changes observed in the forestomach were hyperplasia (20/20, 19/19 for treated and control rats, respectively), papilloma (19/20, 13/19), carcinoma *in situ* (8/20, 11/19), and squamous cell carcinoma (15/20, 5/19). Squamous cell carcinoma in treated group was significant change, compared to control group. Leiomyosarcoma was induced in one treated rat with MNNG treatment. As histological change of the glandular stomach, adenocarcinoma of fundic region was only observed in one of treated rats. No tumors were observed in the other organs examined such as the esophagus and intestines.

In this two-stage study, p-t-butylphenol alone was not carcinogenic at least for one year exposure but had promoting activity of forestomach carcinogenesis (papilloma and squamous carcinoma) in rats treated with MNNG. However, there is a possibility of carcinogenic potential by the longer exposure, concerning the structural relationship with BHA (2(3)-tert-butyl-methoxylphenol), which is a clear carcinogen described on Section i) 3.

i) Any other human health related information that is available

1: Specific toxicities

Depigmentation
There were many data on depigmentation of p-t-butylphenol.

0.1 ml solution of p-t-butylphenol in various solvents was applied daily to the shaved skin of black guinea pigs for up to three weeks. 5 mg and 10 mg of p-t-butylphenol in acetone (5 % and 10 %) induced no depigmentation. However, 10 mg of this chemical both in DMSO (10 %) and in propylene glycol (10 %) induced strong pigmentation potency. (Gellin *et al.*: 1970)

Depigmentation tests using black C 57 male mice were conducted. Oral administration (3 times a week for 6 months) of 0.2 M of p-t-butylphenol in 0.2 mL olive oil induced diffuse or patchy depigmentation in the majority of the animals. Subcutaneous injection (6 times a week for 7 months) of 0.01 M p-t-butylphenol in 0.05 mL olive oil also induced depigmentation 12 weeks after the beginning of the injection. (Hara and Uda: 1966, Hara: 1967, Hara and Nakajima: 1969) Vitiligo-like depigmentation of black mice was also achieved as much by ingestion as by inhalation of p-t-butylphenol, although cutaneous application in different solvents and at different concentrations did not elicit any skin changes. (Forck *et al*.: 1981)

Intramuscular injection of this chemical (7.5 mg/kg and 10 mg/kg) to black rabbits induced a greying 12-24 days after the beginning of the injection. The same change was also induced by oral administration (given their fodder containing 7.5 mg/kg p-t-butylphenol). (Malten *et al.*: 1971)

Other three reports also indicated p-t-butylphenol induced depigmentation in animal studies (Malten *et al.*: 1971, Gellin *et al*.: 1979, Zavadsky & Khovanova: 1975)

In the section of experience with human exposure, it was reported that depigmentation was also observed in workers handling p-t-butylphenol in the factory. In a Russian factory producing p-t-butylphenol and p-t-butylphenol-formaldehyde resin, depigmentation was observed in 23 of 52 workers. The first 3 cases of them occurred one year after the start of the work and in 21 workers of them the vitiligo had a symmetrical distribution. (Chumakov *et al*.: 1962) In Germany, 23 workers handling p-t-butylphenol (chemical factory, Westfalia) showed depigmentation on the skin of hands and arms after a few months to 2 years of exposure. Some patients exhibited symmetrical depigmentation of body regions covered with clothing. (Forck *et al.*: 1981)

Several other reports also showed p-t-butylphenol induced depigmentation by occupational exposure (Rodermund *et al.*: 1975a, b, Rodermund and Wieland: 1975a, b, Budde and Stary: 1988, Goldmann and Thiess: 1975, 1976, Ebner *et al.*: 1979, Gebhart *et al.*: 1980, James *et al*.: 1977, Wozniak and Harmm: 1977, Bleehen and Sharquie: 1981).

Based on these data, p-t-butylphenol was considered to induce pigmentation on the skin. This change was likely induced by exposure to this chemical not only via direct contact but also via inhalation or ingestion route.

Electron microscopic investigations of biopsies of depigmented skin areas from five patients exposed to p-t-butylphenol revealed a lack of melanocytes in 4 of 5 biopsies. In the biopsy of the 5th patient, melanocytes could be found but with difficulty (these cells showed swollen mitochondria, many vacuoles and only premelanosomes with an abacus type of pigment distribution instead of the solid pigment of mature melanosomes). There were no important deviations in the keratinocytes surrounding these defective melanocytes. In the border zone and in normal areas no deviations from normal were observed. (Malten *et al.*: 1971) In another microscopic evaluation to ten workers exposed to p-t-butylphenol, the absence or reduction of melanine and melanocytes was observed. Dermal macrophages containing melanine were found. No hyperpigmentation occurred in the border zone to normal areas. (Ebner et al.: 1979, Gebhart et al.: 1980)

Biochemical effects

In biochemical investigation, p-t-butylphenol influenced the cresolase activity of tyrosinase in such a way to elongate the induction period and suppress the reaction velocity of this enzyme significantly (Nakajima and Ito: 1967, Hara and Nakajima: 1969). In another study, this chemical inhibited the dihydroxyphenylalanine (DOPA) oxidation activity of epidermal tyrosinase from Rana pipiens (enzyme involved in melanin synthesis). It was reported that this chemical might be also an effective competitive inhibitor of the oxidation of tyrosine by Rana pipiens tyrosinase. (McGuire & Hendee: 1971) Therefore, as one mechanism of depigmentation of this chemical, inhibition of enzyme necessary for synthesis of melanin was considered.

Estrogenic activity

In yeast transfected with two plasmids, one carrying human estrogen receptor gene and the other carrying estrogen responsive element and reporter gene Lac-Z, p-t-butylphenol indicated very weakly estrogenic activity (Routledge & Sumpter: 1997). The estrogenic transcriptional activity of p-t-butylphenol was 1.5 x 10^6 fold less potent than 17β-estradiol, although that of t-octylphenol was 1 x 10^3 fold less potent than 17β-estradiol.

2: Experience with human exposure

There were many data on workers handling p-t-butylphenol in the factory. Typical symptoms they showed were depigmentation on the skin.

10 male workers (25 - 53 years old) occupationally exposed to p-t-butylphenol, formaldehyde and derivatives developed vitiligo 10 months to 7 years after the beginning of their exposure (p-t-butylphenol concentration in dust: 0.12 - 0.96 mg/m^3 air). This symptom occurred especially at the skin of exposed body sites like hands and forearms and consisted of more or less intensively spread finger-nail to palm-sized depigmented spots with irregular configuration. Visible mucous membranes, hair and nails were without any findings. No irritation occurred prior to or during the development of vitiligo. An enlarged liver and spleen was observed in 4 and 1 of these vitiligo patients, respectively. Some liver enzyme activities were increased in two cases, of which one case showed increase in the BSP clearance. In thyroid gland, one patient showed microsomal auto-antibodies (titer: 1 : 25600) and thyreoglobuline-auto-antibodies (titer: 1 : 25), and another showed struma diffusa of grade 1 (WHO classification). A stringent combination of vitiligo, hepatosplenopathy and struma could not be found in any patient. (Ebner *et al.*: 1979, Gebhart *et al.*: 1980))

In 1975, a survey of vitiligo in workers at a factory manufacturing p-t-butylphenol was started. Vitiligo was observed in 54 of 198 examinees who had been exposed to p-t-butyl-phenol. One year later, partial resolution of depigmentation could be seen in 16 of 35 men reexamined (exposure situation not specified). Some of the affected body sites had not been directly in contact with p-t-

butylphenol. Therefore, the authors suggested an induction of depigmentation by systemic absorption of p-t-butylphenol. No evidence of an association with autoimmune disease was found. Neither thyroid enlargement, thyroid disease, chronic liver disease, significant liver enlargement nor splenomegaly was detected. There were no abnormalities in the full blood cell counts, blood urea or electrolyte levels and no glucosuria. 20 of the 54 men were patch tested with 2 % p-t-butylphenol and all were negative. (James *et al*.: 1977)

23 workers handling p-t-butylphenol (chemical factory, Westfalia, Germany) showed depigmentation on the skin of hands and arms after a few months to 2 years of exposure. Some patients exhibited symmetrical depigmentation of body regions covered with clothing. No other abnormal changes, especially in liver and thyroid, were observed (data not given). (Forck *et al.*: 1981)

Between 1956 and 1974, 12 cases of occupational vitiligo due to p-t-butylphenol were observed in a p-t-butylphenol manufacturing factory, further 12 cases of vitiligo were judged not to be occupationally caused because of the lacking of direct contact with suspicious substances. Almost all patients showed slight to moderate struma euthyreotica (21 of 24) and chronic hepatitis (10 of 12 occupational cases of leukoderma showed an increased BSP-clearance) (Goldmann and Thiess: 1975, 1976).

In a Russian factory producing p-t-butylphenol and p-t-butylphenol-formaldehyde resin, depigmentation was observed in 23 of 52 workers. The first 3 cases of them occurred one year after the start of the work and in 21 workers of them the vitiligo had a symmetrical distribution. In addition, some workers suffered from headache, dizziness, thirst, hyperhydrosis, disturbed sleep and neurological and otolaryngological disturbances. In this factory, p-t-butylphenol was produced from phenol and isobutyl alcohol in the presence of sulfuric acid and subsequently p-t-butylphenol formaldehyde resin was produced from p-t-butylphenol and formaldehyde in alkaline medium. The end product is washed with water, ground and packed. The measured concentrations of phenol and formaldehyde in the air were considered frequency to surpass the maximal allowable concentration. (Chumakov *et al*.: 1962)

3: Information on the structural related chemicals

Carcinogenic effects

Systematic studies of more than 10 phenolic antioxidants on carcinogenic potential or promoting action were conducted.

Ito *et al.* (1986) showed that BHA (2(3)-tert-butyl-methoxylphenol) (CAS 25013-16-5) induced squamous-cell carcinomas in the forestomach of rats and hamsters, and 2-tert-Butyl-4-methylphenol (TBMP) (CAS 2409-55-4) also induced pronounced hyperplasia and papillomas in the hamster forestomach. Hirose *et al*. (1986) reported that BHA, TBMP and p-t-butylphenol strongly induced hyperplasia and tumorous lesions in the forestomach of male Syrian Golden hamsters. Catechol (CAS 120-80-9), p-methylphenol (PMYP) (CAS 106-44-5), p-methoxyphenol (PMOP) (CAS 150-76-5), caffeic acid (CAS 331-39-5), methylhydroquinone (MHQ) (CAS 95-71-6) and pyrogallol (CAS 87-66-1) were less active, and resorcinol (CAS 108-46-3), hydroquinone (CAS 123-31-9), propylparabene (CAS 94-13-3) and tert-butylhydroquinone (TBHQ) (CAS 1948-33-0) were not active. Authors concerned that p-t-butylphenol and TBMP may be carcinogenic for hamster forestomach after long-term administration, and that both one hydroxy and tert-butyl substituents may be important for induction of hamster forestomach tumors. Hirose et al. (1988) indicated the treatment with catechol, TBMP, or 4-methoxyphenol alone induced forestomach hyperplasia.

Ito *et al.* (1986) showed BHA enhanced forestomach carcinogenesis initiated in rats by N-methyl-N'-nitro-N-nitrosoguanidine or N-methylnitrosourea (MNU) and enhanced urinary bladder carcinogenesis initiated by MNU or N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN). BHT (2,6-bis-tert-butyl-methoxyphenol) (CAS 128-37-0) promoted urinary bladder carcinogenesis initiated by BBN or MNU and thyroid carcinogenesis initiated by MNU. Hirose et al. (1988) investigated promoting effects of phenolic compounds on N-methyl-N'-nitro-N-nitrosoguanidine (MNNG)-initiated forestomach and glandular stomach carcinogenesis in male F344 rats. The incidence of squamous cell carcinoma of the forestomach in MNNG-treated animals was significantly elevated by catechol (2-hydroxyphenol) (CAS 120-80-9), TBMP and p-t-butylphenol.

4.3 Initial Assessment for Human Health

Acute toxicity of p-t-butylphenol is low via any administration routes. This chemical is considered as an irritant to the skin, eyes and respiratory tract. Animal experiment (OECD TG 406) indicated no skin sensitization but some positive results were reported in human patch tests. The depigmentation was observed on the skin of various animals and human exposed to this chemical. The depigmentation was observed on the skin of various animals and human exposed to this chemical. This change was likely induced by exposure to this chemical not only via direct contact but also via inhalation or ingestion route. In OECD combined repeat dose and reproductive/developmental screening toxicity test of rats by gavage, this chemical showed neither systemic toxicity nor reproductive toxicity even at the highest dose of 200 mg/kg/day. Although a noisy respiratory sound was induced in a few females at 200 mg/kg/day, it is considered due to irritation of this chemical to respiratory tract. In a dose-finding study (14 days), this became to respiratory difficulty, especially at 1,000 mg/kg/day. In other studies by the longer and higher exposure in diet, forestomach hyperplasia was induced. This chemical showed negative result in gene mutation test. In chromosomal aberration study, CHL/IU cells indicated structural chromosome aberration and polyploidy with metabolic activation although two other studies in rat lymphocytes and in rat liver epithelial-type cells showed negative results. As a two-stage carcinogenicity study indicated this chemical has promoting activity of forestomach carcinogenesis (papilloma and squamous carcinoma) in rats treated with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), a carcinogenic potential of this chemical could not be ruled out. In transcriptional assay using transfected yeast, this chemical showed very weakly estrogenic activity.

