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

<table>
<thead>
<tr>
<th>CAS NO.</th>
<th>99-96-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHEMICAL NAME</td>
<td>4-Hydroxybenzoic acid</td>
</tr>
<tr>
<td>Structural formula</td>
<td></td>
</tr>
</tbody>
</table>

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 Pow 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 toxicity 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 $4.4 \times 10^9$ 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
### PHYSICAL-CHEMICAL

<table>
<thead>
<tr>
<th>SPECIES</th>
<th>PROTOCOL</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 Melting Point</td>
<td></td>
<td>216.2 °C</td>
</tr>
<tr>
<td>2.2 Boiling Point</td>
<td></td>
<td>Decomposed</td>
</tr>
<tr>
<td>2.3 Density</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.4 Vapour Pressure</td>
<td>OECD TG 104</td>
<td>3.9 x 10^{-3} Pa at 100 °C</td>
</tr>
<tr>
<td>2.5 Partition Coefficient</td>
<td>OECD TG 107</td>
<td>1.37</td>
</tr>
<tr>
<td>2.6 A. Water Solubility</td>
<td>OECD TG 105</td>
<td>6 g/l at 25 °C</td>
</tr>
<tr>
<td>B. pH</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.12 Oxidation: Reduction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### ENVIRONMENTAL FATE AND PATHWAY

<table>
<thead>
<tr>
<th>SPECIES</th>
<th>PROTOCOL</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1.1 Photodegradation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.1.2 Stability in Water</td>
<td>OECD TG 111</td>
<td>Stable at pH4,7 and 9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pK₁ = 4.582</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pK₂ = 9.23</td>
</tr>
<tr>
<td>3.2 Monitoring Data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.3 Transport and Distribution</td>
<td>Calculated</td>
<td>Release: 100% to Water</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In Air   0.0 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In Water 99.5 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In Sediment 0.0 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In Soil 0.5 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(local exposure) 9.7 x 10^{4} mg/L (Japan)</td>
</tr>
<tr>
<td>3.5 Biodegradation</td>
<td>OECD 301C</td>
<td>Readily biodegradable 100% in 28 days</td>
</tr>
</tbody>
</table>

### ECOTOXICOLOGY

<table>
<thead>
<tr>
<th>SPECIES</th>
<th>PROTOCOL</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1 Acute/Prolonged Toxicity to Fish</td>
<td>OECD TG 203</td>
<td>LC₅₀ (48hr) = &gt; 100 mg/l</td>
</tr>
<tr>
<td>4.2 Acute Toxicity to Aquatic Invertebrates</td>
<td>OECD TG 202</td>
<td>EC₅₀ (48hr): 135.7 mg/l</td>
</tr>
<tr>
<td>4.3 Toxicity to Aquatic Plants e.g. Algae</td>
<td>OECD TG 201</td>
<td>LC₅₀ (72hr) = 92.8 mg/l</td>
</tr>
<tr>
<td>4.5.2 Chronic Toxicity to Aquatic Invertebrates (Daphnia)</td>
<td>OECD TG 202</td>
<td>EC₅₀ (21d, Repro) = &gt; 100 mg/l</td>
</tr>
<tr>
<td>4.6.1 Toxicity to Soil Dwelling Organisms</td>
<td></td>
<td>None</td>
</tr>
</tbody>
</table>
### TOXICITY

| 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<sub>50</sub> = 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 | Japanese TG and OECD TG 471 & 472 | - (With metabolic activation) |
| | E. coli WP2 | | | - (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.
1. **IDENTITY**

- **OECD Name:** 4-Hydroxybenzoic acid
- **Synonym:** 4-Hydroxybenzenecarboxylic acid
- **CAS Number:** 99-96-7
- **Empirical Formula:** C₇H₆O₃
- **Structural Formula:**

![Structural Formula Image]

