FOREWORD

INTRODUCTION

**BENZOATES**

*CAS N°: 65-85-0, 532-32-1, 582-25-2, 100-51-6*
SIDS Initial Assessment Report
for
13th SIAM
(Bern, 7th - 9th November 2001)

Chemical Name: Benzoates: Benzoic acid, Sodium benzoate, Potassium benzoate, Benzyl alcohol

CAS No: 65-85-0, 532-32-1, 582-25-2, 100-51-6

Sponsor Country: The Netherlands

National SIDS Contact Point in Sponsor Country: Mr. Dick Sijm

HISTORY:
In 2001 ICCA asked The Netherlands to be the sponsor country for the benzoates

no testing (X )
testing ( )

COMMENTS:
The Benzoates were already discussed in other frameworks such as the WHO. Therefore the original data were not again evaluated. The conclusions of other frameworks are discussed in the SIAR. This SIAR can be considered as a state of the art report on benzoates.

Deadline for circulation:

Date of Circulation:
(To all National SIDS Contact Points and the OECD Secretariat)
## SIDS INITIAL ASSESSMENT PROFILE

**Benzoates Category**

<table>
<thead>
<tr>
<th>CAS No.</th>
<th>Chemical Name</th>
<th>Structural Formula</th>
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<tr>
<td>65-85-0</td>
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<tr>
<td>532-32-1</td>
<td>Sodium benzoate</td>
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<tr>
<td>582-25-2</td>
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</tr>
<tr>
<td>100-51-6</td>
<td>Benzyl alcohol</td>
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</table>

### RECOMMENDATIONS

The chemicals are currently of low priority for further work.

### SUMMARY CONCLUSIONS OF THE SIAR

Benzyl alcohol, benzoic acid and its sodium and potassium salt can be considered as a single category regarding human health, as they are all rapidly metabolised and excreted via a common pathway within 24hrs. Systemic toxic effects of similar nature (e.g. liver, kidney) were observed. However with benzoic acid and its salts at higher doses than with benzyl alcohol. For environmental effects the category is less clear, however all are readily biodegradable, non-bioaccumulative and acute toxicity values are similar. For human health all exposure routes are possible, despite benzoic acid and its salts being solids and benzyl alcohol being a liquid. For workers it will mainly be by inhalation and by skin, whereas for consumers it will mainly be by oral and dermal routes.

### Human Health

The compounds exhibit low acute toxicity as for the oral and dermal route. The LD50 values are > 2000 mg/kg bw except for benzyl alcohol which needs to be considered as harmful by the oral route in view of an oral LD50 of 1610 mg/kg bw. The 4 hrs inhalation exposure of benzyl alcohol or benzoic acid at 4 and 12 mg/l as aerosol/dust respectively gave no mortality, showing low acute toxicity by inhalation for these compounds.

Benzoic acid and benzyl alcohol are slightly irritating to the skin, while sodium benzoate was not skin irritating. No data are available for potassium benzoate but it is also expected not to be skin irritating. Benzoic acid and benzyl alcohol are irritating to the eye and sodium benzoate was only slightly irritating to the eye. No data are available for potassium benzoate but it is expected also to be only slightly irritating to the eye.

The available studies for benzoic acid gave no indication for a sensitizing effect in animals, however occasionally very low positive reactions were recorded with humans (dermatological patients) in patch tests. The same occurs for sodium benzoate. It has been suggested that the very low positive reactions are non-immunologic contact urticaria. Benzyl alcohol gave positive and negative results in
animals. Benzyl alcohol also demonstrated a maximum incidence of sensitization of only 1% in human patch testing. Over several decades no sensitization with these compounds has been seen among workers.

For benzoic acid repeated dose oral toxicity studies give a NOAEL of 800 mg/kg/day. For the salts values > 1000 mg/kg/day are obtained. At higher doses increased mortality, reduced weight gain, liver and kidney effects were observed. For benzyl alcohol the long-term studies indicate a NOAEL > 400 mg/kg bw/d for rats and > 200 mg/kg bw/d for mice. At higher doses effects on bodyweights, lesions in the brains, thymus, skeletal muscle and kidney were observed. It should be taken into account that administration in these studies was by gavage route, at which saturation of metabolic pathways is likely to occur.

It can be concluded that benzoic acid and its salts exhibit very low repeated dose toxicity. Benzyl alcohol exhibits low repeated dose toxicity.

All chemicals showed no mutagenic activity in in vitro Ames tests. Various results were obtained with other in vitro genotoxicity assays. Sodium benzoate and benzyl alcohol showed no genotoxicity in vivo. While some mixed and/or equivocal in vitro chromosomal/chromatid responses have been observed, no genotoxicity was observed in the in vivo cytogenetic, micronucleus, or other assays. The weight of the evidence of the in vitro and in vivo genotoxicity data indicates that these chemicals are not mutagenic or clastogenic. They also are not carcinogenic in long-term carcinogenicity studies.

In a 4-generation study with benzoic acid no effects on reproduction were seen (NOAEL ≥ 750 mg/kg). No compound related effects on reproductive organs (gross and histopathology examination) could be found in the (sub) chronic studies in rats and mice with benzyl acetate, benzyl alcohol, benzaldehyde, sodium benzoate and supports a non-reprotoxic potential of these compounds. In addition, data from reprotoxicity studies on benzyl acetate (NOAEL > 2000 mg/kg bw/d; rats and mice) and benzaldehyde (tested only up to 5 mg/kg bw/d; rats) support the non-reprotoxicity of benzyl alcohol and benzoic acid and its salts.

In rats for sodium benzoate dosed via food during the entire gestation developmental effects occurred only in the presence of marked maternal toxicity (reduced food intake and decreased body weight) (NOAEL = 1400 mg/kg bw). For hamster (NOEL: 300 mg/kg bw), rabbit (NOEL: 250 mg/kg bw) and mice (CD-1 mice, NOEL: 175 mg/kg bw) no higher doses (all by gavage) were tested and no maternal toxicity was observed. For benzyl alcohol: NOAEL= 550 mg/kg bw (gavage; CD-1 mice). LOAEL = 750 mg/kg bw (gavage mice). In this study maternal toxicity was observed e.g. increased mortality, reduced body weight and clinical toxicology. Benzyl acetate: NOEL = 500 mg/kg bw (gavage rats). No maternal toxicity was observed.

Environment

From the data (fish, daphnia, algae, bacteria) it is obvious that neutralization of the pH greatly reduces (up to one order of magnitude) the acute toxicity of benzoic acid. This is also supported by the lower toxicity observed with sodium benzoate. Under environmental relevant conditions therefore the acute toxicity of benzoic acid, sodium benzoate and potassium benzoate for all four trophic levels is > 100 mg/l. Under environmental relevant conditions the acute toxicity of benzyl alcohol for fish, daphnia and bacteria is > 100 mg/l. For algae, an EC 50 3hrs of 95 mg/l is reported. Under environmental relevant conditions, benzoic acid and its salts have very low acute toxicity, whereas benzyl alcohol has low to moderate acute toxicity.
Exposure

Worldwide production capacity of benzoic acid is estimated at 700 kt per year. The major outlet (75%) for benzoic acid is as a chemical intermediate in the production of phenol, which in turn is mainly used to produce caprolactam. The next largest outlet is as a feedstock for sodium benzoate (10%) and chemical synthesis of plasticizers (5%).

Worldwide production capacity of sodium benzoate is estimated at 100 kt per year. The major outlet for sodium benzoate is as preservative in food and beverages (60%). Second most important market is cooling liquids (10%). The main function of sodium benzoate in most applications is as preservative.

Worldwide production capacity of potassium benzoate is estimated at 7 kt per year. It is used as a preservative in nonalcoholic beverages.

Worldwide production capacity of benzyl alcohol is estimated at 50 kt. Major use for benzyl alcohol is as curing agent in epoxy coatings (30%), where it becomes chemically bounded after reaction. Other important uses include the use as a solvent in low concentrations in waterborne coatings (10%) and use in paint strippers (10%) and chemical intermediate for synthesis for benzyl esters that are used in the flavor and fragrance industry (10%). The use in paint strippers is limited to uses in industrial settings.

Benzyl alcohol, benzoic acid and its sodium and potassium salt are also used in pharmaceuticals, cosmetics and/or food. Consumer exposure in these specific applications are controlled by the fact that, for all these applications, specific regulatory frameworks (regional and/or national) with authorization/approval procedures and specific advisory bodies exist (inter alia: the US FDA, WHO JECFA, EU SCF, etc), including, on a regular basis, reevaluation of approvals, hazardous properties and factual exposures. According to information from products registers, uses that are not specifically regulated include uses of the substances in different kinds of products e.g. paints, varnishes solvents, cleaning and washing agents, photochemicals and antifreeze agents.

Benzoic acid is a white solid, with a solubility in water of 2.9 g/l and with a vapour pressure of 0.0011 hPa at 20 °C. The log octanol/water partition coefficient was measured to 1.88; the Henry’s law constant = 0.0046-0.022 Pa*m³/mol; and the pKa = 4.2. Sodium benzoate and potassium benzoate are white solids, with solubility in water of 556 g/l and with a vapour pressure of <0.0011 hPa at 20 °C. The log octanol/water partition coefficient were measured to –2.269. Benzyl alcohol is a colorless liquid, with a solubility in water of 40 g/l and with a vapour pressure of 0.13 hPa at 20°C. The log octanol/water partition coefficient was measured to 1.1.

The distribution modeling according to Mackay Level III indicates soil and water to be the favored compartments for the chemicals. However, physical chemical properties and use patterns indicate water to be the main compartment for these substances. None are expected to hydrolyze. All are readily biodegradable. None has bioaccumulative potential.

NATURE OF FURTHER WORK RECOMMENDED

Regarding all the information provided, the substances have low priority for further work.
1. **IDENTITY**

**Category name:** Benzoates

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<td>Benzyl alcohol</td>
<td>100-51-6</td>
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**Physico-chemical properties:**

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<th>Chemical</th>
<th>Appearance</th>
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<th>Boiling point @ 1013 hPa</th>
<th>Vapor pressure (at 20°C)</th>
<th>octanol/water partition coefficient (LogP)</th>
<th>Water Solubility (at 20°C)</th>
<th>Henry’s law constant</th>
<th>pKa</th>
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<td>556 g/l</td>
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<tr>
<td>Potassium benzoate *</td>
<td>White solid</td>
<td>330.6°C</td>
<td>464.9°C</td>
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<td>556 g/l</td>
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*) No data for Potassium benzoate were available, but they are expected to be the same as for sodium benzoate.

**Category Justification:**

The proposed category of this ICCA HPV Benzoates submission consists of the following chemicals:

- **Benzoic Acid**
  - CAS# 65-85-0
- **Benzyl Alcohol**
  - CAS# 100-51-6
Sodium Benzoate
CAS# 532-32-1

Potassium Benzoate
CAS# 582-25-2

The following chemicals (benzylacetate and benzaldehyde) are being used in this ICCA HPV benzoates submission only for supportive data purposes. They are not as such included in this category submission for reasons stated below:

Benzyl Acetate
CAS# 140-11-4

Benzoaldehyde
CAS# 100-52-7

Sponsored in the US EPA HPV Program
Completed SIDS/SIAR
by the Flavor and Fragrance High Production
Volume Consortia (FFHPVC)

The common metabolic pathway of all these substances, adapted from JECFA 1997 and the American Conference of Governmental Industrial Hygienists Documentation of the Threshold Limit Values and Biological Exposure Indices, is provided below (ACGIH, 1986):

R = Na, K, or H
The sodium and potassium salts of benzoic acid are expected to immediately dissociate and form benzoic acid in an aqueous environment. The benzylicacetate, benzylalcohol, benzaldehyde and benzoic acid and its sodium and potassium salt were considered as a single category regarding human health by JECFA as they are all rapidly metabolized and excreted via a common pathway within 24hrs (JECFA 1997). Benzyl acetate, the first compound in the metabolic pathway diagram, is very rapidly hydrolyzed by esterases in several species including man to benzyl alcohol and acetic acid. The benzylalcohol is then very rapidly metabolized as shown in the above diagram and only at very high dose (> 500 mg/kg/day by oral gavage route) some saturation of metabolic pathways occurs. This is among others very well shown in studies on benzylicacetate (see below; from JECFA 1997).

Male B6C3F1 mice and Fischer 344 rats treated either intravenously or orally with 14C-benzyl acetate. The intravenous dose was equivalent to 10 mg/kg bw for mice and 5 mg/kg bw for rats. For oral administration, benzyl acetate was dissolved in corn oil and administered at doses equivalent to 10, 100, or 1000 mg/kg bw for mice and 5, 50, or 500 mg/kg bw for rats. The compound was readily absorbed from the gastrointestinal tract of both species, and about 90% of the total dose was recovered as urinary metabolites after 24h. A small proportion (0.3-1.3%) of the total dose was excreted in the faeces after both intravenous and oral administration. Elimination of benzyl acetate as carbon dioxide or volatile substances was minimal after intravenous treatment and consequently was not determined after oral treatment. Analysis of tissues of animals sacrificed 24 h after intravenous or oral administration of labelled compound showed no 14C activity, indicating that elimination of the label was virtually complete by this time. This clearance pattern indicates that benzyl acetate is readily absorbed and excreted after oral administration. The relative amounts of benzyl acetate absorbed, metabolized, and excreted were unaffected by the size or number of doses administered. Repeated treatment of rats with benzyl acetate at 500 mg/kg bw per day for 14 days, followed by a single dose of labelled compound did not change the clearance pattern. More than 90% of the radio-label in the urine was present as hippuric acid, with minor amounts as benzyl alcohol and benzylmercapturic acid (up to 4%); no unchanged benzyl acetate was found, and the levels of benzoyl glucuronide were not measured. There was no evidence to suggest saturation or reduction of metabolic capacity in either species over the dose range tested. At much higher dosing the proportion of the dose present as benzoyl glucuronide increased with dose, indicating a limited capacity for glycine conjugation only at extreme high dose levels. These studies clearly show, that the compound is rapidly absorbed from the gastrointestinal tract of rats and mice, and about 90% of the total dose is recovered as urinary metabolites after 24h. More than 90% of the radio-label in the urine is present as hippuric acid, with minor amounts as benzyl alcohol and benzylmercapturic acid (up to 4%); no unchanged benzyl acetate was found. Only at very high doses, saturation of these pathways will occur. This clearly shows the rapid pathway of hydrolysis to benzyl alcohol and subsequent oxidation to benzaldehyde to benzoic acid and subsequent conjugation to the hippuric acid. All supports a very rapid absorption, distribution, biotransformation, and excretion of these substances by the common pathway given above.

Repeated dose toxicity studies (information in this SIAR) reveal only sytemic toxic effects (e.g. liver, kidney) of similar nature, at high dose.

For environmental effects the category is less clear, however all are readily biodegradable, non-bioaccumulative and acute toxicity values for water organisms under environmental relevant conditions are similar.

For human health all exposure routes are possible, despite benzoic acid and its salts being solids and benzylalcohol being a liquid. For workers exposure will mainly be by inhalation and by skin, whereas for consumers it will mainly be oral and dermal.
2. GENERAL INFORMATION ON EXPOSURE

Production and use:

Benzoic Acid
Worldwide production capacity is estimated at 700 kt per year. Average operating rate is at max 80% resulting in a production of 560 kt benzoic acid per year. The major outlet (75%) for benzoic acid is in the production of phenol, which in turn is mainly used to produce caprolactam. The next biggest outlet is as a feedstock for sodium benzoate (10%) and chemical synthesis of plasticizers (5%). Benzoic acid is therefore mainly (>80%) used as a chemical intermediate for synthesis of other chemicals, as well as for the production of sodium salt (10%). So it has mainly a controlled use in industrial settings.

Sodium Benzoate
Worldwide production capacity is estimated at 100 kt per year. Average operating rate is at max 75% resulting in a production of 75 kt sodium benzoate per year. The major outlet for sodium benzoate is as a preservative in food and beverages (60%). Second most important market is cooling liquids (10%). The main function of sodium benzoate in most applications is as a preservative.

Potassium Benzoate:
Worldwide production capacity is estimated at 7 kt per year. It is used as a preservative in nonalcoholic beverages.

Benzyl Alcohol
Worldwide production capacity is estimated at 50 kt per year. Average operating rate is at max 80% resulting in a production of 40 kt benzyl alcohol per year. The major use for benzyl alcohol is as a curing agent in epoxy coatings (30%), where it becomes chemically bound after reaction. Other important uses are as a solvent in low concentrations in waterborne coatings (10%), and use in paint strippers (10%) and as chemical intermediate for synthesis of benzyl esters that are used in the Flavor and Fragrance industry (10%). The use in paint strippers is limited to uses in industrial settings.

Benzylalcohol, benzoic acid and its sodium and potassium salt have been used for decades in pharmaceuticals, cosmetics and/or food as preservatives and flavoring/fragrance agents

Information in Product registers:
According to information in Product Registers the substances are used in different kinds of products e.g. paints, varnishes, solvents, cleaning and washing agents, photochemicals and antifreeze agents.

Release into the environment during production and use:
In DSM Geleen The Netherlands, during production, about 650 kg/year of benzylalcohol are emitted into the atmosphere (< 0.01 % of production volume). Based on the amount benzylalcohol discharged to the DSM WWTP, it can be calculated that the influent concentration of the WWTP is at about 1 ug/l. Because of its ready biodegradability and the existing dilution of effluent to the receiving water, the concentration in the receiving water will be < 0.01 ug/l.
In DSM Rotterdam The Netherlands, during production sodium benzoate is emitted to air at < 0.01 % of the production volume. For benzoic acid this is < 0.001 %.
2.1 Environmental Exposure and Fate

Distribution modelling using Mackay Level III (the EPA default: equal releases (10,000 kg/hr) and equal distribution to all compartments was used) indicates water (34.8-50%) and soil (48.4-64.2%) to be the main compartment for all four chemicals. None are expected to volatilize to the atmosphere (< 1.51%), nor to adsorb to sediment (< 0.09 %) (Meylan & Howard, 1999). However physical chemical properties and use patterns indicate water to be the main compartment for these substances.

### Distribution (%) according to Fugacity Level III

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<th>Water</th>
<th>Soil</th>
<th>Sediment</th>
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<tbody>
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<td>Potassium benzoate</td>
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<td>1.61e-007</td>
<td>45.3</td>
<td>54.6</td>
<td>0.0755</td>
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<tr>
<td>Benzyl alcohol</td>
<td>100-51-6</td>
<td>1.51</td>
<td>50.0</td>
<td>48.4</td>
<td>0.0923</td>
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</tbody>
</table>

Based on structure and organic chemistry rules (e.g. bonding in organic molecules, activation energy, reactivity, transformations, addition, substitution, elimination) no hydrolysis is expected at pH ranges of 4 - 11.

The calculated photodegradation for benzyl alcohol and the benzoates are 50% after 1.3 to 3 days (Meylan and Howard, 1999), and the measured photodegradation for benzoic acid is 90% after 140 minutes (Matthews, 1990).