Occupational exposure
p-t-Butylphenol is used as an intermediate in a closed system at industries, and workers wear protective gloves and respiratory protective equipments during operation in present time. The major exposure route is an inhalation and skin in limited workers. The daily intake through inhalation in occupational situation is calculated as 0.087 mg/kg/day as the worst case. As for systemic toxicity, occupational risk is presumably low because the margin of safety is 2.30×10^3. However, many reports indicated depigmentation on skin occurred by occupational exposure. Therefore, irritation and sensitisation in addition to depigmentation on skin might be concerned to be risk at work place.

Consumer exposure
Consumer exposure is expected to be low because of its use pattern.

Indirect exposure via environment
As for indirect exposure via environment, PEC_{local} of 5.8×10^{-3} mg/l from local exposure scenario was used for the estimation. The daily intake through drinking water or fish is calculated as 1.9×10^{-4} mg/kg/day or 1.0×10^{-3} mg/kg/day. Therefore, health risk via environment is presumably low,

because the margin of safety is very large such as 1.05 x 10^6 for drinking water and 2.00 x 10^5 for fish.

5. CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

Exposure
The production volume of this chemical was ca. 5,000 tonnes/year in 1993 in Japan. This chemical is used as an intermediate for phenol resins and polycarbonate resins. It is also used as a raw material for construction elements and floors in buildings. The potential environmental distribution of p-t-butylphenol obtained from a generic fugacity model (Mackey level III) shows that it will be mainly distributed to water. The main route of human exposure is inhalation with a limited numbers of workers potentially exposed during sampling and bag or tank filling operations.

Hazards to the Environment
p-t-Butylphenol is stable solid and is classified as a readily biodegradable chemical (OECD TG 301). Bioaccumulation factor is 34-120.

The lowest acute and chronic toxicity data were 48h EC_{50} (3.4 mg/l) of *Daphnia magna* and 21d NOEC (0.73 mg/l) of *Daphnia magna*, respectively. Assessment factor of 100 was chosen to the chronic toxicity data (NOEC), because only two NOEC values (algae and *Daphnia*) were available. Thus, PNEC of p-t-butylphenol is 7.3 x 10^{-3} mg/l in this report. p-t-Butylphenol may have potential chronic toxicity to aquatic organisms, because NOEC of *Daphnia* is relatively low and the chemical has moderately bioaccumulative potential.

Human Health Hazards
Acute toxicity of p-t-butylphenol is low via any administration routes. This chemical is considered as an irritant to the skin, eyes and respiratory tract. The possibility of skin sensitization in human still remains because of negative result in animal experiment (OECD TG 406) but some positive results in human patch tests. The depigmentation was observed on the skin of various animals and human exposed to this chemical. This change was likely induced by exposure to this chemical not only via direct contact but also via inhalation or ingestion route. In OECD combined repeat dose and reproductive/developmental screening toxicity test (TG 422) of rats by gavage at doses of 20, 60 and 200 mg/kg/day for 46 days, this chemical showed neither systemic toxicity nor reproductive toxicity even at the highest dose of 200 mg/kg/day. Although a noisy respiratory sound was induced in a few females at 200 mg/kg/day, it is considered due to irritation of this chemical to respiratory tract. In a dose-finding study (14 days), this change became to respiratory difficulty, especially at 1,000 mg/kg/day. In other studies by the longer and higher exposure in diet (approx. 1 g/kg b.w./day, for 20 or 51 weeks), forestomach hyperplasia was induced. This chemical showed clear negative results in gene mutation tests. However, one chromosomal aberration study indicated structural chromosome aberration and polyploidy with metabolic activation in CHL/IU cells (OECD TG 473) although other studies in rat lymphocytes (OECD TG 473) and in rat liver epithelial-type cells resulted in negative. Therefore, the possibility of *in vivo* genotoxicity still remains. There was no sufficient carcinogenicity study and no evidence of carcinogenesis in manufacturing workers, however, a two-stage carcinogenicity study indicated this chemical has promoting activity of forestomach carcinogenesis (papilloma and squamous carcinoma) in rats treated with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). Furthermore, since structural related chemical, BHA, (2(3)-tert-butyl-methoxylphenol) is a clear carcinogen, a carcinogenic potential of this chemical could not be ruled out.

5.2 Recommendations

Human Health
In *vivo* genotoxicity study such as *in vivo* micronucleus test is recommended because *in vitro* chromosomal aberration test indicates clear positive results.

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REVISED OECD HPV FORM 1

SIDS DOSSIER ON THE HPV PHASE-4 CHEMICAL

p-tert-Butylphenol

CAS No. 98-54-4

Sponsor Country: Japan

DATE: December 1, 1999

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

1. GENERAL INFORMATION

1.01 SUBSTANCE INFORMATION

***A. Cast number** 98-54-4

B. Name *(IUPAC name)* p-tert-Butylphenol

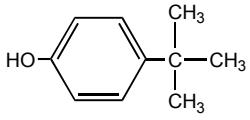
***C. Name** *(OECD name)* p-tert-Butylphenol

†D. CAS Descriptor

E. EINECS-Number 202-679-0

F. Molecular Formula $C_{10}H_{14}O$

***G. Structural Formula**



H. Substance Group

I. Substance Remark

J. Molecular Weight 150.22

1.02 OECD INFORMATION

A. Sponsor Country: Japan

B. Lead Organisation:

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

Contact person: Mr. Kazuhide Ishikawa
Director, Second International Organization Bureau
Ministry of Foreign Affairs

Address:

Street: 2-2-1 Kasumigaseki, Chiyoda-ku, Tokyo 100, Japan
Tel: 81-3-3581-0018
Fax: 81-3-3503-3136

C. Name of responder

Name: Same as above contact person

1.1 GENERAL SUBSTANCE INFORMATION

A. Type of Substance

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

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

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

C. Purity

99.9%

1.2 SYNONYMS

4-Hydroxy-tert-butylbenzene

1.3 IMPURITIES

Unknown

1.4 ADDITIVES

None

*1.5 QUANTITY

(1) 5,000 tonnes/year in 1993 (Japan)
(2) 11,000 tonnes/year in 1990 (USA)

Remarks:

Reference: (1) MITI, Japan (1997)
(2) ECDIN Database

1.6 LABELLING AND CLASSIFICATION

1.6.1 Labelling

No data are available.

1.6.2 Classification

No data are available.

*1.7 USE PATTERN

A. General

	Type of Use:	Category:
(a)	main	Intermediate
	industrial	Intermediate in closed system

		use	Intermediate for antioxidants, oil-soluble phenolic resins, pour point depressors and emulsion breakers for petroleum oil and some plastics; insecticides; industrial perfumes.
	(b)	main	Direct use
		industrial	Plasticizer
		use	Plasticizer for cellulose acetate

Reference: ECDIN Database

B. Uses in Consumer Products

No consumer use is known in Japan

Reference: MITI, Japan (1997)

1.8 OCCUPATIONAL EXPOSURE LIMIT

No occupational exposure limit value is available in Japan.

Type of limit: TWA
Limit value: 0.08 ppm (0.5 mg/m^3)
Country: Germany, Austria, Switzerland
Source: RTECS Database

Type of limit: TWA
Limit value: 10 ppm (60 mg/m^3)
Country: Australia
Source: RTECS Database

*** 1.9 SOURCES OF EXPOSURE**

Source:	Media of release:	Bay
	Quantities per media:	12,000 kg/year
Reference:	Company data	

1.10 ADDITIONAL REMARKS

A. Options for disposal

Remarks: Treatment in sewage plant, then release 4.4 x 10^{10} l/year of effluent to bay.
Reference: Company data

B. Other remarks

None

2. PHYSICAL-CHEMICAL DATA

***2.1 MELTING POINT**

Value: 99.3 °C
Decomposition: Yes **[ ]** No **[X]** Ambiguous **[ ]**

Sublimation: Yes **[ ]** No **[X]** Ambiguous **[ ]**
Method:
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks:
Reference: Tokyo Kasei Chemical Co.

***2.2 BOILING POINT**

(a)
Value: 237 °C
Pressure: at 1,013 hPa
Decomposition: Yes **[ ]** No **[X]** Ambiguous **[ ]**
Method: Unknown
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Remarks:
Reference: The Merck Index (11th edition)

(b)
Value: 237 °C
Pressure: at 1,013 hPa
Decomposition: Yes **[ ]** No **[X]** Ambiguous **[ ]**
Method: Unknown
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Remarks:
Reference: IUCLID Database (Huels AG Marl)

***2.3 DENSITY (relative density)**

Type: Bulk density **[ ]**; Density **[X]**; Relative Density **[ ]**
Value: 0.92 g/cm^3
Temperature: 110 °C
Method: unknown
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Reference: IUCLID Database (Huels AG Marl)

***2.4 VAPOUR PRESSURE** *(if more than one, identify the recommended value)*

(a)
Value: 1.3 x 10^2 Pa
Temperature: 60 °C
Method: calculated **[ ]**; measured **[X]**
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks:
Reference: The Sigma-Aldrich Library of Regulatory and Safety Data

(b)
Value: 0.3 hPa
Temperature: 50 °C
Method: calculated **[ ]**; measured **[X]**
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks:
Reference: IUCLID Database (Huels AG Marl)

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

(a)
Log Pow: 3.29
Temperature: 25 °C
Method: calculated **[ ]**; measured **[** X **]**
OECD TG 107
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Remarks:
Reference: MITI, Japan (1997)

(b)
Log Pow: 2.44
Temperature: °C
Method: calculated **[ ]**; measured **[** X **]**
OECD TG 107 (Flask-shaking method)
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Remarks:
Reference: IUCLID Database (Huels AG Marl)

***2.6 WATER SOLUBILITY**

A. Solubility

Value: 610 mg/l
Temperature: 25 °C
Description: Miscible **[ ]**; Of very high solubility **[ ]**;
Of high solubility **[ ]**; Soluble **[ ]**; Slightly soluble **[X]**;
Of low solubility **[ ]**; Of very low solubility **[ ]**; Not soluble **[ ]**
Method: OECD TG 105
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Remarks:
Reference: MITI, Japan (1997)

B. pH Value, pKa Value

pKa value 10.16 at 25°C
Method OECD TG 112 (Photo absorption method)
GLP: Yes **[x]** No **[x]** ? **[ ]**
Remarks:
Reference: MITI, Japan (1997)

2.7 FLASH POINT *(liquids)*

Value: ca. 115 °C
Type of test: Closed cup **[ ]**; Open cup **[ ]**; Other **[X]**
Method: Open cup (DIN ISO 2592)
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Remarks:
Reference: IUCLID Database (Huels AG Marl)

2.8 AUTO FLAMMABILITY *(solid/gases)*

No data are available.

2.9 FLAMMABILITY

No data are available.

2.10 EXPLOSIVE PROPERTIES

No data are available.

2.11 OXIDISING PROPERTIES

None

†2.12 OXIDATION: REDUCTION POTENTIAL

No data are available.

2.13 ADDITIONAL DATA

A. pKa

Value:	10.39
Method:	unknown
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Remarks:	measured value
Reference:	IUCLID Database (Huels AG Marl)

B. Other data

None

3. ENVIRONMENTAL FATE AND PATHWAYS

3.1 STABILITY

***3.1.1 PHOTODEGRADATION**

***3.1.1 PHOTODEGRADATION**

Type:	Air **[X]**; Water **[ ]**; Soil **[ ]**; Other **[ ]**
Light source:	Sun light **[ ]**; Xenon lamp **[ ]**; Other **[ ]**
Light spectrum:	
Relative intensity:	.
Spectrum of substance:	
Concentration of Substance:	
Temperature:	
Direct photolysis:	
Half life:	
Degradation:	
Quantum yield:	
Indirect Photolysis:	
Type of sensitizer:	OH
Concentration of sensitizer:	
Rate constant (radical):	43.4* 10^{-12} cm3/molecule*sec
Degradation:	
Method:	calculated **[X];** measured **[ ]**
GLP:	Yes **[ ]** No **[ ]** ? **[ ]**

Test substance:
Remarks: Half-life of 8.9 hour is calculated based on the rate constants (43.4 * 10^{-12} cm3/molecule*sec) by using the concentration of OH-radicals of 500000 molecule/cm3 in atmosphere
Reference: IUCLID Database (Huels AG Marl)

***3.1.2 STABILITY IN WATER**

Type: Abiotic (hydrolysis) **[ ]**; biotic (sediment)**[ ]**
Degradation: Stable at pH 4, 7 and 9 at 25 °C
Method: OECD TG 111
GLP: Yes **[x]** No **[ ]** ? **[ ]**
Test substance: p-t-Butyl phenol, purity: 99%
Remarks:
Reference: MITI, Japan (1997)

3.1.3 STABILITY IN SOIL

No data are available.

