FOREWORD INTRODUCTION

4-HYDROXYBENZOIC ACID

CAS N°: 99-96-7

SIDS Initial Assessment Report
for
9th SIAM

(France, June 29-July 1, 1999)

Chemical Name: 4-Hydroxybenzoic acid
CAS No: 99-96-7
Sponsor Country: Japan

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

HISTORY:

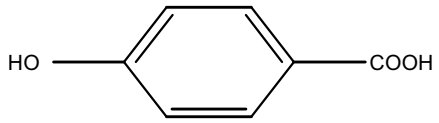
SIDS Testing Plan were reviewed in SIDS Review Process, where the following SIDS Testing Plan was agreed:

no testing ( )
testing (X) Water solubility, Vapour pressure, Octanol/water partition coefficient, Stability in water, Biodegradation

Chronic toxicity to daphnia
Combined repeat dose and reproductive toxicity,
Gene mutation, Chromosomal aberration test in vitro

Deadline for circulation: March 31, 1999
Date of Circulation: March 30, 1999
(To all National SIDS Contact Points and the OECD Secretariat)

SIDS INITIAL ASSESSMENT PROFILE

CAS NO.	99-96-7
CHEMICAL NAME	4-Hydroxybenzoic acid
Structural formula	

RECOMMENDATIONS OF THE SPONSOR COUNTRY

The chemical is currently of low priority for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE RECOMMENDATIONS

4-Hydroxybenzoic acid is readily biodegradable (OECD 301C: 100 % after 28-day), and low bioaccumulative based on Log P_{ow} value (1.37 at 25 °C).

Toxicity of this chemical seems to be relatively low to aquatic organisms because all toxicity data to test organisms belonging to three trophic levels were higher than 32 mg/l. For the algal test (*Selenastrum capricornutum*), 72-h EC_{50}, 72-h NOEC and 96-h EC_{50} are 68.5 mg/l, 32.0 mg/l and 42.8 mg/l, respectively. For testing in daphnids, *Daphnia magna*, both 48-h EC_{50} for immobilisation and 21-day EC_{50} for reproduction were more than 100 mg/l. LC_{50}s of *Oryzias latipes* were >100 mg/l (48 hours), 92.8 mg/l (72 hours) and 92.8 mg/l (72 hours), 14-day LC_{50} was 66.5 mg/l. No data are available for effects on terrestrial organisms.

Oral LD_{50} of 4-hydroxy benzoic acid for rats is more than 2,000 mg/kg. This chemical is considered to be slightly irritating to skin and moderate to eyes, and a mild skin sensitizer. In an OECD combined repeat dose and reproductive/developmental toxicity study in rats at 40, 200 and 1,000 mg/kg/day, this chemical induced rale and rhinorrhea, indicative of imitation to respiratory tract irritation, and small fluctuation of blood chemistry with no changes of histopathological findings and organ weights. These changes of blood chemistry are considered not to be adverse. Therefore, no sign of toxic effects in repeated dose toxcity testing were detected at the highest dose of 1,000 mg/kg/day. Reproductive toxicity was not observed up to the highest test dose of 1000 mg/kg/day, suggesting no reason for concern. This chemical is not genotoxic, based on negative results of bacterial mutation test and chromosomal aberration test *in vitro*. In vaginal cornification and uterotrophic assay of mice, this chemical showed estrogenic response.

It is produced ca. 10,000 tons/year by one company in Japan, and 142 tons (ca. 1.4 %) is wasted through a waste-water treatment plant with a removal rate of 97 % together with 4.4×10^9 L/year effluent into sea. This chemical is used as intermediate for pesticide, antiseptics and pharmaceuticals. No consumer use is reported.

A generic fugacity model (Mackey level III) shows that most (99.5%) of this chemical will be distributed in water phase after discharged into water.

IF FURTHER WORK IS RECOMMENDED, SUMMARISE ITS NATURE

FULL SIDS SUMMARY

CAS NO: 99-96-7		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point			216.2 °C
2.2	Boiling Point			Decomposed
2.3	Density			
2.4	Vapour Pressure		OECD TG 104	3.9×10^{-3} Pa at 100 °C
2.5	Partition Coefficient (Log Pow)		OECD TG 107	1.37
2.6 A.	Water Solubility		OECD TG 105	6 g/l at 25 °C
B.	pH			
	pKa			
2.12	Oxidation: Reduction Potential			
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation			
3.1.2	Stability in Water		OECD TG 111	Stable at pH4,7 and 9 $pK_1 = 4.582$ $pK_2 = 9.23$
3.2	Monitoring Data			
3.3	Transport and Distribution		Calculated (Fugacity Level III type)	Release: 100% to Water In Air 0.0 % In Water 99.5 % In Sediment 0.0 % In Soil 0.5 %
			(local exposure)	9.7×10^{-4} mg/L (Japan)
3.5	Biodegradation		OECD 301C	Readily biodegradable 100% in 28 days
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	*Oryzias latipes*	OECD TG 203	LC_{50} (48hr) = > 100 mg/l LC_{50} (72hr) = 92.8 mg/l LC_{50} (96hr) = 92.8 mg/l LC_{50} (14d) = 66.5 mg/l
4.2	Acute Toxicity to Aquatic Invertebrates *Daphnia*	*Daphnia magna*	OECD TG 202	EC_{50} (48hr): 135.7 mg/l
4.3	Toxicity to Aquatic Plants e.g. Algae	*Selenastrum capricornutum*	OECD TG 201	EC_{50} (72hr) = 68.5 mg/l NOEC = 32 mg/l
4.5.2	Chronic Toxicity to Aquatic Invertebrates (*Daphnia*)	*Daphnia magna*	OECD TG 202	EC_{50} (21d, Repro)= > 100 mg/l NOEC = > 100 mg/l
4.6.1	Toxicity to Soil Dwelling Organisms			None

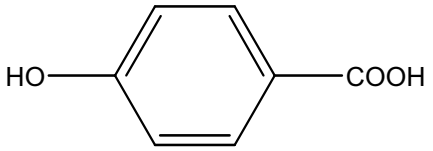
4.6.2	Toxicity to Terrestrial Plants			None
4.6.3	Toxicity to Other Non-Mammalian Terrestrial Species (Including Birds)			None
	TOXICOLOGY			
5.1.1	Acute Oral Toxicity	Rat	Other (unknown)	LD_{50} = 6,000 mg/kg
5.1.2	Acute Inhalation Toxicity			No data
5.1.3	Acute Dermal Toxicity			No data
5.2.1	Skin Irritation/Corrosion	Rabbit	Other (unknown)	Slightly irritating
5.2.2	Eye Irritation/Corrosion	Rabbit	Other (unknown)	Moderate irritating
5.3	Skin Sensitisation	Guinea pig	Guinea pig maximization test	Mildly sensitising
5.4	Repeated Dose Toxicity	Rat	OECD Combined	NOAEL = 1,000 mg/kg/day
5.5	Genetic Toxicity In Vitro			
A.	Bacterial Test (Gene mutation)	*S. typhimurium* *E. coli* WP2	Japanese TG and OECD TG 471 & 472	- (With metabolic activation) - (Without metabolic activation)
B.	Non-Bacterial In Vitro Test (Chromosomal aberrations)	Chinese hamster CHL cells	Japanese TG and OECD TG 473	- (With metabolic activation) - (Without metabolic activation)
5.6	Genetic Toxicity In Vivo			No data
5.8	Toxicity to Reproduction	Rat	OECD combined	NOAEL = 1,000 mg/kg/day
5.9	Developmental Toxicity/ Teratogenicity			No available data
5.11	Experience with Human Exposure			No available data

[Note] Data beyond SIDS requirements can be added if the items are relevant to the assessment of the chemical, e.g. corrosiveness/irritation, carcinogenicity.

SIDS INITIAL ASSESSMENT REPORT

1. IDENTITY

- OECD Name: 4-Hydroxybenzoic acid
- Synonym: 4-Hydroxybenzenecarboxylic acid
- CAS Number: 99-96-7
- Empirical Formula: $C_7H_6O_3$
- Structural Formula:



- Degree of Purity: 99.7%
- Major Impurity: None
- Essential Additives: None
- Physical-chemical properties
  - Melting Point: 216.2 °C
  - Vapour pressure: 3.9×10^{-3} Pa at 100 °C
  - Water solubility: 6,000 mg/L
  - Log Pow: 1.37

2. GENERAL INFORMATION ON EXPOSURE

2.1 Production and import

The production volume of 4-hydroxybenzoic acid in Japan is 10,000 tonnes/year in 1995.