### Biodegradation and Bioaccumulation

All four chemicals are readily biodegradable (> 90% after 28 days) both aerobically (MITI, 1992; Zahn & Wellens, 1980; Salanitro et al., 1988) and anaerobically (Battersby & Wilson, 1989; Horowitz et al., 1982).

*(Benzoic acid is used as positive control in OECD Guideline for ready biodegradability testing).*

From the results of numerous removal experiments the main elimination pathway for the chemicals is biotic mineralization.

The octanol/water partition coefficient of all compounds indicates a low potential for bioaccumulation. This is also supported by the rapid biotransformation and/or excretion of these compounds in urine in mammals.

2.2 Human Exposure

For human health all exposure routes are possible, despite benzoic acid and its salts being solids and benzyl alcohol being a liquid. For workers exposure will mainly be by inhalation and by skin, whereas for consumers it will mainly be oral and dermal.
Consumer exposure:

Benzoic acid, benzylalcohol, sodium benzoate and potassium benzoate are widely used in food, cosmetic and pharmaceutical applications as preservatives and flavoring/fragrance agents. Benzoic acid and benzylalcohol are naturally occurring (Merck Index, 1996). Consumer exposure in these specific applications are controlled by specific regulatory frameworks (regional and/or national) with authorization/approval procedures and specific advisory bodies (among others US FDA, WHO JECFA, EU SCF, etc). A re-evaluation of approvals, hazardous properties and factual exposures (among others compliance to the ADI) inclusive, are performed on a regular basis. According to information in Product Registers the substances are used in different kinds of products e.g. paints, varnishes, solvents, cleaning and washing agents, photo chemicals and antifreeze agents. Benzoic acid and sodium benzoate are under re-evaluation at the EU Scientific Committee for Food. From preliminary information (June 2001) re-approval is expected for these substances. The Joint FAO/WHO Expert Committee on Food Additives (JEFCA) has established a group Acceptable Daily Intake (ADI) for benzoic acid and its salts and benzyl alcohol, benzyl acetate and benzaldehyde of 5 mg benzoic acid equivalent/kg bodyweight. This group ADI is based on the structural similarity and common metabolic fate of these chemicals (WHO, 1997).

Worker exposure:

Companies have provisionally advised exposure limits for benzoic acid and its salts as well as for benzyl alcohol. Also the US WEEL (Workplace Environmental Exposure Limit) Committee of the AIHA has set limits for benzyl alcohol at a value of 10-ppm (44 mg/m$^3$) 8hr TWA.

In the several past decades of production, no cases of health complaints (sensitisation inclusive) have occurred.

Also from companies that use the substances no health complaints (sensitisation inclusive) have ever been reported.
3. **HUMAN HEALTH**

3.1 Effects on Human Health

**In general:**

- Benzoate from potassium benzoate and sodium benzoate will change from the ionized form to the undissociated benzoic acid molecule under physiological conditions.
- Benzyl acetate, benzyl alcohol and benzaldehyde are all metabolized to benzoic acid and it is therefore reasonable to assume that the results of studies on members of the group will apply to the others.
- All benzyl compounds are rapidly absorbed, and rapidly and completely excreted in the urine. The main transformation of benzoic acid is the formation of hippuric acid.
- It is considered also that data gaps for one substance can be adequately addressed by the existing data for the other compounds.

Only the results of the critical studies are given, but for most endpoints additional studies exist (see full IUCLID documents), that support the results in the critical studies.

3.1.1 Acute Oral Toxicity

Three of the four compounds were tested according to Guideline methods. All demonstrated very low or low toxicity, especially the benzoate salts. Only benzyl alcohol has a LD50 slightly less than 2000mg/kg bw and should therefore be considered as harmful. Although the studies on potassium benzoate were not Guideline studies, these were accepted because the results showed low toxicity, similar to the sodium salt.
### 3.1.2 Acute Dermal Toxicity

Two of the compounds were tested for acute dermal toxicity. Both demonstrated low toxicity.

<table>
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<th>Chemical</th>
<th>Species</th>
<th>Protocol</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
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### Chemical Species  Protocol Result  Reference

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<th>Protocol</th>
<th>Result</th>
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<td>LD50 = &gt;10,000 mg/kg</td>
<td>Kravets-Bekker &amp; Ivanova, 1970</td>
</tr>
<tr>
<td></td>
<td>mouse</td>
<td>other</td>
<td>LD50 = &gt;10,000 mg/kg</td>
<td>Kravets-Bekker &amp; Ivanova, 1970</td>
</tr>
<tr>
<td></td>
<td>guinea pig</td>
<td>other</td>
<td>LD50 = &gt;10,000 mg/kg</td>
<td>Kravets-Bekker &amp; Ivanova, 1970</td>
</tr>
</tbody>
</table>
3.1.3 Acute Inhalation Toxicity

Two of the compounds were tested for acute inhalation toxicity according to Guideline procedures; both demonstrating very low toxicity.

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Species</th>
<th>Protocol</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzoic acid</td>
<td>rat</td>
<td>EPA OTS 798.1150</td>
<td>LC50 = &gt;12.2 mg/l/4h. No mortality at 12.2 mg/l as dust.</td>
<td>IRDC#163-282, 1974</td>
</tr>
<tr>
<td>Benzyl alcohol</td>
<td>rat</td>
<td>OECD Guide-line 403 and GLP</td>
<td>LC_{50} = &gt; 4.178 mg/l/4h. No mortality at 4.178 mg/l as aerosol</td>
<td>Bayer AG, 1990</td>
</tr>
</tbody>
</table>

In conclusion: The compounds exhibit low acute toxicity, except benzylalcohol that has an oral LD50 slightly less than 2000 mg/kg bw and should therefore be considered as harmful by the oral route.

3.1.4 Skin Irritation

Three of the compounds were tested for skin irritation according to Guideline procedures; the potassium salt should be similar to the sodium salt, therefore being non-irritating.

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Species</th>
<th>Protocol</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzoic acid</td>
<td>Rabbit</td>
<td>EPA OTS 798.4470</td>
<td>not irritating</td>
<td>IRDC # 163-282</td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td>Rabbit</td>
<td>OECD Guide-line 404</td>
<td>not irritating</td>
<td>RCC NOTOX - study no. 014658</td>
</tr>
</tbody>
</table>

3.1.5 Eye Irritation

Three of the compounds were tested for eye irritation according to Guideline procedures; the potassium salt should be similar to the sodium salt, therefore being non-to slightly irritating.
<table>
<thead>
<tr>
<th>Chemical</th>
<th>Species</th>
<th>Protocol</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzoic acid</td>
<td>Rabbit</td>
<td>Directive 84/449/EEC</td>
<td>highly irritating</td>
<td>RCC NOTOX - study no. 0847/1084, 1988</td>
</tr>
<tr>
<td></td>
<td>rabbit</td>
<td>EPA OTS 798.4500</td>
<td>severely irritating</td>
<td>IRDC #163-282</td>
</tr>
<tr>
<td></td>
<td>rabbit</td>
<td>OECD Guide-line 405</td>
<td>slightly irritating</td>
<td>RCC NOTOX - study no. 014669, 1988</td>
</tr>
<tr>
<td></td>
<td>rabbit</td>
<td>Other: limited data</td>
<td>highly irritating</td>
<td>Smyth, H. F. et al., 1951; reported in US NTP: TR 343, 1989</td>
</tr>
</tbody>
</table>

**In conclusion:** Benzoic acid and benzyl alcohol are slightly irritating to the skin, while sodium and potassium benzoate are not skin irritating. Benzoic acid and benzyl alcohol are irritating to eyes, and sodium and potassium benzoate are only slightly irritating to eyes.

### 3.1.6 Sensitization

The available studies for benzoic acid gave no indication for a sensitizing effect in animals, however some weak positive reactions were recorded with the human patch test. Benzyl alcohol was non-sensitizing in the Draize and Guinea Pig Maximization Tests, but a positive sensitizer in the Freund’s Complete Adjuvant Test and the guinea pig Open Cutaneous Test and demonstrated a maximum incidence of sensitization of 1% in clinical human patch testing. A clinical dermatological study showed positive patch test reactions in 0.2% of the patients treated with 5% sodium benzoate in petrolatum. It has been suggested that this very low potential of sodium benzoate to elicit a non-immunologic contact urticaria may be due to the formation of benzoic acid at skin contact.
Chemical | Species | Protocol | Result | Reference |
---|---|---|---|---|
Benzoic acid | guinea pig | Draize | not sensitizing | BRL #9347, 1979 |
| guinea pig | Guinea pig maximization test | not sensitizing | Gad, 1986 |
| human | Patch test | occasional positive result | Rademaker & Forsyth, 1989; Forsbeck & Skog, 1977 |
Sodium benzoate | Human | Patch test | 5 of 2045 patients positive | Brasch, J. et al., 1993 |
| human | Patch test | nonimmunologic contact urticaria | Nethercott, J.R., 1984 |
Benzyl alcohol | guinea pig | Draize Test | not sensitizing | Klecak, G. et al., 1977 |
| guinea pig | Guinea pig maximization test | not sensitizing | Klecak, G. et al., 1977 |
| guinea pig | Freund's complete adjuvant test | sensitizing | Klecak, G. et al., 1977 |
| guinea pig | Open epicutaneous test | sensitizing | Klecak, G. et al., 1977 |
| human | Patch-Test | sensitizing | Malten, K. E. et al., 1984; Mitchell, J. C. et al., 1982; Nethercott, J. R., 1982 |

**In conclusion:** No firm conclusion on the sensitizing potential of benzyl alcohol can be made due to the varied results with the various tests. Both benzoic acid and sodium benzoate were non-sensitizing in animal test but showed a very low incidence in humans (patients) tested by the patch test.

CICAD conclusion on benzoic acid and sodium benzoate was: “However, both substances are known to cause non-immunologic immediate contact reactions. This effect is scarce in healthy subjects, while in patients with frequent urticaria or asthma, symptoms or exacerbation of the symptoms were observed”.

**3.1.7 Repeat Dose Toxicity**

Several short term repeated dose toxicity studies are available (see IUCLID documents) on compounds of the group (as well as benzaldehyde and benzyl acetate) and support the outcome and No Observed Adverse Effect Level (NOAEL) of the longer term studies given below.
In a 4-generation study 20 rats/sex/group were dosed continuously by diet with 375 or 750 mg/kg/day benzoic acid. In all 4 generations no influence on growth (weight, weight gain and food efficiency (measured by protein efficiency)) and organ weights was found. The animals of the 3rd generation were killed and examined histopathologically after 16 weeks (after lactation of the pups). No histo-pathological findings were found. In the paper, no information is given on the organs investigated, however the robustness of the total study, the reputation of the investigators, as well as the reputation of the Professor who did the histopathologic investigation, a high scientific quality has to be assumed even though the studies were performed many years ago. From other parameters it can be assumed that as a minimum the brains, heart, liver, kidney, testis and spleen were examined.

Feeding of 375 mg/kg/day led to prolongation of survival compared to controls
NOAEL ≥ 750 mg/kg/day
(Kieckebusch & Lang, 1960)

Due to missing hematological and clinical chemistry investigations in all studies only a preliminary NO(A)EL of about 800 mg/kg can be derived for rats which is based on the studies from Kieckbusch & Lang (1960), Kreis et al. (1967) and Bio-Fax (1973) (Details to be found in the IUCLID).

A 21 day dermal study with male/female New Zealand white rabbits dosed with 100, 500, or 2500 mg/kg bw benzoic acid 5 days/week showed no compound related effects in behavior, body weight organ weights, clinical laboratory tests or survival. Very slight dermal irritation was noted for 1/8 rabbits at the 2500 mg/kg level.
NOAEL = 2500 mg/kg/day
(IRDC# 163-675, 1981)

Four groups of 10 CD rats/sex/group were exposed to 0, 25, 250 or 1200 mg benzoic acid dust aerosol/m³ (analytical concentration; MMAD 4.7 µm) for 6 hours/day and 5 days/week over 4 weeks. At ≥ 25 mg/m³ an increased incidence of interstitial cell infiltrate and interstitial fibrosis in the lungs in treated animals compared with controls was seen. However, there was no clear dose-dependency. A concentration of ≥ 250 mg/m³ resulted in upper respiratory tract irritation and decreased absolute kidney weights in females. In the highest-dose group one rat/sex died and the body weight gain was decreased in males and females. Other effects included a decrease in platelets (males/females), absolute/relative liver weights (males) and trachea/lung weights (females).
LOAEC (local effect) = 25 mg/m³ (However no clear dose-response was observed).
NOAEC (systemic) = 25 mg/m³
(IRDC# 163-676,1981)

In a 10-day study, rats received sodium benzoate in feed. At the lowest tested concentration of 1358 mg/kg changes in serum cholesterol levels occurred in females. At doses of 1568 mg/kg and above changes in further serum parameters and an increased relative liver weight were described. Histopathological changes of the liver, increased relative kidney weights and disorders of the central nervous system were seen after dosing via diet with ≈ 1800 mg/kg.(Fujitani, 1993)

A 90-day study with male/female Sherman rats given 640, 1280, 3145, or 6290 mg/kg/day USP sodium benzoate continuously in feed showed no adverse effects at ≤ 3145 mg/kg bw. There was increased mortality (4/8 died); reduced weight gain; increased weight of livers and kidneys; pathological lesions (not specified) in livers and kidneys at 6290 mg/kg bw.
NOAEL = 3145 mg/kg bw/day
(Deuel, 1954)
For mice the NO(A)EL of sodium benzoate is higher. According to a 35 day study (by drinking water) no effects were observed at 3000 mg/kg bw. At this dose level also in a chronic study no toxic effects were found in histopathological examinations (see 3.1.9 paragraph 2, Toth, 1984).

A 13-week study with male/female F344/N rats given 50, 100, 200, 400, or 800 mg/kg/day benzyl alcohol by gavage showed staggering, respiratory difficulty, and lethargy in rats of the high dose group. Hemorrhages occurred around the mouth and nose, and there were histologic lesions in the brain, thymus, skeletal muscle, and kidney. There were reductions in relative weight gain in male rats dosed with 800 mg/kg and in female rats dosed with 200 mg/kg or more. No notable changes in bw gain or compound-related histopathologic lesions were observed in rats from the lower dose groups.

In the 2-y study (see 3.1.9 paragraph 3), however, no notable changes were found on bw or bw gain at 200 or 400 mg/kg/d. The NOAEL in this 2-y rat study was 400 mg/kg/day, the highest dose tested.

NOAEL = 400 mg/kg/day (based on investigated parameters and taking into account the bw results of the 2-y study)


A 13-week study with male/female B6C3F1 mice given 50, 100, 200, 400, or 800 mg/kg/day benzyl alcohol by gavage showed staggering in mice dosed with 800 mg/kg, after dosing during the first 2 weeks of the study. Staggering after dosing occurred during the first 2 w of the study in mice dosed with 800 mg/kg. There were reductions in relative weight gain in male mice dosed with 400 or 800 mg/kg, and in female mice dosed with 200 mg/kg or more. No notable changes in bw gain or compound-related histopathologic lesions were observed in mice from the lower dose groups.

In the 2-y study (see 3.1.9 paragraph 4), however no notable changes were found on bw or bw gain at 200 mg/kg/d. The NOAEL in this 2-y mice study was 200 mg/kg/day the highest dose tested.

NOAEL = 200 mg/kg/day (based on reduction of relative weight gain only and taking into account the bw results of the 2-y study).


It should be noted: these studies were done by gavage (leading to greater toxicity due to the “bolus effect”). The administration of the benzyl compounds by gavage are likely to reveal changes at lower doses compared to studies where the substances are applied in the diet, leading to a distribution in the body over time.

In conclusion: For benzoic acid repeated dose (long-term inclusive) oral toxicity gives a NOAEL of 800 mg/kg/day. For the salts values > 1000 mg/kg/day are obtained. At higher doses increased mortality, reduced weight gain, liver and kidney effects were observed. For benzyl alcohol taking into account also the results of the long-term studies indicate a NOAEL > 400 mg/kg bw/d for rats and > 200 mg/kg bw/d for mice, however it should be taken into account that in these studies administration was by gavage, at which bolus dosing occurs and saturation of metabolic pathways is likely to occur. At high doses, effects on bodyweights, lesions in the brains, thymus, skeletal muscle and kidney were observed.

It can be concluded that benzoic acid and its salts exhibit very low repeated dose toxicity. Benzyl alcohol exhibits low repeated dose toxicity.
3.1.8 Genetic Toxicity

3.1.8.1 Genetic Toxicity in vitro

**Benzoic acid** was not mutagenic in Ames tests with and without metabolic activation (EGG# 580-192-1-78, 1978). The Sister Chromatid Exchange assay with human lymphocytes was negative - no metabolic activation was used (Jansson, 1988; Tohda, 1980). A Chromosome Aberration study with CHL cells was ambiguous - no metabolic activation was used (Ishidate, et al., 1984). A recombination assay with *Bacillus subtilis* H17 and M45 was positive (reported with minimal documentation in an abstract, Nonaka, 1989).

**Sodium benzoate** was not mutagenic in Ames tests with and without metabolic activation (Ishidate, et al., 1984). A cytogenetic assay using anaphase preparations of cultured human embryonic lung cells was negative - no metabolic activation was used (FDA PB 245453, 1974). An *Escherichia coli* reverse mutation assay was negative with and without metabolic activation (Prival, 1991). A cytogenetic assay using CHL cells was positive without metabolic activation (Ishidate, et al., 1984; Ishidate & Odashima, 1977). Sister Chromatid Exchange assays using Chinese hamster cells or human lymphocytes were positive without metabolic activation (Abe & Saski, 1977; Xing & Zhang, 1990). A recombination assay with *Bacillus subtilis* H17 and M45 was positive (reported with minimal documentation in an abstract, Nonaka, 1989).

**Potassium benzoate** tested positive in a recombination assay using *Bacillus subtilis* H17 and M45, with and without metabolic activation (Ishizaki & Ueno, 1989).