***3.2 MONITORING DATA (ENVIRONMENTAL)**

(a)
Type of Measurement: Background **[ ]**; At contaminated site **[ ]**; Other **[x]**
Media: Surface water (sea)
Results: ND (Detection limits: 0.0005 mg/l) in 4 areas in Japan as of 1977
Remarks: ND: Not detected
Reference: Chemicals in the environment, EA, Japan (1977)

(b)
Type of Measurement: Background **[ ]**; At contaminated site **[ ]**; Other **[x]**
Media: Surface water (river)
Results: ND (Detection limits: 0.002 mg/l) in 4 areas in Japan as of 1977
Remarks: ND: Not detected
Reference: Chemicals in the environment, EA, Japan (1977)

(c)
Type of Measurement: Background **[ ]**; At contaminated site **[ ]**; Other **[x]**
Media: Surface water (estuary)
Results: ND (Detection limits: 0.005 mg/l) in 2 areas in Japan as of 1977
Remarks: ND: Not detected
Reference: Chemicals in the environment, EA, Japan (1977)

(d)
Type of Measurement: Background **[ ]**; At contaminated site **[ ]**; Other **[x]**
Media: Sediment (sea)
Results: ND (Detection limits: 0.03 mg/kg) in 4 areas in Japan as of 1977
Remarks: ND: Not detected
Reference: Chemicals in the environment, EA, Japan (1977)

(e)
Type of Measurement: Background **[ ]**; At contaminated site **[ ]**; Other **[x]**
Media: Sediment (river)
Results: ND (Detection limits: 0.04 mg/kg) in 4 areas in Japan as of 1977
Remarks: ND: Not detected
Reference: Chemicals in the environment, EA, Japan (1977)

(f)

Type of Measurement:	Background **[ ]**; At contaminated site **[ ]**; Other **[x]**
Media:	Sediment (estuary)
Results:	ND (Detection limits: 0.25 mg/kg) in 2 areas in Japan as of 1977
Remarks:	ND: Not detected
Reference:	Chemicals in the environment, EA, Japan (1977)

(g)

Type of Measurement:	Background **[X]**; At contaminated site **[ ]**; Other **[ ]**
Media:	Surface water
Results:	4-tert-Butylphenol was identified in 5 of 16 samples from the river Rhein (Weil, Mainz; Germany) aand in 1 of 5 samples from the river Main (Kostheim, Germany); no further information available.
Remarks:	GC/MS analysis
Reference:	IUCLID Database (Huels AG Marl)

(h)

Type of Measurement:	Background **[ ]**; At contaminated site **[X]**; Other **[ ]**
Media:	Ground water
Results:	Concentration for gas-chromatographic peaks likely identified as 4-tert-butylphenol via relative flame ionization detector (FID) response: 0.035 - 0.118 ug/l; ground water samples were taken from February to March 1980 beneath a rapid infiltration site for wastewater (secondary effluent) in Phoenix, Alizona, USA.
Remarks:	XAD-2 analysis
Reference:	IUCLID Database (Huels AG Marl)

(i)

Type of Measurement:	Background **[ ]**; At contaminated site **[X]**; Other **[ ]**
Media:	Waste water, receiving water and sediment
Results:	Concentration of 4-tert-butylphenol in waste water from a specialty chemicals manufacturing plant: 1 - 150 ug/l; concentration of waste water receiving river water: 3 ug/l (detected only one sample); concentration in related sediment: 0.2 -7 ug/g; samples were taken in 1975 and 1976; Brackish River, USA.
Remarks:	
Reference:	IUCLID Database (Huels AG Marl)

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

*3.3.1 TRANSPORT

No data are available.

*3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

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:

Compartment	Release 100% to air	Release 100% to water	Release 100% to soil
Air	39.7 %	0.2 %	0.0 %
Water	23.3 %	95.3 %	0.4 %
Soil	35.9 %	0.2 %	99.6 %
Sediment	1.1 %	4.4 %	0.0 %

Remarks:
Reference:

3.4 IDENTIFICATION OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE

No information is available.

*3.5 BIODEGRADATION

Type: aerobic **[X]**; anaerobic **[ ]**
Inoculum: adapted **[ ]**; non-adapted **[X]**;
Concentration of the chemical: 30 mg/l in organic carbon
related to COD **[ ]**; DOC **[X]**; test substance **[ ]**
Medium: water **[ ];** water-sediment **[ ];** soil **[ ];** sewage treatment **[ ]**
Degradation: 98 % after 28 days
Results: readily biodeg. **[X];** inherently biodeg. **[ ]**; under test condition no biodegradation observed **[ ]**, other **[ ]**
Method: Directive EEC/92/69, Part II, C. 4-A DOC Die Away Test
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: purity: unknown
Remarks:
Reference: IUCLID Database (Huels AG Marl)

3.6 BOD_5, COD OR RATIO BOD_5/COD

No data are available.

3.7 BIOACCUMULATION

(a)
Species: Fish (*Leuciscus idus melanotus*)
Exposure period:
Temperature: 22.5 °C
Concentration: 46 ug/l
BCF: 120
Elimination: Yes **[ ]** No **[ ]** ? **[X]**
Method: Other, bioaccumulation test
Type of test: calculated **[ ]**; measured **[X]**
static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other **[ ]**
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: 14C-labelled 4-t-butylphenol; Purity: >= 98%
Remarks: Static procedure; 5 fishes/10 l water (5 l tap water of 160-170 mg CaO/l hardness + 5 l deionized water)
Reference: IUCLID Database (Huels AG Marl)

(b)
Species: Algae (*Chlorella fusca*)
Exposure period: 24

Temperature:	22.5 °C
Concentration:	50 ug/l
BCF:	34
Elimination:	Yes **[X]** No **[ ]** ? **[ ]**
Method:	Other, bioaccumulation test
Type of test:	calculated **[ ]**; measured **[X]** static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other **[ ]**
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance:	14C-labelled 4-t-butylphenol; Purity: >= 98%
Remarks:	Static procedure; concentration of algae: 100 mg dry weight/l (50 mg wet weight/l); BCF was related to wet weight of the algae.
Reference:	IUCLID Database (Goyer et al., Chemosphere, 10, 1307 (1981))

3.8 ADDITIONAL REMARKS

A. Sewage treatment *(information on treatability of the substance)*

None

B. Other information

None

4. ECOTOXICITY

*4.1 ACUTE/PROLONGED TOXICITY TO FISH

(a)

Type of test:	static **[ ]**; semi-static **[X]**; flow-through **[ ]**; other *(e.g. field test)* **[ ]** open-system **[X]**; closed-system **[ ]**
Species:	Medaka (*Oryzias latipes*)
Exposure period:	96 h
Results:	LC_{50} (24h) = 5.1 mg/l LC_{50} (48h) = 5.1 mg/l LC_{50} (72h) = 5.1 mg/l LC_{50} (96h) = 5.1 mg/l
Analytical monitoring:	Yes **[ ]** No **[X]** ? **[ ]**
Method:	OECD TG 203 (1992)
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	As prescribed by 1.1 - 1.4, purity: 99.5%
Remarks:	Group of ten Medaka were exposed to nominal concentrations of 2.0, 3.0, 4.5, 6.8 and 10 mg/l. 100 mg/l DMSO & HCO-40 (4:1 weight ratio,) was used as solubilizer. 100 mg/l solubilizer and dechlorinated tap water were used as control. The LC_{50} (96h) was determined to be 5.1 mg/l with 95 % confidence limits of 4.7 mg/l to 5.8 mg/l.
Reference:	Environment Agency of JAPAN (1995)

(b)

Type of test:	static **[ ]**; semi-static **[X]**; flow-through **[ ]**; other *(e.g. field test)* **[ ]** open-system **[ ]**; closed-system **[ ]**
Species:	Fathead minnow (*Pimephales promelas*)
Exposure period:	96 h
Results:	LC_{50} (24h) = 6.2 mg/l LC_{50} (48h) = 5.7 mg/l

	LC_{50} (72h) = 5.3 mg/l
	LC_{50} (96h) = 5.1 mg/l
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**
Method:	Fifty fathead minnows (25 per duplicate tank) were exposed to five test concentrations in flow-through aquaria (7.3 1, flow rate= 83 ml/min) for 96 hr.
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test Substance:	Purity: > 99%
Remarks:	Water for testing was obtained from Lake Superior. Age of fathead minnows, 31 to 35-day-old; Water temperature, 24.5°C; DO, 7.4 mg/l; hardness, 44.9 mg/l as $CaCO_3$; Toxicity tests were conducted together with 24 chemicals.
Reference:	Holcombe G.W., Phipps, G.L., Knuth, M.L. and Felhaber, T. (1984) Environ. Pollut. (Ser. A) 35, 367-381.

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

*A. Daphnia

(a)

Type of test:	static **[ ]**; semi-static **[X]**; flow-through **[ ]**; other *(e.g. field test)* **[ ]**; open-system **[X]**; closed-system **[ ]**
Species:	*Daphnia magna*
Exposure period:	48 h
Results:	EC_{50} (24h) = 7.3 mg/l EC_{50} (48h) = 6.7 mg/l NOEC < 1.0 mg/l
Analytical monitoring:	Yes **[ ]** No **[X]** ? **[ ]**
Method:	OECD TG 202
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	As prescribed by 1.1 - 1.4 , purity: 99.5 %
Remarks:	20 daphnids (4 replicates; 5 organisms per replicate) were exposed to nominal concentrations of 1.0, 1.8, 3.2, 5.6 and 10 mg/l. 10 mg/l DMSO & HCO-40 (4:1 weight ratio) was used as solubilizer. 10 mg/l solubilizer and dechlorinated tap water was used as control. The EC_{50} (48h) was determined to be 6.7 mg/l with 95 % confidence limits of 5.2 mg/l to 9.7 mg/l.
Reference:	Environment Agency of JAPAN (1995)

(b)

Type of test:	static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other *(e.g. field test)* **[ ]**; open-system **[ ]**; closed-system **[ ]**
Species:	*Daphnia magna*
Exposure period:	48 h
Results:	EC_{50} (24h) = 3.4 mg/l EC_{50} (48h) = 3.4 mg/l EC_0 (48h) = 0.34 mg/l
Analytical monitoring:	Yes **[ ]** No **[X]** ? **[ ]**
Method:	Ten test animals (6-24 h old) were exposed to this chemical dissolved into the dilution water (pH, 8.0 + 0.2, kept at 20°C) in a 50 ml beaker for 48h. Daphnids of swimming were counted.
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance:	
Remarks:	Daphnids (5-24 h old) were exposed to 3 to 4 concentrations to calculate EC_{50}. DO value was not below 4.0 mg/l. Toxicity tests were conducted together with 50 chemicals.

Reference: Kuhn, R., Pattard, M., Pernak, K.D. and Winter, A. (1989) Water Res., 23, 495-499.

B. Other aquatic organisms

No data are available.

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

Species:	*Selenastrum capricornutum* ATCC 22662	
Endpoint:	Biomass **[X]**; Growth rate **[ ]**; Other **[ ]**	
Exposure period:	72 h.	
Results:	Biomass	EC_{50} (72h) = 22.7 mg/l
	(Endpoint)	NOEC = 9.53 mg/l
		LOEC = 17.2 mg/l
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**	
Method:	OECD TG 201 (1984)	
	open-system **[X]**; closed-system **[ ]**	
GLP:	Yes **[ ]** No **[X]** ? **[ ]**	
Test substance:	As prescribed by 1.1 - 1.4, purity: 99.5 %	
Remarks:	Static test. The EC_{50} value for biomass change (% inhibition) was calculated based on five nominal concentrations (9.53, 17.2, 30.9, 55.6 and 100 mg/l). Minimal amount of Tween 80 - acetone (1:1) or DMSO - HCO-40 (9:1) is used as solubilizer.	
Reference:	Environment Agency of JAPAN (1995)	

4.4 TOXICITY TO BACTERIA

Type:	Aquatic **[X]**; Field **[ ]**; Soil **[ ]**; Other **[ ]**
Species:	*Pseudomonas putida*
Exposure Period:	6 hr
Results:	EC10 = 145 mg/l
Analytical monitoring:	Yes **[ ]** No **[ ]** ? **[X]**
Method:	Other (Huels-Methode) LTwS-Nr. 10.
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	Purity: unknown
Remarks:	Test for inhibition of oxygen consumption by *Pseudomonas putida*
Reference:	IUCLID Database (Huels AG Marl)

4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS

4.5.1 CHRONIC TOXICITY TO FISH

No data are available.

(*)4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Type of test:	static **[ ]**; semi-static **[X]**; flow-through **[ ]**; other *(e.g. field test)* **[ ]**; open-system **[X]**; closed-system **[ ]**	
Species:	*Daphnia magna*	
Endpoint:	Mortality **[ ]**; Reproduction rate **[X]**; Other **[X]**	
Exposure period:	21 d	
Results:	Reproduction rate:	EC_{50} (21 d) = 2.0 mg/l
	(Endpoint)	NOEC = 0.73 mg/l
		LOEC = 2.3 mg/l

Analytical monitoring:	Yes **[ ]** No **[X]** ? **[ ]**
Method:	OECD TG 202(1984)
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	As prescribed by 1.1 - 1.4, purity: 99.5 %
Remarks:	40 daphnids (4 replicates; 10 daphnids per replicate) were exposed to five concentrations (0.073, 0.23, 0.73, 2.3, 7.3 mg/l) in dechlorinated tap water (pH: 7.6 to 8.0; Hardness: 48 to 111 mg/l). DMSO and HCO-40 (4:1 mixture, 7.3 mg/l) is added as solubilizer.
Reference:	Environment Agency of JAPAN (1995)

4.6 TOXICITY TO TERRESTRIAL ORGANISMS

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

No data are available.

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

No data are available.

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

No data are available.

4.7 BIOLOGICAL EFFECTS MONITORING (INCLUDING BIOMAGNIFICATION)

No data are available.

4.8 BIOTRANSFORMATION AND KINETICS

No data are available.