2.2 Use pattern

All of 4-hydroxybenzoic acid produced in Japan are used as a monomer unit of polymer and as an intermediate of pesticide and antiseptics, and no consumer use is reported.

2.3 Other information

None

3. ENVIRONMENT

3.1 Environmental Exposure

3.1.1 General Discussion

4-Hydroxybenzoic acid is readily biodegradable (OECD 301C: 100 % after 28d). Although direct photodegradation is expected because 4-hydroxybenzoic acid has absorption band in UV and VIS region, the data of half-lifetime is not available.

4-Hydroxybenzoic acid is low bioaccumulative based on Log Pow (1.37 at 25 °C).

The potential environmental distributions of 4-hydroxybenzoic acid obtained from a generic Mackay level III fugacity model is shown in Table 1. Parameters used for this model are shown as Annex to this report. The results show that, if 4-hydroxybenzoic acid is released into water, it is unlikely to be distributed into other compartments. If 4-hydroxybenzoic acid is released into air or soil, it is likely to be distributed in other compartments.

Table 1
Environmental distribution of 4-hydroxybenzoic acid
Using a generic level III fugacity model.

Compartment	Release 100% to air	Release 100% to water	Release 100% to soil
Air	0.0 %	0.0 %	0.0 %
Water	28.5 %	99.5 %	23.3 %
Soil	71.4 %	0.0 %	76.6 %
Sediment	0.1 %	0.5 %	0.1 %

As this chemical is used in closed system as a monomer unit of polymer or an intermediate of pesticide, and is not included in consumer products, its release to the environment may occur only from the production site.

3.1.2 Predicted Environmental Concentration

As 4-hydroxybenzoic acid is produced under the well-controlled closed system, amount of release to air phase is negligibly small. The waste of 4-hydroxybenzoic acid from the production system is released to water phase after treated its own wastewater treatment plant. Therefore, Predicted Environmental Concentration (PEC) will be calculated only for the water environment.

a. Regional exposure

According to report from a Japanese manufacturer, 142 tonnes/year (measured) of 4-hydroxybenzoic acid are treated in its own wastewater treatment plant with 97% of removal rate (Plant 1:80%, Plant 2:85%) and released with 4.4 x 10^9 L/year of effluent into sea. Local Predicted Environmental Concentration (PEC_{local}) is calculated to be 9.7 x 10^{-4} mg/L as a worst case scenario, employing the following calculation model and dilution factor of 1000 (default).

$$\frac{\text{Amount of release } (1.42 \times 10^{11} \text{ mg/y}) \times (1 - \text{Removal rate } (97\ \%))}{\text{Volume of effluent } (4.4 \times 10^{9} \text{ L/y}) \times \text{Dilution Factor } (1000)}$$

A. Effects on the Environments

3.2.1 Effects on aquatic organisms

Acute and chronic toxicity data of 4-hydroxybenzoic acid to test organisms are summarized below (Table 2). Toxicity of this chemical to aquatic organisms seems relatively low, because NOEC values of *Selenastrum* and *Oryzias latipes* are 32.0 mg/l and 66.5 mg/l, respectively. PNEC of this chemical was determined mainly based on the toxicity data obtained by the Environment Agency of Japan through a GLP-laboratory. Concentrations of the chemical were

kept at the levels of 84 to 105 % of the nominal concentrations in all toxicity tests. Several data by different organizations were available in the AQUIRE and IUCLID. As the lowest acute and chronic toxicity data, 14d LC_{50} of fish and NOEC of algae were adopted, respectively (Table 2).

The assessment factors of 100 were used to both acute and chronic toxicity data to determine PNEC, according to the OECD Provisional Guidance for Initial Assessment of Aquatic Effects (EXCH/MANUAL/96-4-5.DOC/May 1996), because chronic toxicity data for fish was absent.

From acute toxicity data (14d LC_{50} of fish):

PNEC = 66.5/100 = 0.665 mg/l

From chronic toxicity data (72h NOEC of algae):

PNEC = 32.0/100 = 0.32 mg/l

Thus, PNEC of 4-hydroxybenzoic acid is 0.32 mg/l.

Table 2
Acute and chronic toxicity data of 4-hydroxybenzoic acid to aquatic organisms at different trophic levels. The data were obtained by the Environmental Agency of Japan based on the OECD Test Guide Lines and GLP.

Species	Endpoint	Conc. (mg/l)	Remarks
Selenastrum capricornutum (algae)	Bms 72 h EC50	68.5	A, 1)
	Bms 72 h NOEC	32.0	C, 1), C
Chlorella pyrenoidosa (algae)	Bms 96 h EC50	42.8	a, 2), A
Daphnia magna (Water flea)	Imm 48 h EC50	135.7	a, 1), A
	Rep 21 d EC50	> 100	c, 1)
	Rep 21 d NOEC	> 100	c, 1), C
Daphnia magna	Imm 48 h EC50	173.0	a, 3)
Oryzias latipes (fish, Medaka)	Mor 48h LC50	> 100	a, 1)
	Mor 72h LC50	92.8	a, 1)
	Mor 96h LC50	92.8	a, 1)
	Mor 14d LC50	66.5	a, 1), A
Oncorhynchus mykiss (Rainbow trout)	Mor 96h LC50	> 99.4	a, 4)

Notes: Bms; biomass, Mor; mortality, Rep; reproduction
A), C); the lowest values among the acute or chronic toxicity data of algae, cladocera (water flea) and fishes to determine PNEC of 4-hydroxybenzoic acid.

References in Table 2: (1) Toxicity tests were conducted by the Environment Agency of Japan based on OECD Test GuideLines and GLP; (2) Larson, L.J. (1991); (3) Kuhn, R., Pattard, M., Pernak, K., and Winter, A. (1989); (4) Hodson, P.V., and Kaiser, K.L. (1984)

3.2.2 Terrestrial effects

No data available

3.2.3 Other effects

No data available

3.3 Initial Assessment for the Environment

Predicted No Effect Concentration (PNEC) of this chemical has been calculated as 0.32 mg/l.

PEC from Japanese local exposure scenario is 9.7×10^{-4} mg/l.

Thus, PEC_{local} / PNEC = 9.7×10^{-4}/ 0.32 = 0.003 < 1

Therefore, it is currently considered of low potential risk for environments and low priority for further work.

4. HUMAN HEALTH

4.1 Human Exposure

4.1.1 Occupational exposure

4-Hydroxybenzoic acid is produced in closed systems and used as an intermediate for agricultural chemical synthesis and antiseptics. The occupational exposures are expected through inhalation and the dermal route is assumed negligible because this chemical is solid. As the atmospheric concentration in plant was not measured, the maximum exposure levels are estimated according to working schedules as follows. If a single worker (body weight; 70 kg, respiratory volume; 1.25 m^3/hr) is assigned to implement these two bag filling operations without protection, the highest daily intake (combined EHE) is calculated as 0.067 mg/kg/day as the worst cases. Practically, workers always wear protective gloves and respiratory protective equipment (mask) during the operation.

	Frequency Times/day	Duration hr	Working hr/day	Concentration mg/m^3	EHE mg/kg/day	Combined EHE mg/kg/day
Bag Filling	0.44	2	0.88	2.99	0.04700	
Bag Filling	0.058	6.6	0.38	2.99	0.02000	0.067

EHE: Estimated Human Exposure

4.1.2 Consumer exposure

As all of 4-hydroxybenzoic acid produced in Japan are used as a monomer unit of polymer and as an intermediate of pesticide, and no consumer use is reported in Sponsor country, consumer exposure is not expected.

4.1.3 Indirect exposure via the environment

Although 4-hydroxybenzoic acid is readily biodegradable and low 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.

The concentration in drinking water should be estimated to be equal to PEC calculated in Section 3.1, i.e. 9.7 x 10^{-4} mg/l. The daily intake through drinking water is calculated as 3.23 x 10^{-5} mg/kg/day (2 l/day, 60 kg b.w.).

Using the bioconcentration factor of 5.0 estimated from log Pow (1.37), the concentration of this chemical in fish can be calculated as follows:

$$PEC_{fish} = (9.70 \times 10^{-4} \text{ mg/l}) \times 5.0 = 4.85 \times 10^{-6} \text{ mg/g-wet}$$

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 7.28 x 10^{-6} mg/kg/day.