**Benzyl alcohol** was not mutagenic in Ames tests with and without metabolic activation (US NTP Technical Report No. TR 343, 1989). *Escherichia coli* reverse mutation assay was negative with and without metabolic activation (Leifer et al., 1981). A cytogenetic assay using CHO cells was negative without metabolic activation and positive with metabolic activation (Anderson et al., 1990; Zeiger et al., 1990). A Sister Chromatid Exchange assay using CHO cells was ambiguous with and without metabolic activation (US NTP Technical Report No. TR 343, 1989). A recombination assay with *Bacillus subtilis* H17 and M45 was positive (reported with minimal documentation, Kuroda et al., 1984).
## Summary of (non-Ames) in vitro results:

<table>
<thead>
<tr>
<th>Species (test system)</th>
<th>End-point</th>
<th>without metabolic activation</th>
<th>with metabolic activation</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzoic acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human lymphoblastoid cells (transformed by Epstein-Barr virus)</td>
<td>Sister chromatid exchange</td>
<td>Negative</td>
<td>NT</td>
<td>tested positive (no further information available, only summary given) result given as negative in: Ishidate et al. (1984)</td>
</tr>
<tr>
<td><strong>Bacillus subtilis</strong> H17, M45</td>
<td>Recombination assay</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese hamster cells (CHL)</td>
<td>Chromosome aberration</td>
<td>?</td>
<td>NT</td>
<td></td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human embryonic lung cells</td>
<td>Anaphase preparation</td>
<td>Negative</td>
<td>NT</td>
<td></td>
</tr>
<tr>
<td><strong>E.coli</strong> WP2</td>
<td>Reverse mutation assay</td>
<td>Negative</td>
<td>Negative</td>
<td>tested positive (no further information available, only summary given)</td>
</tr>
<tr>
<td><strong>Bacillus subtilis</strong> H17, M45</td>
<td>Recombination assay</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese hamster cells (CHL)</td>
<td>Chromosome aberration</td>
<td>Positive</td>
<td>NT</td>
<td></td>
</tr>
<tr>
<td>Chinese hamster cells (DON)</td>
<td>Sister chromatid exchange</td>
<td>Positive?</td>
<td>NT</td>
<td>slight increase without dosage effect</td>
</tr>
<tr>
<td>Human lymphocytes</td>
<td>Sister chromatid exchange</td>
<td>Positive</td>
<td>NT</td>
<td></td>
</tr>
<tr>
<td>Potassium benzoate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bacillus subtilis</strong> H17, M45</td>
<td>Recombination assay</td>
<td></td>
<td></td>
<td>tested positive (limited data)</td>
</tr>
<tr>
<td>Benzyl alcohol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>E.coli</strong></td>
<td>Reverse mutation assay</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Chinese hamster cells (CHO)</td>
<td>Cytogenetic assay</td>
<td>Negative</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Chinese hamster cells (CHO)</td>
<td>Sister chromatid exchange</td>
<td>?</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td><strong>Bacillus subtilis</strong> H17, M45</td>
<td>Recombination assay</td>
<td></td>
<td></td>
<td>tested positive (limited data)</td>
</tr>
</tbody>
</table>

? = ambiguous
NT = not tested

**In conclusion:** Studies of these chemicals in the Ames point mutation assay do not show evidence of mutagenicity. However, some have been reported to be positive in the less commonly used Bacillus subtilis recombination assay. In a number of cases adverse effects on the chromosome could be noticed, however also negative and/or equivocal results were reported.
However many higher-level *in vivo* tests (clastogenicity inclusive) were negative (see 3.1.8.2).

### 3.1.8.2 Genetic Toxicity *in vivo*

General remark: Since the sodium salt of benzoic acid instantaneously dissociates to the benzoic acid, the studies with sodium benzoate are also representative for benzoic acid and potassium benzoate.

A cytogenic assay in male rats given single or multiple gavage doses of 50, 500, or 5,000 mg/kg **sodium benzoate** showed no significant increase in chromosomal aberrations in the bone marrow.

(FDA PB 245453, 1974)

A dominant lethal assay using male rats given single or multiple gavage doses of 50, 500, or 5,000 mg/kg **sodium benzoate** was non-mutagenic.

(FDA PB 245453, 1974)

**Remark:** IPCS CICAD 26 (2000) mentioned this dominant lethal assay as a positive result, however evaluation of the raw data in the original report (by experts of the industry consortium and a recent independent review by Prof. R. Kroes) gives no support for this. In addition the authors of the study clearly conclude negative. FDA also evaluated this study as negative. In addition sodium benzoate doesn’t contain a structural alert for genotoxicity.

A host mediated assay using male rats given multiple gavage doses of 50, 500, or 5,000 mg/kg **sodium benzoate** showed no elevation of mutant frequencies in *Salmonella typhimurium* G46; no elevation of mutant frequencies in *Salmonella typhimurium* TA 1530; no increase in recombinant frequencies in *Saccharomyces cerevisiae* D3.

(FDA PB 245453, 1974)

A host mediated assay using male rats given a single gavage dose of 50, 500, or 5,000 mg/kg **sodium benzoate** showed an elevation of mutant frequencies in *Salmonella typhimurium* TA 1530 in the intermediate dose level; the other doses were negative.

(FDA PB 245453, 1974)

A Mouse Micronucleus assay using 50, 100, 200 mg/kg **benzyl alcohol** by i.p. injection was negative at all doses tested.

(Hayashi et al., 1988)

A Replicative DNA Synthesis assay using male Fischer 344 rats given a single dose of 0, 300 or 600 mg/kg bw **benzyl alcohol** by gavage was negative at all doses tested.

(Uno et al., 1994)

A Replicative DNA Synthesis assay using male B6C3F1 male mice given a single dose of 0, 400 or 800 mg/kg bw **benzyl alcohol** by gavage was negative at all doses tested.

(Miyagawa et al., 1995)

A Drosophila melanogaster SRL assay with **benzylalcohol** 5000 ppm (feed) and 8000 ppm (injection) was negative (Fourman, et al., 1994)

**Summary of genetic toxicity *in vivo* results:**
<table>
<thead>
<tr>
<th>Species (test system)</th>
<th>End-point</th>
<th>Results</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium benzoate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male Sprague Dawley rats</td>
<td>Cytogenetic Assay (bone marrow)</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>male ICR mice</td>
<td>Host-Mediated Assay (tester strains Salmonella typhimurium TA 1530, G 46 and Saccharomyces cerevisiae D3)</td>
<td>Negative</td>
<td>elevated mutant frequency with TA 1530 in the intermediate single gavage dosing only (clear negative after multiple gavage dosing)</td>
</tr>
<tr>
<td>male random bred rats</td>
<td>Dominant Lethal Assay</td>
<td>Negative</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Benzyl alcohol</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>male mice</td>
<td>Mouse Micronucleus Assay</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>male Fischer 344 rats</td>
<td>Replicative DNA Synthesis</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>male B6C3F1</td>
<td>Replicative DNA Synthesis</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Drosophila melanogaster</td>
<td>SLR assay</td>
<td>Negative</td>
<td></td>
</tr>
</tbody>
</table>

In addition data from *in-vivo* genotoxicity studies on benzyl acetate and benzaldehyde (JECFA report, 1997) are supportive evidence for the non-genotoxicity of benzyl alcohol and benzoic acid and its salts.
Summary genetic toxicity \textit{in vivo} results:

<table>
<thead>
<tr>
<th>Species (test system)</th>
<th>Endpoint</th>
<th>Dose</th>
<th>Results</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzaldehyde</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>\textit{Drosophila melanogaster}</td>
<td>Sex-linked recessive lethal mutation</td>
<td>150 ppm (feed), 2500 ppm (injection)</td>
<td>Negative</td>
<td>Woodruff et al. (1985); US NTP (1990)</td>
</tr>
<tr>
<td><strong>Benzyl acetate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>\textit{Drosophila melanogaster}</td>
<td>Sex-linked recessive lethal mutation</td>
<td>300 ppm (feed), 20,000 ppm (injection)</td>
<td>Negative</td>
<td>US National Toxicology Program (1993)</td>
</tr>
<tr>
<td>Mouse bone-marrow cells</td>
<td>Chromosomal aberration</td>
<td>325-1700 mg/kg bw (i.p.)</td>
<td>Negative</td>
<td>US National Toxicology Program (1993)</td>
</tr>
<tr>
<td>Mouse bone-marrow cells</td>
<td>Micronucleus formation</td>
<td>312-1250 mg/kg bw (i.p.)</td>
<td>Negative</td>
<td>US National Toxicology Program (1993)</td>
</tr>
<tr>
<td>Mouse peripheral blood</td>
<td>Micronucleus formation</td>
<td>3130-50 000 ppm in diet</td>
<td>Negative</td>
<td>US National Toxicology Program (1993)</td>
</tr>
<tr>
<td>Mouse bone-marrow cells</td>
<td>Sister chromatid exchange</td>
<td>325-1700 mg/kg bw (i.p.)</td>
<td>Negative</td>
<td>US National Toxicology Program (1993)</td>
</tr>
</tbody>
</table>

In conclusion: The compounds exhibit no genotoxicity in several \textit{in-vivo} assays evaluating different endpoints.

3.1.9 Carcinogenicity

In a 2-year carcinogenicity study, groups of 50 male and 52 female Fischer 344 rats, four to five weeks old, received diets containing 1% (500 mg/kg bw per day) or 2% (1000 mg/kg bw per day) \textit{sodium benzoate} for 18-24 months. Controls, consisting of 25 male and 43 female rats, received basal diet. Food intake was adequately controlled to avoid an excess; tap water was available \textit{ad libitum}. Survival was very poor in all groups, due to intercurrent sialodacryoadenitis and mycoplasma infections. All surviving animals were sacrificed between 18 and 25 months, all were autopsied, and various tissues were examined histopathologically. No adverse clinical signs directly attributable to treatment were observed, and only negligible differences in average body weight and mortality rate were seen between the treated and control groups. Although a variety of tumors occurred among treated and control rats of each sex, they were of similar type and incidence. (Sodemoto & Enomoto, 1980)

Poor survival in all groups, due to infections, limits the usefulness of this study.

A lifelong study using male/female Swiss Albino mice given 2% \textit{sodium benzoate} continuously in drinking water showed no carcinogenic effect.

In the main study, a 2% solution of sodium benzoate (purity, 99%) was administered in the drinking water to groups of 50 male and 50 female five-week-old mice for their lifetime. Groups of 100 males and 100 females were used as untreated controls. Both treated and control animals were ‘carefully checked'; their body weights were measured weekly, and gross pathological changes were recorded. The animals were either allowed to die or were sacrificed when moribund. Complete necropsies were performed on all animals, and the liver, spleen, kidneys, bladder, thyroid, heart, pancreas, testes, ovaries, brain, nasal turbinates, at least four lobes of the lungs, and organs with
gross pathological changes were examined histologically. The average daily intake of sodium benzoate was 124.0 mg for males and 119.2 mg for females on the basis of daily water consumption of 6.2 and 5.9 ml, respectively. The dose of sodium benzoate was equivalent to 6200 mg/kg bw per day for males and 5960 mg/kg bw per day for females. Treatment had no effect on survival or the incidence of tumors.

(Toth, 1984).
This study is sufficiently reliable due to the number of animals and detailed histopathological examinations.

In a 2-year carcinogenicity study, benzyl alcohol was administered in corn oil by gavage to groups of 50 Fischer 344/N rats of each sex at a dose of 0, 200, or 400 mg/kg bw per day on five days a week for 103 weeks. The rats were observed twice daily, and body weights were recorded weekly for the first 12 weeks and once a month thereafter. Gross necropsy was performed on all animals and 49 tissues and organs, including brain, kidney, pancreas, and skeletal muscle, from all female rats and from male rats in the vehicle control and high-dose groups and those in the other groups that died before 22 months or which had gross lesions were examined histologically. The mean body weights of treated and control animals were comparable throughout the study. No compound-related clinical signs were observed, although a sialoadenitis viral infection was widespread among the study animals in the third month. The survival of treated females was significantly lower than that of vehicle controls: 70% of controls, 34% of low-dose females, and 34% of high-dose females; this was due to a much higher incidence of accidental deaths related to the gavage process. Survival among the male rats was comparable in all groups: 56% of controls, 54% at the low dose, and 48% at the high dose. Cataracts and retinal atrophy were observed at increased incidences in rats at the high dose. The authors attributed this effect to the proximity of this group of animals to fluorescent light for most of the study. An increased incidence of hyperplasia of the forestomach epithelium was seen (not statistically significant) in male rats: control, 0/48; low dose, 0/19; high dose, 4/50. Hemorrhage and foreign material in the respiratory tract seen in treated rats that died before the end of the study were suggested by the authors to have been the result of either direct deposition of material into the lung during gavage 'accidents' or the anaesthetic properties of benzyl alcohol resulting in reflux of gavage material and aspiration into the lungs. No pancreatic acinar-cell adenomas were reported, and no other effects of treatment were seen at gross necropsy or histopathological examination.

(US National Toxicology Program, 1989)

In conclusion: The compounds exhibit no carcinogenicity.
3.1.10 Toxicity to Reproduction

In a 4-generation study 20 rats/sex/group were dosed continuously by diet with 375 or 750 mg/kg/day benzoic acid. In all 4 generations, no effects on fertility (“Fortpflanzung”) and lactation (“Aufzugt der Jungen”) were found. In addition a so-called “Alters Paarung” after 48 weeks gave no influence on start of menopause.

NOAEL (Parental)  > 750 mg/kg/day
NOAEL (F1 Offspring)  > 750 mg/kg/day
NOAEL (F2 Offspring)  > 750 mg/kg/day
(Kieckebusch & Lang, 1960)

In addition data from reprotoxicty studies on benzyl acetate and benzaldehyde (JECFA report 1997) give supportive evidence for the non-reprotoxicity of benzyl alcohol and benzoic acid and its salts.

The potential reproductive toxicity of benzyl acetate was assessed by examining sperm morphology, vaginal cytology, and the weights of male reproductive organs at the end of the 13-week feeding study (US National Toxicology Program, 1993) in mice. Dietary levels of 3130-50 000 ppm benzyl acetate (> 3000 mg/kg bw/d) had no effect on the weights of the epididymis, cauda epididymis, or testis or on sperm motility or density or the percent of abnormal sperm. The mean length of the estrous cycle of mice at the high dose was significantly greater than that of the control group. This effect was associated with a significant decrease in body weight.

(Morrissey et al., 1988)

The potential reproductive toxicity of benzyl acetate was assessed by examining sperm morphology, vaginal cytology, and the weights of male reproductive organs at the end of the 13-week feeding study in rats. Dietary levels of 3130-50 000 ppm benzyl acetate (> 2000 mg/kg bw/d) had no effect on the weights of the epididymis, cauda epididymis, or testis, on sperm motility, or on the density or percent of abnormal sperm.

(US National Toxicology Program, 1993)

A single study was conducted to examine the potential reproductive toxicity of benzaldehyde, and the report was available as a translation from Romanian. A group of 10 rats of breeding age were given 2 mg benzaldehyde in oil (type not specified) by gavage every other day for 32 weeks, equivalent to about 5 mg/kg bw per day. Ten controls were used. Two pregnancies in each rat, one at 75 days and one at 180 days, were studied. The end-points examined included the number of pregnant females, number of offspring born, pup body weight at days 7 and 21 post partum, and pup viability.

At the end of treatment, the body weights of control and treated rats were similar: 265 g and 260 g, respectively. It was reported that fewer females in the group given benzaldehyde than in the control group became pregnant; however, no data or statistical analyses were presented. The authors concluded that treatment did not significantly modify any of the parameters studied. No further details were available.

The NOAEL was about 5 mg/kg bw per day.

(Sporn et al., 1967)

In addition to compound related effects on reproductive organs (gross and histopathology examination) could be found in the (sub) chronic studies in rats and mice with benzyl acetate, benzyl alcohol, benzaldehyde, sodium benzoate and supports a non-reprotoxic potential of these compounds (see studies in sections on repeated dose toxicity and carcinogenicity).

In conclusion: According to IPCS CICAD 26 (2000) (only evaluating benzoic acid and sodium benzoate), no clear statement on the reproductive effects can be given on basis of the Kieckebusch & Lang (1960) and Toth (1984) studies only. However, critical evaluation of the original paper of
the Kieckebusch & Lang study gives confidence of an adequately performed study although it was performed many years ago. In addition, reprotoxicity studies on benzaldehyde and benzylacetate and the fact that no compound related effects on reproductive organs were found in the (sub)chronic studies with all the compounds supports the lack of reproductive potential. Therefore the available consistent data on compounds in this group (data on benzyl acetate and benzaldehyde inclusive) taken as a whole are sufficient to demonstrate the lack of reprotoxic potential.

3.1.11 Developmental Toxicity

Pregnant Wistar rats were treated on day 9 of gestation with one dose of 510 mg/kg benzoic acid in carboxymethylcellulose. Animals were sacrificed on Day 20 of gestation and the uterus observed in situ for implantation and resorption sites. Live fetuses were removed, examined for gross malformations, weighed, and prepared for histopathological examination. Treatment with benzoic acid resulted in no dead or resorbed implants and 3% abnormal survivors, rates comparable to the control animals.

NOAEL Maternal toxicity: 510 mg/kg bw
NOAEL Teratogenicity: 510 mg/kg bw
(Kimmel et al., 1971)

A 4-generation study with female rats dosed with 375 or 750 mg/kg/day benzoic acid during pregnancy and lactation showed no effects on the dams or on the growth and development of the offspring.

NOAEL Maternal toxicity: ≥ 750 mg/kg/day
NOAEL Teratogenicity: ≥ 750 mg/kg/day
(Kieckebusch & Lang, 1960)

Studies on the developmental toxicity of sodium benzoate administered by gavage to multiple species (rat, mice, rabbit, hamster) were conducted by Food and Drug Research Labs, Inc. (1972):

A study using pregnant Wistar rats, dosed with 1.75, 8, 38 or 175 mg/kg sodium benzoate by gavage on Days 6-15 of gestation showed no effect on nidation or on maternal or fetal survival; the number of abnormalities of soft and skeletal tissues did not differ from controls.

NOAEL Maternal toxicity: 175 mg/kg bw
NOAEL Teratogenicity: 175 mg/kg bw
(FDA PB# 221777, 1972)

A study using pregnant CD-1 mice, dosed with 1.75, 8, 38 or 175 mg/kg sodium benzoate by gavage on Days 6-15 of gestation showed no effect on nidation or on maternal or fetal survival; the number of abnormalities of soft and skeletal tissues did not differ from controls.

NOAEL Maternal toxicity: 175 mg/kg bw
NOAEL Teratogenicity: 175 mg/kg bw
(FDA PB# 221777, 1972)

A study using pregnant Dutch-belted rabbits, dosed with 2.5, 12, 54 or 250 mg/kg sodium benzoate by gavage on Days 6-18 of gestation showed no effect on nidation or on maternal or fetal survival; the number of abnormalities of soft and skeletal tissues did not differ from controls.

NOAEL Maternal toxicity: 250 mg/kg bw
NOAEL Teratogenicity: 250 mg/kg bw
(FDA PB# 221777, 1972)
A study using pregnant Golden hamsters, dosed with 3, 14, 65 or 300 mg/kg sodium benzoate by gavage on Days 6-10 of gestation showed no effect on nidation or on maternal or fetal survival; the number of abnormalities of soft and skeletal tissues did not differ from number in controls.

**NOAEL Maternal toxicity:** 300 mg/kg bw  
**NOAEL Teratogenicity:** 300 mg/kg bw  
(FDA PB# 221777, 1972)

A study using pregnant Wistar rats, dosed with 700, 1400, 2800, 5600 mg/kg sodium benzoate in the diet during the entire gestation showed no statistical difference in organ and bone abnormalities of fetuses between experimental groups and controls; growth of treated offsprings was similar to controls in rats dosed with 1400 mg/kg/day; reduced food intake and decreased body weight of the pregnant rats especially in the 5600 mg/kg group; 100% perinatal death rate; organ abnormalities of fetuses involved eye, brain and kidneys, in addition abnormalities of the skeletal system were found in rats dosed with ≥2800 mg/kg/day. The authors concluded that the effects on the dams and fetuses at the 2800 and 5600 levels were due to reduced maternal feed intake in these groups, leading to malnutrition.