- **Degree of Purity:** 99.7%
- **Major Impurity:** None
- **Essential Additives:** None
- **Physical-chemical properties**
  - **Melting Point:** 216.2 °C
  - **Vapour pressure:** 3.9 x 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>
<thead>
<tr>
<th>Compartment</th>
<th>Release 100% to air</th>
<th>Release 100% to water</th>
<th>Release 100% to soil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>0.0 %</td>
<td>0.0 %</td>
<td>0.0 %</td>
</tr>
<tr>
<td>Water</td>
<td>28.5 %</td>
<td>99.5 %</td>
<td>23.3 %</td>
</tr>
<tr>
<td>Soil</td>
<td>71.4 %</td>
<td>0.0 %</td>
<td>76.6 %</td>
</tr>
<tr>
<td>Sediment</td>
<td>0.1 %</td>
<td>0.5 %</td>
<td>0.1 %</td>
</tr>
</tbody>
</table>

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 10⁹ L/year of effluent into sea. Local Predicted Environmental Concentration (PEClocal) 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).

\[
\text{Amount of release (1.42 x 10^{11} mg/y) x (1 – Removal rate (97 %))} \\
\text{Volume of effluent (4.4 x 10^9 L/y) x Dilution Factor (1000)} \\
\]

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):

$$\text{PNEC} = \frac{66.5}{100} = 0.665 \text{ mg/l}$$

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

$$\text{PNEC} = \frac{32.0}{100} = 0.32 \text{ mg/l}$$

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

**Table 2**

<table>
<thead>
<tr>
<th>Species</th>
<th>Endpoint</th>
<th>Conc. (mg/l)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Selenastrum capricornutum</em> (algae)</td>
<td>Bms 72 h EC50</td>
<td>68.5</td>
<td>A, 1)</td>
</tr>
<tr>
<td></td>
<td>Bms 72 h NOEC</td>
<td>32.0</td>
<td>C, 1), C</td>
</tr>
<tr>
<td></td>
<td>Bms 96 h EC50</td>
<td>42.8</td>
<td>a, 2), A</td>
</tr>
<tr>
<td><em>Chlorella pyrenoidosa</em> (algae)</td>
<td>Imm 48 h EC50</td>
<td>135.7</td>
<td>a, 1), A</td>
</tr>
<tr>
<td></td>
<td>Rep 21 d EC50</td>
<td>&gt; 100</td>
<td>c, 1)</td>
</tr>
<tr>
<td></td>
<td>Rep 21 d NOEC</td>
<td>&gt; 100</td>
<td>c, 1), C</td>
</tr>
<tr>
<td></td>
<td>Imm 48 h EC50</td>
<td>173.0</td>
<td>a, 3)</td>
</tr>
<tr>
<td><em>Daphnia magna</em> (Water flea)</td>
<td>Imm 48 h EC50</td>
<td>135.7</td>
<td>a, 1), A</td>
</tr>
<tr>
<td></td>
<td>Rep 21 d EC50</td>
<td>&gt; 100</td>
<td>c, 1)</td>
</tr>
<tr>
<td></td>
<td>Rep 21 d NOEC</td>
<td>&gt; 100</td>
<td>c, 1), C</td>
</tr>
<tr>
<td></td>
<td>Imm 48 h EC50</td>
<td>173.0</td>
<td>a, 3)</td>
</tr>
<tr>
<td><em>Oryzias latipes</em> (fish, Medaka)</td>
<td>Mor 48h LC50</td>
<td>&gt; 100</td>
<td>a, 1)</td>
</tr>
<tr>
<td></td>
<td>Mor 72h LC50</td>
<td>92.8</td>
<td>a, 1)</td>
</tr>
<tr>
<td></td>
<td>Mor 96h LC50</td>
<td>92.8</td>
<td>a, 1)</td>
</tr>
<tr>
<td></td>
<td>Mor 14d LC50</td>
<td>66.5</td>
<td>a, 1), A</td>
</tr>
<tr>
<td></td>
<td>Mor 96h LC50</td>
<td>&gt; 99.4</td>
<td>a, 4)</td>
</tr>
</tbody>
</table>

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 \(9.7 \times 10^{-4}\) mg/l.