4.2 Effects on Human Health

a) Acute toxicity

[SIDS data] The oral LD_{50} value for 4-hydroxybenzoic acid was 6,000 mg/kg for rats (Ueno Pharm. Inc.).

In another oral study, the LD_{50} value was 2,200 mg/kg for mice (Drug Standards: 1952).

The intraperitoneal LD_{50} value was 340 and 210 mg/kg for rats (Gigiena i Sanitariya: 1986) and mice (J Am Pharm Assoc, Sci Ed: 1956), respectively. Muscle weakness was observed in rats and flaccid paralysis without anesthesia (usually neuromuscular blockage), somnolence (general depressed activity), and ataxia were observed in mice.

The subcutaneous LD_{50} was 1,050 mg/kg for mice (Arch Intl Pharmacodyn Ther: 1960).

b) Irritation

4-Hydroxybenzoic acid was reported to be slightly irritating to skin and moderate to eyes in Bayer Report (1980a,b).

This chemical (500 mg) was applied to the clipped skin with occlusive dressing for 24 hours. Erythema and edema were observed but these changes were very weak. Erythema was reversible within 8 days but edema was not.

As for eye irritation, this chemical (100 µg) was applied to conjunctivae under the right eyelid. Corneal opacity, conjunctival redness, and chemosis were observed. These signs of irritation were not reversible within 8 days.

Based on these observations, this chemical is considered to be slightly irritating to skin and moderate to eyes.

c) Sensitisation

4-Hydroxybenzoic acid was reported as a mild sensitizer by guinea pig maximization test (Scholes *et al.*; 1992). In this test, 10 animals (4 animals in control group) were induced intradermally at 1.0 % and topically at 20 % six to eight days later. After 12-14 days, all animals were challenged by 20 %. The sensitization potential was 20 % (the percentage of animals exhibiting a reaction significantly greater than control animals).

On the other hand, the local lymph node assay in mice showed that this chemical was not a sensitizer (Scholes *et al.*; 1992). In this assay, 4 animals were inducted by daily topical application of 2.5 – 15.0 % for three consecutive days. Five days after the initiation of exposure, [^{3}H] methyl thymidine was injected and the labeling in lymph node cells was measured. The ratio of labeling incorporation by tested lymph node cells to that recorded for control lymph node cells, (T/C) ratio was 0.6 – 1.5 (more than 3.0 is positive).

d) Repeated toxicity

[SIDS data] Oral toxicity study was performed in SD (Crj: CD) rats by an OECD combined repeat dose and reproductive/developmental toxicity screening test. 4-Hydroxybenzoic acid was administered by gavage at doses of 40, 200 and 1,000 mg/kg for 45 days in males and from 14 days before mating to day 3 of lactation in females. (MHW, Japan: 1997)

All animals survived at all treated groups. 4-Hydroxybenzoic acid induced rale and temporary salivation (sometimes accompanied by rhinorrhea) at 1,000 mg/kg and slightly at 200 mg/kg. These changes were suggesting the irritation of this chemical to respiratory tract. There were no adverse effects on body weight change and food consumption. At necropsy, no histological and morphological changes were observed. In hematological and blood chemical findings of males, decrease in the percentage of lymphocytes and the blood glucose at 200 mg/kg or more groups and decrease in total protein and increase in A/G ratio, GPT and GOT at 1,000 mg/kg were observed. These changes were significant, but not considered adverse effects. Therefore, NOAEL for systemic toxicity was considered to be 1,000 mg/kg/day.

e) Reproductive/developmental toxicity

Reproductive toxicity

[SIDS data] Oral toxicity study was performed in SD (Crj: CD) rats by an OECD combined repeated dose and reproductive/developmental toxicity screening test. 4-Hydroxybenzoic acid was administered by gavage at doses of 40, 200 and 1,000 mg/kg for 45 days in males and from 14 days before mating to day 3 of lactation in females. (MHW, Japan: 1997)

4-Hydroxybenzoic acid showed no adverse effects on copulation, fertility, maintenance of pregnancy, parturition and lactation, as well as viability, sex ratio, body weights and morphological appearance of pups at all treated groups. The NOAEL of reproductive toxicity for parents and offsprings was considered to be 1,000 mg/kg/day.

Developmental toxicity

Single oral toxicity study (day 11 of gestation) was performed in Sprague-Dawley rats at doses of 333, 667, 1,000 mg/kg. 4-Hydroxybenzoic acid showed no maternal toxicity, including death and change in body weight gain at 24 and 72 hours after treatment. In addition, no developmental toxicity was observed, including change in litter size, pup weight, and total litter weight at 1 and 6 days after birth, and overt malformation. Therefore, NOAEL was considered to be 1,000 mg/kg. (Kavlock *et al.*: 1990)

Some other developmental toxicity studies by a single administration were performed. No teratogenic effect was observed after subcutaneous application to rats at day 9 of gestation or intramuscular application to mice at day 9 or 12 of gestation (Details were not clear, Larsson and Bostrom: 1965, Koshakji and Scheulert: 1973).

However, any above experiments does not fully support no developmental toxicity of 4-hydroxybenzoic acid, because the exposure conditions were not suitable as the developmental toxicity study.

There was a data on developmental toxicity of ethylparaben (102-47-8). This chemical was shown to hydrolyse to 4-hydroxybenzoic acid rapidly in liver and kidney tissue taken from dogs (Jones *et al.*: 1956) and almost completely after intravenous injection or injected directly into the small intestine in rats (Kiwada et al: 1979 & 1980). In this study, a diet containing 0.1, 1 or 10 % ethylparaben (around 60, 540 and 2800 mg/kg/day) was given to rats on days 8 – 15 of pregnancy. In the 10 % group, some fetuses showed low body weight, and there were some instances of malformations of bones and viscera. However, these changes were considered due to malnutrition of dams. Neonatal growth curves showed no abnormal trends. No signs of teratogenicity were observed in fetuses. (Moriyama *et al*: 1975)

f) Genetic toxicity

Bacterial test

[SIDS data] Gene reverse mutation was negative in *S. Typhimurium* TA100, TA98, TA1535, TA1537 and *E.coli* WP2 *uvr*A with and without metabolic activation (MHW, Japan: 1997).

Non-bacterial test *in vitro*

[SIDS data] Chromosomal aberration test was conducted at concentrations of 0, 0.18, 0.35, 0.70 mg/ml with and without metabolic activation in cultured Chinese hamster lung (CHL/IU) cells. 4-Hydroxybenzoic acid induced structural chromosomal aberrations at 0.70 mg/ml with short-term treatment with metabolic activation and with continuous treatment. Polyploidy was also induced at 0.70 mg/ml with 48 hr continuous treatment, and at 0.70 and 0.18 mg/ml with short-term treatment with metabolic activation. Since this chemical decreased pH in the medium, a confirmation test was conducted under pH-adjusted conditions. As a result, no chromosomal aberrations were observed. As the further study, micronucleus in those cells under the same exposure condition was analysed. Although sufficient increase in micronucleus (Type 2: typical micronucleus) was observed, occurrence was low (1.9 %) and other micronucleus was not observed. Therefore, it was suggested that chromosomal aberrations induced by this chemical were not caused by the direct effects on DNA. (MHW. Japan: 1997)

Based on these results, 4-hydroxybenzoic acid was considered not to be genotoxic.

g) Specific toxicity

It is reported that various phenyl and phenolic acids inhibit the incorporation of mevalonate into cholesterol by homogenates of rat liver and of rat brain. In order to find the specificity and mechanism of this inhibition, a study on various phenyl and phenolic acids was conducted with homogenate of rat liver. As a result, 4-hydroxybenzoic acid competed with the substrate mevalonate 5-pyrophosphate, and inhibited mevalonate pyrophosphate decarboxylase. And this chemical also inhibited mevalonate phosphate kinase. (Shama Bhat and Ramasarma: 1979) However, since no change in cholesterol level was observed in all toxicity studies, this result is considered not to be important for toxicity of this chemical.

Estrogenic effect of 4-hydroxybenzoic acid was examined in vaginal cornification and uterotrrophic assay (Lemini *et al.*: 1997). Immature intact and adult ovariectomized female mice (CD1) were treated subcutaneously daily for 3 days with vehicle (corn oil, 0.3 ml/100 g), E2 (1 μg/100 g), and 4-hydroxybenzoic acid (0.5, 5, 50, and 500 μg/100 g).