**NOAEL Maternal toxicity:** 1400 mg/kg bw  
**NOAEL Teratogenicity:** 1400 mg/kg bw  
(Onodera et al., 1978)

Fifty female mice were given benzyl alcohol at 550 mg/kg bw per day by gavage on days 6-15 of gestation; a further 50 mice received the corn oil vehicle. All dams were allowed to deliver naturally, and pups and dams were observed until day 3 post partum, when the experiment was terminated. Body weight, clinical observations, and mortality were recorded daily throughout treatment and up to day 3 post partum. Mortality was not significantly increased in animals given benzyl alcohol over that in the control group. One treated mouse showing languid behaviour, laboured breathing, and a rough coat died, but no other deaths or clinical signs were reported. Maternal body weight and body-weight gain during treatment and up to day 3 post partum were virtually identical for treated and control animals. All other parameters examined, including gestation index, average number of live pups per litter, and postnatal survival and pup body weight on days 0 and 3 post partum, were not significantly different from the control values. The authors concluded that, at the predicted LD10, benzyl alcohol had no significant effects on the development of CD-1 mice.

**NOAEL = 550 mg/kg bw per day**  
(York et al., 1986; JECFA, 1997).

**Benzyl alcohol** dissolved in distilled water was administered by gavage at a dose of 750 mg/kg bw per day to 50 CD-1 mice on days 7-14 of gestation; evidence of copulation was considered the first day of gestation. A control group of 50 animals received distilled water only. All animals were allowed to deliver their litters and nurse their pups for three days, at which time necropsies were performed. Maternal body-weight gain and mortality, mating, gestation, numbers of live and dead pups per litter, total litter weight on days 1 and 2 post partum, litter weight change between days 1 and 3 post partum, and pup survival on days 1 and 3 post partum were recorded. During the treatment period, 18 deaths were reported, all of which were attributed to treatment; a further death was reported on day 15 of gestation, the day after treatment was terminated. Clinical signs of toxicity, including hunched posture, tremors, inactivity, prostration, hypothermia, ataxia, dyspnoea, swollen or cyanotic abdomen, and piloerection, were reported in up to 20 mice during treatment. Piloerection was also reported in some animals up to day 3 post partum, but no other clinical signs were seen after the period of administration. No differences were observed in the mating or gestation indices, the total number of resorptions, the mean length of gestation, or the number of live pups per litter between treated and control groups. Maternal body weight, measured on days 4 and 7 of gestation, was not significantly different from control values; however, statistically...
significant reductions were reported on day 18 of gestation ($P < 0.001$) and on day 3 post partum ($P < 0.05$). Maternal body-weight gain during days 7-18 of gestation was significantly lower than that of controls ($P < 0.001$). Significant reductions in pup body weight were reported, including a lower mean pup weight per litter on days 1 ($P < 0.01$) and 3 post partum ($P < 0.001$), a mean litter weight change between day 1 and day 3 post partum ($P < 0.05$), and a mean pup weight change between days 1 and 3 post partum ($P < 0.001$). No differences in pup survival were observed by day 3 post partum. The authors concluded that benzyl alcohol may be a reproductive hazard, apparently on the basis of the reductions in pup body weights, an effect that was observed in conjunction with maternal toxicity evidenced by increased mortality, reduced body weights, and clinical toxicity during the period of administration. As effects were seen on the dams and fetuses at the only dose used in this study, there was no NOAEL.

LOAEL = 750 mg/kg bw per day


In a developmental toxicity study in rats, benzyl acetate given by gavage did not show teratogenic effects and on the basis of fetotoxic effects a NOEL of 500 mg/kg/day could be established.

(Ishiguro et al., 1993)

Many of these studies were done by gavage (leading to greater toxicity due to the “bolus effect”). In these studies NOEL of $\geq 500$ mg/kg were found. Thus, studies on reproductive and/or developmental toxicology performed by the administration of the benzyl compounds by gavage are likely to reveal changes at lower doses compared to studies where the substances are applied in the diet, leading to a distribution in the body over time.

**In conclusion:** The compounds exhibit no developmental toxicity and a NOEL of 500 mg/kg/day can be established for developmental effects for this group of substances.
4  HAZARDS TO THE ENVIRONMENT

4.1  Aquatic Effects

The studies used as the basis for the following data did not always state whether effect values were based on nominal or measured concentrations. However, because of the good water solubility, their insignificant volatility and low adsorption potential, all nominal concentrations of the test substances are expected to correspond to effective concentrations even in tests with open systems and longer exposure durations.

Acute toxicity to fish

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Species</th>
<th>Protocol</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzoic acid</td>
<td><em>Lepomis macrochirus</em></td>
<td>EPA-660/3-75-009</td>
<td>(LC_{50}) (96 h) = 44.6 mg/l (LC_{0}) = 180 mg/l (pH control)</td>
<td>UCES#11506-03-85, 1979</td>
</tr>
<tr>
<td></td>
<td><em>Salmo gairdneri</em></td>
<td>EPA-660/3-75-009</td>
<td>(LC_{50}) (96 h) = 47.3 mg/l</td>
<td>Buzzel et al 1968</td>
</tr>
<tr>
<td></td>
<td><em>Leuciscus idus</em></td>
<td>other</td>
<td>(LC_{50}) (48 h) = 460 mg/l (pH 7 – 8)</td>
<td>Juhnke &amp; Luedemann, 1978</td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td><em>Pimephales promelas</em></td>
<td>EPA OPP 72-1</td>
<td>(LC_{50}) (96 h) = 484 mg/l (pH 7.4, flow-through, measured concentrations)</td>
<td>Geiger et al., 1985</td>
</tr>
<tr>
<td></td>
<td><em>Pimephales promelas</em></td>
<td></td>
<td>(LC_{50}) (96 h) &gt; 100 mg/l</td>
<td>Ewell et al 1986</td>
</tr>
<tr>
<td>Benzylic alcohol</td>
<td><em>Pimephales promelas</em></td>
<td>EPA OPP 72-1</td>
<td>(LC_{50}) (96 h) = 460 mg/l</td>
<td>Mattson, V.R., et al., EPA-600/3-76-097, PB-262897, 1976</td>
</tr>
<tr>
<td></td>
<td><em>Leuciscus idus</em></td>
<td>DIN 38412 Teil 15</td>
<td>(LC_{50}) (48 h) = 646 mg/l</td>
<td>Knie et al., 1983</td>
</tr>
<tr>
<td>Benzylic alcohol</td>
<td>Specific acute spill testing (*)</td>
<td></td>
<td>(LC_{50}) (96 h) 10 and 15 mg/l</td>
<td>Dawson et al 1975/1977</td>
</tr>
</tbody>
</table>

No data for potassium benzoate were identified, but it should be similar to sodium benzoate.

(*) REMARK: For benzylalcohol two valuable guideline studies gave acute toxicity values > 100 mg/l. Dawson et al, however reported acute toxicity values 10 – 15 mg/l. Their static tests however were directed to simulate acute spill circumstances. The test substances were pipetted or poured undiluted directly into the aquaria with fish. So without preparing defined concentrations according to guideline. No analytical monitoring was done. Aeration was not used during the first 24 hrs thus allowing chemicals to act in an uninterrupted state at the onset of the test period. For environmental relevant conditions and for derivation of a PNECaqua a benzylalcohol acute toxicity (LC50 96 hrs) to fish of > 100 mg/l should therefore be used.
### Acute toxicity to aquatic invertebrates

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Species</th>
<th>Protocol</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzoic acid</td>
<td><em>Daphnia magna</em></td>
<td>EPA-6603-75-009</td>
<td>EC$_{50}$ (48 h) $\geq$ 100 mg/l (pH 8.4)</td>
<td>UCES#11506-03-80, 1979</td>
</tr>
<tr>
<td></td>
<td></td>
<td>other</td>
<td>EC$_{50}$ (24 h) = 500 mg/l (with neutralization)</td>
<td>Bringmann, &amp; Kuehn, 1982</td>
</tr>
<tr>
<td></td>
<td></td>
<td>other</td>
<td>EC$_{50}$ is 102 mg/l (without neutralization)</td>
<td>Bringmann, &amp; Kuehn, 1982</td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td><em>Daphnia magna</em></td>
<td>DIN 38412 Teil 11</td>
<td>EC$_{50}$ (48 h) $\geq$ 100 mg/l</td>
<td>Ewell et al., 1986</td>
</tr>
<tr>
<td>Benzylic alcohol</td>
<td><em>Daphnia magna</em></td>
<td>other</td>
<td>EC$_{50}$ (24 h) $=$ 400 mg/l</td>
<td>Knie et al., 1983</td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td><em>Daphnia magna</em></td>
<td>other</td>
<td>EC$_{50}$ (48 h) $=$ 360 mg/l</td>
<td>Bringmann &amp; Kuehn, 1959</td>
</tr>
</tbody>
</table>

No data for potassium benzoate were identified, but it should be similar to sodium benzoate.

### Acute toxicity to aquatic plants (algae)

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Species</th>
<th>Protocol</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzoic acid</td>
<td><em>Scenedesmus quadricauda</em></td>
<td>other</td>
<td>EC$_{50}$ (3 h) = 75 mg/l</td>
<td>Stratton &amp; Corke, 1982</td>
</tr>
<tr>
<td></td>
<td><em>Scenedesmus quadricauda</em></td>
<td>cell</td>
<td>Inhibition starts at 1630 mg/l (96 hr)</td>
<td>Bringmann &amp; Kuehn, 1977</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mutiplication</td>
<td>(pH = 7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>inhibition test;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>static</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Chlorella pyrenoidosa</em></td>
<td>other</td>
<td>EC$_{50}$ (3 h) = 60 mg/l</td>
<td>Stratton &amp; Corke, 1982</td>
</tr>
<tr>
<td></td>
<td><em>Anabaena variabilis</em></td>
<td>other</td>
<td>EC$_{50}$ (14d) $&gt;10$ mg/l</td>
<td>Stratton &amp; Corke, 1982</td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td>Green algae</td>
<td>ECOSAR</td>
<td>EC$_{50}$ (96 h) = 478 mg/l</td>
<td></td>
</tr>
<tr>
<td>Benzylic alcohol</td>
<td><em>Chlorella pyrenoidosa</em></td>
<td>other</td>
<td>EC$_{50}$ (3 h) = 95 mg/l</td>
<td>Stratton &amp; Corke, 1982</td>
</tr>
<tr>
<td></td>
<td><em>Haematococcus pluvialis</em></td>
<td>other</td>
<td>EC$_{50}$ (4 h) = 2600 mg/l</td>
<td>Knie et al., 1983</td>
</tr>
<tr>
<td></td>
<td><em>Scenedesmus quadricauda</em></td>
<td>cell</td>
<td>Inhibition starts at 640 mg/l (96 h)</td>
<td>Bringmann &amp; Kuehn 1959</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mutiplication</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>inhibition test</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Remark: The studies are no guideline studies, but despite this shortcoming they indicate a moderate to low acute toxicity. The Scenedesmus study of Stratton and Cork was not used because the endpoint is about the inhibition of the photosynthesis and not growth (rate). The blue green algae were left out because they are not directly used for the effect assessment for the aquatic.
environment and the endpoint was inhibition of the photosynthesis and not growth (rate). No data for potassium benzoate were identified, but it should be similar to sodium benzoate.

**Acute toxicity to micro-organisms (bacteria)**

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Species</th>
<th>Protocol</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzoic acid</td>
<td>activated sludge</td>
<td>OECD 209 (respiration inhibition)</td>
<td>EC₅₀ (3 h) &gt; 1000 mg/l (pH 7.5)</td>
<td>Klecka et al., 1985</td>
</tr>
<tr>
<td></td>
<td>Photobacterium phosphoreum</td>
<td>Static</td>
<td>EC₅₀ (30 min) = 16.85 mg/l</td>
<td>Kaiser, 1987</td>
</tr>
<tr>
<td></td>
<td>Pseudomonas putida</td>
<td>Static</td>
<td>Inhibition starts at 480 mg/l (16 h) (pH neutral)</td>
<td>Cicad 2000</td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td>Achromobacter liquefaciens</td>
<td>other: static</td>
<td>EC₅₀ (24 h) &gt; 3000 mg/l</td>
<td>Nikkilae, 1955</td>
</tr>
<tr>
<td></td>
<td>Micrococcus flavus</td>
<td>other: static</td>
<td>EC₅₀ (24 h) &gt; 500 mg/l</td>
<td>Nikkilae, 1955</td>
</tr>
<tr>
<td>Benzylic alcohol</td>
<td>Escherichia coli</td>
<td>cell multiplication inhibition test</td>
<td>EC₅₀ (48 h) = 1000 mg/l</td>
<td>Bringmann &amp; Kuhn, 1959</td>
</tr>
<tr>
<td></td>
<td>Pseudomonas putida</td>
<td>cell multiplication inhibition test</td>
<td>EC₅₀ (16-18 h) = 658 mg/l</td>
<td>Knie et al., 1983</td>
</tr>
</tbody>
</table>

No data for potassium benzoate were identified, but it should be similar to sodium benzoate.

**In conclusion:**

From the data (fish, daphnia, algae, bacteria) it is obvious that neutralization of the pH greatly reduces (up to one order of magnitude) the acute toxicity of benzoic acid. This is also supported by the lower toxicity observed with the sodium benzoate. Under environmental relevant conditions therefore the acute toxicity of benzoic acid, sodium benzoate and potassium benzoate for all four trophic levels is > 100 mg/l.

Under environmental relevant conditions the acute toxicity of benzylalcohol for fish, daphnia and bacteria is > 100mg/l. For algae an acute EC 50 3hrs of 95 mg/l.

Therefore it can be concluded that under environmental relevant conditions, benzoic acid and its salts have very low acute toxicity, whereas benzylalcohol has low to moderate acute toxicity.

### 4.2 Terrestrial Effects

There were no available studies on terrestrial organisms.

IPCS CICAD 26 (2000) concluded for benzoic acid and sodium benzoate: No information on toxic effects of benzoic acid and sodium benzoate on plants, earthworms or other terrestrial organisms or on ecosystems were identified. Only antimicrobial properties were identified preventing bacterial or fungal growth. Based on these data they conclude a low toxicity potential of benzoic acid and sodium benzoate in the terrestrial environment.
5. CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

Benzylalcohol, benzoic acid and its sodium and potassium salt can be considered as a single category regarding human health, as they are all rapidly metabolised and excreted via a common pathway within 24hrs.

Systemic toxic effects of similar nature (e.g liver, kidney) were observed. However, with benzoic acid and its salts at higher doses than with benzylalcohol. For environmental effects the category is less clear, however all are readily biodegradable, non-bioaccumulative and acute toxicity values are similar.

For human health all exposure routes are possible, despite benzoic acid and its salts being solids and benzylalcohol being a liquid. For workers exposure will mainly be by inhalation and by skin, whereas for consumers it will mainly be by oral and dermal route.

Human Health:

The compounds exhibit low acute toxicity as for the oral and dermal route. The LD50 values are > 2000 mg/kg bw except for benzylalcohol which needs to be considered as harmful by oral route in view of an oral LD50 of 1610 mg/kg bw. The 4 hrs inhalation exposure of benzylalcohol or benzoic acid at 4 and 12 mg/l as aerosol/dust respectively gave no mortality, showing low acute toxicity by inhalation for these compounds.

Benzoic acid and benzyl alcohol are slightly irritating to the skin, while sodium benzoate was not skin irritating. No data are available for potassium benzoate but it is also expected not to be skin irritating. Benzoic acid and benzyl alcohol are irritating to the eye and sodium benzoate was only slightly irritating to the eye. No data are available for potassium benzoate but it is expected also to be only slightly irritating to the eye.

The available studies for benzoic acid gave no indication for a sensitizing effect in animals, however occasionally very low positive reactions were recorded with humans (dermatological patients) in patch tests. The same occurs for sodium benzoate. It has been suggested that the very low positive reactions are a non-immunologic contact urticaria. Benzyl alcohol gave positive and negative results in animals. Benzyl alcohol also demonstrated a maximum incidence of sensitization of only 1% in human patch testing. Over several decades no sensitization with these compounds has been seen among workers.

For benzoic acid repeated dose oral toxicity studies give a NOAEL of 800 mg/kg/day. For the salts values > 1000 mg/kg/day are obtained. At higher doses increased mortality, reduced weight gain, liver and kidney effects were observed.

For benzyl alcohol the long-term studies indicate a NOAEL > 400 mg/kg bw/d for rats and > 200 mg/kg bw/d for mice. At higher doses effects on bodyweights, lesions in the brains, thymus, skeletal muscle and kidney were observed. It should be taken into account that administration in these studies was by gavage route, at which saturation of metabolic pathways is likely to occur. It can be concluded that benzoic acid and its salts exhibit very low repeated dose toxicity. Benzylalcohol exhibits low repeated dose toxicity.

All chemicals showed no mutagenic activity in in vitro Ames tests. Various results were obtained with other in vitro genotoxicity assays.

Sodium benzoate and benzyl alcohol showed no genotoxicity in vivo.
While some mixed and/or equivocal in vitro chromosomal/chromatid responses have been observed, no genotoxicity was observed in the in vivo cytogenetic, micronucleus, or other assays. The weight of the evidence of the *in vitro* and *in vivo* genotoxicity data indicates that these chemicals are not mutagenic or clastogenic. They also are not carcinogenic in long-term carcinogenicity studies. In addition data from *in-vivo* genotoxicity studies on benzyl acetate and benzaldehyde (JECFA report, 1997) support the non-genotoxicity of benzylalcohol and benzoic acid and its salts.

Carcinogenicity studies (2-year) with sodium benzoate and benzyl alcohol showed no evidence of carcinogenic activity.

In a 4-generation study with benzoic acid no effects on reproduction were seen (NOAEL ≥ 750 mg/kg). No compound related effects on reproductive organs (gross and histopathology examination) could be found in the (sub) chronic studies in rats and mice with benzyl acetate, benzyl alcohol, benzaldehyde, sodium benzoate and supports a non-reprotoxic potential of these compounds. In addition, data from reprotoxicity studies on benzyl acetate (NOAEL >2000 mg/kg bw/d; rats and mice) and benzaldehyde (tested only up to 5 mg/kg bw; rats) support the non-reprotoxicity of benzyl alcohol and benzoic acid and its salts.

In rats for sodium benzoate dosed via food during the entire gestation developmental effects occurred only in the presence of marked maternal toxicity (reduced food intake and decreased body weight) (NOAEL = 1400 mg/kg bw). For hamster (NOEL : 300 mg/kg bw), rabbit (NOEL :250 mg/kg bw) and mice (CD-1 mice, NOEL : 175 mg/kg bw) no higher doses (all by gavage) were tested and no maternal toxicity was observed. For benzyl alcohol: NOAEL= 550 mg/kg bw (gavage; CD-1 mice). LOAEL = 750 mg/kg bw (gavage mice). In this study maternal toxicity was observed e.g. increased mortality, reduced body weight and clinical toxicology. Benzyl acetate: NOEL = 500 mg/kg bw (gavage rats). No maternal toxicity was observed.