Thus, \(\frac{\text{PEC}_{\text{local}}}{\text{PNEC}} = \frac{9.7 \times 10^{-4}}{0.32} = 0.003 < 1\)

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.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Duration</th>
<th>Working</th>
<th>Concentration</th>
<th>EHE</th>
<th>Combined EHE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Times/day</td>
<td>hr/day</td>
<td>hr/day</td>
<td>mg/m(^3)</td>
<td>mg/kg/day</td>
<td>mg/kg/day</td>
</tr>
<tr>
<td>Bag Filling</td>
<td>0.44</td>
<td>2</td>
<td>0.88</td>
<td>2.99</td>
<td>0.04700</td>
</tr>
<tr>
<td>Bag Filling</td>
<td>0.058</td>
<td>6.6</td>
<td>0.38</td>
<td>2.99</td>
<td>0.02000 0.067</td>
</tr>
</tbody>
</table>

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. $9.7 \times 10^{-4}$ mg/l. The daily intake through drinking water is calculated as $3.23 \times 10^{-5}$ 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:

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

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 $7.28 \times 10^{-6}$ 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 uvrA 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/1U) 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 uterotrophic 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 ovarietomized 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 ovarietomized 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/cm², 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/m³), toluene (1.3-2.13 mg/m³), and diphenylolpropen, 4-hydroxybenzoic acid, N-glycidyl-m-aminobenzoic acid, and isophthalic acid (2-5 mg/m³) 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 LD₅₀ 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 without 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 10⁴. 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\textsubscript{local} of $9.70 \times 10^{-4} \text{ mg/l}$ from local exposure scenario was used for the estimation. The daily intakes through drinking water and fish are calculated as $3.23 \times 10^{-5} \text{ mg/kg/day}$ and $7.28 \times 10^{-6} \text{ mg/kg/day}$, respectively. Since the margin of safety is very large, such as $3.09 \times 10^{7}$ for drinking water and $1.37 \times 10^{8}$ 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 $1.49 \times 10^{4}$ and $3.09 \times 10^{7}$ or $1.37 \times 10^{8}$ (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

6. REFERENCES

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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.

\[
PEC_{local} (\text{mg/L}) = \frac{Co \cdot Q + Cs \cdot Qs}{Q + Qs}
\]  

(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.

\[
R = \frac{Cs}{Co} = \frac{(Q + Qs)}{Qs}
\]  

(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.

\[
\text{Flow rate at dry season} = \text{mean flow late} / 2.5
\]  

(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 Yi “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 no any effect of tidal current.
6. Decomposition of pollutant can be ignored.
\[
C(x) = (C_s - C(r)) \left(1 - \exp\left(-\frac{1}{dp \cdot x \cdot r}\right)\right) + C(r) \tag{4}
\]

Where
- \(C(x)\): Concentration of pollutant at distance \(x\) (m) from release point
- \(C_s\): Concentration of pollutant in effluent
- \(C(r)\): Concentration of pollutant at distance \(r\) (m) from release point
- \(Q_s\): Flow rate of effluent (m³/day)
- \(\theta\): Opening angle of seacoast (rad.)
- \(d\): Thickness of diffusion layer (m)
- \(P\): Diffusion velocity (m/day) (1.0 0.5 cm/sec)

When \(C(x) = 0\) at \(r = \) and density stratification is ignored for simplification, Joseph-Sendner's equation (4) is simplified to equation (5)

\[
C(x) = C_s \left(1 - \exp\left(-\frac{Q_s}{dp \cdot x}\right)\right) \tag{5}
\]

Because of \(Q_s/ dp \cdot x << 1\) except vicinity of release point, dilution factor in distance \(x\) from release point \(R(x)\) can be shown with equation (6).

\[
R(x) = \frac{C_s}{C(x)} = \frac{dp \cdot x}{Q_s} \tag{6}
\]

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

\[
P = 1 \text{ cm/sec (860 m/day)}
\]

\[
= 3.14
\]

\[
d = 10 \text{ m}
\]

\[
x = 1000 \text{ m}
\]

\[
R = 2.7 \times 10^7/Q_s \tag{7}
\]

\(Q_s\): volume of effluent (m³/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
CONTENTS

Sids Profile

Sids Summary

1. General Information

1.01 Substance Information
   * A. Cas-Number
   B. Name (Iupac-Name)
   * C. Name (Oecd Name)
   † D. Cas Descriptor
   E. Eincs-Number
   F. Molecular Formula
   * G. Structural Formula
   H. Substance Group
   I. Substance Remark
   J. Molecular Weight