Four days after treatment, a dose-dependent response on vaginal cornification and uterotrophic activity was observed in both immature intact and adult ovariectomized mice treated with this chemical. The relative uterotrophic potency of this chemical (500 µg/100 g) to estradiol (1 µg m/100 g) was 0.0011 in immature and 0.0018 in ovarectomized animals.

h) Toxicokinetics

Toxicokinetics study was performed in Fischer 344 female rats (29 days old) to examine the disposition of 4-hydroxybenzoic acid 120 hr after i.p. (2.5 µg, approx. 1 µCi) and dermal (5 µg, 3.9 µg/cm^2, approx. 2 µCi) administration (Hughes and Hall: 1997). Urinary excretion was the predominant means of elimination and occurred primarily within 24 hr after i.p. and dermal administration. The 120 hr cumulative excretion after i.p. administration was 86.5 % in urine and 3.4 % in faeces, and 10.2 % was detected in the carcasses of treated animals. The dermal absorption was very low (2 %). The major portion of the dose not absorbed dermally in 24 hr was washed from the skin. The 120 hr cumulative excretion after dermal administration was 1.9 % in urine and 0.04 % in faeces. 2 % and 0.28 % was detected in the treated skin and the carcasses of treated animals, respectively. In this study, the skin irritation did not occur because of very small amount application to skin.

i) Experience with human exposure

Occupational exposure to airborne epichlorohydrin (0.9-1.5 mg/m^3), toluene (1.3-2.13 mg/m^3), and diphenylolpropane, 4-hydroxybenzoic acid, N-glycidyl-m-aminobenzoic acid, and isophthalic acid (2-5 mg/m^3) at the manufacture of epoxy resins induced contact and allergic dermatitis and sensitization to bacterial and chemical allergens. However, any further detailed information is not given. (Chernykh and Savchenko: 1988)

4.3 Initial Assessment for Human Health

Oral LD_{50} of 4-hydroxy benzoic acid for rats is more than 2,000 mg/kg. This chemical is considered to be slightly irritating to skin and moderate to eyes, and a mild skin sensitizer. In an OECD combined repeat dose and reproductive/developmental toxicity study in rats at 40, 200 and 1,000 mg/kg/day, this chemical induced rale and rhinorrhea, indicative of imitation to respiratory tract irritation, and small fluctuation of blood chemistry with no changes of histopathological findings and organ weights. As these changes of blood chemistry are considered not to be adverse, NOAEL for systemic toxicity is 1,000 mg/kg/day. Reproductive toxicity was not observed (NOAEL = 1,000 mg/kg/day). This chemical is not genotoxic, based on negative results of bacterial mutation test and chromosomal aberration test *in vitro*. In vaginal cornification and uterotrophic assay of mice, this chemical showed estrogenic response *in vivo*.

Occupational exposure

4-Hydroxybenzoic acid is used in a closed system at industries. Although the occupational exposure route is expected as an inhalation in limited workers, there is no available data of the atmosphere concentration. Based on the predicted high concentration and the possibility of exposure period, the daily intake is calculated as 0.067 mg/kg/day as the worst cases. Occupational risk is presumably low because the margin of safety is 1.49 x 10^4. Although this chemical is considered as an irritant for the skin and eyes, and a skin sensitizer, the risk is probably low because workers wear protective gloves and respiratory protective equipment (mask) during the operation.

Consumer exposure
No consumer exposure is expected because of use pattern.

Indirect exposure via environment
As for indirect exposure via environment, PEC_{local} of 9.70 x 10^{-4} mg/l from local exposure scenario was used for the estimation. The daily intakes through drinking water and fish are calculated as 3.23 x 10^{-5} mg/kg/day and 7.28 x 10^{-6} mg/kg/day, respectively. Since the margin of safety is very large, such as 3.09 x 10^{7} for drinking water and 1.37 x 10^{8} for fish, health risk is presumably low.

5. CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

4-Hydroxybenzoic acid is readily biodegradable (OECD 301C: 100 % after 28-d) and low bioaccumulative judging from a relative low Pow value (1.37 at 25 °C). Toxicity of this chemical seems relatively low to aquatic organisms because all toxicity data to test organisms belonging to three trophic levels are higher than 32 mg/l. PEC/PNEC ratio is less than 1 based on the local exposure scenario in the Sponsor country. It is currently considered of low potential risk for the environment and low priority for further work.

4-Hydroxybenzoic acid showed no systemic and reproductive toxicity in an OECD combined repeat dose and reproductive/developmental toxicity study. This chemical is not genotoxic and considered to be slightly irritating to skin and moderate to eyes, and a mild skin sensitizer. The margin of safety for occupational and indirect exposure is calculated as 1.49 x 10^{4} and 3.09 x 10^{7} or 1.37 x 10^{8} (through drinking water or fish), respectively. Therefore, it is currently considered of low potential human risk and low priority for further work.

5.2 Recommendations

No recommendation

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Appendix 1

Method for Prediction of Environmental Concentration of Pollutant in Surface Water

1. Predicted environmental concentration in the local environment (PEC_{local}) with effluent release into river

When decomposition, precipitation and vaporization of pollutant can be ignored, it is used that simplified equation by complete mixing model shown with equation (1) to calculate predicted environmental concentration in the local environment (PEC_{local}) as for release effluent into river.

$$PEC_{local}\ (mg/L) = \frac{Co\ Q + Cs\ Qs}{Q + Qs} \qquad (1)$$

Where

Co: Concentration of pollutant in upper stream of release point (mg/L)
Cs: Concentration of pollutant in effluent (mg/L)
Q: Flow rate of river (m^3/day)
Qs: Flow rate of effluent released into river (m^3/ day)

At the equation (1), when Co can be considered as 0, dilution factor of pollutant in the river (R) can be shown with following equation.

$$R = Cs/C = (Q + Qs) / Qs \qquad (2)$$

As the worst case, it is used to employ a flow rate at dry season as flow rate of river (Q). When flow rate at dry season is indistinct, it is estimated using the following equation in Japan.

$$\text{Flow rate at dry season} = \text{mean flow late} / 2.5 \qquad (3)$$

2. Predicted environmental concentration in the local environment (PEC_{local}) with effluent release into sea

For prediction of concentration of pollutant in the sea water with effluent, it is employed generally Joseph-Sendnersymbol 146 ¥f ″Times New Roman″ ¥s 11'}s equation (4). This equation is one of analytic solution led under the following conditions from diffusion equation.

1 It is adopted large area of sea or lake.
2 The flow rate of effluent and concentration of pollutant in the effluent are constant, and distribution of concentration is able to regard as equilibrium state.
3 Effluent is distributed uniformly to vertical direction, and it spreads in a semicircle or segment to horizontal direction.
4 Diffusion coefficient of pollutant at the sea is in proportion to distance from release point of effluent.
5 There is not any effect of tidal current.
6 Decomposition of pollutant can be ignored.

$$C(x) = (C_s - C(r))\left(1 - \exp\left(-\frac{Q_s}{d\,p}\left(\frac{1}{x} - \frac{1}{r}\right)\right)\right) + C(r) \qquad (4)$$

Where

C (x): Concentration of pollutant at distance x (m) from release point
Cs: Concentration of pollutant in effluent
C (r): Concentration of pollutant at distance r (m) from release point
Qs: Flow rate of effluent (m^3/day)
: Opening angle of seacoast (rad.)
d: Thickness of diffusion layer (m)
P: Diffusion velocity (m/day) (1.0 0.5 cm/sec)

When C(x) is 0 at r = and density stratification is ignored for simplification, Joseph-Sendnersymbol 146 ¥f ″Times New Roman″ ¥s 11'}s equation (4) is simplified to equation (5)

$$C(x) = C_s\left(1 - \exp\left(-\frac{Q_s}{d\,p\,x}\right)\right) \qquad (5)$$

Because of Qs/ d p x << 1 except vicinity of release point, dilution factor in distance x from release point R(x) can be shown with equation (6).

$$R(x) = C_s/C(x) = d\,p\,x/Q_s \qquad (6)$$

When it is employed following parameters in equation (6) as default, dilution factor R can be shown with equation (7).