**Environment:**

From the data (fish, daphnia, algae, bacteria) it is obvious that neutralization of the pH greatly reduces (up to one order of magnitude) the acute toxicity of benzoic acid. This is also supported by the lower toxicity observed with sodium benzoate. Under environmental relevant conditions therefore the acute toxicity of benzoic acid, sodium benzoate and potassium benzoate for all four trophic levels is > 100 mg/l. Under environmental relevant conditions the acute toxicity of benzylalcohol for fish, daphnia and bacteria is > 100mg/l. For algae an acute EC 50 3hrs of 95 mg/l is reported. Therefore it can be concluded that under environmental relevant conditions benzoic acid and its salts have very low acute toxicity, whereas benzylalcohol has low to moderate acute toxicity.

**Exposure:**

Worldwide production capacity of benzoic acid is estimated at 700 kt per year. The major outlet (75%) for benzoic acid is as a chemical intermediate in the production of phenol, which in turn is mainly used to produce caprolactam. The next largest outlet is as a feedstock for sodium benzoate (10%) and chemical synthesis of plasticizers (5%). Worldwide production capacity of sodium benzoate is estimated at 100 kt per year. The major outlet for sodium benzoate is as preservative in food and beverages (60%). Second most important market is cooling liquids (10%). The main function of sodium benzoate in most applications is as preservative.
Worldwide production capacity of potassium benzoate is estimated at 7 kt per year. It is used as a preservative in nonalcoholic beverages.

Worldwide production capacity of benzyl alcohol is estimated at 50 kt. Major use for benzyl alcohol is as a curing agent in epoxy coatings (30%), where it becomes chemically bound after reaction. Other important uses include the use as a solvent in low concentrations in waterborne coatings (10%) and use in paint strippers (10%) and chemical intermediate for synthesis for benzyl esters that are used in the flavor and fragrance industry (10%). The use in paint strippers is limited to uses in industrial settings.

Benzyl alcohol, benzoic acid and its sodium and potassium salt are also used in pharmaceuticals, cosmetics and/or food. Consumer exposure in these specific applications are controlled by the fact that for all these applications specific regulatory frameworks (regional and/or national) with authorization/approval procedures and specific advisory bodies exist (among others US FDA, WHO JECFA, EU SCF, etc), with on regular basis reevaluation of approvals, hazardous properties and factual exposures inclusive. According to information from products registers uses that are not specifically regulated includes uses of the substances in different kinds of products e.g. paints, varnishes solvents, cleaning and washing agents, photochemicals and antifreeze agents.

Benzoic acid is a white solid, with solubility in water of 2.9 g/l and with a vapor pressure of 0.0011 hPa at 20 °C. The octanol/water partition coefficient was measured to 1.88; the Henry’s law constant = 0.0046-0.022 Pa·m³/mol; and the pKa = 4.2.

Sodium benzoate and potassium benzoate are white solids, with solubility in water of 556 g/l and with a vapor pressure of <0.0011 hPa at 20 °C. The octanol/water partition coefficient were measured to –2.269.

Benzyl alcohol is a colorless liquid, with solubility in water of 40 g/l and with a vapor pressure of 0.13 hPa at 20 °C. The octanol/water partition coefficient was measured to 1.1.

The distribution modeling according to Mackay Level III indicates soil and water to be the favored compartments for the chemicals. None are expected to hydrolyze. All are classified as readily biodegradable. None has bioaccumulative potential.

### 5.2 Recommendations

Several of the toxicological studies on benzyl alcohol and benzoic acid and its salts were carried out some years ago and do not always fulfill for 100% present-day guidelines. However, well-known research groups and/or test laboratories ran the studies according to scientific standards and or accepted protocols at that time. They did appear to be acceptable studies for evaluation. Also, all were peer-reviewed and published in high quality scientific literature. Most of them have been reviewed and accepted by other fora like FDA, JECFA, and IPCS as acceptable studies. In addition, there is good consistency in the individual data for a substance in the group as well as between members of the group (benzyl acetate and benzaldehyde data inclusive). Therefore, taken as a whole, the available studies give a robust database for hazard assessment and hazard evaluation of these compounds and further studies are not indicated. The JECFA Committee (1997) concluded that the data reviewed for compounds in this group were sufficient to demonstrate lack of teratogenic, reproductive or carcinogenic potential. Consequently, the Committee concluded that further studies were not required.

Taking into account the rapid biodegradability, the low bioaccumulation potential, the low to moderate toxicity to most aquatic species, and the rapid metabolism of these substances, these substances will pose a minimal risk to the aquatic environment.
Taking into account the rapid metabolism and excretion, the non-bioaccumulation, the low toxicity after acute and repeated exposures, the non-reprotoxicity, the non-genotoxicity and the non-carcinogenicity, the low irritating and non- to very low sensitizing properties of these substances, as well as the controlled (industrial settings) and /or regulated (pharma, cosmetics and /or food) uses, these substances will pose a minimal risk to humans (workers and consumers).

Therefore these substances have low priority for further work.
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I U C L I D D a t a S e t

Existing Chemical       ID: 65-85-0
CAS No.                 65-85-0
EINECS Name            benzoic acid
EC No.                 200-618-2
TSCA Name              Benzoic acid
Molecular Formula      C7H6O2

Producer Related Part
  Company:             Bayer Corporation
  Creation date:       21-OCT-1999

Substance Related Part
  Company:             Bayer Corporation
  Creation date:       21-OCT-1999

Memo:                  Bayer Corporation

Printing date:          14-FEB-2002
Revision date:
Date of last Update:   14-FEB-2002

Number of Pages:        82

Chapter (profile):      Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile):  Reliability: without reliability, 1, 2, 3, 4
Flags (profile):
1.0.1 Applicant and Company Information

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<th>Date</th>
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<td>American Chemistry Council (formerly Chemical Manufacturers Association, HPV Benzoates Panel)</td>
<td>United States</td>
<td>14-AUG-2001</td>
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<td>cooperating company</td>
<td>ATOFINA Chemicals, Inc.</td>
<td>United States</td>
<td>14AUG-2001</td>
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<td>Netherlands</td>
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<td>21-MAY-2001</td>
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<tr>
<td>lead organisation</td>
<td>American Chemistry Council, Benzoates Panel</td>
<td>United States</td>
<td>16-JAN-2001</td>
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1.0.2 Location of Production Site, Importer or Formulator

1.0.3 Identity of Recipients

1.0.4 Details on Category/Template
1.1.0 Substance Identification

1.1.1 General Substance Information

1.1.2 Spectra

1.2 Synonyms and Tradenames

1.3 Impurities

1.4 Additives

1.5 Total Quantity

1.6.1 Labelling

1.6.2 Classification

1.6.3 Packaging

1.7 Use Pattern

1.7.1 Detailed Use Pattern

1.7.2 Methods of Manufacture

1.8 Regulatory Measures

1.8.1 Occupational Exposure Limit Values

1.8.2 Acceptable Residues Levels

1.8.3 Water Pollution

1.8.4 Major Accident Hazards

1.8.5 Air Pollution

1.8.6 Listings e.g. Chemical Inventories
1.9.1 Degradation/Transformation Products

1.9.2 Components

1.10 Source of Exposure

1.11 Additional Remarks

1.12 Last Literature Search

Type of Search: Internal and External
Date of Search: 07-SEP-1999

Remark: Only HPV endpoints: TOXLINE data base and internal studies.
14-AUG-2001

1.13 Reviews
2.1 Melting Point

Value: = 122.4 degree C  
Method: other: measured  
Test substance: other TS: benzoic acid; purity not noted  
Reliability: (2) valid with restrictions  
Flag: Critical study for SIDS endpoint

Value: = 122 degree C  
15-JAN-2001  
Value: = 121.7 degree C  
15-JAN-2001

2.2 Boiling Point

Value: = 249.2 degree C at 1013 hPa  
Method: other: measured  
Test substance: other TS: benzoic acid; purity not noted  
Reliability: (2) valid with restrictions  
Flag: Critical study for SIDS endpoint  
14-AUG-2001  
Value: = 250 degree C at 1013 hPa  
15-JAN-2001

Value: = 249 degree C at 1013 hPa  
15-JAN-2001

2.3 Density

Type: density  
Value: = 1.2659 at 15 degree C  
Method: other:
OECD SIDS  BENZOATES

2. PHYSICO-CHEMICAL DATA

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
14-AUG-2001 (1)

Type: density
Value: = 1.321 g/cm³ at 20 degree C
15-JAN-2001 (6)

2.3.1 Granulometry

2.4 Vapour Pressure

Value: = .0011 hPa at 20 degree C
Method: other (measured): Handbook Value
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
14-AUG-2001 (7)
Value: = .0053 hPa at 20 degree C
Flag: Critical study for SIDS endpoint
15-JAN-2001 (8)

2.5 Partition Coefficient

log Pow: = 1.88
Method: other (measured): centrifugal distribution chromatography
Year: 1988
Reliability: (2) valid with restrictions
Meet generally accepted scientific method and is described in sufficient detail
Flag: Critical study for SIDS endpoint
14-AUG-2001 (9)
log Pow: = 1.9
Year: 1991
2.6.1 Solubility in different media

Solubility in: Water
Value: = 2.931 g/l at 20 degree C

Method: other: similar to OECD Guideline 105
Test substance: other TS: Research grade benzoic acid (Merck)

Remark: pH-Value: no data
Result: 2.45 g/l at 15 degree C (0.0210 mol/l at 288K)
2.93 g/l at 20 degree C (0.0240 mol/l at 293K)
3.47 g/l at 25 degree C (0.0284 mol/l at 298K)

Reliability: (2) valid with restrictions
Meets generally accepted scientific standards,
Well documented and acceptable for assessment
Flag: Critical study for SIDS endpoint

2.6.2 Surface Tension

2.7 Flash Point

Value: = 121 degree C
Method: other: no data

Remark: nicht angegeben
15-JAN-2001

2.8 Auto Flammability

Value: = 574 degree C at 1013 hPa

Method: other

Year: 1990

GLP: no
15-JAN-2001

2.9 Flammability

Remark: Not applicable.
14-AUG-2001

2.10 Explosive Properties

Remark: Dust explosions possible. LEL 0.95 % and UEL 8.2 %
14-AUG-2001

2.11 Oxidizing Properties

Remark: Not applicable.
14-AUG-2001

2.12 Dissociation Constant

2.13 Viscosity

2.14 Additional Remarks

Remark: Henry-constant (Pa * m3/mol):
0.0046 - 0.022 (calculated as quotient of vapour pressure and water solubility at 20 degree C)

Flag: Critical study for SIDS endpoint
14-AUG-2001
Remark: Dissociation-constant (25 degree C): pKa = 4.1951
Flag: Critical study for SIDS endpoint
14-AUG-2001

Remark: Dissociation-constant (20 degree C): pKa = 4.21
Flag: Critical study for SIDS endpoint
14-AUG-2001

Remark: Dissociation-constant pKa (25 degree C): 3.99–4.205 (various methods; summarized values)
14-AUG-2001

Remark: Begin of sublimation at ca. 100 degree C. At ca. 150 degree C formation of anhydride, at ca. 370 degree C decarboxylation. Volatile with steam.
14-AUG-2001

Remark: pH-value: 3.1 at 1 g/l water (roomtemperature)
14-AUG-2001

Remark: pH-value: 2.8 (saturated solution, 25 degree C)
14-AUG-2001
3.1.1 Photodegradation

Type:    other: mineralization in aqueous TiO2
Light source: other: 20W NEC blacklight blue fluorescent tube
Light spect.: <= 350 nm
Conc. of subst.: 50 mg/l at 40 degree C

INDIRECT PHOTOLYSIS
Sensitizer: other: aqueous TiO2
Conc. of sens.: 40 mg/l
Degradation: 90 % after 140 minute(s)

Method: other measured: mineralization in aqueous TiO2
Year: 1990
GLP: no data
Test substance: other TS: benzoic acid, purity not noted

Remark: Photochemical dissociation of benzoic acid by irradiation with UV light if fixed on solid carriers: 90 % mineralization in aqueous TiO2-suspension after 2-3 h of irradiation with sunlight on 1 m2 water surface (concentration 50 mg/l related to test substance)
This endpoint has been studied several times by several other investigators/groups and all support the result of the study mentioned above.

Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment
Flag: Critical study for SIDS endpoint
14-FEB-2002

Type: other: calculated
Light source: Sun light
Conc. of subst.: at 25 degree C

INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 1560000 molecule/cm³
Rate constant: ca. .000000000001242 cm³/(molecule * sec)
Degradation: 50 % after 8.6 day(s)

Method: other (calculated): AOPWin version 1.89
Year: 1999
Test substance: other TS: molecular structure
3. ENVIRONMENTAL FATE AND PATHWAYS

Reliability: (2) valid with restrictions
Accepted calculation method

Flag: Critical study for SIDS endpoint
14-AUG-2001

Remark: UV-Spectrum lambda max (nm):
227.5 (Methanol; lg epsilon: 4.27)
222 (Methanol/KOH; lg epsilon: 4.07)
15-JAN-2001

Remark: photochemical dissociation of benzoic acid by
UV-irradiation if fixed on solid carriers
(SiO2): -10.2 % mineralization after 17 h
irradiation with light (lambda > 290 nm) (no data
concerning concentration)
15-JAN-2001

Remark: photochemical dissociation of benzoic acid by
Irradiation with UV light if fixed on solid
carriers: - 67 % mineralization in aqueous ZnO-
suspension after 24 h of irradiation with
sunlight (concentration 100-200 mg/l
related to DOC)
15-JAN-2001

Remark: Formation of a small amount of photochemical
aerosols after irradiation of some crystals
of benzoic acid with a deuterium lamp (180 <
lambda < 400 nm) in a laboratory reactor.
15-JAN-2001

3.1.2 Stability in Water

Result: Based on structure and organic chemistry rules
(e.g. bonding in organic molecules, activation
energy, reactivity, transformations, addition,
substitution, elimination) no hydrolysis will
occur at pH ranges 4 - 11.
26-JAN-2001

3.1.3 Stability in Soil

Remark: Not available.
14-AUG-2001
3.2.1 Monitoring Data (Environment)

Remark: Not available.
14-AUG-2001

3.2.2 Field Studies

3.3.1 Transport between Environmental Compartments

Type: adsorption
Media: water - soil
Method: other: see below

Method: 14C-labeled benzoic acid (767MBq mmol-1) of radiochemical purity greater than 98.5% was prepared in 0.01 M calcium nitrate in concentrations of 0.01, 0.1, 1.0, 10 mg/l. The solutions were added to three types of autoclaved, dry soils (2 g) and allowed to equilibrate on a mechanical shaker for 72 hrs at 6C.

The soil types were sandy till, clayey till, and melt water sand.

The suspension was allowed to settle and the supernatant liquid tested for 14C activity. Adsorption constants were determined.

Result: No adsorption was observed for benzoic acid in melt water sand and clayey till; very low adsorption was observed in sandy till (K=0.23).

Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment

Flag: Critical study for SIDS endpoint
14-AUG-2001

Type: fugacity model level III
Media: other: air - water - soil - sediment
Method: other: EPIWin Modeling Program
Remark: Modeling was performed using equal releases (10,000 kg/hr) and equal distribution to all compartments.
### 3. ENVIRONMENTAL FATE AND PATHWAYS

**SUBSTANCES ID: 65-85-0**

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<th>Distribution (percent)</th>
<th>Half-Life (hr)</th>
<th>Emissions (kg/hr)</th>
<th>Fugacity (atm)</th>
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<td>1000</td>
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<td>Water</td>
<td>34.8</td>
<td>360</td>
<td>1000</td>
<td>6.11e-013</td>
</tr>
<tr>
<td>Soil</td>
<td>64.2</td>
<td>360</td>
<td>1000</td>
<td>1.22e-011</td>
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<tr>
<td>Sediment</td>
<td>0.093</td>
<td>1.44e+003</td>
<td>0</td>
<td>4.73e-013</td>
</tr>
</tbody>
</table>

Persistence Time: 421 hr  
Reaction Time: 516 hr  
Advection Time: 2.28e+003 hr  
Percent Reacted: 81.5  
Percent Advected

Reliability: (2) valid with restrictions  
Accepted calculation method  
Flag: Critical study for SIDS endpoint

#### 3.3.2 Distribution

#### 3.4 Mode of Degradation in Actual Use

**Remark:** Benzoic acid is readily biodegradable, and in production and use in chemical industry it is biodegraded in a waste water treatment plant. In many species, benzoic acid is rapidly absorbed, conjugated with glycine and excreted as hippuric acid.

23-OCT-1995

#### 3.5 Biodegradation

**Type:** aerobic  
**Inoculum:** activated sludge, industrial, non-adapted  
**Concentration:** 1000 mg/l related to COD (Chemical Oxygen Demand)  
508 mg/l related to Test substance  
**Degradation:** > 90 % after 2 day(s)

**Method:** OECD Guide-line 302 B "Inherent biodegradability: Modified Zahn-Wellens Test"

**Year:** 1981  
**GLP:** no data  
**Test substance:** other TS: reagent grade benzoic acid
Reliability: (1) valid without restriction
Guideline study

Flag: Critical study for SIDS endpoint
14-FEB-2002

Type: anaerobic
Inoculum: anaerobic sludge
Concentration: 73 mg/l related to Test substance
Contact time: 28 day(s)
Degradation: 96 - 100 % after 7 day(s)

Method: other: see below
GLP: no data
Test substance: other TS: commercial grade benzoic acid, purity > 95%

Method: A 10% anaerobic sludge inoculum was transferred to 160 ml serum bottles previously amended with 50 ppm Carbon (related to test substance) using strict anaerobic techniques. Methane production from test bottles vs. controls monitored weekly for 4 weeks or until net production occurred. At that time, the bottles were amended again with the same substrate and methane production monitored to confirm the observation. All data were obtained from duplicate bottles. Methane was measured using a flame ionization detector on a Perkin-Elmer Model 900 GC equipped with a 3-m Tenax-G.C. column

Remark: 96 % mineralisation (CH4-Production) in 1 week with sludge from Jackson, MI waste-treatment plant 100 % mineralisation (CH4-Production) in 2 weeks with sludge from Adrian, MI waste-treatment plan

Test condition: The test bottles were incubated at 35 degree C in the dark. Substrates were kept under an atmosphere of 90% N2 and 10% H2

Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment

Flag: Critical study for SIDS endpoint
14-AUG-2001

Type: anaerobic
Concentration: 50 µg/l related to DOC (Dissolved Organic Carbon)
Contact time: 2 month
Degradation: > 75 % after 2 month

Method: other: see below
GLP: no data
Test substance: other TS: benzoic acid, purity not noted

Method: Sludge samples collected from primary and Secondary anaerobic digesters were diluted to 10% and incubated anaerobically with 50 µg Carbon per ml (related to test substance). All compounds were tested in triplicate. Gas production was measured by gas chromatography and by a pressure transducer. Biodegradation was determined by net increase in gas pressure in bottles amended with test chemicals over non-amended controls.