4.9 ADDITIONAL REMARKS

None

5. TOXICITY

*5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

(a)

Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Rat
Value:	4,000 mg/kg b.w.
Method:	OECD TG 401 (1981)
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	purity: unknown
Remarks:	
Reference:	Huels-Bericht: 1985

(b)

Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Sprague-Dawley rat
Value:	male: 5,360 mg/kg b.w. female: 3,620 mg/kg b.w.
Method:	Other
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	purity: 99 %
Remarks:	p-t-Butylphenol was treated by stomach intubation at 2,500, 3,500, 5,000 mg/kg and 10,000 mg/kg (males only) as a 25 % (w/v) suspension in corn oil. Sluggishness, unsteady gait, prostration, unkempt appearance, and nasal discharge were observed as the principal signs of toxicity. Signs of toxicity subsided in survivors at 3 to 7 days after dosing. Deaths were induced from 2 hours to 5 days after dosing. In rats died during the study, there were mottling of the lungs and livers as the principal macroscopic lesions in female but no significant gross lesions in male.
Reference:	Klonne *et al.*: 1988

(c)

Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Rat
Value:	2,990 mg/kg b.w.
Method:	Other
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	purity: unknown
Remarks:	
Reference:	Smyth *et al.*: 1969

(d)

Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Rat
Value:	ca. 3,500 mg/kg b.w.
Method:	Other (BASF-Test)
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance:	purity: unknown
Remarks:	
Reference:	BASF AG: 1971

(e)

Type:	LD_0 **[X]**; LD_{100} **[ ]**; LD_{50} **[ ]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Guinea pig
Value:	400 mg/kg b.w.
Method:	Other
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance:	purity: 99 %
Remarks:	The 100 % lethal dose was found to be greater than 1,400 mg/kg and probably 2,000 mg/kg.
Reference:	The Dow Chemical Company: 1997a

5.1.2 ACUTE INHALATION TOXICITY

(a)

Type:	LC_0 **[X]**; LC_{100} **[ ]**; LC_{50} **[ ]**; LCL_0 **[ ]**; Other **[ ]**

Species/strain: Rat
Exposure time: 8 hours
Value: See Remarks
Method: Other (BASF Test)
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: purity: unknown
Remarks: No lethal effects were observed in 12 rats exposed to an atmosphere saturated with the test substance at 20 degree C.
Reference: BASF AG: 1971

(b)
Type: LC_0 **[ ]**; LC_{100} **[ ]**; LC_{50} **[ ]**; LCL_0 **[ ]**; Other **[X]**
Species/strain: Sprague-Dawley rat
Exposure time: 4 hours
Value: See remarks
Method: Other
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: purity: 99 %
Remarks: Exposure to p-t-butylphenol was conducted as dust aerosol of 5,600 mg/cm^3 with additional vapour component of 30 mg/cm^3. Within one to two days following exposure, 1/5 rat of each sex died, which showed dark red of purple discoloration of the lungs and/or kidneys but not survivors. On post exposure day 7, a loss of mean body weight was observed for both sexes but body weight gains were exhibited on day 14. Clinical signs observed on the day of exposure and up to 7 days postexposure included signs of mucosal irritation (perinasal, perioral, and periocular encrustation) and signs of respiratory distress (audible respiration, gasping, and a deceased respiration rate).
Reference: Klonne *et al*.: 1988

(c)
Type: LC_0 **[X]**; LC_{100} **[ ]**; LC_{50} **[ ]**; LCL_0 **[ ]**; Other **[ ]**
Species/strain: Sprague-Dawley rat
Exposure time: 6 hours
Value: See Remarks
Method: Other
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: purity: 99 %
Remarks: Exposure to a statically generated substantially saturated vapour did not effect on body weight, clinical signs, mortality, or necropsy observations.
Reference: Klonne *et al*.: 1988

5.1.3 ACUTE DERMAL TOXICITY

(a)
Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Rabbit
Value: 2,318 mg/kg b.w.
Method: Other
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: purity: unknown
Remarks:
Reference: Smyth et al.: 1969

(b)

Type:	LD_0 **[X]**; LD_{100} **[ ]**; LD_{50} **[ ]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	New Zealand white rabbit
Value:	16,000 mg/kg b.w.
Method:	Other
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	purity: 99 %
Remarks:	Ground p-t-butylphenol, which was moistened with distilled water, was applied to the clipped skin of the trunk at 2,000, 8,000, 16,000 mg/kg and covered with Vetrap (3M) Bandaging Tape. Signs of severe skin irritation (erythema, edema, fissuring, desquamation and/or necrosis) were observed in both sexes of all groups. However, the sign of toxicity was only prostration in one female at 12,000 mg/kg and no significant lesions were observed at necropsy.
Reference:	Klonne *et al*.: 1988

(c)

Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[ ]**; LDL_0 **[ ]**; Other **[X]**
Species/strain:	Rabbit
Value:	See remarks
Method:	Other
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance:	a mixture of 66.3 % p-t-butylphenol, 13.4 % o-t-butylphenol, 19.8 % phenol and 0.5 % di-t-butylphenol
Remarks:	The subject material as a 50 % solution in ethanol was applied to the clipped bellies of rabbits restrained on animal boards. An hour later, the animals were released, bandaged so that they could not lick themselves, and returned to their respective cages. At a dose of 3,000 mg/kg, tremors were caused in 15 minutes, which were typical change of phenol poisoning. In addition, in 1.5 hours after the application, severe burning of the skin and death was observed. At a dose of 1,000 mg/kg, tremors were also caused and severe burning was observed. The animals survived for 24 hours. At a dose of 300 mg/kg, severe burns were only observed and all animals survived.
Reference:	The Dow Chemical Company: 1997b

(d)

Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[ ]**; LDL_0 **[ ]**; Other **[X]**
Species/strain:	Guinea pig
Value:	See Remarks
Method:	Other
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance:	purity: 99 %
Remarks:	A single dose of 10 % solutions in olive oil and in alcohol was applied to the clipped bellies of guinea pigs. With the olive oil solution, no death was induced at doses of up to and including 2,000 mg/kg. While one of 5 animals died from doses of 2,000 mg/kg and 3,000 mg/kg when alcoholic solution was used as solvent.
Reference:	The Dow Chemical Company: 1997a

5.1.4 ACUTE TOXICITY, OTHER ROUTES OF ADMINISTRATION

(a)
Type: LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; Other [ ]
LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Rat
Route of Administration: i.m. [ ]; i.p. [X]; i.v. [ ]; infusion [ ]; s.c. [ ]; other [ ]
Exposure time:
Value: ca. 225 mg/kg b.w.
Method: Other (BASF Test)
GLP: Yes [ ] No [X] ? [ ]
Test substance: purity: unknown
Remarks:
Reference: BASF AG: 1971

(b)
Type: LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; Other [ ]
LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Mouse
Route of Administration: i.m. [ ]; i.p. [X]; i.v. [ ]; infusion [ ]; s.c. [ ]; other [ ]
Exposure time:
Value: 78.46 mg/kg b.w.
Method: Other
GLP: Yes [ ] No [X] ? [ ]
Test substance: purity: unknown
Remarks: Single administration (p-t-butylphenol in dimethyl sulfoxide)
Observation period: 24 hours
Reference: Biagi *et al.*: 1975

5.2 CORROSIVENESS/IRRITATION

5.2.1 SKIN IRRITATION/CORROSION

(a)
Species/strain: New Zealand white rabbit
Results: Highly corrosive [ ]; Corrosive [ ]; Highly irritating [ ];
Irritating [ ]; Moderate irritating [X]; Slightly irritating [ ];
Not irritating [ ]
Classification: Highly corrosive (causes severe burns) [ ];
Corrosive (causes burns) [ ]; Irritating [ ]; Not irritating [ ]
Method: Standard Draize test
GLP: Yes [ ] No [X] ? [ ]
Test substance: purity: 99 %
Remarks: Dose: 500 mg (moistened with distilled water)
Exposure period: 4 hours
Majority of rabbits (4/6) showed no signs of skin irritation. However, in another rabbit, minor, transient erythema and desquamation was evident. The remaining rabbit exhibited slight edema, dermal necrosis, scab formation, and desquamation. The skin appeared to be normal on postexposure day 17.
Reference: Klonne *et al.*: 1988

(b)
Species/strain: Rabbit
Results: Highly corrosive [ ]; Corrosive [ ]; Highly irritating [ ];
Irritating [ ]; Moderate irritating [X]; Slightly irritating [ ];
Not irritating [ ]

Classification: Highly corrosive (causes severe burns) **[ ]**;
Corrosive (causes burns) **[ ]**; Irritating **[ ]**; Not irritating **[ ]**
Method: Standard Draize test
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: purity: unknown
Remarks: Exposure period: 500 mg/24 hours
Reference: *Prehled Prumyslove Toxikologie*: 1986

(c)
Species/strain: Rabbit
Results: Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**;
Irritating **[ ]**; Moderate irritating **[X]**; Slightly irritating **[ ]**;
Not irritating **[ ]** *See Remarks
Classification: Highly corrosive (causes severe burns) **[ ]**;
Corrosive (causes burns) **[ ]**; Irritating **[ ]**; Not irritating **[ ]**
Method: Other
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: purity: unknown
Remarks: Uncovered application of 0.01 ml on the rabbit belly.

Irritation was induced, and the injury grade was described as 6 of 10 in IUDLID Database.
Reference: Smyth *et al*.: 1969

(d)
Species/strain: Rabbit
Results: Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**;
Irritating **[X]**; Moderate irritating **[ ]**; Slightly irritating **[ ]**;
Not irritating **[ ]** *See Remarks
Classification: Highly corrosive (causes severe burns) **[ ]**;
Corrosive (causes burns) **[ ]**; Irritating **[ ]**; Not irritating **[ ]**
Method: OECD Guideline No. 404 "Acute Dermal Irritation/Corrosion"
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: purity: unknown
Remarks: Irritation was induced, but the severity was not described in IUCLID Database.
Reference: Huels-Bericht: 1985

(e)
Species/strain: Rabbit
Results: Highly corrosive **[ ]**; Corrosive **[X]**; Highly irritating **[ ]**;
Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[ ]**;
Not irritating **[ ]** *See Remarks
Classification: Highly corrosive (causes severe burns) **[ ]**;
Corrosive (causes burns) **[ ]**; Irritating **[ ]**; Not irritating **[ ]**
Method: Other (BASF test)
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: purity: unknown
Remarks: Corrosion was induced, but the severity was not described in IUCLD Database.
Reference: BASF: 1971

(f)
Species/strain: Rabbit
Results: Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**;

Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[X]**;
Not irritating **[ ]** *See Remarks

Classification: Highly corrosive (causes severe burns) **[ ]**;
Corrosive (causes burns) **[ ]**; Irritating **[ ]**; Not irritating **[ ]**

Method: Other (BASF test)

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

Test substance: purity: 99 %

Remarks: When butyl carbitol acetate was used as solvent, repeat application of 10 % solution produced only very slight simple irritation, and 0.1 and 1 % solution caused no irritation. On the other hands, repeat application of 10 % solution in olive oil produced a marked simple irritation and 5 %, 1 % and 0.1 % solution in olive oil were slightly irritating. However, it was believed that most of the irritation in these instances was due to the olive oil.

Reference: The Dow Chemical Company: 1997a

(g)

Species/strain: Rabbit

Results: Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[X]**;
Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[ ]**;
Not irritating **[ ]** *See Remarks

Classification: Highly corrosive (causes severe burns) **[ ]**;
Corrosive (causes burns) **[ ]**; Irritating **[ ]**; Not irritating **[ ]**

Method: Other

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

Test substance: a mixture of 66.3 % p-t-butylphenol, 13.4 % o-t-butylphenol, 19.8 % phenol and 0.5 % di-t-butylphenol

Remarks: The subject material was applied both dry and wet with water to the shaven abdomen of rabbits for various periods of time, and then removed by washing with alcohol. As a result, severity of skin irritation was as followed.
1.0 minutes of exposure time: + for wet and ± for dry
5.0 minutes of exposure time: ++ for wet and + for dry
15.0 minutes of exposure time: +++ for wet and +++ for dry
30.0 minutes of exposure time: ++++ for wet and ++++ for dry
60.0 minutes of exposure time: ++++ for wet and ++++ for dry

Reference: The Dow Chemical Company: 1997b

5.2.2 EYE IRRITATION/CORROSION

(a)

Species/strain: New Zealand white rabbit

Results: Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[X]**;
Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[ ]**;
Not irritating **[ ]**

Classification: Irritating **[ ]**; Not irritating **[ ]**; Risk of serious damage to eyes **[ ]**

Method: Standard Draize test

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

Test substance: purity: 99 %

Remarks: Dose: 10 or 80 mg (dry, finely ground powder)
Severe corneal injury, iritis, and severe conjunctival irritation was observed and generally persisted for 21 days after exposure. This effect was severe and moderate to severe at 80 mg and 10 mg, respectively. At 10 mg, the severity of this effect decreased with time.

Reference: Klonne *et al*.: 1988

(b)

Species/strain:	Rabbit
Results:	Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[X]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[ ]**; Not irritating **[ ]**
Classification:	Irritating **[ ]**; Not irritating **[ ]**; Risk of serious damage to eyes **[ ]**
Method:	Standard Draize test
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance:	purity: unknown
Remarks:	Dose: 50 µg/24 hours
Reference:	*Prehled Prumyslove Toxikologie*: 1986

(c)

Species/strain:	Rabbit
Results:	Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[X]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[ ]**; Not irritating **[ ]** *See Remarks
Classification:	Irritating **[ ]**; Not irritating **[ ]**; Risk of serious damage to eyes **[ ]**
Method:	Other
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	purity: unknown
Remarks:	Application of excess of 1 % solution in water or propylene glycol to the centre of the cornea and examination after 18 - 24 hours resulted in injury grade 9 of 10 (not classifiable according to current day standards).
Reference:	Smyth *et al*.: 1969

(d)

Species/strain:	Rabbit
Results:	Highly corrosive **[ ]**; Corrosive **[X]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[ ]**; Not irritating **[ ]** *See Remarks
Classification:	Irritating **[ ]**; Not irritating **[ ]**; Risk of serious damage to eyes **[ ]**
Method:	Other: BASF Test
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	purity: unknown
Remarks:	Corrosion was induced, but the severity was not described in IUCLID Database.
Reference:	BASF AG: 1971

5.3 SKIN SENSITISATION

(a)

Type:	Maximisation test
Species/strain:	Dunkin Hartley guinea pig (male)
Results:	Sensitizing **[ ]**; Not sensitizing **[X]**; Ambiguous **[ ]**
Classification:	Sensitizing **[ ]**; Not sensitizing **[ ]**
Method:	OECD Guidelines for Testing of Chemicals, Section 4, No. 406, "Skin Sensitization"
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	purity: 99.89 %
Remarks:	Three pairs of intracutaneous injections of 0.5 % p-t-butylphenol (0.1 cm^3 volume) were given in the bare skin of shoulder region, one of each pair on either side of the midline. After one week, a filter paper was covered with the 10 % p-t-butylphenol or with the vehicle (about 0.4 g/patch) and placed onto the shoulder region of the animals on top of the injections and held in place

by an occlusive patch and fixed with a bandage for 48 hours. For the challenge treatment after 2 weeks, surgical gauze was covered with 0.2g of the 1 % test substance in Vaseline and placed onto the clipped right flank of the animals. An occlusive patch with the vehicle alone was applied to the left flank. The patches were held in contact with the skin by an occlusive patch and fixed with a bandage for 24 hours. Assessment took place 48 and 72 hours after administration.