P = 1 cm/sec (860 m/day)
= 3.14
d = 10 m
x = 1000 m

$$R = 2.7\ 10^7/Q_s \qquad (7)$$

Qs: volume of effluent (m^3/day)

REVISED OECD HPV FORM 1

SIDS DOSSIER
ON THE HPV PHASE 5 CHEMICAL

4-Hydroxybenzoic acid

CAS No. 99-96-7

Sponsor Country: Japan

DATE: March 15, 1999

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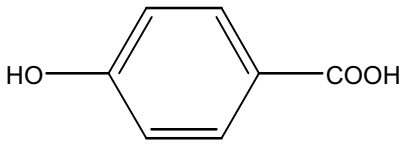
Appendix

Note: *; Data Elements In The Sids
†; Data Elements Specially Required For Inorganic Chemicals

S I D S P R O F I L E

1.01 A.	**CAS No.**	99-96-7
1.01 C.	**CHEMICAL NAME (OECD Name)**	4-Hydroxybenzoic acid
1.01 D.	**CAS DESCRIPTOR**	
1.01 G.	**STRUCTURAL FORMULA**	
	OTHER CHEMICAL IDENTITY INFORMATION	
1.5	**QUANTITY**	10,000 tonnes/year in Japan
1.7	**USE PATTERN**	Intermediate for pesticides and preservatives in closed system.
1.9	**SOURCES AND LEVELS OF EXPOSURE**	142 tonnes/year Release into Bay
ISSUES FOR DISCUSSION (IDENTIFY, IF ANY)	SIDS testing required: Water solubility, Vapour pressure, Octanol/water partition coefficient, Stability in water, Biodegradation Combined repeat dose and reproductive toxicity, Gene mutation, Chromosomal aberration test in vitro	

S I D S S U M M A R Y

CAS NO: 99-96-7		Information	OECD Study	GLP	Other Study	Estimation Method	Acceptable	SIDS Testing Required
STUDY		**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**
PHYSICAL-CHEMICAL DATA								
2.1	Melting Point	Y	N	N	Y	N	Y	N
2.2	Boiling Point	Y	N	N	Y	N	Y	N
2.3	Density	N						N
2.4	Vapour Pressure	N						Y
2.5	Partition Coefficient	N						Y
2.6	Water Solubility	N						Y
	pH and pKa values	N						N
2.12	Oxidation: Reduction potential	N						N
OTHER P/C STUDIES RECEIVED								
ENVIRONMENTAL FATE and PATHWAY								
3.1.1	Photodegradation	N						N
3.1.2	Stability in water	N						Y
3.2	Monitoring data	N						N
3.3	Transport and Distribution	N						N
3.5	Biodegradation	N						Y
OTHER ENV FATE STUDIES RECEIVED								
ECOTOXICITY								
4.1	Acute toxicity to Fish	Y	N	N	Y	N	N	Y
4.2	Acute toxicity to Daphnia	Y	N	N	Y	N	N	Y
4.3	Toxicity to Algae	Y	N	N	Y	N	N	Y
4.5.2	Chronic toxicity to Daphnia	N						Y
4.6.1	Toxicity to Soil dwelling organisms	N						N
4.6.2	Toxicity to Terrestrial plants	N						N
4.6.3	Toxicity to Birds	N						N
OTHER ECOTOXICITY STUDIES RECEIVED								
TOXICITY								
5.1.1	Acute Oral	Y	N	N	Y	N	Y	N
5.1.2	Acute Inhalation	N						N
5.1.3	Acute Dermal	N						N
5.4	Repeated Dose	N						Y
5.5	Genetic Toxicity *in vitro*							
	. Gene mutation	N						Y
	. Chromosomal aberration	N						Y
5.6	Genetic Toxicity *in vivo*	N						N
5.8	Reproduction Toxicity	N						Y
5.9	Development / Teratogenicity	Y	N	N	N	N	Y	N
5.11	Human experience	Y	N	N	N	N	Y	N
OTHER TOXICITY STUDIES RECEIVED								

1. GENERAL INFORMATION

1.01 SUBSTANCE INFORMATION

***A. CAS number** 99-96-7

B. Name *(IUPAC name)*

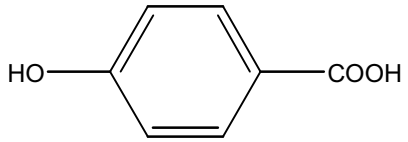
***C. Name** *(OECD name)* 4-Hydroxybenzoic acid

†D. CAS Descriptor

E. EINECS-Number 202-804-9

F. Molecular Formula $C_7H_6O_3$

***G. Structural Formula**



H. Substance Group

I. Substance Remark

J. Molecular Weight 138.13

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)
Environmental Agency (EA)
Ministry of Labour (MOL)

Contact person: Mr. Kazuhide Ishikawa
Economic International Bureau
Second International Organisation Division
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 99.7%

1.2 SYNONYMS 4-Hydroxybenzenecarboxylic acid

1.3 IMPURITIES

None

1.4 ADDITIVES

None

***1.5 QUANTITY**

Remarks: 4,044 tonnes/year
Reference: MITI, Japan

1.6 LABELLING AND CLASSIFICATION

None

***1.7 USE PATTERN**

A. General

Type of Use:	**Category:**
main industrial use	Intermediate Intermediate in closed system Intermediate for pesticides and preservatives

Remarks: None
Reference: MITI, Japan

1.8 OCCUPATIONAL EXPOSURE LIMIT

None

*** 1.9 SOURCES OF EXPOSURE**

In Japan, 4-hydroxybenzoic acid is produced in 1 company.

Source:	Media of release: Bay
	Quantities per media: 142 tonnes/year
Remarks:	
Reference:	MITI, Japan

2. PHYSICAL-CHEMICAL DATA

*2.1 MELTING POINT

Value:	216.2 °C
Decomposition:	Yes **[ ]** No **[X]** Ambiguous **[ ]**
Sublimation:	Yes **[ ]** No **[X]** Ambiguous **[ ]**
Method:	
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Remarks:	
Reference:	Company data

*2.2 BOILING POINT

Value:	Decompose
Pressure:	
Decomposition:	Yes **[X]** No **[ ]** Ambiguous **[ ]**
Method:	
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Remarks:	
Reference:	Company data

*2.4 VAPOUR PRESSURE

Value:	< 3.9 x 10^{-3} Pa
Temperature:	100 °C
Method:	calculated **[ ]**; measured **[X]**
	OECD TG 104
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	purity: 99.9 %
Remarks:	
Reference:	MITI, Japan

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

Log Pow:	1.37
Temperature:	25 °C
Method:	calculated **[ ]**; measured **[X]**
	OECD TG 107
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	purity: 99.9 %
Remarks:	
Reference:	MITI, Japan.

*2.6 WATER SOLUBILITY

A. Solubility

Value:	6.0 g/L
Temperature:	25 °C
Description:	Miscible **[ ]**; Of very high solubility **[ ]**; Soluble **[ ]**; Slightly soluble**[X]**; Of low solubility **[ ]**; Of very low solubility **[ ]**; Not soluble **[ ]**
Method:	OECD TG 105
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	purity: 99.9 %
Remarks:	
Reference:	MITI, Japan.

B. pH Value, pKa Value

Value:	pK1 = 4.582 pK2 = 9.23
Reference:	Lang's Handbook of Chemistry (13th Edition)

3. ENVIRONMENTAL FATE AND PATHWAYS

3.1 STABILITY

*3.1.2 STABILITY IN WATER

Type:	Abiotic (hydrolysis) **[X]**; biotic (sediment)**[ ]**
Half life:	Stable at pH 4, 7, 9 at 25 °C
Method:	OECD TG 111
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	purity: 99.9 %
Remarks:	
Reference:	MITI, Japan

*3.2 MONITORING DATA (ENVIRONMENTAL)

No studies located

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

*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	0.0 %	0.0 %	0.0 %
Water	28.5 %	99.5 %	23.3 %
Soil	71.4 %	0.0 %	76.6 %
Sediment	0.1 %	0.5 %	0.1 %

Remarks: Appendix 1
Reference: MITI, Japan

*3.5 BIODEGRADATION

Type: aerobic **[X]**; anaerobic **[ ]**
Inoculum: adapted **[ ]**; non-adapted **[X]**;
Concentration of the chemical: related to COD **[ ]**; DOC **[ ]**; test substance **[X]**
Medium: water **[X];** water-sediment **[ ];** soil **[ ];** sewage treatment **[ ]**
Degradation: 90 % by BOD after 14 days
100 % by TOC after 14 days
100 % by GC after 14 days
Results: readily biodeg. **[X];** inherently biodeg. **[ ]**; under test condition no biodegradation observed **[ ]**, other **[ ]**
Method: OECD TG 301C
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: purity: 99.9 %
Reference: MITI, Japan