Result: Degradation is expressed as percentage of Theoretical Methane production based on the stoichiometry of degradation.

Test condition: The test bottles were incubated at 35 degree C in the dark.
Substrates were kept under atmospheres of 10% CO2 and 90% N2.

Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, Well documented and acceptable for assessment
Flag: Critical study for SIDS endpoint
14-AUG-2001 aerobic
Type: activated sludge, industrial
Degradation: 86.9 % after 5 day(s)

Test substance: other TS: benzoic acid-1-14C (0.026mC/mg) obtained from NewEngland Nuclear Corporation, Boston, Massachusetts.

Method: Radio-respirometric study using radio-labeled chemicals by activated sludge and in a complex photographic processing effluent using acclimated industrial sludge. Concentration of test substance was 0.1 or 0.2ml of radioactive substrate (27,000-400,000 dpm). Samples were incubated in the dark at ambient temperature.
**Result:**
14CO2 recovery without effluent = 68.2% after 5 days
14CO2 recovery in presence of effluent = 86.9% after 5 days

**30-JAN-2001**

**Inoculum:** activated sludge, domestic
**Concentration:** 10 mg/l related to Test substance
**Degradation:** 74 % after 5 day(s)

**Method:** other: BOD test; 20 degree C; pH 7.0; minimal medium

**Remark:** Degradation after 20 d: 78 %
t 1/2 for TOC: 1 d
BOD: 2 d
no lag phase

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**14-FEB-2002**

**Inoculum:** activated sludge, non-adapted
**Concentration:** 100 mg/l related to Test substance

**Method:** other: Respirometer, 20 degree C; pH 7

**Remark:** Degradation after 65-80 h: 61-69 %; 5-20 h lag phase

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**14-FEB-2002**

**Inoculum:** activated sludge, domestic
**Concentration:** 500 mg/l related to Test substance
**Degradation:** after 6 day(s)

**Method:** other: Warburg-Respirometer, 20 degree C

**Remark:** Measured O2-consumption (graphically determined; considering endogenous respiration): ca. 525-750 mg/l = ca. 1050-1500 mg O2/g substance (ThOD 1967 mg O2/g substance)

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**15-JAN-2001**

**Inoculum:** activated sludge, non-adapted
**Concentration:** 500 mg/l related to Test substance

**Method:** other: Warburg-Respirometer; 20 degree C

**Remark:** Measured O2-consumption (graphically determined;
Considering endogenous respiration): after 1 d
ca. 410 mg/l = ca. 820 mg O2/g substance (ThOD
1967 mg O2/g substance).
Benzoic acid had an initial toxic effect on
two of three samples of activated sludge from
different communal purification plants, after
24 hours degradation started in these samples,
too.

15-JAN-2001

Inoculum: activated sludge, adapted
Concentration: 200 mg/l related to COD (Chemical Oxygen
Demand)
Degradation: 99 % after 5 day(s)
Method: other: aerobic degradation, 20 degree C
Remark: Concentration related to 101.7 mg substance/l
20 days adaption, degradation 88.5 mg COD/g.h

14-FEB-2002

Inoculum: activated sludge, domestic
Concentration: 16 mg/l related to Test substance
Degradation: 100 % after 1 day(s)
Method: other: aerobic degradation, static, 30 degree C; pH 7.3
Remark: Substance specific analysis

14-FEB-2002

Inoculum: activated sludge, domestic
Concentration: .059 mg/l related to Test substance
Degradation: 99.5 % after 7 day(s)
Method: other: aerobic degradation; 29 degree C;
measurement of radioactivity (C14 labelled at
the carboxygroup) (CO2-formation)
Remark: Test with trace concentrations

15-JAN-2001

Inoculum: activated sludge, industrial
Concentration: 150 mg/l related to Test substance
Degradation: 86 % after 1 day(s)
Method: other: aerobic degradation; semi-continuous; 25–30 degree C; pH 7; parameter: TOC

Remark: 1 day acclimation
15–JAN–2001

Inoculum: activated sludge, domestic, adapted
Concentration: 1000 mg/l related to COD (Chemical Oxygen Demand)
Degradation: 97 % after .2 day(s)

Method: other: aerobic degradation; static; test temperature 30 degree C; pH 7.2

Remark: Concentration equivalent to 508 mg substance/l 20 days adaptation with glucose as additional C-source
14–FEB–2002

Inoculum: other bacteria: obligatory anaerobic species from sludge of the first purification step
Concentration: 300 mg/l related to Test substance
Degradation: 91 % after 18 day(s)

Method: other: anaerobic degradation, enrichment culture; 35 degree C; parameter: gas production

Remark: 8 days lag phase
Degradation after 18 d: 91 +- 7.8 %
14–FEB–2002

Inoculum: other bacteria: anaerobic sludge, domestic
Concentration: 50 mg/l related to Test substance
Degradation: after 21 day(s)

Method: other: anaerobic degradation, static, 35 degree C, adding of test substance in solid form; parameter: gas production

Remark: Degradation: 110.5 %
14–FEB–2002

Inoculum: other bacteria: anaerobic sludge, domestic, washed
Concentration: 50 mg/l related to Test substance
### 3. ENVIRONMENTAL FATE AND PATHWAYS

**OECD SIDS**  |  **BENZOATES**  |  **DATE:** 14-FEB.-2002  
**SUBSTANCES ID:** 65-85-0

| Degradation: | 89.5 % after 35 day(s) |
| Method: | other: anaerobic degradation, static, 35 degree C, adding of test substance in solid form; parameter: gas production |

**15-JAN-2001**  
**Inoculum:** other bacteria: anaerobic laboratory sludge, adapted  
**Concentration:** 24 mg/l related to Test substance  
**Degradation:** 86 - 93 % after 23 day(s)

| Method: | other: anaerobic degradation, static, parameter: gas production, 37 degree C |

**15-JAN-2001**

| Inoculum: | other bacteria: activated sludge, domestic/industrial sewage |
| Concentration: | .8 mg/l related to Test substance |
| Degradation: | > 71.5 % after 5 day(s) |
| Method: | other: closed bottle-test |

**15-JAN-2001**

| Inoculum: | activated sludge, domestic |
| Concentration: | 700 mg/l related to Test substance |
| Degradation: | 76 % after 5 day(s) |
| Method: | other: respirometric determination of BOD; 20 degree C |

**15-JAN-2001**

### 3.6 BOD5, COD or BOD5/COD Ratio

| Method: |  |
| Year: |  |
| Method: |  |
| Remark: | BOD5/COD ratio is 0.72, indicating readily biodegradation. |

**14-AUG-2001**
3.7 Bioaccumulation

BCF: 3.16

Method: other: BCF Program (v2.13)
Year: 1999
Test substance: other TS: molecular structure

Result: Estimated Log BCF = 0.500 (BCF = 3.162)
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
14-AUG-2001

Remark: Based on the log P and the fact that many species absorb benzoic acid rapidly and rapidly metabolize it to hippuric acid that is excreted in urine, no bioaccumulation is indicated.
15-JAN-2001

3.8 Additional Remarks

Remark: Soil sorption coefficient Kd at 50 ug/l
Loamy sand: 0.4 m depth: 1.92
Sand: 18.9 m depth: 0.62

23-OCT-1995

Remark: Biomagnification factors (modell ecosystem)
(0.01-0.1 ppm; radiolabelled):
Gambusia affinis (mosquito fish) 21
Daphnia magna 1772
Oedogonium cardiacum (green algae) 102
Culex quinquifasciatus (midge, larvae) 138
Physa (snail) 2786

Duration of test: 48 h

Fishes were added after 24 h; no differentiation between bioaccumulation and magnification.
There is no evidence whether a plateau was achieved; the depuration rate is unknown.

23-OCT-1995
Remark:Bioconcentration factor:
Selenastrum capricornutum (green algae) 7.6
23-OCT-1995 (46)

Remark:Bioconcentration factors:
Leuciscus idus (golden orfe)< 10(fresh weight) (3 d)
Chlorella fusca (green algae)< 10(fresh weight) (1 d)
activated sludge 1300 (dry weight) (5 d)
There is no evidence whether a plateau was achieved; the depuration rate is unknown.
23-OCT-1995 (23)

Remark:Bioconcentration factor (calculated):
Oncorhynchus mykiss (rainbow trout, muscle) 14
23-OCT-1995 (47)

Remark:Degradation in soil:
Half life in soil: 35 d
(Determination of mineralization by radioactive labelling)
(loamy sand/sand, independent of depth 3-18 m)
23-OCT-1995 (44)

Remark:Degradation in soil:
Inoculum: soil microorganisms ("septic tank tile fields")
Method: anaerobic degradation, static;
parameter: 14 CO2;
20 degree C
Concentration: 1 mg/kg related to soil
Half life: 18.2 h
23-OCT-1995 (48)

Remark:Degradation in sea water:
Inoculum: sea water
Method: Determination of BOD

Concentration: 2 mg/l related to test substance
Degradation after 5 d: 74.9 %
No further information about test conditions
14-AUG-2001 (49)

Remark:Degradation in sea water:
Inoculum: sea water (New York, USA)
Method: aerobic degradation, static; 29 degree C; measurement of radioactivity of the 14C-labelled substance (at carboxyl group)
Concentration: 0.059 mg/l related to test substance
Degradation after 7 d: 98.7%
Determination with trace concentrations

14-AUG-2001

Remark: Degradation in marine ecosystems:
Benzoic acid can be degraded by different marine yeasts (9 of 12 tested species: Saccharomyces rosei, S. italicus, S. chevaliero, Cryptococcus laurentii, C. luteolus, C. neoformans, Rhodotorulus rubra, R. glutinis, Hansenula anomala). No information about test conditions.

23-OCT-1995

Remark: Elimination in rainwater:
Inoculum: rainwater
Method: aerobic degradation; 22 degree C
Concentration: 0.001 mg/l related to test substance
Degradation after 7 d: 22-40 %
Degradation after 45 d: 100 %

23-OCT-1995

Remark: Inoculum: Basische Parabraunerde (ueber p-Hydroxybenzoesaeure isoliertes Inokulum)
Method: aerobic degradation, static, room temperature
Concentration: 20 mg test substance/kg soil
Degradation after 3 d: 40 %
Degradation after 7 d: 44 %
Degradation after 70 d: 63 % related to the release of labelled CO2 in % applied radioactivity (labelled benzene ring)

23-OCT-1995

Remark: Inoculum: soil microorganisms (loamy sand)
Method: aerobic degradation, static, 30 degree C, pH = 7.3
Concentration: 16 mg/l related to test substance
Degradation after 1 d: 100 % substance specific analysis
23-OCT-1995

Remark: Inoculum: soil microorganisms (sandy soil in 18.3 m depth)
Method: aerobic degradation, static, 24 degree C
Concentration: 0.05 mg/kg related to test substance
Degradation after 15 d: 40 %
Half life: 35 d (graphically determined)

14-AUG-2001

Remark: Inoculum: soil microorganisms (loam)
Method: aerobic degradation, static, 25 degree C
Concentration: 25 mg/l related to test substance
Degradation after 1 d: 100 %
The cleavage of the benzene ring was detected by UV adsorption.
AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: static
Species: Lepomis macrochirus (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l
NOEC: 10
LC50: 44.6

Method: other: Test conducted according to EPA-660/3-75-009 except that replicate concentrations were not used.

Year: 1975
GLP: no data
Test substance: other TS: technical grade benzoic acid

Remark: Higher LC50s were seen with other species.
Result: 24 hr LC50 = >56.0 mg/l; 48 hr LC50 = 46.0 mg/l; 72 hr LC50 = 46.0 mg/l

Test condition: Purified, deionized water reconstituted to pH of 7.49, total hardness of 44 mg/l CaCO₃, total alkalinity of 31 mg/l CaCO₃.
Reliability: (2) valid with restrictions
Flag: Guideline study with acceptable restrictions

Type: static
Species: Salmo gairdneri (Fish, estuary, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l
NOEC: 10
LC50: 47.3

Year: 1979
GLP: no data
Test substance: other TS: technical grade benzoic acid

Method: Test conducted according to EPA-660/3-75-009 except that replicate concentrations were not used.
Result: 24 hr LC50 = 47.3 mg/l; 48 hr LC50 = 47.3 mg/l; 72 hr LC50 = 47.3 mg/l
Test condition: Purified, deionized water reconstituted to pH of 7.44, total hardness of 36 mg/l CaCO3, total alkalinity of 27 mg/l CaCO3.

Reliability: (2) valid with restrictions Guideline study with acceptable restrictions

Flag: Critical study for SIDS endpoint 14-AUG-2001

Type: static
Species: Leuciscus idus (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no data
LC0: 400
LC50: 460
LC100: 600

Method: other: Fish test acc. to Deutsche Einheitsverfahren zur Wasser-,Abwasser- und Schlammuntersuchung L15
Year: 1976
GLP: no data
Test substance: other TS: benzoic acid, purity not noted

Remark: pH 7 - 8
Reliability: (2) valid with restrictions Meets generally accepted scientific standards, well documented and acceptable for assessment

Flag: Critical study for SIDS endpoint 14-AUG-2001

Type: static
Species: Lepomis macrochirus (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: 180
LC0: 180

Method: other: aerated; 19.5-20.5 degree C; pH control 15-JAN-2001

Species: Carassius auratus (Fish, fresh water)
Unit: mg/l Analytical monitoring: 200
LC100: 200

Method: other: no data
4. ECOTOXICITY

SUBSTANCES ID: 65-85-0

Remark: exposure period: 7-96 h
15-JAN-2001 (57)

Species: Lepomis humilis (Fish, fresh water)
Exposure period: 1 hour(s)
Unit: mg/l Analytical monitoring:
LC100: 550 - 570

Method: other: no data
15-JAN-2001 (57)

4.2 Acute Toxicity to Aquatic Invertebrates

Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no data
EC0: 260
EC50: 500
EC100: 1000

Method: other: Immobilization test at 20 degree C; pH 8.0
Year: 1982
GLP: no data
Test substance: other TS: benzoic acid, purity not noted

Remark: standardized culture without neutralization

<table>
<thead>
<tr>
<th>Test</th>
<th>EC0</th>
<th>EC50</th>
<th>EC100</th>
</tr>
</thead>
<tbody>
<tr>
<td>standardized culture</td>
<td>77 mg/l</td>
<td>102 mg/l</td>
<td>136 mg/l</td>
</tr>
</tbody>
</table>

Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment

Flag: Critical study for SIDS endpoint
14-AUG-2001 (58)

Type: static

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no
NOEC: 100
EC50: > 100
Method: other: EPA-660/3-75-009  
Year: 1979  
GLP: no data  
Test substance: other TS: technical grade benzoic acid  
Test condition: The water was vigorously aerated and determined by analysis to have pH of 8.45, total hardness of 250 mg/l CaCO3, total alkalinity of 141 mg/l CaCO3.  
Reliability: (2) valid with restrictions  
Flag: Guideline study  
14-FEB-2002 (59)  
Species: Daphnia magna (Crustacea)  
Exposure period: 24 hour(s)  
Unit: mg/l  
Analytical monitoring:  
EC0: 540  
EC50: 1540  
Method: other: Immobilization test (neutralization); 20-22 degree C; pH 7.6 - 7.7  
Remark: wild population  
06-JUN-2001 (60)  
Species: Daphnia magna (Crustacea)  
Exposure period: 24 hour(s)  
Unit: mg/l  
Analytical monitoring:  
EC50: 300  
Method: other: Immobilization test acc. to Bringmann & Kuehn  
15-JAN-2001 (61)  

4.3 Toxicity to Aquatic Plants e.g. Algae  
Species: Scenedesmus quadricauda (Algae)  
Endpoint: other: Inhibition of photosynthesis  
Exposure period: 3 hour(s)  
Unit: mg/l  
Analytical monitoring: no data  
EC50: 75  
Method: other: see below
Year: 1982  
GLP: no data  
Test substance: other TS: >95% pure, purchased from Aldrich Chemical Co. Milwaukee, Wisconsin, USA  
Method: Photosynthesis was assayed by following the uptake of (14C)O2 from NaH(14C)O2. Plastic culture flasks contained 9.9ml cell suspension (containing 1.0 E+5 algalcells/ml), 0.1ml radioisotope, and 0.1ml of test chemical. The flasks were incubated for 3 hours and photosynthetic activity assayed. Five replicates of five concentrations, ranging from 0 to 100 mg/ml, were used. Per cent inhibition was calculated relative to photosynthetic activity in the controls. EC50 values were determined by probit (Finney DJ. 1971. Probit Analysis, 3rd ed). Analyses for significant differences (p=0.05) were performed using Dunnett's test (Winer BJ. 1971. Stat. Prin. in Exp. Design, 2nd ed).  
Test condition: 20 degree C; 12 h light/dark-cycle; light intensity 7000 lux  
Reliability: (2) valid with restrictions  
Meets generally accepted scientific standards, Well documented and acceptable for assessment  
Flag: Critical study for SIDS endpoint  
14-FEB-2002  
Species: Scenedesmus quadricauda (Algae)  
Exposure period: 8 day(s)  
Unit: mg/l  
Analytical monitoring:  
TGK : 1630  
Method: other: static, inhibition of cell multiplication; 27 degree C; pH 7  
Reliability: (2) valid with restrictions  
Meets generally accepted scientific standards, Well documented and acceptable for assessment  
Flag: Critical study for SIDS endpoint  
14-AUG-2001  
Species: Scenedesmus quadricauda (Algae)  
Endpoint: growth rate  
Exposure period: 14 day(s)  
Unit: mg/l  
Analytical monitoring:
EC50: > 10

Test substance: other TS: >95% pure, purchased from Aldrich Chemical Co. Milwaukee, Wisconsin, USA

Method: Growth was assessed by measuring the absorbance of cultures with time using a Bausch and Lomb Spectronic 20 spectrophotometer. The wavelength employed (420 nm) was determined by the method of Sorokin C. (1973. Handbook of Phycological Methods). Sidearm flasks containing 94.9 ml of medium and 0.1 ml of test chemical were inoculated with 5 ml of an active culture (containing 6.5 E+4 cyanobacterial and 1.0 E+5 algal cells per ml) and incubated for 12 - 14 days. Five replicates of five concentrations of test chemical, ranging from 0 to 10 mg/ml, were used. Optical densities of treated cultures were determined daily and per cent inhibition was calculated relative to the controls. Growth rates were determined by Sorokin C (1973) and EC50 values were determined by probit (Finney DJ. 1971. Probit Analysis, 3rd ed).