Reference: Hüls Infracor GmbH: 1998

(b)
Type:
Species/strain: Guinea pig
Results: Sensitizing **[X]**; Not sensitizing **[ ]**; Ambiguous **[ ]**
Classification: Sensitizing **[ ]**; Not sensitizing **[ ]**
Method: Other
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: purity: unknown
Remarks: 20 white female guinea pigs were painted daily on the bare skin behind their ears with one drop of 30 % solution of a p-t-butylphenol resin in ethyl acetate for three weeks followed by a two weeks rest. 0.5 % resin and 1 % p-t-butylphenol in ethyl acetate was applied behind the right and left nipple, respectively and biopsies were conducted after 48 hours. In histological examination, 15 of 20 guinea pigs showed contact allergic reactions to the resin. 7 of these 15 animals showed positive reactions to p-t-butylphenol and in 8 of these 15 animals sensitization appears not to be based upon a demonstrable sensitivity to p-t-butylphenol. Starting with an application of 30 % p-t-butylphenol behind both ears followed by application of 1 % p-t-butylphenol and 0.5 % resin behind the right and left ear, respectively, 14 animals were sensitized with p-t-butylphenol and 9 of these also reacted to the resin (procedure as described above).
Reference: Malten: 1967

*5.4 REPEATED DOSE TOXICITY

(a)
Species/strain: Rats/Crj:CD (SD)
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**
Route of Administration: Oral (gavage)
Exposure period: 14 days
Frequency of treatment: Daily
Post exposure observation period: 1 day
Dose: 0 (Vehicle), 250, 500, 1,000 mg/kg/day
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**; 0.5% aqueous methyl cellulose
Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**; Historical **[ ]**
NOEL:
LOEL: 250 mg/kg/day
Results: At 1,000 mg/kg, the body weights were 10% lower than control at day 9, and 3/5 females and 1/5 male died up to day 9. At this time, all other survivors were dissected but no toxic sign was observed by necropsy. Two females continuously showed difficulty of breathing with noisy respiratory sound.

At 500 mg/kg, abnormality was only noisy respiratory sound in 3/5 animals of both sexes. At 250 mg/kg, 1/5 female showed noisy respiratory sound.
Method: Other (Dose finding study)
GLP: Yes **[ ]** No **[X]** ? **[ ]**

Test substance: purity: 99.9%
Remarks: Author considered there was no systemic toxicity of this chemical but the tolerable dose of this chemical would be around 250 mg/kg/day for OECD Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test, because of difficulty of breathing, probably causing by irritation.
Reference: MHW, Japan: Unpublished

(b)
Species/strain: Rat/Crj:CD (SD)
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**
Route of Administration: Oral (gavage)
Exposure period: Male: 44 days
Female: from 14 days before mating to day 4 of lactation
Frequency of treatment:
Post exposure observation period:
Dose: 0 (Vehicle), 20, 60, 200 mg/kg/day
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**; 0.5% aqueous methyl cellulose
Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**; Historical **[ ]**
NOAEL: 200 mg/kg/day as systemic toxicity
LOAEL:
Results: No treatment related changes were observed except noisy respiratory sound in a few females of the 200 mg/kg. Only plasma albumin in the 200 mg/kg males was decreased.
Method: OECD Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test (OECD TG 422)
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Remarks: Author considered the noisy respiratory sound was likely related to irritation of the respiratory tract caused by the oral administration of the chemical.
Test substance: purity: 99.9%
Reference: MHW, Japan: 1996

(c)
Species/strain: Syrian Golden hamsters
Sex: Female **[ ]**; Male **[X]**; Male/Female **[ ]**; No data **[ ]**
Route of Administration: Oral (feed)
Exposure period: 20 weeks
Frequency of treatment: Daily
Post exposure observation period:
Dose: 15 g/kg diet (calculated daily dose as 120 g of body weight and 10 g/day of food consumption: 1.25 g/kg b.w.)
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**; basal diet
Concurrent no treatment **[X]**; Concurrent vehicle **[ ]**; Historical **[ ]**
NOAEL:
LOAEL: 1,250 mg/kg/day
Results: Body weights were decreased by 5 % and relative liver weights were increased, compared to the control group. In histological examination, grossly prominent thickening of the forestomach epithelium with a keratin-like white substance was observed in the posterior and anterior walls along the lesser curvature and adjacent to the esophagus. Hyperplasia observed in the forestomach was classified into three types, mild (< 0.1 mm; 15/15 and 7/15 in treated and control group, respectively), moderate (0.1 - 0.5 mm; 12/15 and 1/15) and severe (> 0.5 mm; 11/15 and 0/15). Another category of changes was papillomatous lesions (7/15 and 0/15), in which the epithelium showed papillary upward projection with slight atypia of cells,

or nestic downward growth beyond the muscularis mucosa. No abnormal findings were observed in liver, kidneys, cheek pouch, lung, pancreas and urinary bladder.

Method: Other
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: purity: > 95 %
Remarks: [^{3}H]thymidine incorporation study was also conducted together with this study. See Section 5.10.A.
Reference: Hirose *et al.*: 1986

(d)
Species/strain: Fischer 344 rats
Sex: Female **[ ]**; Male **[X]**; Male/Female **[ ]**; No data **[ ]**
Route of Administration: Oral (feed)
Exposure period: 51 weeks
Frequency of treatment:
Post exposure observation period: 1 week
Dose: 15 g/kg diet (calculated daily dose as 420 g of body weight and 30 g/day of food consumption: 1.07 g/kg b.w.)
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[X]**; Concurrent vehicle **[ ]**; Historical **[ ]**
Results: Decrease in the final body weight and increase in relative liver and kidney weights were observed in treated rats. Histological changes observed in the forestomach were hyperplasia (14/15, 0/10 for treated and control rats, respectively) but papilloma (1/14, 1/15), carcinoma *in situ* (0/15, 0/15) and squamous cell carcinoma (0/15, 0/10) were no changes. No tumors were observed in the other organs examined such as the esophagus and intestines.
Method: Other
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: purity: > 95 %
Remarks: Major purpose of this study was to examine the promoting property of phenolic antioxidants including p-t-butylphenol by two-stage protocol. The result was given at section 5.7.
Reference: Hirose *et al.*: 1988

*5.5 GENETIC TOXICITY IN VITRO

A. BACTERIAL TEST

(a)
Type: Bacterial gene mutation assay
System of testing: *S. typhimurium* TA98, TA100, TA1535, TA1537
E. coli WP2 *uvrA*
Dose: -S9 mix: 0, 15.6, 31.3, 62.5, 125, 250 and 500 μg/plate (TA100, TA1535, TA98, TA1537), 0, 31.3 - 1000 μg/plate (WP2)
+S9 mix: Same as -S9 mix.
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
S9: Rat liver, induced with phenobarbital and 5,6-benzoflavone
Plate/test 3
Number of replicates: 2
Results:
Cytotoxicity conc: With metabolic activation: 500 μg/plate (five strains)
Without metabolic activation: 500 μg/plate (TA100, TA1535, TA1537) 1000 μg/plate (WP2 and TA98)

Precipitation conc:
Genotoxic effects: + ? -
With metabolic activation: **[ ] [ ] [X]**
Without metabolic activation: **[ ] [ ] [X]**
Method: Guidelines for Screening Mutagenicity Testing of Chemicals Japan, and OECD TG (471 and 472)
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: purity: 99.9%
Remarks:
Reference: MHW, Japan: 1996

(b)
Type: Bacterial gene mutation assay
System of testing: *S. typhimurium* TA1535, TA1537, TA98, TA100
E. coli WP2 *uvrA*$^{-}$
Test method:
Solvent: Dimethyl sulfoxide
Dose: 1.6, 8, 40, 200, 1,000 μg/ml
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
Results:
Cytotoxicity conc: With metabolic activation: 1,000 μg/ml (all strains)
Without metabolic activation: 1,000 μg/ml (all strains)
Precipitation conc:
Genotoxic effects: + ? -
With metabolic activation: **[ ] [ ] [X]**
Without metabolic activation: **[ ] [ ] [X]**
Method: Guidelines for bacterial mutagenicity testing published by the major Japanese Regulatory Authorities including MITI, MHW, MOL and MAFF
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Except that the concentration, homogeneity and stability of test material preparations were not determined by analysis and that this specific study may not have been subject to procedure inspection by the Quality Assurance Unit
Test substance: purity: unknown
Remarks: Positive control:
With metabolic activation:
2-Aminoanthracene at 2 μg/plate for TA 1535 and 10 μg/plate for WP2 *uvrA*$^{-}$
Benzo(a)pyrene at 5 μg/plate for TA 100, TA1537 and TA 98
Without metabolic activation:
N-ethyl-N'-nitro-N-nitrosoguanidine at 2 μg/plate for WP2 *uvrA*$^{-}$, 3 μg/plate for TA100 and 8 μg/plate for TA 1535
9-Aminoacridine at 80 μg/plate for TA 1537
4-Nitroquinoline-1-oxide at 0.2 μg/plate for TA 98
Reference: Safepharm Laboratories Ltd.: 1992a

(c)
Type: Bacterial gene mutation assay
System of testing: *S. typhimurium* TA1535, TA1537, TA1538, TA98, TA100, *E. coli* WP2, WP2 *uvrA*, *S. cerevisiae* JD1
Test method:
Solvent: Dimethyl sulfoxide or Hexane
Dose: Up to 5.0 mg/ml
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
Results:
Cytotoxicity conc: With metabolic activation:

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

Method: Other
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: purity: > 95 %
Remarks:
Reference: Dean *et al.*: 1985

B. NON-BACTERIAL IN VITRO TEST

(a)
Type: Chromosomal aberration test
Type of cells used: Chinese hamster lung (CHL/IU) cell
Test method:
Solvent: Dimethylsulfoxide
Positive control: -S9, Mitomycin C; +S9, Cyclophosphamide
Dose: -S9 (continuous treatment): 0, 0.013, 0.025, 0.05 mg/ml
-S9 (short-term treatment): 0, 0.02, 0.04, 0.08 mg/ml
+S9 (short-term treatment): 0, 0.013, 0.025, 0.05 mg/ml
S-9: Rat liver, induced with phenobarbital and 5,6-benzoflavone
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
Plates/test: 2
Results:
Cytotoxicity conc: Without metabolic activation: (continuous treatment): 0.025 mg/ml
Without metabolic activation (short-term treatment): 0.08 mg/ml
With metabolic activation: (short-term treatment): not observed
Precipitation conc:

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

Method: Guidelines for Screening Mutagenicity Testing of Chemicals, Japan and OECD TG 473
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: purity: 99.9%
Remarks: Structural chromosome aberration was observed in CHL/IU cells with exogenous metabolic activation by short-term treatment in 6.5 - 12.0 % of cells at all concentrations studied. This chemical also induced polyploidy with and without an exogenous metabolic activation system. The high incidences of polyploidy cell were observed after 48 hr continuous treatment but the response was apparent only at cytotoxic concentrations. Other increases of polyploidy were small incidences.
Reference: MHW, Japan: 1996

(b)
Type: Chromosomal aberration test
Type of cells used: Rat lymphocytes
Test method:
Solvent: Dimethylsulfoxide
Positive control: -S9: Ethyl methanesulphonate at 500 μg/ml
+S9: Cyclophosphamide at 4.2 μg/ml
Dose: -S9 (20-hour cultures): 1.0 – 125 μg/ml

+S9 (20-hour cultures): 1.88 –120 μg/ml
+S9 (30-hour cultures): 1.88 – 60 μg/ml
S-9: Rat liver, induced with Aroclor 1254
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
Plates/test: 2
Results:
Cytotoxicity conc: With metabolic activation: 60.0 μg/ml and more dose (20- and 30-hour cultures)
Without metabolic activation: 30.0 μg/ml and more dose
Precipitation conc:
Genotoxic effects:

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

Method: OECD Guidelines for Testing of Chemicals (1981) No. 473 "Genetic Toxicology: Chromosome Aberration Test" and Method B10 of Commission Directive 84/449/EEC
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Except that the concentration, homogeneity and stability of test material preparations were not determined by analysis and that this specific study may not have been subject to procedure inspection by the Quality Assurance Unit
Test substance: purity: unknown
Remarks:
Reference: Safepharm Laboratories Ltd.: 1992b

(c)
Type: Chromosomal aberration test
Type of cells used: Rat liver epithelial-type cells
Test method: Other
Solvent: Dimethyl sulfoxide
Dose: Up to 0.5 mg/ml GI50 (50 % growth inhibition dose)
Metabolic activation: With **[ ]**; Without **[X]**; With and Without **[ ]**; No data **[ ]**
Results:
Cytotoxicity conc: With metabolic activation:
Without metabolic activation:
Precipitation conc:
Genotoxic effects:

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

Method: Other
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: purity: > 95 %
Remarks: The cells were treated for 24 hr and 100 cells were analyzed microscopically. As for polyploidy, it is not mentioned
Reference: Dean *et al.*: 1985

(d)
Type: Mutation of L5178Y mouse lymphoma cells at the thymidine kinase TK +/- locus. Fluctuation assay
Type of cells used: L5178Y mouse lymphoma cells (heterozygous at the thymidine kinase locus)
Test method:
Solvent: Dimethylsulfoxide
Positive control: -S9: Ethyl methanesulphonate at 931.5 μg/ml
+S9: Cyclophosphamide at 5 μg/ml
Dose: 5.0, 10.0, 20, 40, 80 μg/ml

S-9: Rat liver, induced with Aroclor 1254
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
Plates/test: 2
Dose:
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
Results:
Cytotoxicity conc: 80 µg/ml
Precipitation conc:

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

Method: Other
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Except that the concentration, homogeneity and stability of test material preparations were not determined by analysis and that this specific study may not have been subject to procedure inspection by the Quality Assurance Unit
Test substance: purity: unknown
Remarks:
Reference: Safepharm Laboratories Ltd.: 1992c

* 5.6 GENETIC TOXICITY IN VIVO

Type:
Species/strain: Drosophila melanogaster
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[ ]**; No data **[X]**
Route of Administration: Oral feed in the larval stage
Exposure period: No data
Doses: No data
Results: p-t-Butylphenol induced a change of the colour of body and wings of adult flies; nearly 100 % of the flies showed disturbed wing development; p-t-butylphenol did not cause any mutagenic effect in cells of imaginal buds.
Effect on mitotic index or P/N ratio:

Genotoxic effects:	+	?	-
	[ ]	**[X]**	**[ ]**

Method: Other: Morphogenetic Test
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: purity: unknown
Remarks: Due to poor documentation of this (Russian) publication, it is not possible to evaluate the results of this study.
Reference: Zavadsky & Khovanova: 1975

5.7 CARCINOGENICITY

Species/strain: Fischer 344 rats
Sex: Female **[ ]**; Male **[X]**; Male/Female **[ ]**; No data **[ ]**
Route of Administration: Oral (feed)
Exposure period: 51 weeks
Frequency of treatment: Daily
Post exposure observation period: 1 week
Dose: 15 g/kg diet (calculated daily dose as 420 g of body weight and 30 g/day of food consumption: 1.07 g/kg b.w.)
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[X]**; Concurrent vehicle **[ ]**; Historical **[ ]**

Results: Rats were administered with or without N-Methyl-N'-nitro-N-nitrosoguanidine (MNNG) at 150 mg/kg b.w. by stomach tube and given diet containing p-t-butylphenol or basal diet one week later.

[Without MNNG pretreatment] Decrease in the final body weight and increase in relative liver and kidney weights were observed in p-t-butylphenol treated rats. Histological changes observed in the forestomach were hyperplasia (14/15, 0/10 for treated and control), papilloma (1/14, 1/15), carcinoma *in situ* (0/15, 0/15), and squamous cell carcinoma (0/15, 0/10). No tumors were observed in the other organs examined such as the esophagus and intestines.

[With MNNG pretreatment] Decrease in the final body weight and increase in relative liver and kidney weights were observed in p-t-butylphenol treated rats. Grossly, small papillary or polypoid tumours were found in the forestomach of control rats, while very large single or multiple tumor masses occupied the forestomach in treated rats. Histological changes observed in the forestomach were hyperplasia (20/20, 19/19 for treated and control), papilloma (19/20, 13/19), carcinoma *in situ* (8/20, 11/19), and squamous cell carcinoma (15/20, 5/19). Squamous cell carcinoma in treated group was significant change, compared to control group. Leiomyosarcoma was induced in one treated rat. As histological change of the glandular stomach, adenocarcinoma of fundic region was only observed in one of treated rats. No tumors were observed in the other organs examined such as the esophagus and intestines.

Method: Other
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: purity: > 95 %
Reference: Hirose *et al.*: 1988

*5.8 TOXICITY TO REPRODUCTION

Type: Fertility **[ ]**; One-generation study **[ ]**; Two-generation study **[ ]**; Other **[X]**
Species/strain: Rats/Crj:CD (SD)
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**
Route of Administration: Oral (gavage)
Exposure period: Male: 44 days
Female: from 14 days before mating to day 3 of lactation
Frequency of treatment:
Post exposure observation period:
Premating exposure period: male: 14 days, female: 14 days
Duration of the test:
Doses: 0 (Vehicle), 20, 60, 200 mg/kg/day
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**; 0.5% aqueous methyl cellulose
Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**; Historical **[ ]**
NOEL Parental: 200 mg/kg/day
NOEL F1 Offspring: 200 mg/kg/day
NOEL F2 Offspring:
Results: There were no treatment related toxic effects on pregnant and lactating females or their offspring.
Method: OECD Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: purity: 99.9%

Reference: MHW, Japan: 1996

***5.9 DEVELOPMENTAL TOXICITY/ TERATOGENICITY**

No data are available.

5.10 OTHER RELEVANT INFORMATION

A. Specific toxicities

(a)
Type: Depigmentation test
Results: 0.1 ml solution was applied daily to 9 cm^2 of the shaved skin of 12 male and female black guinea pigs for up to three weeks.
5 mg in acetone (5 %): mildly irritating; no depigmentation
10 mg in acetone (10 %): strongly irritating (erythema and edema extending beyond area of application); no depigmentation
10 mg in DMSO (10 %): moderate irritating; strong depigmentation potency
10 mg in propylene glycol (10 %): moderate irritating; strong depigmentation potency
1 mg in any vehicle caused no irritation.
Remarks: Observation period was 3 months.
Reference: Gellin *et al.*: 1970

(b)
Type: Depigmentation test
Results: 0.2 mL olive oil, to which 0.2 M of p-t-butylphenol was added, was administered orally to black C 57 male mice 3 times a week for 6 months. Diffuse or patchy depigmentation was observed in the majority of the animals.
Remarks:
Reference: Hara: 1967, Hara and Nakajima: 1969

(c)
Type: Depigmentation test
Results: 0.05 mL olive oil, to which 0.01 M of p-t-butylphenol was added, was injected subcutaneously to black C 57 male mice 6 times a week for 7 months. 12 weeks after the beginning of the injection, depigmentation was observed.
Remarks:
Reference: Hara and Uda: 1966, Hara and Nakajima: 1969

(d)
Type: Depigmentation test
Results: Vitiligo-like depigmentation of black mice was achieved as much by ingestion as by inhalation of p-t-butylphenol. Cutaneous application in different solvents and at different concentrations did not elicit any skin changes. A modified Kligman solution (p-t-butylphenol, vitamin A acid and dexamethasone) caused distinct depigmentation (no further data available).
Remarks:
Reference: Forck *et al.*: 1981

(e)
Type: Depigmentation test
Results: p-t-Butylphenol (10 mg/kg/day) in peach oil was injected intramuscularly to black rabbits (no data on the number of used animals) daily for 6 weeks. 20 - 24 days after the beginning of the treatment, small areas of grey hair were observed on the flanks and backs of the animals. In four rabbits, there was a spastic paralysis of the hind legs.
Remarks: In four rabbits, inhalation exposure to formaldehyde vapour was performed together with the above treatment, but there was no effect on the greying.
Reference: Malten *et al.*: 1971

(f)
Type: Depigmentation test
Results: 0.5 % p-t-butylphenol (7.5 mg/kg) in ol. persicarium was injected intramuscularly to eight black rabbits (no data on exposure period). On the other hands, four other rabbits were given their fodder containing this chemical of the same amount. 12 – 20 days after the beginning of the treatment, an apparent greying was observed without previous browning. 2 years after the end of the treatment, grey hair still remained in 3/8 animals injected intramuscularly. Between two routes of the treatment, there were no differences in the effects of this chemical.
Remarks:
Reference: Malten *et al.*: 1971

(g)
Type: Depigmentation test
Results: Emulsions was made of 9 g of emulgide in 1,000 ml water, to which 600 mg of p-t-butylphenol was added during mixing. This emulsions, equal to 7.5 mg/kg b.w., was treated to 10 wild coloured guinea pigs by gavage 5 days per week for 10 months. Several animals died, due to well known difficulties with tube feeding. Clear-cut depigmentation was not observed within the limits of accuracy of judging depigmentation even with colour photographs.
Remarks:
Reference: Malten *et al.*: 1971

(h)
Type: Depigmentation test
Results: 0.1 ml aliquot of p-t-butylphenol was applied to adult black guinea pigs on the dorsal epilated surface (eight sites, 3 cm x 3 cm), and the unepilated skin of ears and nipples. Various solvent was used such as DMSO, acetone and hydrophilic ointment, and the concentration of this chemical ranged from 0.01 M to 1.0 M for various liquid solvents and from 0.1 % to 10 % for solid ointment bases. p-t-Butylphenol induced definite, but moderate depigmentation (uniform hypopigmentation) on the back and ear, but not on nipple. Minimal eliciting concentration was 0.25 M in DMSO and 10 % in hydrophilic ointment on the back, and 0.25 M in DMSO on the ear. Minimal time for the appearance of maximum depigmentation was 23 days after applications of 0.25 M in DMSO on the back and the ear. The longest time required to induce maximal depigmentation was 112 days for 1 M in acetone on the back.

In addition, this chemical induced severe and moderate irritation to the skin of the back and the ear, respectively.

Remarks: The solvent control sites included at least one sector on the back, an ear and one nipple.
Reference: Gellin *et al.*: 1979

(i)
Type: Depigmentation test
Results: p-t-Butylphenol was applied to the skin of 4 black guinea pigs for 4 - 5 days. Depigmentation occurred without preceding inflammation. Spots of depigmented (white) skin and hairs were surrounded by a zone of hyperpigmentation. Leukoderma was irreversible in some cases and exhibited a tendency to progressing and spontaneous dissemination (no further data available).
Remarks: 15 black guinea pigs were used as a control group.
Reference: Zavadsky & Khovanova: 1975

(j)
Type:
Results: p-t-Butylphenol (500 mg/kg/day) in a mixture of 5 ml propylene glycol plus 50,000 mg polyethyleneglycol was applied on the skin of rabbits daily for 20 weeks. There was an increase in the incidence of a capillaritis consisting of perivascular infiltration and formation of thrombi.
Remarks:
Reference: Malten *et al.*: 1971 (Hara and Okumura: 1962)

(k)
Type: Biochemical investigation
Results: p-t-Butylphenol influenced the cresolase activity of tyrosinase in such a way to elongate the induction period and suppress the reaction velocity of this enzyme significantly. On the other hands, this chemical delayed the reaction inactivation to increase the catecholase activity.
Remarks: The tyrosinase was prepared from potato by Kubowitz's method and determined by Warburg's oxygen consumption method using p-cresol as a substance in a medium of propylene glycol.
Reference: Malten *et al.*: 1971 (Nakajima and Ito: 1967, Hara and Nakajima: 1969)

(l)
Type: Biochemical investigation
Results: p-t-Butylphenol inhibited the dihydroxyphenylalanine (DOPA) oxidation activity of epidermal tyrosinase from Rana pipiens (enzyme involved in melanin synthesis) and Ki was estimated as 2.02×10^{-4} mol/l. This chemical might be also an effective competitive inhibitor of the oxidation of tyrosine by Rana pipiens tyrosinase. Km for tyrosine and Ki for p-t-butylphenol was estimated as 2.2×10^{-3} mol/l and 1.95×10^{-4} mol/l, respectively.
Remarks:
Reference: McGuire & Hendee: 1971

(m)
Type: Chemobiokinetics general studies
Results: p-t-Butylphenol was incubated with UDP-glucuronyltransferase for 10 min or sulfotransferase for 30 min at 37 degree C.
UDP-glucuronyltransferase; Km = 0.03 ± 0.01 mmol/l
Vmax = 4.08 ± 0.53 nmol/min/mg
Sulfotransferase; Km = 110 ± 32.5 μmol/l
Vmax = 0.58 ± 0.42 nmol/min/mg

Remarks: These enzymes were prepared from human liver.
Reference: Temellini *et al.*: 1991

(n)
Type: Chemobiokinetics general studies
Results: Male Sprague-Dawley rats were administered p-t-butylphenol by gavage at a single dose of 2 and 10 mg/kg b.w. As a result, aminopyrine demethylase activity was inhibited. Microsomal cytochrome b5 and P-450 contents were increased 1, 12 and 24 h after administration. Although ascorbate-dependent lipid peroxidation of mitochondria and microsomes were increased, NADPH-dependent lipid peroxidation was decreased. Swelling and decrease of rough endoplasmic reticulum and increase of smooth endoplasmic reticulum was observed.
Remarks:
Reference: Nakayama *et al.*: 1988

(o)
Type: Radioimmunoassay
Results: p-t-Butylphenol showed less than 10 % competition for the thyroxin (T4) binding site of transthyretin at a concentration level of 15 mg/l.
Remarks:
Reference: Van den Berg *et al.*: 1991

(p)
Type: Cytotoxicity
Results: Hemolytic activity in rat erythrocytes was examined at 37 degree C. Incubation period was 3 hours. As a result, the value of EC_{50} was 120.1 mg/l.
Remarks: Data were expressed as percentage of total hemolysis provoked by distilled water.
Reference: Biagi *et al.*: 1975

(q)
Type: [^{3}H]-Thymidine incorporation study
Results: Male Syrian Golden hamsters were given diet containing p-t-butylphenol at 15 g/kg diet daily for 20 weeks, followed by single i.p. injection of 1 mCi/kg bw [methyl-^{3}H]-thymidine 1 h before killing the hamsters. Hamsters in treated group showed a significantly increased labelling index in the forestomach, but no significant change in the pyloric region and urinary bladder.
Remarks: For analysis of the labeling index, counts were made on 4000 cells of the urinary bladder epithelium, 3000 cells of pyloric gland epithelium and 2000 basal cells each of the forestomach epithelium.
Reference: Hirose *et al.*: 1986

(r)
Type: Estrogenic activity
Results: In yeast transfected with two plasmids, one carrying human estrogen receptor gene and the other carrying estrogen responsive element and reporter gene Lac-Z, p-t-butylphenol indicated very weakly estrogenic activity. The estrogenic transcriptional activity of p-t-butylphenol was 1.5 x 10^6 fold less potent than 17β-estradiol, although that of t-octylphenol was 1 x 10^3 fold less potent than 17β-estradiol.
Remarks:
Reference: Routledge & Sumpter: 1997

B. Toxicodynamics, toxicokinetics

(a)
Type: Metabolism
Results: ^{14}C-labelled p-t-butylphenol was given intravenously to male Wistar rats at a single dose of 1.2 - 10.4 mg/kg b.w. Subsequently, bile and urine was collected for 4 hours. 65 - 71 % and 17 - 21 % of the applied dose were excreted as glucuronide conjugate and sulfate conjugate, respectively (total recovery of radioactivity: 91 - 93 %). The ratio of glucuronidation and sulfation was not dose-dependent.
Remarks: D-Mannitol was infused to stimulate diuresis during the experiment. ^{14}C-labelled p-t-butylphenol dissolved in saline at pH 10.5 before dilution to the required concentration with saline.