4. ECOTOXICITY

*4.1 ACUTE/PROLONGED TOXICITY TO FISH

(a) Type of test: static **[ ]**; semi-static **[ ]**; flow-through **[X]**; other *(e.g. field test)* **[ ]** open-system **[X]**; closed-system **[ ]**
Species: *Oryzias latipes* (Himedaka)
Exposure period: 96 h
Results: LC_{50} (96 h) = 92.8 mg/l
Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**
Method: OECD TG 203 (1992)
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: As prescribed by 1.1 - 1.4, purity: > 95 %
Remarks: Groups of ten Himedaka were exposed to the nominal concentrations of 30.9, 55.6 and 100 mg/l, and laboratory water control. No solubilizer was used. Concentrations of the chemical were kept within ± 20% changes from the nominal concentrations throughout the test period.
Reference: Environment Agency of Japan (1995)

(b) Type of test: static **[ ]**; semi-static **[ ]**; flow-through **[X]**; other *(e.g. field test)* **[ ]** open-system **[X]**; closed-system **[ ]**
Species: *Poecilia reticulata* (Guppy)
Exposure period: 14 d
Results: LC_{50} (14d) = 66.5 mg/l
Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**
Method: No data
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: As prescribed by 1.1 - 1.4, purity: > 95 %
Remarks: Groups of ten Himedaka were exposed to the nominal concentrations of 9.5, 17.1, 30.9, 55.6 and 100 mg/l, and laboratory water control. No solubilizer was used. Concentrations of the chemical were kept within ± 20% changes from the nominal concentrations throughout the test period. Toxicity data was calculated based on nominal concentrations.
Reference: Environment Agency of Japan (1995)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

*A. Daphnia

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} (48 h) = 135.7 mg/l
Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**
Method: OECD TG 202
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: As prescribed by 1.1 - 1.4, purity: > 95 %
Remarks: 20 daphnids (4 replicates of 5 organisms) were exposed to nominal concentrations of 26, 42, 67, 107, 172 and 275 mg/l, and laboratory water control (M4-medium). The measured concentrations were within 95.0 to 99.7% of the nominal concentrations throughout the test period. No solubilizer was used.
Reference: Environment Agency of Japan (1995)

*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 *(Endpoint)* EC_{50} (72h) = 68.5 mg/l; NOEC = 32 mg/l
Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**
Method: OECD TG 201 (1984)
open-system **[X]**; closed-system **[ ]**
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: As prescribed by 1.1 - 1.4, purity: > 95 %

Remarks:	Static test. The EC_{50} value for growth rate (% inhibition) was calculated based on 5 nominal concentrations (20, 32, 51, 82, 131 and 210 mg/l). No solubilizer was used. Measured concentrations were within 98.5 to 101.3 of the nominal concentrations after 3 days test period.
Reference:	Environment Agency of Japan (1995)

4.4 TOXICITY TO BACTERIA

No data

4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS

4.5.1 CHRONIC TOXICITY TO FISH

No data

(*) 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): > 100 mg/l *(Endpoint)* NOEC: > 100 mg/l
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**
Method:	OECD TG 202(1984)
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	As prescribed by 1.1 - 1.4, purity: > 95 %
Remarks:	40 daphnids (4 replicates of 10 daphnids) were exposed to the nominal concentrations of 100 mg/l and laboratory water control (M4-medium). No solubilizer used.
Reference:	Environment Agency of Japan (1995)

4.6 TOXICITY TO TERRESTRIAL ORGANISMS

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

No data

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

No data

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

No data

4.7 BIOLOGICAL EFFECTS MONITORING (INCLUDING BIOMAGNIFICATION)

No data

4.8 BIOTRANSFORMATION AND KINETICS

No data

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: Rats
Value: 6,000 mg/kg b.w.
Method: Other
GLP: Yes [ ] No [X] ? [ ]
Test substance: purity: unknown
Remarks:
Reference: Ueno Pharm Inc

(b) Type: LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Mice
Value: 2,200 mg/kg b.w.
Method: Other
GLP: Yes [ ] No [X] ? [ ]
Test substance: purity: unknown
Remarks:
Reference: Drug Standards: 1952

5.1.2 ACUTE INHALATION TOXICITY

No data

5.1.3 ACUTE DERMAL TOXICITY

No data

5.1.4 ACUTE TOXICITY, OTHER ROUTES OF ADMINISTRATION

(a) Type: LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Rats
Route of Administration: i.m. [ ]; i.p. [X]; i.v. [ ]; infusion [ ]; s.c. [ ]; other [ ]
Exposure time:
Value: 340 mg/kg

Method: Other
GLP: Yes [ ] No [X] ? [ ]
Test substance: purity: unknown
Remarks: Muscle weakness
Reference: Gigiena i Sanitariya: 1986

(b) Type: LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Mice
Route of Administration: i.m. [ ]; i.p. [X]; i.v. [ ]; infusion [ ]; s.c. [ ]; other [ ]
Exposure time:
Value: 210 mg/kg
Method: Other
GLP: Yes [ ] No [X] ? [ ]
Test substance: purity: unknown
Remarks: Flaccid paralysis without anesthesia (usually neuromuscular blockage), somnolence (general depressed activity), and ataxia
Reference: J Am Pharm Assoc, Sci Ed: 1956

(c) Type: LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Mice
Route of Administration: i.m. [ ]; i.p. [ ]; i.v. [ ]; infusion [ ]; s.c. [X]; other [ ]
Exposure time:
Value: 1,050 mg/kg
Method: Other
GLP: Yes [ ] No [X] ? [ ]
Test substance: purity: unknown
Remarks:
Reference: Arch Intl Pharmacodyn Ther: 1960

5.2 CORROSIVENESS/IRRITATION

5.2.1 SKIN IRRITATION/CORROSION

Species/strain: New Zealand white rabbits
Results: Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[X]**; Not irritating **[ ]**
Classification: *(If possible, according to EC Directive 67/548/EEC)*
Highly corrosive (causes severe burns)**[ ]**; Corrosive (causes burns)**[ ]**; Irritating **[ ]**; Not irritating **[ ]**
Method: Other (according Code of Federal Regulation (CFR))
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: purity: unknown
Remarks: 4-Hydroxybenzoic acid (500 mg) was applied to the clipped skin with occulusive dressing for 24 hours. Cutaneous reaction was evaluated approximately 24, 48 and 72 hours, and 8 days after the test beginning. Erythema and edema were observed but these changes were very weak. Erythema was reversible within 8 days but edema was not.
Reference: Bayer Report: 1980a

5.2.2 EYE IRRITATION/CORROSION

Species/strain:	New Zealand white rabbits
Results:	Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[X]**; Slightly irritating **[ ]**; Not irritating **[ ]**
Classification:	*(if possible, according to EC Directive 67/548/EEC)* Irritating**[ ]**; Not irritating **[ ]**; Risk of serious damage to eyes **[ ]**
Method:	Other (according Code of Federal Regulation (CFR))
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance:	purity: unknown
Remarks:	4-Hydroxybenzoic acid (100 µg) was applied to conjunctivae under the right eyelid. The eye was closed for 1 second and not washed. As control, left eye remained. Eye reaction was evaluated approximately 24, 48, and 72 hours, and 8 days after the test beginning. Corneal opacity, conjunctival redness, and chemosis were observed. These signs of irritation were not reversible within 8 days.
Reference:	Bayer Report: 1980b

5.3 SKIN SENSITISATION

(a)

Type:	Guinea pig maximization test
Species/strain:	Guinea pigs/Dunkin Hartley strain
Results:	Sensitizing [X]; Not sensitizing [ ]; Ambiguous [ ]
Classification:	Sensitizing [ ]; Not sensitizing [ ]
Method:	Other
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	purity: unknown
Remarks:	10 animals (4 animals in control group) were inducted intradermally at 1.0 % and topically at 20 % six to eight days later. After 12-14 days, all animals were challenged at 20 %. Mild response was induced. The sensitization potential was 20 % (the percentage of animals exhibiting a reaction significantly greater than control animals).
Reference:	Scholes *et al.*: 1992

(b)

Type:	Local lymph node assay
Species/strain:	Mice/CBA/Ca strain/female
Results:	Sensitizing [ ]; Not sensitizing [X]; Ambiguous [ ]
Classification:	Sensitizing [ ]; Not sensitizing [ ]
Method:	Other
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	purity: unknown
Remarks:	Four animals were inducted by daily topical application of 2.5 – 15.0 % for three consecutive days. Five days after the initiation of exposure, [^{3}H] methyl thymidine was injected and the labeling in lymph node cells was measured.