Test condition: 20 degree C; 12 h light/dark-cycle; light intensity 7000 lux

Reliability: (2) valid with restrictions

Meet generally accepted scientific standards, well documented and acceptable for assessment

Flag: Critical study for SIDS endpoint

Species: Chlorella pyrenoidosa (Algae)

Endpoint: other: inhibition of photosynthesis

Exposure period: 3 hour(s)

Unit: mg/l Analytical monitoring: no data

EC50: 60

Method: other: see below

Year: 1982

GLP: no data

Test substance: other TS: >95% pure, purchased from Aldrich Chemical Co. Milwaukee, Wisconsin, USA
Method: Photosynthesis was assayed by following the uptake of (14C)O2 from NaH(14C)O2. Plastic culture flasks contained 9.9ml cell suspension (containing 1.0 E+5 algal cells/ml), 0.1ml radioisotope, and 0.1ml of test chemical. The flasks were incubated for 3 hours and photosynthetic activity assayed. Five replicates of five concentrations, ranging from 0 to 100 mg/ml, were used. Per cent inhibition was calculated relative to photosynthetic activity in the controls. EC50 values were determined by probit (Finney DJ. 1971. Probit Analysis, 3rd ed). Analyses for significant differences (p=0.05) were performed using Dunnett’s test (Winer BJ. 1971. Stat. Prin. in Exp. Design, 2nd ed).

Test condition: 20 degree C; 12 h light/dark-cycle; light intensity 7000 lux

Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, Well documented and acceptable for assessment

Flag: Critical study for SIDS endpoint
14-AUG-2001

Species: Chlorella pyrenoidosa (Algae)
Endpoint: growth rate
Exposure period: 14 day(s)
Unit: mg/l

EC50: > 10

Test substance: other TS: >95% pure, purchased from Aldrich Chemical Co. Milwaukee, Wisconsin, USA

Method: Growth was assessed by measuring the absorbance of cultures with time using a Bausch and Lomb Spectronic 20 spectrophotometer. The wavelength employed(420 nm) was determined by the method of Sorokin C. (1973. Handbook of Phycological Methods). Sidearm flasks containing 94.9ml of medium and 0.1 ml of test chemical were inoculated with 5 ml of an active culture (containing 6.5 E+4 cyanobacterial and 1.0 E+5 algal cells per ml) and incubated for 12 - 14 days.
Five replicates of five concentrations of test chemical, ranging from 0 to 10 mg/ml, were used. Optical densities of treated cultures were determined daily and per cent inhibition was calculated relative to the controls. Growth rates were determined by Sorokin C (1973) and EC50 values were determined by probit (Finney DJ. 1971. Probit Analysis, 3rd ed.).

**Test condition:** 20 degree C; 12 h light/dark-cycle; light intensity 7000 lux

**Reliability:** (2) valid with restrictions

Meets generally accepted scientific standards, well documented and acceptable for assessment

**Flag:** Critical study for SIDS endpoint

14-AUG-2001

**Species:** Anabaena variabilis (Algae)

**Endpoint:** growth rate

**Exposure period:** 14 day(s)

**Unit:** mg/l Analytical monitoring: no data

**EC50:** > 10

**Method:** other: see below

**GLP:** no data

**Test substance:** other TS: >95% pure, purchased from Aldrich Chemical Co. Milwaukee, Wisconsin, USA

**Method:** Growth was assessed by measuring th absorbance of cultures with time using a Bausch and Lomb Spectronic 20 spectrophotometer. The wavelength employed (420nm) was determined by the method of Sorokin C. (1973. Handbook of Phycological Methods).

Sidearm flasks containing 94.9ml of medium and 0.1 ml of test chemical were inoculated with 5 ml of an active culture (containing 6.5 E+4 cyanobacterial and 1.0 E+5 algal cells per ml) and incubated for 12 - 14 days. Five replicates of five concentrations of test chemical, ranging from 0 to 10 mg/ml, were used. Optical densities of treated cultures were determined daily and per cent inhibition was calculated relative to the controls.
Growth rates were determined by Sorokin C (1973) and EC50 values were determined by probit (Finney DJ. 1971. Probit Analysis, 3rd ed).

Test condition: 20 degree C; 12 h light/dark-cycle; light intensity 7000 lux

Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, Well documented and acceptable for assessment

Flag: Critical study for SIDS endpoint
14-AUG-2001 (62)

Species: Anabaena cylindrica (Algae)
Endpoint: other: inhibition of photosynthesis
Exposure period: 3 hour(s)
Unit: mg/l
Analytical monitoring:
EC50: 60

Test substance: other TS: >95% pure, purchased from Aldrich Chemical Co. Milwaukee, Wisconsin, USA

Method: Photosynthesis was assayed by following the uptake of (14C)O2 from NaH(14C)O2. Plastic culture flasks contained 9.9ml cell suspension (containing 1.0 E+5 algal cells/ml), 0.1ml radioisotope, and 0.1ml of test chemical. The flasks were incubated for 3 hours and photosynthetic activity assayed. Five replicates of five concentrations, ranging from 0 to 100 mg/ml, were used. Per cent inhibition was calculated relative to photosynthetic activity in the controls. EC50 values were determined by probit (Finney DJ. 1971. Probit Analysis, 3rd ed).
Analyses for significant differences (p=0.05) were performed using Dunnett's test (Winer BJ. 1971. Stat. Prin. in Exp. Design, 2nd ed).

Test condition: 20 degree C; 12 h light/dark-cycle; light intensity 7000 lux
Reliability: (2) valid with restrictions
23-MAY-2001 (62)

Species: Microcystis aeruginosa (Algae, blue, cyanobacteria)
Exposure period: 8 day(s)
Unit: mg/l  Analytical monitoring:
TGK: 55

Method: other: inhibition of cell multiplication at 27 degree C; pH 7

15-JAN-2001

Species: Anabaena inaequalis  (Algae)
Endpoint: growth rate
Exposure period: 14 day(s)
Unit: mg/l  Analytical monitoring:
EC50: 9

Test substance: other TS: >95% pure, purchased from Aldrich Chemical Co. Milwaukee, Wisconsin, USA

Method: Growth was assessed by measuring the absorbance of cultures with time using a Bausch and Lomb Spectronic 20 spectrophotometer. The wavelength employed (600 nm) was determined by the method of Sorokin C. (1973. Handbook of Phycological Methods). Sidearm flasks containing 94.9ml of medium and 0.1 ml of test chemical were inoculated with 5 ml of an active culture (containing 6.5 E+4 cyanobacterial and 1.0 E+5 algal cells per ml) and incubated for 12 - 14 days. Five replicates of five concentrations of test chemical, ranging from 0 to 10 mg/ml, were used. Optical densities of treated cultures were determined daily and per cent inhibition was calculated relative to the controls. Growth rates were determined by Sorokin C (1973) and EC50 values were determined by probit (Finney DJ. 1971. Probit Analysis, 3rd ed).

Test condition: 20 degree C; 12 h light/dark-cycle; light intensity 7000 lux
Reliability: (2) valid with restrictions

13-DEC-2000

Species: Anabaena cylindrica  (Algae)
Endpoint: growth rate
Exposure period: 14 day(s)
Unit: mg/l  Analytical monitoring:
EC50: > 10

Test substance: other TS: >95% pure, purchased from Aldrich Chemical Co. Milwaukee, Wisconsin, USA

Method: Growth was assessed by measuring the absorbance of cultures with time using a Bausch and Lomb Spectronic 20 spectrophotometer. The wavelength employed (600 nm) was determined by the method of Sorokin C. (1973. Handbook of Phycological Methods).
Sidearm flasks containing 94.9 ml of medium and 0.1 ml of test chemical were inoculated with 5 ml of an active culture (containing 6.5 E+4 cyanobacterial and 1.0 E+5 algal cells per ml) and incubated for 12 - 14 days. Five replicates of five concentrations of test chemical, ranging from 0 to 10 mg/ml, were used. Optical densities of treated cultures were determined daily and percent inhibition was calculated relative to the controls. Growth rates were determined by Sorokin C (1973) and EC50 values were determined by probit (Finney DJ. 1971. Probit Analysis, 3rd ed).

Test condition: 20 degree C; 12 h light/dark-cycle; light intensity 7000 lux

Reliability: (2) valid with restrictions

EC50: 5

Test substance: other TS: >95% pure, purchased from Aldrich Chemical Co. Milwaukee, Wisconsin, USA

Method: Photosynthesis was assayed by following the uptake of (14C)O2 from NaH(14C)O2. Plastic culture flasks contained 9.9 ml cell suspension (containing 1.0 E+5 algal cells/ml), 0.1 ml radioisotope, and 0.1 ml of test chemical. The flasks were incubated for 3 hours and photosynthetic activity assayed.
Five replicates of five concentrations, ranging from 0 to 100 mg/ml, were used. Per cent inhibition was calculated relative to photosynthetic activity in the controls. EC50 values were determined by probit (Finney DJ. 1971. Probit Analysis, 3rd ed).
Analyses for significant differences (p=0.05) were performed using Dunnett's test (Winer BJ. 1971. Stat. Prin. in Exp. Design, 2nd ed).

Test condition: 20 degree C; 12 h light/dark-cycle; light intensity 7000 lux
Reliability: (2) valid with restrictions

Species: Anabaena variabilis (Algae)
Endpoint: other: Inhibition of photosynthesis
Exposure period: 3 hour(s)
Unit: mg/l
EC50: 55

Method: other: inhibition of photosynthesis;
20 degree C; 12 h light/dark-cycle; light intensity 7000 lux

Test substance: other TS: >95% pure, purchased from Aldrich Chemical Co. Milwaukee, Wisconsin, USA

Method: Photosynthesis was assayed by following the uptake of (14C)O2 from NaH(14C)O2. Plastic culture flasks contained 9.9ml cell suspension (containing 1.0 E+5 algal cells/ml), 0.1ml radioisotope, and 0.1ml of test chemical. The flasks were incubated for 3 hours and photosynthetic activity assayed.
Five replicates of five concentrations, ranging from 0 to 100 mg/ml, were used. Per cent inhibition was calculated relative to photosynthetic activity in the controls. EC50 values were determined by probit (Finney DJ. 1971. Probit Analysis, 3rd ed).
Analyses for significant differences (p=0.05) were performed using Dunnett's test (Winer BJ. 1971. Stat. Prin. in Exp. Design, 2nd ed).

Test condition: 20 degree C; 12 h light/dark-cycle; light intensity 7000 lux
Reliability: (2) valid with restrictions
4.4 Toxicity to Microorganisms e.g. Bacteria

Species: activated sludge
Exposure period: 3 hour(s)
Unit: mg/l
EC50: > 1000

Method: OECD Guide-line 209 "Activated Sludge, Respiration Inhibition Test"
Year: 1984
Test substance: other TS: benzoic acid; purity not noted
Remark: pH 7.5
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint

Species: Photobacterium phosphoreum (Bacteria)
Exposure period: 30 minute(s)
Unit: mg/l
EC50: 16.85

Method: other: static at 15 degree C; Microtox-Test
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

Species: Pseudomonas putida (Bacteria)
Exposure period: 16 hour(s)
Unit: mg/l
TGK: 480

Method: other: static; 25 degree C; pH 7
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
Species: Pseudomonas fluorescens (Bacteria)  
Exposure period: 24 hour(s)  
Unit: mg/l  
EC0: 1000  
Method: other: Bestimmung der biologischen Schadwirkung toxischer Abwaessergegen Bakterien. DEV, L 8 (1968) modifiziert

Species: other bacteria: Pseudomonas Stamm Berlin  
Exposure period: 1 hour(s)  
Unit: mg/l  
EC10: 50  
Method: other: Oxygen consumption test acc. to Robra, GWF-Wasser/Abwasser 117,80-86 (1976)

Species: other bacteria: population of microorganisms from communal sewage  
Exposure period: 24 hour(s)  
Unit: mg/l  
Tlm : 500  
Method: other: static, inhibition of cell multiplication; 37 degree C; pH 6.9

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

Remark: No data available.

4.5.2 Chronic Toxicity to Aquatic Invertebrates

Remark: No data available.
TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Sediment Dwelling Organisms

4.6.2 Toxicity to Terrestrial Plants

Remark: No data available. 14-AUG-2001

4.6.3 Toxicity to Soil Dwelling Organisms

Remark: No data available. 14-AUG-2001

4.6.4 Toxicity to other Non-Mamm. Terrestrial Species

Remark: No data available. 14-AUG-2001

4.7 Biological Effects Monitoring

Remark: No data available. 14-AUG-2001

4.8 Biotransformation and Kinetics

Remark: No data available. 14-AUG-2001

4.9 Additional Remarks

Remark: Toxicity to protozoa:
TT (Chilomonas paramaecium): 48 h EC5 356 mg/l (cell multiplication) pH 6.9 23-OCT-1995 (67)

Remark: Toxicity to protozoa:
Entosiphon sulcatum 72 h EC5: 218 mg/l (cell multiplication) 23-OCT-1995 (68)

Remark: Toxicity to protozoa:
Uronema parduczi 20 h TT: 31 mg/l, pH 6.9 (cell multiplication)
Remark: Toxicity to yeast: 6 w MIC (pH 3.5; 25 degree C adapted non-adapted)
- Saccharomyces cerevisiae St 1297 170 mg/l 100 mg/l
- Kluveromyces fragilis 173 125
- Kloeckera apiculata 188 125
- Hansenula anomala 223 140
- Candida crusei 440 300
- Saccharomycodes ludwigi 650 300
- Schizosaccharomyces pombe 567 325
- Zygosaccharomyces bailii 1250 600

Remark: Toxicity to fungi: Fusarium oxysporum:
Test concentration: 610 mg/l
Growth inhibition at
pH 4.0 : 83.5 %
pH 4.8 : 74.6 %
pH 5.6 : 57.9 %
pH 6.4 : 39.5 %
pH 7.2 : 23.7 %

Remark: Antimicrobial effects (pH 6):
Minimal microbicidal minimal inhibitory
Conc. (MMC) Conc. (MIC)
(serial dilution test)
- Aspergillus niger 1000 mg/l 500-1000 mg/l
- Candida albicans 1200 500-1000
- Escherichia coli 160 100-200
- Klebsiella pneumoniae 160 100-200
- Penicillium notatum 1000 500-1000
- Pseudomonas aeruginosa 160 200-500
- Pseudomonas cepacia 160
- Pseudomonas fluorescens 160 200-500
- Staphylococcus aureus 20 50-100
5.0 Toxicokinetics, Metabolism and Distribution

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Sex: male/female
No. of Animals: 50
Vehicle: other: corn oil
Value: 2565 mg/kg bw

Method: Directive 84/449/EEC, B.1 "Acute toxicity (oral)"
GLP: no data
Test substance: other TS: technical grade benzoic acid

Method: 25 male and 25 female Spartan rats weighing 200 to 250 grams were used for this study. The test compound was suspended in corn oil and administered orally at the following dosage levels: 500, 1250, 1984, 3150, and 5000 mg/kg. Five rats of each sex were used at each dosage level. Volumes of 10 ml/kg bw were administered at all dosage levels. All rats were observed for mortality continuously during the first 4 hours after dosing, at 24 hours and once daily thereafter for a total of 14 days. Body weights were recorded initially and at 14 days.

Result: All surviving rats, males and females, exhibited normal body weight gains during the 14 day observation period. The acute oral LD50 of benzoic acid in male albino rats was calculated to be 2742 mg/kg (2279-3299 mg/kg). The acute oral LD50 of benzoic acid in female albino rats was calculated to be 2360 mg/kg (2042-2726 mg/kg). A combined acute oral LD50 for benzoic acid in male and female albino rats was calculated to be 2565 mg/kg (2292-2870 mg/kg).
LD50 calculations were done according to WR Thompson. 1947. Bact. Rev. 11:115-145.

<table>
<thead>
<tr>
<th>Dose level (mg/kg)</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
<td>0/5</td>
</tr>
<tr>
<td>1250</td>
<td>0/5</td>
</tr>
<tr>
<td>1984</td>
<td>0/5</td>
</tr>
<tr>
<td>3150</td>
<td>4/5</td>
</tr>
<tr>
<td>5000</td>
<td>5/5</td>
</tr>
</tbody>
</table>

Reliability: (1) valid without restriction
Flag: Guideline study

**14-FEB-2002**

Type: LD50
Species: mouse
Sex: male/female
No. of Animals: 60
Vehicle: other: Tween 80 (1.5%)
Value: 2250 mg/kg bw

Method: EPA OPPTS 870.1100
Year: 1979
GLP: no data
Test substance: other TS: Commercial Grade benzoic acid (Velsicol lot #52829055)

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint

**14-FEB-2002**

Type: LD50
Species: rat
Value: = 1700 mg/kg bw

**26-JAN-2001**

Type: LD50
Species: rat
Value: = 3040 mg/kg bw
5. TOXICITY

<table>
<thead>
<tr>
<th>Type</th>
<th>LD50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species</td>
<td>rat</td>
</tr>
<tr>
<td>Value</td>
<td>= 2530 mg/kg bw</td>
</tr>
<tr>
<td>26-JAN-2001</td>
<td>(76)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type</th>
<th>LD50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species</td>
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</tr>
<tr>
<td>Value</td>
<td>= 1940 mg/kg bw</td>
</tr>
<tr>
<td>26-JAN-2001</td>
<td>(77)</td>
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</table>

<table>
<thead>
<tr>
<th>Type</th>
<th>LD50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species</td>
<td>mouse</td>
</tr>
<tr>
<td>Value</td>
<td>= 2370 mg/kg bw</td>
</tr>
<tr>
<td>26-JAN-2001</td>
<td>(78)</td>
</tr>
</tbody>
</table>

5.1.2 Acute Inhalation Toxicity

<table>
<thead>
<tr>
<th>Type</th>
<th>LC50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species</td>
<td>rat</td>
</tr>
<tr>
<td>Sex</td>
<td>male/female</td>
</tr>
<tr>
<td>No. of Animals</td>
<td>10</td>
</tr>
<tr>
<td>Exposure time</td>
<td>4 hour(s)</td>
</tr>
<tr>
<td>Value</td>
<td>&gt; 12.2 mg/l</td>
</tr>
<tr>
<td>Method</td>
<td>EPA OTS 798.1150</td>
</tr>
<tr>
<td>Year</td>
<td>1974</td>
</tr>
<tr>
<td>GLP</td>
<td>no data</td>
</tr>
<tr>
<td>Test substance</td>
<td>other TS: technical grade benzoic acid</td>
</tr>
</tbody>
</table>

Method:
Ten rats (4 units of 2 or 3 rats/unit to prevent piling) were placed in a sealed 59.1 liter glass chamber and exposed to a dynamic atmosphere containing the dust of the test material. A Wright Dust Feeder controlled addition of the test substance; airflow regulated by a flowmeter. The rats were observed continuously during the 4-hour exposure, and for a period of 14 days following exposure.

Result:
All of the rats survived the 4-hour exposure and the 14-day observation period. Signs during the exposure period included occasional increased motor activity and slight erythema. At the conclusion of exposure, 1 rat exhibited salivation.
At 24 hours and through the 14-day observation period, all rats appeared normal and exhibited normal body weight gains.