1.02 Oecd Information
   A. Sponsor Country
   B. Lead Organisation
   C. Name Of Responder (Company)

1.1 General Substance Information
   A. Type Of Substance
   B. Physical State
   C. Purity

1.2 Synonyms

1.3 Impurities

1.4 Additives

1.5 * Quantity

1.6 Labelling And Classification (Use And/Or Transportation)

1.7 * Use Pattern
   A. General Use Pattern
   B. Uses In Consumer Products

1.8 Occupational Exposure Limit Value

1.9 * Sources Of Exposure

1.10 Additional Remarks
   A. Options Of Disposal
   B. Other Remarks.

2. Physical-Chemical Data

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2.2 * Boiling Point

2.3 † Density (Relative Density)

2.4 * Vapour Pressure

2.5 * Partition Coefficient N-Octanol/Water

2.6 * Water Solubility
   A. Solubility
   B. Ph Value, Pka Value
2.7 Flash Point (Liquids)
2.8 Auto Flammability (Solid/Gases)
2.9 Flammability
2.10 Explosive Properties
2.11 Oxidising Properties
2.12 Oxidation: Reduction Potential
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   3.1.1 Photodegradation
   3.1.2 Stability In Water
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4.2 Acute Toxicity To Aquatic Invertebrates
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   B. Other Aquatic Organisms
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5.7 Carcinogenicity  
5.8 * Toxicity To Reproduction  
5.9 * Developmental Toxicity / Teratogenicity  
5.10 Other Relevant Information  
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   B. Toxicodynamics, Toxicokinetics  
5.11 * Experience With Human Exposure

6. **References**

**Appendix**

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

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#### 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
## SIDS SUMMARY

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<td>Acute Oral</td>
<td>Y</td>
<td>N</td>
<td>N</td>
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<td>N</td>
<td>Y</td>
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<td>5.1.2</td>
<td>Acute Inhalation</td>
<td>N</td>
<td></td>
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<td>5.1.3</td>
<td>Acute Dermal</td>
<td>N</td>
<td></td>
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<tr>
<td>5.4</td>
<td>Repeated Dose</td>
<td>N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Y</td>
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<tr>
<td>5.5</td>
<td>Genetic Toxicity in vitro</td>
<td>N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Y</td>
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<tr>
<td>5.5.1</td>
<td>Genetic Toxicity in vitro</td>
<td>N</td>
<td></td>
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<td></td>
<td>Y</td>
<td></td>
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<tr>
<td>5.6</td>
<td>Reproduction Toxicity</td>
<td>N</td>
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<td></td>
<td></td>
<td></td>
<td>Y</td>
<td></td>
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<tr>
<td>5.9</td>
<td>Development / Teratogenicity</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td></td>
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<tr>
<td>5.11</td>
<td>Human experience</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td></td>
</tr>
</tbody>
</table>

### OTHER TOXICITY STUDIES RECEIVED
1. **GENERAL INFORMATION**

1.01 **SUBSTANCE INFORMATION**

*A. CAS number*  
99-96-7

*B. Name (IUPAC name)*  
4-Hydroxybenzoic acid

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

†D. **CAS Descriptor**

E. **EINECS-Number**  
202-804-9

F. **Molecular Formula**  
C₇H₆O₃

*G. **Structural Formula**

```
HO-       COOH
```

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

<table>
<thead>
<tr>
<th>Type of Use</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>main</td>
<td>Intermediate</td>
</tr>
<tr>
<td>industrial use</td>
<td>Intermediate in closed system</td>
</tr>
<tr>
<td></td>
<td>Intermediate for pesticides and preservatives</td>
</tr>
</tbody>
</table>

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 %
*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: 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: 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:

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Release 100% to air</th>
<th>Release 100% to water</th>
<th>Release 100% to soil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>0.0 %</td>
<td>0.0 %</td>
<td>0.0 %</td>
</tr>
<tr>
<td>Water</td>
<td>28.5 %</td>
<td>99.5 %</td>
<td>23.3 %</td>
</tr>
<tr>
<td>Soil</td>
<td>71.4 %</td>
<td>0.0 %</td>
<td>76.6 %</td>
</tr>
<tr>
<td>Sediment</td>
<td>0.1 %</td>
<td>0.5 %</td>
<td>0.1 %</td>
</tr>
</tbody>
</table>

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.
4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

*A. Daphnia*

Type of test: static [ ]; semi-static [ ]; flow-through [X]; other (e.g. field test) [ ]
Species: Daphnia Magna.
Exposure period: 48 h
Results: EC₅₀ (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.