The ratio of labeling incorporation by test lymph node cells to that recorded for control lymph node cells, (T/C) ratio was 0.6 – 1.5 (more than 3.0 is positive).

Reference: Scholes *et al.*: 1992

*5.4 REPEATED DOSE TOXICITY

Species/strain: Rats/Crj: CD (SD)
Sex: Female [ ]; Male [ ]; Male/Female [X]; No data [ ]
Route of Administration: Oral (by gavage)
Exposure period: Male: 42 days
Female: From 14 days before mating to day 3 of lactation
Frequency of treatment: Daily
Post exposure observation period:
Dose: 0, 40, 200, 1,000 mg/kg/day
Control group: Yes [X]; No [ ]; No data [ ]; 0.5 % CMC-Na
Concurrent no treatment];Concurrent vehicle[X]; Historical[ ]
NOAEL: Male: 1,000 mg/kg/day, Female: 1,000 mg/kg/day
LOAEL: All animals survived at all treated groups. 4-Hydroxybenzoic acid induced rale and temporary salivation (sometimes accompanied by rhinorrhea) at 1,000 mg/kg and slightly at 200 mg/kg. These changes were suggesting the irritation of this chemical to respiratory tract. There were no adverse effects on body weight change and food consumption. At necropsy, no histological and morphological changes were observed. In hematological and blood chemical findings of males, decrease in the percentage of lymphocytes and the blood glucose at 200 mg/kg or more groups and decrease in total protein and increase in A/G ratio, GPT and GOT at 1,000 mg/kg were observed. These changes were significant, but not considered adverse effects. Therefore, NOAEL for systemic toxicity was considered to be 1,000 mg/kg/day.
Method: OECD Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test
GLP: Yes [X] No [ ] ? [ ]
Test substance: purity: 99.7 %
Reference: MHW, Japan: 1997

*5.5 GENETIC TOXICITY IN VITRO

A. BACTERIAL TEST

Type: Gene mutation test
System of testing: *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, *Escherichia coli* WP2 *uvr*A
Concentration: +S9 mix; 0, 78.1, 156, 313, 625, 1250, 2500, 5000 µg/plate (TA1537)
0, 313, 625, 1250, 2500, 5000 µg/plate (TA100, TA1535, TA98 and WP2)
-S9 mix; 0, 78.1, 156, 313, 625, 1250, 2500, 5000 µg/plate (TA98 and TA1537)

0, 313, 625, 1250, 2500, 5000 µg/plate (TA100, TA1535, and WP2)

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

S9; Rat liver, induced with phenobarbital and 5,6-benzoflavone,

Results:

Cytotoxicity conc: With metabolic activation: not observed

Without metabolic activation: 5000 µg/plate (observed only in TA100, TA98, TA1537)

Precipitation conc: 5000 µg/plate

Genotoxic effects:

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

Method: Guidelines for Screening Mutagenicity Testing of Chemicals (Japan) and OECD Guideline No. 471 and 472

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

Test substance: purity: 99.7 %

Remarks: Positive control:

With metabolic activation: 2-Aminoantthracene (five strains)

Without metabolic activation:

Sodium azide (TA 1535)

9-Aminoacridine (TA1537)

2-(2-Furyl)-3-(5-nitro-2-furyl) acrylamide

(TA100, TA98, WP2)

Reference: MHW, Japan: 1997

B. NON-BACTERIAL IN VITRO TEST

Type: Chromosomal aberration test

System of testing: Chinese hamster lung (CHL/IU) cells

Concentration: +S9 mix (short-term treatment): 0, 0.18, 0.35, 0.70 mg/ml

-S9 mix (short-term treatment): 0, 0.18, 0.35, 0.70 mg/ml

-S9 mix (continuous treatment): 0, 0.18, 0.35, 0.70 mg/ml

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

S9: Rat liver, induced with phenobarbital and 5,6-benzoflavone.

Results: Structural chromosomal aberrations were observed at 0.70 mg/ml with short-term treatment with metabolic activation and with continuous treatment. Polyploidy was also induced at 0.70 mg/ml with 48 hr continuous treatment, and at 0.70 and 0.18 mg/ml with short-term treatment with metabolic activation. Since 4-hydroxybenzoic acid decreased pH in the medium, a confirmation test was conducted under pH-adjusted conditions. As a result, no chromosomal aberrations were observed.

Cytotoxicity conc: 0.70 mg/ml (observed only with short-term treatment with metabolic activation)

Precipitation conc:

Genotoxic effects:

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

Method: Guide for Screening Mutagenicity Testing of Chemicals (Japan), and OECD TG No.473.

GLP: Yes [X] No [ ] ? [ ]
Test substance: purity: 99.7%
Remarks: Exposure period: short-term treatment: 6 hr
continuous treatment: 24 or 48 hr
Positive control: -S9: Mitomycin, +S9: Cyclophosphamide
Reference: MHW, Japan: 1997

* 5.6 GENETIC TOXICITY IN VIVO

No data

5.7 CARCINOGENICITY

No data

*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 (by gavage)
Exposure period: Male: From 14 days before mating to 14 days after mating
Female: From 14 days before mating to day 3 of lactation
Frequency of treatment: Daily
Post exposure observation period:
Premating exposure period: 14 days
Duration of the test:
Dose: 0, 40, 200, 1,000 mg/kg/day
Control group: Yes [X]; No [ ]; No data [ ]; 0.5 % CMC-Na
Concurrent no treatment[ ];Concurrent vehicle[X]; Historical[ ]
NOAEL Parental: 1,000 mg/kg/day
NOAEL F1 Offspring: 1,000 mg/kg/day
NOAEL F2 Offspring:
Results:
General parental toxicity:
4-Hydroxybenzoic acid showed no adverse effects on copulation, fertility, maintenance of pregnancy, parturition and lactation at all treated groups.
Toxicity to offspring:
4-Hydroxybenzoic acid showed no adverse effects on viability, sex ratio, body weights and morphological appearance of pups at all treated groups.
Method: OECD Combined Repeat Dose and Reproductive/ Developmental Toxicity Screening Test
GLP: Yes [X] No [ ] ? [ ]
Test substance: purity: 99.7 %
Remarks:
Reference: MHW, Japan: 1997

*5.9 DEVELOPMENTAL TOXICITY/ TERATOGENICITY

Species/strain: Rats/Sprague-Dawley
Sex: Female [X]; Male [ ]; Male/Female [ ]; No data [ ]
Route of Administration: Oral (a single dose)
Duration of the test: Until weaning
Exposure period: Day 11 of gestation
Frequency of treatment:
Doses: 0, 333, 667, 1,000 mg/kg
Control group: Yes [X]; No [ ]; No data [ ]; consisting of water, Tween 20, propylene glycol, and ethanol in a ratio of 4: 4: 1: 1
Concurrent no treatment[ ]; Concurrent vehicle[X];Historical[ ]
NOAEL Maternal Toxicity: 1,000 mg/kg
NOAEL teratogenicity: 1,000 mg/kg
Results:
Maternal general toxicity:
No significant change was observed in the mortality and body weight at 24 and 72 hr, compared to vehicle control.
Pregnancy/litter data:
There was no significant change in the number of pregnancy, the number of implantation scars in the uterus, the number of perinatal loss of offspring (calculated as the difference between the number of implantation sites and the litter size on 6 day after birth), and litter size, total litter weight and litter biomass at 1 and 6 days, compared to vehicle control.
Foetal data: No significant change in pup weight and overt malformation were observed.
Method: Other
GLP: Yes [ ] No [X] ? [ ]
Test substance: purity: unknown
Remarks:
Reference: Kavlock *et al.*: 1990

5.10 OTHER RELEVANT INFORMATION

A. Specific toxicities

Type: Inhibitory effect on hepatic enzyme
Results: 4-Hydroxybenzoc acid competed with the substrate mevalonate 5-pyrophosphate, and inhibited mevalonate pyrophosphate decarboxylase. And this chemical also inhibited mevalonate phosphate kinase.
Remarks: Male albino rats were killed and the liver were quickly removed, chilled and homogenised in 0.25 M sucrose. The homogenate was centrifuged at 38,000 x g for 40 min and the resultant supernatant was used as the source of enzyme.
As the substrate, (R)-[1-^{14}C] mevalonate 5-phosphate and (R)-[1-^{14}C] mevalonate 5-pyrophosphate was used.
Reference: Shama Bhat & Ramasarma: 1979

Type: Estrogenic assay (vaginal cornification and uterotrophic assay)

Results: A dose-dependent response on vaginal cornification and uterotrophic activity was observed in both immature intact and adult ovariectomized mice treated with 4-hydroxybenzoic acid. The relative uterotrophic potency of this chemical (500 µg/100 g) to estradiol (1 µg /100 g) was 0.0011 and 0.0018 in immature and ovariectomized animals, respectively.