In vitro incubation of isolated hepatocytes with 3.6 - 120.2 mg/l at 37 degree C for 1 hour supported these results concerning the ratio of conjugates and dose-dependency.
Reference: Koster *et al.*: 1981

(b)
Type: Metabolism
Results: [U-^{14}C]p-t-butylphenol was given intravenously to rats at a dose of 18 mg/kg b.w.. Urine and bile were collected during 24 hr and analyzed by thin layer chromatography. 1.5 ± 0.2 µmol was excreted as sulfate in the urine, while no significant amounts were found in the biliary excretes.
Remarks:
Reference: Nanbo: 1991

(c)
Type: Metabolism
Results: *In vitro* incubation of 112.65 mg [U-^{14}C]p-t-butylphenol with rat liver cytosol at 37 degree C for 1 h yielded 65.5 +/- 11.8 nmol/min/mg protein-1 of sulfated TS.
Remarks:
Reference: Nanbo: 1991

(d)
Type: Distribution and Excretion
Results: ^{14}C-labelled p-t-butylphenol (147 µg/kg/day) in Keltrol solution was administered to male Wistar rats by gavage daily for 3 days. Urine and feces were collected daily. 26.7 % and 72.9 % of the applied dose was eliminated via feces and urine, respectively. Distribution in tissues and organs was as follows: retention in abdominal adipose tissue: not detectable (< 0.01 %/g), liver: 0.02 %, lung: not detectable (< 0.01 %), carcass: 0.1 % (data in percent of the applied doses)
Remarks: Post observation period was 4 days.
Reference: Freitag *et al.*: 1982

*** 5.11 EXPERIENCE WITH HUMAN EXPOSURE**

A. Skin sensitization

(a)
Type: Patch Test
Results: Sensitizing **[X]**; Not sensitizing **[ ]**; Ambiguous **[ ]** *See Remarks

Classification: Sensitizing **[ ]**; Not sensitizing **[ ]**
Method: Other (Al-test and Dermicel tape (trade name) (1976))
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: purity: unknown
Remarks: In routine test series of the North American Contact Dermatitis Group in 1974/75, 1900 patients with contact dermatitis revealed 1.9 % positive reactions to 2 % of p-t-butylphenol. The test series in 1975/76 with 900-2000 contact dermatitis patients revealed 1.1 % positive reactions to 2 % of p-t-butylphenol. Tests were read at 48 and 96 hour.
Reference: Rudner: 1977

(b)
Type: Patch Test
Results: Sensitizing **[X]**; Not sensitizing **[ ]**; Ambiguous **[ ]**
Classification: Sensitizing **[ ]**; Not sensitizing **[ ]**
Method: Other
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: purity: unknown
Remarks: Eight workers working in two factories (Derfesa and Givaudan) where they were handling with p-t-butylphenol showed leukoderma on the hands and forearms, sometimes wrists, neck and neckline. They were patch-tested with 1 % p-t-butylphenol in petrolatum. All tests were positive. The four patients from Derfesa showed an achromic response to the patch test between 8 and 15 days later. The workers from Givaudan were positive after 48 and 96 hours. Patch tests with the standard Spanish Contact Dermatitis Research Group series were all negative (Spain, 1979).
Reference: Romaguera and Grimalt: 1981

(c)
Type: Patch Test
Results: Sensitizing **[X]**; Not sensitizing **[ ]**; Ambiguous **[ ]**
Classification: Sensitizing **[ ]**; Not sensitizing **[ ]**
Method: Other
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: purity: unknown
Remarks: 10 shoemakers with eczema due to occupational exposure to p-t-butylphenol containing glues were patch-tested for sensitization in 1957. Positive reactions to the glue, its ingredients formaldehyde-p-t-butylphenol resin (50 % in ethyl acetate; three patients: 75 % in ethyl acetate) and p-t-butylphenol (50 % in ethyl acetate) were observed in all patients. After 24 hours, reaction in the p-t-butylphenol test was erythema, edema or papules, and some patients showed a few vesicles. After 48 hours, all patients showed these symptoms (The Netherlands, 1957).
Reference: Malten: 1958, 1977

(d)
Type: Patch Test
Results: Sensitizing **[ ]**; Not sensitizing **[X]**; Ambiguous **[ ]**
Classification: Sensitizing **[ ]**; Not sensitizing **[ ]**
Method: Other
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: purity: unknown
Remarks: 7 persons with spectacle frame dermatitis were tested and showed no reaction to 5 % p-t-butylphenol in vaseline.
Reference: Hausen and Jung: 1985

(e)

Type:	Patch Test
Results:	Sensitizing **[ ]**; Not sensitizing **[X]**; Ambiguous **[ ]**
Classification:	Sensitizing **[ ]**; Not sensitizing **[ ]**
Method:	Other
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance:	purity: unknown
Remarks:	Two patients with contact dermatitis reacting positively to p-t-butylphenol-formaldehyde resins in a patch test showed a negative reaction to 2 % p-t-butylphenol in petrolatum.
Reference:	Bruze *et al*.: 1985

(f)

Type:	Patch Test
Results:	Sensitizing **[ ]**; Not sensitizing **[X]**; Ambiguous **[ ]**
Classification:	Sensitizing **[ ]**; Not sensitizing **[ ]**
Method:	Other
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance:	purity: unknown
Remarks:	Three patients with vitiligo occupationally exposed to p-t-butylphenol showed negative reactions to 0.01, 0.05, 0.1 and 0.5 % test substance in 70 % ethanol and vaseline. Tests were read at 48 hours, 72 hours and 14 days.
Reference:	Budde & Stary: 1988

B. Toxicokinetics and toxicodynamics

(a)

Results:	Urine samples of workers engaged in packing of p-t-butylphenol (bagging, weighing and sealing of the bags) were collected for 24 h after the start of each shift. Acid-hydrolyzed samples were analyzed by GC. Mean level in urine was 4.20 µg/ml at day shift and 6.12 µg/ml at night shift. Mean total urinary excretion (24 h) was 2.31 mg, estimated respiratory absorption (during substantial working time; workers were wearing respirators) was 0.74 mg, and 8 h-TWA (time weighted average value for workers ambient air) was 0.39 mg/m^3. p-t-Butylphenol was even qualitatively detected by GC in an diethyl ether extract of acid-hydrolyzed sweat collected from the back of workers immediately after bathing. In contrast to the urine samples, no free p-t-butylphenol could be detected (Japan, not dated).
Remarks:	
Reference:	Kosaka *et al*.: 1989

(b)

Results:	Urine samples of male workers engaged in the production of p-t-butylphenol were collected during shift and during the half-a-day period after the shift. Mean concentrations were from 0.5 µg/ml (engineers) to 6.3 µg/ml (product packers). After introduction of semi-automatization of weighing and bag sealing, and installation of mighty local exhaust systems, concentration in urine samples decreased to a range from traces (engineers) to 2.2 µg/ml (product packers). In another factory with semi-automatization, non-detectable amounts to traces were found in the urine of plant operators and 1.55 - 3.34 µg/ml were found in urine of 3 product packers (time averages). The biological half-life of p-t-butylphenol in urine taken from these 3 examinees was calculated to be 4 h on average. (Japan, not dated)

Remarks: Samples were acid-hydrolyzed and analyzed by gaschromatography. Detection limit in urine was 0.2 µg/ml.
Reference: Ikeda *et al.*: 1978

C. Effects of occupational exposure

(a)
Results: In a Russian factory producing p-t-butylphenol and p-t-butylphenol-formaldehyde resin, depigmentation was observed in 23 of 52 workers. The first 3 cases of them occurred one year after the start of the work and in 21 workers of them the vitiligo had a symmetrical distribution. In addition, some workers suffered from headache, dizziness, thirst, hyperhidrosis, disturbed sleep and neurological and otolaryngological disturbances.
Remarks: In this factory, p-t-butylphenol was produced from phenol and isobutylalchohol in the presence of sulfuric acid and subsequently p-t-butylphenol formaldehyde resin was produced from p-t-butyl phenol and formaldehyde in alkaline medium. The end product is washed with water, ground and packed. The measured concentrations of phenol and formaldehyde in the air were considered frequency to surpass the maximal allowable concentration.
Reference: Chumakov *et al.*: 1962

(b)
Results: 23 workers handling p-t-butylphenol (chemical factory, Westfalia, Germany) showed depigmentation on the skin of hands and arms after a few months to 2 years of exposure. Some patients exhibited symmetrical depigmentation of body regions covered with clothing. No other abnormal changes, especially in liver and thyroid, were observed (data not given).
Remarks:
Reference: Forck *et al.*: 1981

(c)
Results: 3 patients occupationally exposed to p-t-butylphenol showed hepatosplenopathy and a goiter (euthyreotic struma diffusa grade II) with disorder of the synthesis of thyroid hormone, auto-antibodies against thyroid material and vitiliginous depigmentation. (Germany, 1974).
Remarks: The systemically disseminated depigmentation was concluded to be caused by inhalation or ingestion of p-t-butylphenol.
Reference: Rodermund *et al.*: 1975a, b, Rodermund and Wieland: 1975a, b

(d)
Results: Three male patients (22, 23 and 51 years old) occupationally exposed to fine dusts of p-t-butylphenol developed vitiligo 18 months to 6 years after the beginning of their exposure. This symptom occurred especially at the skin of exposed body sites like hands and forearms, but no skin irritation occurred prior to or during the development of vitiligo. No sensitization was found. All patients developed antibodies against thyroid-microsomes and parietal cells and 2 of 3 patients developed antibodies against thyreoglobulin. Serum transaminases were unremarkable (Germany, not dated).
Remarks:
Reference: Budde and Stary: 1988

(e)

Results: Between 1956 and 1974, 12 cases of occupational vitiligo due to p-t-butylphenol were observed in a p-t-butylphenol manufacturing factory, further 12 cases of vitiligo were judged not to be occupationally caused because of the lacking of direct contact with suspicious substances. Almost all patients showed slight to moderate struma euthyreotica (21 of 24) and chronic hepatosis (10 of 12 occupational cases of leukoderma showed an increased BSP-clearance) (Germany, 1956 - 1974).

Remarks:

Reference: Goldmann and Thiess: 1975, 1976

(f)

Results: 10 male workers (25 - 53 years old) occupationally exposed to p-t-butylphenol, formaldehyde and derivatives developed vitiligo 10 months to 7 years after the beginning of their exposure. This symptom occurred especially at the skin of exposed body sites like hands and forearms and consisted of more or less intensively spread finger-nail to palm-sized depigmented spots with irregular configuration. In microscopic evaluation, the absence or reduction of melanine and melanocytes was observed. Dermal macrophages containing melanine were found. No hyperpigmentation occurred in the border zone to normal areas. Visible mucous membranes, hair and nails were without any findings. No irritation occurred prior to or during the development of vitiligo. An enlarged liver and spleen was observed in 4 and 1 of these vitiligo patients, respectively. Some liver enzyme activities were increased in two cases, of which one case showed increase in the BSP clearance. In thyroid gland, one patient showed microsomal auto-antibodies (titer: 1 : 25600) and thyreoglobuline-auto-antibodies (titer: 1 : 25), and another showed struma diffusa of grade 1 (WHO classification). A stringent combination of vitiligo, hepatosplenopathy and struma could not be found in any patient. (Austrian resin factory, 1979 and 1980)

Remarks: Dust concentration: 0.48 - 1.52 mg/m^3 air
p-t-Butylphenol concentration in dust: 0.12 - 0.96 mg/m^3 air

Reference: Ebner *et al.*: 1979, Gebhart *et al.*: 1980

(g)

Results: In 1975, a survey of vitiligo in workers at a factory manufacturing p-t-butylphenol was started. Vitiligo was observed in 54 of 198 examinees who had been exposed to p-t-butyl-phenol. One year later, partial resolution of depigmentation could be seen in 16 of 35 men reexamined (exposure situation not specified). Some of the affected body sites had not been directly in contact with p-t-butylphenol. No evidence of an association with autoimmune disease was found. Neither thyroid enlargement, thyroid disease, chronic liver disease, significant liver enlargement nor splenomegaly were detected. There were no abnormalities in the full blood-count, blood urea or elctrolyte levels and no glucosuria. (England, 1975).