*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 EC₅₀ (72h) = 68.5 mg/l
(Endpoint) NOEC = 32 mg/l
Analytical monitoring: Yes [X] No [ ] ? [ ]
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.


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 [ ]; ? [ ]
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.

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)
5. TOXICITY

*5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

(a) Type: \( \text{LD}_0 \); \( \text{LD}_{100} \); \( \text{LD}_{50} \); \( \text{LDL}_0 \); 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: \( \text{LD}_0 \); \( \text{LD}_{100} \); \( \text{LD}_{50} \); \( \text{LDL}_0 \); Other
Species/strain: Mice
Value: 2,200 mg/kg b.w.
Method: Other
GLP: Yes [ ] No [X] ? [ ]
Test substance: purity: unknown

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: \( \text{LD}_0 \); \( \text{LD}_{100} \); \( \text{LD}_{50} \); \( \text{LDL}_0 \); Other
Species/strain: Rats
Route of Administration: i.m. [ ]; i.p. [X]; i.v. [ ]; infusion [ ]; s.c. [ ]; other [ ]
Exposure time:
Value: 340 mg/kg
OECD SIDS 4-HYDROXYBENZOIC ACID

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

(b) Type: LD₀ [ ]; LD₁₀₀ [ ]; LD₅₀ [X]; LD₀ [ ]; 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

(c) Type: LD₀ [ ]; LD₁₀₀ [ ]; LD₅₀ [X]; LD₀ [ ]; 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: Flaccid paralysis without anesthesia (usually neuromuscular blockage), somnolence (general depressed activity), and ataxia

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 occlusive 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.

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, [3H] 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 uvrA
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)
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.
**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

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: 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-^14C] mevalonate 5-phosphate and (R)-[1-^14C] mevalonate 5-pyrophosphate was used.
Reference: Shama Bhat & Ramasarma: 1979

Type: Estrogenic assay (vaginal cornification and uterotrophic assay)
**OECD SIDS**

**4 -HYDROXYBENZOIC ACID**

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

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**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/cm², 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 CO₂ 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

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**5.11 EXPERIENCE WITH HUMAN EXPOSURE**

Results: Occupational exposure to airborne epichlorohydrin, 0.9-1.5 mg/m³; toluene, 1.3-2.13 mg/m³; and diphenylolpropane, p-hydroxybenzoic acid, N-glycidyl-m-aminobenzoic acid, and isophthalic acid, 2-5 mg/m³ at the manufacture of epoxy resins induced contact and allergic dermatitis and sensitization to bacterial and chemical allergens.

Remarks:
6. REFERENCES

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- Gigiena i Sanitariya. For English translation, see HYSAAV. (V/O Mezhdunarodnaya Kniga, 113095 Moscow, USSR), 51(1), 85 (1986)
- Kavlock, R.J. et al., Teratology, 41(1), 43 (1990)
- Ueno Pharmaceutical Incorporation, unpublished data
### Appendix 1

#### scenario 1

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EXTRACT FROM IRPTC LEGAL FILES

entry date: SEP 1987    effective date: 1JAN1988


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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*, HYGIENIC PREDPISY MINISTERSTVA ZDRAVOTNICTVI CSR(HYGIENIC REGULATIONS OF MINISTRY OF HEALTH OF CSR), 43, 1978

amendment: HPMZC*, HYGIENIC PREDPISY MINISTERSTVA ZDRAVOTNICTVI CSR(HYGIENIC REGULATIONS OF MINISTRY OF HEALTH OF CSR), 61, 1986