Remarks: Immature intact and adult ovariectomized female mice (CD1) were treated subcutaneously daily for 3 days with vehicle (corn oil, 0.3 ml/100 g), estradiol (1 µg /100 g), and 4-hydroxybenzoic acid (0.5, 5, 50, and 500 µg/100 g). Four days after treatment, estrogenic effect was analyzed.

Reference: Lemini *et al.*: 1997

B. Toxicodynamics, toxicokinetics

Type: Toxicokinetics

Results: Urinary excretion was the predominant means of elimination and occurred primarily within 24 hr after dermal and i.p. administration. The 120 hr cumulative excretion after i.p. administration was 86.5 % in urine and 3.4 % in faeces, and 10.2 % was detected in the carcasses of treated animals. The dermal absorption was very low (2 %). The major portion of the dose not absorbed dermally in 24 hr was washed from the skin. The 120 hr cumulative excretion after dermal administration was 1.9 % in urine and 0.04 % in faeces. 2 % and 0.28 % was detected in the treated skin and the carcasses of treated animals, respectively.

Remarks: Female Fischer 344 rats (29 days old) were dosed with 4-hydroxybenzoic acid by i.p. (2.5 µg, approx. 1 µCi) and dermal (5 µg, 3.9 µg/cm^2, approx. 2 µCi) route. In the dermally treated animals, treated area was washed 24 hr after dosing. Urine and faces were collected at 4, 8, 12, 24, 48, 72, 96 and 120 hr, weighted after collection and stored at –70 until analysed. The animals were killed by CO_2 asphyxiation at 120 hr after treatment. A sample of treated and untreated skin was removed from the dermally treated animals. The skin and samples of the whole-animal homogenate were weighted, combusted and analysed for radioactivity.

References: Hughes & Hall: 1997

* 5.11 EXPERIENCE WITH HUMAN EXPOSURE

Results: Occupational exposure to airborne epichlorohydrin, 0.9-1.5 mg/m^3; toluene, 1.3-2.13 mg/m^3; and diphenylolpropane, p-hydroxybenzoic acid, N-glycidyl-m-aminobenzoic acid, and isophthalic acid, 2-5 mg/m^3 at the manufacture of epoxy resins induced contact and allergic dermatitis and sensitization to bacterial and chemical allergens.

Remarks:

Reference: Chernykh & Savchenko: 1988

6. REFERENCES

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Appendix 1

scenario 1

	emission rate	conc.	amount	percent	transformation rate [kg/h]	
	[kg/h]	[g/m^3]	[kg]	[%]	reaction	advection
air	1,000	3.6.E-08	3.6.E+02	0.0	9.2E-01	3.6.E+00
water	0	3.9.E-02	7.8.E+05	28.5	6.2E+01	7.8.E+02
soil	0	1.2.E+00	1.9.E+06	71.4	1.6E+02	
sediment		4.0.E-02	4.0.E+03	0.1	3.2E-01	7.9.E-02
		total amount	2.7.E+06			

scenario 2

	emission rate	conc.	amount	percent	transformation rate [kg/h]	
	[kg/h]	[g/m^3]	[kg]	[%]	reaction	advection
air	0	6.1.E-13	6.1.E-03	0.0	1.5.E-05	6.1.E-05
water	1000	4.6.E-02	9.3.E+05	99.5	7.4.E+01	9.3.E+02
soil	0	2.0.E-05	3.3.E+01	0.0	2.6.E-03	
sediment		4.7.E-02	4.7.E+03	0.5	3.8.E-01	9.5.E-02
		total amount	9.3.E+05			

scenario 3

	emission rate	conc.	amount	percent	transformation rate [kg/h]	
	[kg/h]	[g/m^3]	[kg]	[%]	reaction	advection
air	0	1.0.E-10	1.0.E+00	0.0	2.6.E-03	1.0.E-02
water	0	3.7.E-02	7.4.E+05	23.3	6.0.E+01	7.4.E+02
soil	1000	1.5.E+00	2.4.E+06	76.6	2.0.E+02	
sediment		3.8.E-02	3.8.E+03	0.1	3.0.E-01	7.6.E-02
		total amount	3.2.E+06			

scenario 4

	emission rate	conc.	amount	percent	transformation rate [kg/h]	
	[kg/h]	[g/m^3]	[kg]	[%]	reaction	advection
air	600	2.2.E-08	2.2.E+02	0.0	5.5.E-01	2.2.E+00
water	300	4.1.E-02	8.2.E+05	36.6	6.6.E+01	8.2.E+02
soil	100	8.8.E-01	1.4.E+06	63.2	1.1.E+02	
sediment		4.2.E-02	4.2.E+03	0.2	3.4.E-01	8.4.E-02
		total amount	2.2.E+06			

Physico-chemical parameter

molecular weight		138.13	Measured
melting point		216.2	Measured
vapor pressure [Pa]		3.90E-03	Measured
water solubility [g/m^3]		6000	Measured
log Kow		1.37	Measured
half life [h]	in air	272	Estimated
	in water	8640	Estimated
	in soil	8640	Estimated
	in sediment	8640	Estimated

Temp. []	25

Environmental parameter

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

Intermedia Transport Parameters

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

EXTRACT FROM IRPTC LEGAL FILES

File: 17.01 LEGAL **rn : 25998**

```
systematic name:Benzoic acid, 4-hydroxy-
common name    :p-hydroxybenzoic acid
reported name  :4-HYDROXYBENZOIC ACID
cas no         :99-96-7
area          : EEC                 type          : REG
 --------------------------------
|subject|specification|descriptor|
|-------+-------------+----------|
| GOODS |             |   PRMT   |
| GOODS |             |   MXL    |
 --------------------------------
PRESERVATIVE ALLOWED IN COSMETIC PRODUCTS. MEMBER STATES SHALL PROHIBIT
THE MARKETING OFCOSMETIC PRODUCTS CONTAINING THE PRESERVATIVEBEYOND THE
LIMITS AND OUTSIDE THE CONDITIONS LAID DOWN UNLESS OTHER CONCENTRATIONS
ARE USED FOR SPECIFIC PURPOSES APPARENT FROM THE PRESENTATION OF THE
PRODUCT. (COUNCIL DIRECTIVE 76/768/EEC - OJEC L262,169,1976 AS LAST
AMENDED BY THE REFERENCE GIVEN)
entry date: SEP 1987                          effective date:  1JAN1988

amendment: OJEC**, Official Journal of the European (Communities)/Union,
           L56 , , 20 , 1987
```

****

File: 17.01 LEGAL **rn : 401002**

```
systematic name:Benzoic acid, 4-hydroxy-
common name    :p-hydroxybenzoic acid
reported name  :p-hydroxybenzoic acid
cas no         :99-96-7
area          : CSK                 type          : REG
 --------------------------------
|subject|specification|descriptor|
|-------+-------------+----------|
| FOOD  |             |   MPC    |
 --------------------------------
LIMIT OF ADDITIVE PRESENT DUE TO PRODUCTION, PACKING, TRANSPORT AND
STORAGE OF FOOD PRODUCTS: 0.4G/KG.
entry date: DEC 1991                          effective date:  1JUL1986

title: DIRECTIVE NO. 50/1978 ON FOREIGN SUBSTANCES IN FOODSTUFFS
original : HPMZC*, HYGIENICKE PREDPISY MINISTERSTVA ZDRAVOTNICTVI
           CSR(HYGIENIC REGULATIONS OF MINISTRY OF HEALTH OF CSR), 43 ,
           , , 1978
amendment: HPMZC*, HYGIENICKE PREDPISY MINISTERSTVA ZDRAVOTNICTVI
           CSR(HYGIENIC REGULATIONS OF MINISTRY OF HEALTH OF CSR), 61 ,
           , , 1986
```