Remarks: 20 of the 54 men were patch tested with 2 % p-t-butylphenol and all were negative

Reference: James *et al.*: 1977

(h)

Results: A shoemaker who was handling glues containing p-t-butylphenol showed itching eczema at his hands, arms, face and ears. Three years later, irregularly shaped, depigmented spots with sharp edges symmetrically localized on hands, feet and scrotum started to develop, although the p-t-

butylphenol contact ceased. The border zone of the spots was hyperpigmented. Some inflammatory erythema usually occurred prior to the leucoderma. No specific sensitization was found, but 10 % p-t-butylphenol resin in acetone caused a crescendo-typ reaction until 72 h after the epicutane test (no further data available). Neither struma nor hepatosis was observed. (Germany, 1975)

Remarks:
Reference: Wozniak and Harmm: 1977

(i)
Results: In a large automobile factory, the employees applied the glue liberally on a paintbrush without wearing gloves. They soon noticed that the areas of skin on their hands and fingers which were contaminated by the glue became red and felt sore with burning sensation, but there was no frank dermatitis.
Remarks: Neoprene-based adhesives were used as glues in a large automobile factory in Britain, also about 1956. They were used in the manufacture of car seats and for the linings of the roof and sides of the car interiors. They incorporated a high content of a p-t-butylphenol formaldehyde resin, which sometimes formed nearly 50 % of the product.
Reference: Calnan and Cooke: 1974

(j)
Results: Progressive vitiligo-like leukoderma observed in two patients, who were occupationally exposed to p-t-butylphenol, was examined ultrastructurally. In amelanotic areas of skin, melanocytes and melanosomes were almost lacked completely and few remaining melanocytes contained small, round and granular melanosomes. In hypomelanotic areas, some melanosomes appeared to be damaged and contained few melanosomes in various stages of development. Intraepidermal lymphocytes were frequently found. Increased cellularity of the dermis, melanophages containing melanosomal complexes were also present; no abnormality was found in the normally pigmented skin of the patients when compared to biopsies from controls.
Remarks:
Reference: Bleehen and Sharquie: 1981

(k)
Results: Electron microscopic investigations of biopsies of depigmented skin areas from five patients exposed to p-t-butylphenol (no further data available) revealed a lack of melanocytes in 4 of 5 biopsies. In the biopsy of the 5th patient, melanocytes could be found, but with difficulty (these cells showed swollen mitochondria, many vacuoles and only premelanosomes with an abacus type of pigment distribution instead of the solid pigment of mature melanosomes). There were no important deviations in the keratinocytes surrounding these defective melanocytes. In the border zone and in normal areas, no deviations from normal were observed. (The Netherlands, not dated).
Remarks:
Reference: Malten *et al*.: 1971

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EXTRACT FROM IRPTC LEGAL FILES

file: 17.01 LEGAL rn : 302545
systematic name:Phenol, 4-(1,1-dimethylethyl)-
common name :p-tert-butylphenol
reported name :4-tert-Butylphenol
cas no :98-54-4 rtecs no :SJ8925000
area : CAN type : REG

subject	specification	descriptor
USE	OCC	RQR
STORE		
LABEL		

Ingredient Disclosure List - Concentration: 1% weight/weight. The Workplace Hazardous Materials Information System (WHMIS) is a national system providing information on hazardous materials used in the workplace. WHMIS is implemented by the Hazardous Products Act and the Controlled Products Regulations (administered by the Department of Consumer and Corporate Affairs). The regulations impose standards on employers for the use, storage and handling of controlled products. The regulations also address labelling and identification, employee instruction and training, as well as the upkeep of a Materials Safety Data Sheet (MSDS). The presence in a controlled product of an ingredient in a concentration equal to or greater than specified in the Ingredient Disclosure List must be disclosed in the Safety Data Sheet.
entry date: APR 1991 effective date: 31DEC1987

amendment: CAGAAK, CANADA GAZETTE PART II, 122 , 2 , 551 , 1988

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file: 17.01 LEGAL rn : 522433
!!! WARNING - not original IRPTC record - WARNING !!!
systematic name:Phenol, 4-(1,1-dimethylethyl)-
common name :p-tert-butylphenol
reported name :4-tert-Butylphenol
cas no :98-54-4 rtecs no :SJ8925000
area : DEU type : REG

subject	specification	descriptor
AQ		CLASS
USE	INDST	RQR

This substance is classified as hazardous to water (Water Hazard Class: WHC 2). (There are 3 water hazard classes: WHC 3 = severely hazardous; WHC 2 = hazardous; WHC 1 = moderately hazardous; and the classification as "not hazardous to water"). The purpose of the classification is to identify the technical requirements of industrial plants which handle substances hazardous to water.
entry date: SEP 2001 effective date: 01JUN1999

title: Administrative Order relating to Substances Hazardous to Water (Verwaltungsvorschrift wassergefaehrdende Stoffe)
original : BUANZ*, Bundesanzeiger, 51 , 98a , 1 , 1999

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file: 17.01 LEGAL rn : 540139
!!! WARNING - not original IRPTC record - WARNING !!!
systematic name:Phenol, 4-(1,1-dimethylethyl)-
common name :p-tert-butylphenol
reported name :p-tert-Butyl phenol
cas no :98-54-4 rtecs no :SJ8925000
area : DEU type : REC

subject	specification	descriptor
AIR	OCC	MAK

MAK value (8-hour time-weighted average): 0.080 ml/m3 (ppm) or 0.5 mg/m3 (20 C, 1013 hPa). Peak limitation category II,2: Substance with systemic effects, onset of effect within 2 h, half-life 2 h to shift-length; excursion factor = 5 (peak level is 5 x MAK); maximum duration of peaks is 30 minutes, average value; maximum frequency is 2x/shift.
entry date: MAY 2001

title: List of MAK and BAT Values 2000. Maximum Concentrations and Biological Tolerance Values at the Workplace. (MAK- und BAT-Werte-Liste 2000. Maximale Arbeitsplatzkonzentrationen und Biologische Arbeitsstofftoleranzwerte.)
original : MPGFDF, Mitteilung der Senatskommission zur Pruefung gesundheitsschaedlicher Arbeitsstoffe, 36 , , , 2000

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file: 17.01 LEGAL rn : 542511
!!! WARNING - not original IRPTC record - WARNING !!!
systematic name:Phenol, 4-(1,1-dimethylethyl)-
common name :p-tert-butylphenol
reported name :p-tert-Butylphenol
cas no :98-54-4 rtecs no :SJ8925000
area : DEU type : REG

subject	specification	descriptor
AIR	OCC	BAT

Parameter: p-tert-Butylphenol (PTBP). BAT value: 2 mg/l. Assay material: Urine. Sampling time: End of exposure or end of shift. - The BAT value (biological tolerance value for occupational exposures) is defined as the concentration of a substance or its metabolites or the deviation from the norm of biological parameters induced by the substance which generally does not affect the health of the employees adversely.
entry date: JUN 2001 effective date: 01APR2001

title: Technical Regulations for Hazardous Substances (TRGS 903): Biological Tolerance Values for Occupational Exposures. (Technische Regeln fuer Gefahrstoffe (TRGS 903): Biologische Arbeitsplatztoleranzwerte - BAT-Werte -.)
original : BNDSD6, Bundesarbeitsblatt, , 4 , 52 , 2001

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file: 17.01 LEGAL rn : 1322101
systematic name:Phenol, 4-(1,1-dimethylethyl)-

```
common name    :p-tert-butylphenol
reported name  :4-(1,1-Dimethylethyl)phenol
cas no         :98-54-4            rtecs no       :SJ8925000
area          : USA                type          : REG
 ------------------------------
|subject|specification|descriptor|
|-------+-------------+----------|
| CLASS |    PESTI    |   RQR    |
| MANUF |    PESTI    |   PRMT   |
| FOOD  |    ADDIT    |   RQR    |
 ------------------------------
CASE NAME 4-T-BUTYLPHENOL, AND SALTS; Summary - THIS SUBSTANCE IS
INCLUDED ON A LIST OF ACTIVE INGREDIENTS CONTAINED IN A PRODUCT FIRST
REGISTERED BEFORE NOVEMBER 1, 1984, FOR WHICH A REGISTRATION STANDARD
HAS NOT BEEN ISSUED. PUBLICATION OF THIS LIST INITIATES AN ACCELERATED
REREGISTRATION AND DATA C ALL-IN FOR PRODUCTS CONTAINING THE LISTED
ACTIVE INGREDIENTS. IN PARTICULAR THE LIST INCLUDES A NUMBER OF ACTIVE
INGREDIENT CASES HAVING INDIRECT FOOD OR FEED USES.
entry date: JAN 1992                          effective date:      1988

title: FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT PESTICIDES
REQUIRED TO BE REREGISTERED; LIST C.
original : FEREAC, FEDERAL REGISTER, 54 , 140 , 30846 , 1989
amendment: FEREAC, FEDERAL REGISTER, 54 , 140 , 30846 , 1989


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file: 17.01 LEGAL   rn : 1407657
systematic name:Phenol, 4-(1,1-dimethylethyl)-
common name    :p-tert-butylphenol
reported name  :4-tert-Butylphenol
cas no         :98-54-4            rtecs no       :SJ8925000
area          : EEC                type          : REG
 ------------------------------
|subject|specification|descriptor|
|-------+-------------+----------|
| GOODS |    CSMET    |   PRO    |
| GOODS |    CSMET    |   RQR    |
 ------------------------------
THE SUBSTANCE MUST NOT FORM PART OF THE COMPOSITION OF COSMETIC
PRODUCTS. MEMBER STATES SHOULD PROHIBIT THE MARKETING OF COSMETIC
PRODUCTS CONTAINING THE SUBSTANCE.
entry date: SEP 1995                          effective date: 27MCH1978

title: COUNCIL DIRECTIVE OF 27 JULY 1976 ON THE APPROXIMATION OF THE
LAWS OF THE MEMBER STATES RELATING TO COSMETIC PRODUCTS (76/768/EEC)
original : OJEC**, OFFICIAL JOURNAL OF THE EUROPEAN COMMUNITIES, L262 ,
           , 169 , 1976
amendment: OJEC**, OFFICIAL JOURNAL OF THE EUROPEAN COMMUNITIES, L181 ,
           , 31 , 1994


                                *******


file: 17.01 LEGAL   rn : 1408531
systematic name:Phenol, 4-(1,1-dimethylethyl)-
common name    :p-tert-butylphenol
reported name  :4-tert-Butylphenol
cas no         :98-54-4            rtecs no       :SJ8925000
```

area : EEC type : REG

subject	specification	descriptor
FOOD		RQR
GOODS		MXL
GOODS		PRMT

THE SUBSTANCE IS INCLUDED IN THE LIST OF MONOMERS AND OTHER STARTING SUBSTANCES, WHICH MAY CONTINUE TO BE USED FOR THE MANUFACTURE OF PLASTICS AND ARTICLES INTENDED TO COME INTO CONTACT WITH FOODSTUFFS UNTIL 1 JANUARY 1997 PENDING A DECISION ON THEIR INCLUSION IN THE LIST OF AUTHORIZED SUBSTANCES. THE USE OF THE SUBSTANCE IS SUBJECT TO THE RESTRICTIONS SPECIFIED THEREIN. PLASTIC MATERIALS AND ARTICLES SHALL NOT TRANSFER THEIR CONSTITUENTS TO FOODSTUFFS IN QUANTITIES EXCEEDING 10MG/DM2 OF SURFACE AREA OF MATERIAL OR ARTICLE OR 60 MG/KG OF FOODSTUFFS IN THE SPECIFIED CASES. VERIFICATION OF COMPLIANCE WITH THE MIGRATION LIMITS SHALL BE CARRIED OUT IN ACCORDANCE WITH DIRECTIVES 82/711/EEC AND 85/572/EEC.
entry date: SEP 1995 effective date: 01JAN1991

title: COMMISSION DIRECTIVE OF 23 FEBRUARY 1990 RELATING TO PLASTICS MATERIALS AND ARTICLES INTENDED TO COME INTO CONTACT WITH FOODSTUFFS (90/128/EEC)
original : OJEC**, OFFICIAL JOURNAL OF THE EUROPEAN COMMUNITIES, L75 , , 19 , 1990
amendment: OJEC**, OFFICIAL JOURNAL OF THE EUROPEAN COMMUNITIES, L90 , , 26 , 1993

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file: 17.01 LEGAL rn : 1470247
!!! WARNING - not original IRPTC record - WARNING !!!
systematic name:Phenol, 4-(1,1-dimethylethyl)-
common name :p-tert-butylphenol
reported name :4-tert-Butylphenol
cas no :98-54-4 rtecs no :SJ8925000
area : EEC type : REG

subject	specification	descriptor
MANUF	INDST	CLASS
IMPRT	INDST	CLASS

The substance is included in a list of existing substances produced or imported within the Community in quantities exceeding 1000 tonnes per year. - A system of data reporting by any manufacturer who has produced or any importer who has imported the substance, as such or in a preparation, in quanities exceeding 10 tonnes per year is established.
entry date: AUG 1999 effective date: 04JUN1993

title: Council Regulation (EEC) No 793/93 of 23 March 1993 on the evaluation and control of the risks of existing substances
original : OJECFC, Official Journal of the European Communities, L84 , , 1 , 1993