Reliability: (1) valid without restriction
Guideline study
Flag: Critical study for SIDS endpoint
14-FEB-2002

Type: LC50
Species: rat
Exposure time: 1 hour(s)
Value: > .026 mg/l

Remark: exposure to vapor
generalized inactivity, lacrimation at 0.026
mg/l/1h, no mortality

15-JAN-2001

5.1.3 Acute Dermal Toxicity

Type: LD50
Species: rabbit
Sex: male/female
No. of Animals: 4
Vehicle: other: neat
Value: > 2000 mg/kg bw

Method: EPA OTS 798.1100
Year: 1974
GLP: no data
Test substance: other TS: technical grade benzoic acid

Method: The test compound was applied once only to a shaved area of the back of each rabbit at a
dose of 2000 mg/kg bw.
The skin of 1 male and 1 female was abraded with
a scalpel blade prior to test application.
The area was wrapped with a gauze bandage and
occluded with plastic wrap.
The bandages were removed and the backs washed
24 hours after application.
The rabbits were observed for a period of 14
days.

Reliability: (1) valid without restriction
Guideline study
Flag: Critical study for SIDS endpoint
14-FEB-2002

Type: LD50
5. TOXICITY

Species: rabbit
Value: > 10000 mg/kg bw

Remark: mortality: 0/5
15-JAN-2001 (4)

Type: LD50
Species: rabbit
Value: > 5000 mg/kg bw

Remark: mortality: no information
15-JAN-2001 (79)

5.1.4 Acute Toxicity, other Routes

Type: LD50
Species: mouse
Route of admin.: i.p.
Value: = 1460 mg/kg bw

23-MAR-2001 (80)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Concentration: undiluted
Exposure: Semiocclusive
Exposure Time: 4 hour(s)
No. of Animals: 6
PDII: 0
Result: not irritating
EC classificat.: not irritating

Method: EPA OTS 798.4470
GLP: no data
Test substance: other TS: benzoic acid, technical flakes

Remark: Primary Skin Irritation and Corrosive Hazard (Title 49, Transportation, Chapter 1)
Reliability: (1) valid without restriction
Guideline study
Flag: Critical study for SIDS endpoint
14-AUG-2001 (73)

Species: rabbit
Concentration: undiluted
Exposure: Semiocclusive
Exposure Time: 4 hour(s)
No. of Animals: 3
PDII: .5
Result: slightly irritating
EC classification: not irritating

Method: Directive 84/449/EEC, B.4 "Acute toxicity (skin irritation)"
GLP: yes
Test substance: other TS: benzoic acid, purity not noted

Method: The flank site of 3 albino rabbits was exposed to 0.5 g of the test substance moistened with 0.25 ml Milli-RO water for 4 hours using semi-occlusive dressings.
Result: The primary skin irritation index amounted to 0.5; based on these results, the test substance should be considered as minimally irritating to the skin; According to Annex VI of EEC Council Directive 67/548/EEC (amended by Directive 83/467/EEC), the test substance need not be labelled as a skin irritant.

Reliability: (1) valid without restriction
Flag: Guideline study
Species: rabbit
Method: other: see remarks
Remark: irritation score: 1.66/8.00 single application of 500 mg dry powder (no further information), response scored at 24 h and 72 h

Concentration: undiluted
Exposure Time: 24 hour(s)
No. of Animals: 2
Result: not irritating
Method: other:
Test substance: other TS: benzoic acid, purity not noted
Method: 2 animals; application of 500 mg/animal at the inner side of the ear for 24 h
Species: human
Method: other: see remarks
Remark: Chamber-Scarification-Test
threshold irritating concentration:
1) normal skin: 30 % in ethanol
2) scarified skin: 7.5 % in ethanol: moderate irritations;
   application of 15 % in ethanol leads to marked irritation with erosions
23-MAR-2001 (83) (84)

Species: human
Remark: intermittent exposure, total dose applied: 22 mg, duration of exposure: 3 days
   irritation classified as moderate
23-MAR-2001 (85)

Species: human
Method: other: see remarks
Remark: 16 mM benzoic acid (in petrolatum) produced an Erythematous reaction in 12 of 13 healthy
   volunteers on the cheek and in 6 subjects on the forehead, neck and upper back.
   8 mM and 4 mM benzoic acid produced only a reaction on cheek.open application method
23-MAR-2001 (86)

Species: human
Method: other: see remarks
Remark: benzoic acid (in 50 % aqueous isopropanol) was applied to the medial cheek of adult
   volunteers; a 2 % solution led to wheals (11/11), a 0.04 % solution to erythema (11/11)
   and pruritus (4/11)
23-MAR-2001 (87)

Species: human
Method: other: see remarks
Remark: non-immunologic immediate contact reactions 30-45 min after application skin-test with 10 ul doses of 50, 100, 250, 500 or 1000 mM benzoic acid in various vehicles (emollient cream, petrolatum, 2-propyl alcohol/water-mixture (1:1), abs. ethyl alcohol, synthetic lanolin substitute), openly applied on the back of 11 healthy subjects and 3 patients with psoriasis, eczema, and rosacea resp. for 15 min

23-MAR-2001 (88)

5.2.2 Eye Irritation

Species: rabbit
Concentration: undiluted
Dose: .1 ml
Exposure Time: 1 hour(s)
Comment: rinsed after (see exposure time)
No. of Animals: 8
Result: corrosive
EC classificat.: risk of serious damage to eyes

Method: EPA OTS 798.4500
GLP: no data
Test substance: other TS: benzoic acid, technical flakes

Remark: Group I, consisting of 5 rabbits, were exposed to the test compound for 5 minutes; 3 rabbits in Group II were exposed to the test substance for 24 hours. Following the exposure period, the treated eyes were washed with a gentle continuous stream of water for 2 minutes. Eye Irritation Test in Albino Rabbits (21 CFR, Part 191)

Result: Both Group I (5 minute exposure) and Group II (24 hrs exposure) - an extremely irritating and corrosive substance.

Reliability: (1) valid without restriction
Flag: Guideline study
Critical study for SIDS endpoint

14-AUG-2001 (73)

Species: rabbit
Concentration: undiluted
Dose: 77 other: mg
Result: highly irritating
EC classificat.: irritating
Method:              Directive 84/449/EEC, B.5 "Acute toxicity (eye irritation)"
GLP:                yes
Test substance:      other TS: benzoic acid, purity not noted

Remark:             Based on Draize score of 35 the test substance should be classified as severely irritating according to the scheme of Kay & Calandra; according to Annex VI of EEC Council Directive 67/548/EEC (amended by Directive 83/467/EEC), the test substance should be labelled as an eye irritant. Instillation of approx. 77 mg in the eye

Reliability:        (1) valid without restriction
Flag:               Critical study for SIDS endpoint

Species:            rabbit
Method:             other: see remarks
Remark:             Irritation score: 65.0/110
                     Single application of 100 mg dry powder, responses scored at 24, 48 or 72 h

Species:            rabbit
Result:             Slightly irritating
Method:             other: OECD Guideline 405

Species:            rabbit
Result:             Moderately irritating
Method:             other: see remark
Remark:             2 animals; instillation of 50 mg/animal into the conjunctival sac

5.3 Sensitization

Type:               Draize Test
Species:            guinea pig
Concentration 1st:   Induction 500 undiluted occlusive epicutaneous
2nd: Challenge 500 undiluted occlusive epicutaneous

No. of Animals: 10
Result: not sensitizing
Classification: not sensitizing

Method: EPA OPP 81-6
Year: 1959
GLP: yes
Test substance: other TS: benzoic acid, purity not noted

Result: During induction and challenge, the grand mean for erythema and edema at 24 and 48 hours was 0. Based on this study, it was concluded that benzoic acid is neither an irritant nor a sensitizer when applied to guinea pigs.

Reliability: (1) valid without restriction
GLP guideline study
Flag: Critical study for SIDS endpoint 14-AUG-2001

Type: Guinea pig maximization test
Species: guinea pig
Concentration 1st: Induction 10 % intracutaneous
2nd: Induction 20 % semiocclusive
3rd: Challenge 20 % semiocclusive
Result: not sensitizing
Classification: not sensitizing

Method: OECD Guide-line 406 "Skin Sensitization"
GLP: no data
Test substance: other TS: benzoic acid, purity not noted

Remark: test concentrations: intradermal injection 10 %, topical induction 20 %, challenge 20 %

Reliability: (1) valid without restriction
GLP guideline study
Flag: Critical study for SIDS endpoint 14-AUG-2001

Type: Buehler Test
Species: guinea pig
Result: not sensitizing

Test substance: other TS: benzoic acid; purity not noted

Remark: test concentrations: induction 20 %, challenge 20 %

14-AUG-2001

Type: Mouse local lymphnode assay
<table>
<thead>
<tr>
<th>Species</th>
<th>mouse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result</td>
<td>not sensitizing</td>
</tr>
<tr>
<td>Test substance:</td>
<td>other TS: benzoic acid; purity not noted</td>
</tr>
<tr>
<td>Remark</td>
<td>test concentrations: 5, 10 or 20 %</td>
</tr>
<tr>
<td>Date</td>
<td>14-AUG-2001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Species</th>
<th>mouse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result</td>
<td>not sensitizing</td>
</tr>
<tr>
<td>Test substance:</td>
<td>other TS: benzoic acid; purity not noted</td>
</tr>
<tr>
<td>Remark</td>
<td>test concentrations: induction 20 %, challenge 20 %</td>
</tr>
<tr>
<td>Date</td>
<td>14-AUG-2001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Species</th>
<th>guinea pig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method</td>
<td>other: ear swelling test</td>
</tr>
<tr>
<td>Remark</td>
<td>groups of five guinea pigs were challenged by applying various concentrations of benzoic acid to both sides of the earlobe. The thickness of the ear was measured at various time intervals. Benzoic acid was positive (concentration-dependent effect).</td>
</tr>
<tr>
<td>Date</td>
<td>14-AUG-2001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Species</th>
<th>human</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method</td>
<td>other: patch-test</td>
</tr>
<tr>
<td>Test substance:</td>
<td>other TS: benzoic acid; purity not noted</td>
</tr>
<tr>
<td>Remark</td>
<td>3 workers of a pharmaceutical plant with transient urticaria after exposure to sodium benzoate and 3 previously unexposed healthy control subjects were tested. All subjects reacted to benzoic acid at 0.25 % in aqueous solution under occlusion. 1 worker and 2 controls reacted to sodium benzoate at 0.5 % in saline under occlusion, but none reacted to sodium benzoate at 0.5 % in aqueous solution. All 3 workers reacted in a closed patch test to benzoic acid at 5 % in petrolatum.</td>
</tr>
<tr>
<td>Date</td>
<td>14-AUG-2001</td>
</tr>
</tbody>
</table>
The time course of the responses to benzoic acid and sodium benzoate was similar in controls and workers. The potential of sodium benzoate to elicit nonimmunologic contact urticaria may be due to the formation of benzoic acid at skin contact.

14-AUG-2001 (95)

Type: other: see remarks
Species: human
Method: other: patch-test
Remark: 3/5 patients with chronic urticaria developed positive skin reactions in a patch test with benzoic acid (5 % in petrolatum).

14-AUG-2001 (96)

Type: other: see remarks
Species: human
Method: other: patch-test
Test substance: other TS: benzoic acid; purity not noted
Remark: In a patch test with benzoic acid (5 % in petrolatum), 108/113 patients showed no reaction and 5/113 patients showed a 1+ reaction. Benzoic acid was not classified as a sensitizer.

14-AUG-2001 (97)

Type: other: see remarks
Species: human
Method: other: patch-test
Remark: In a study of cosmetic intolerance with patients tested for possible contact dermatitis, 34 (0.7 %) of all patients and 1 (0.6 %) patient with pure allergy to cosmetics reacted positive.
Method: other: patch-test
Test substance: other TS: benzoic acid; purity not noted

Remark: a baker developed dermatitis from flours which contained traces of benzoic acid; patch tests showed contact type eczematous hypersensitivity to benzoic acid (6 % in petrolatum).
14-AUG-2001 (99)

Type: other: see remark
Species: human

Method: other: patch-test
Test substance: other TS: benzoic acid; purity not noted

Remark: 40 children (under 12 years old) were tested for contact urticaria against food additives. 14 of them reacted positive to benzoic acid (no further information).
Reliability: (3) invalid Documentation insufficient for assessment
14-AUG-2001 (100)

Type: other: see remarks
Species: human

Method: other: skin-prick-test
Remark: 23 out of 91 subjects suffering from chronic or recurrent urticaria were tested in a skin test: 10/23 positive subjects (at least one histamine equivalent skin test reaction) reacted to benzoic acid (5 % in petrolatum).
14-AUG-2001 (101)

Type: other: see remarks
Species: human

Method: other: oral provocation test
Remark: a chemical worker suffered from allergic reactions of increasing intensity while being constantly exposed to benzoic acid during work. After oral exposure to sodium benzoate (500 mg) he suffered a severe anaphylactic shock.
He showed similar but milder reaction after consuming food containing benzoic acid.
14-AUG-2001 (102)
5. TOXICITY

Type: other: see remarks
Species: human
Method: other: oral provocation test
Remark: only one out of 7 subjects with a positive skin test for benzoic acid showed a positive response (itching, wealing) after repeated oral exposure

14-AUG-2001 (101)

Type: other: see remarks
Species: human
Method: other: oral provocation test
Remark: to patients suffering from asthma benzoic acid was given orally (no details reported); approx. 50 % of the subjects showed asthmatic hypersensitivity, rhinitis and urticaria.

14-AUG-2001 (103)

Type: other: see remarks
Species: human
Method: other: patch-test
Remark: 7 patients with recurrent episodes of erythema multiforme were found to be sensitive to benzoic acid. Advice on avoidance of benzoic acid resulted in resolution of attacks in 4 patients (3 patients were not able to adhere to an exclusion diet).

14-AUG-2001 (104)

5.4 Repeated Dose Toxicity

Type: Chronic
Species: rat Sex: male/female
Strain: no data
Route of administration: oral feed
Exposure period: generation 1 and 2: lifelong, generation 3: 16 weeks, generation 4: until breeding
Frequency of treatment: continuously in diet
Post exposure period: no
Doses: 0.5 or 1 % in diet (approx. 375 or 750 mg/kg/day)
Control Group: yes
NOAEL: 750 mg/kg bw

Year: 1960
GLP: no
Test substance: other TS: benzoic acid, purity not noted

Method: A robust protocol according to standards at That time was used. Taking into account the reputation of the investigators a high quality has to be assumed.

Remark: 40 rats/group; initial body weight: 40-50 g The mean compound consumption was calculated according to Lehman, A.J., Assoc. Food Drug Off. Q. Bull. 18, 66 (1954).

Result: In all 4 generations no influence on growth (weight, weight gain and food efficiency (measured by protein efficiency)) and organ weights was found. In all 4 generations, no effects on fertility ("Forzplanzung") and lactation ("Aufzugt der Jungen") was found. The animals of the 3rd generation were killed and examined histopathological after 16 weeks (after lactation of the pups.) No histopathological findings were found. In the paper no information is given on the organs investigated, however due to the robustness of the total study, the reputation of the investigators, as well as the reputation of the Professor who did the histopathologic investigation, a high quality has to be assumed. From other parameters it can be assumed that as a minimum the brains, heart, liver, kidney, testis and were examined.

Feeding of 0.5 % led to prolongation of survival compared to controls. In addition a so-called "Alters Paarung" after 48 weeks gave no influence on start of menopause.

Reliability: (2) valid with restrictions

Flag: Critical study for SIDS endpoint

Type: Sub-chronic
Species: rat Sex: male
Strain: no data
Route of administration: oral feed
Exposure period: 28 days
Frequency of treatment: continuously in diet
Post exposure period: no

Doses: 760, 3800 or 7600 ppm (approx. 65, 324.1 or 647.5 mg/kg/day)
Control Group: yes
NOAEL: 647.5 mg/kg bw

Method: other
GLP: no data
Test substance: other TS: benzoic acid; purity not noted

Remark: 10 rats/group; initial body weight: 120 g
mean feed consumption: 85.5; 85.3 or 85.2 g/kg/d

Result: no deaths or signs of intoxication during
experiment, no significant gross pathological
lesions at autopsy

Reliability: (2) valid with restrictions
Meets generally accepted scientific standards,
Well documented and acceptable for assessment

Flag: Critical study for SIDS endpoint

Species: rabbit
Sex: male/female
Strain: New Zealand white
Route of administration: dermal
Exposure period: 21 days
Frequency of treatment: 5 days/week for 3 weeks
Doses: 100, 500, 2500 mg/kg bw
Control Group: yes, concurrent vehicle

NOAEL: 2500 mg/kg bw

GLP: yes
Test substance: other TS: benzoic acid, purity not noted

Method: Four male and four female rabbits were used in
each treatment group and in the control group.
The skin of one-half of the animals was
abraded and the others left intact.
Benzoic acid was applied 5 days a week for 3
weeks at dosage levels of 100, 500, 2500 mg/kg
bw.
The rabbits were observed daily for signs of
dermal irritation and changes in general
behavior and appearance. Individual body
weights were recorded weekly. Hematologic and
biochemical studies were conducted once in the
pretest period and again.
at 21 days of the study. Gross and histopathology was performed on liver, kidneys, thyroid/parathyroid, heart, lung, ovaries, testes, adrenals as well as most gastrointestinal tract and neurological organs.

Result: Very slight dermal irritation was noted for one rabbit at the 2500 mg/kg dosage level. No compound-related effects were seen in general behavior and appearance, body weight, clinical laboratory tests, organ weights, or survival.

Reliability: (1) valid without restriction
Meets generally accepted scientific method and is described in sufficient detail

Flag: Critical study for SIDS endpoint

Type: Sub-chronic
Species: rat Sex: male/female
Strain: Sprague-Dawley
Route of administration: inhalation
Exposure period: 4 weeks
Frequency of treatment: 6 h/d; 5 d/w
Post exposure period: none
Doses: 0, 25, 250, 1200 mg/m³
Control Group: yes
NOAEL: 25 mg/m³
LOAEL: 250 mg/m³

Year: 1981
GLP: yes
Test substance: other TS: technical grade benzoic acid

Method: Four groups of rats (10 animals/sex/group) were exposed to a dust aerosol of benzoic acid at concentrations of 0, 25, 250, 1200 mg/m³, 6 hrs/day, 5 days/week, 4 consecutive weeks. The animals were observed twice daily, pharmacotoxic signs observed weekly, and their body weights recorded prior to exposure and weekly thereafter.

Animals found in a moribund condition were sacrificed. After 4 weeks of exposure, all surviving animals were necropsied and biochemical, hematologic, organ weights and histopathologic evaluations were conducted.
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Result: No compound-related gross lesions were seen in any animal from any dose group.
Compound-related microscopic lesions, consisting of an increase of inflammatory cell infiltrate and an increase in the incidence, intensity, and extent of interstitial fibrosis in lungs of rats from all dose groups (but not dose related), were observed.
1200 mg/m³: 1 animal/sex died; decreased body weight; decrease in platelets; decreased absolute and relative weights of liver (m) and trachea/lung (f); no significant difference in biochemical parameters.
>/>= 250 mg/m³: upper respiratory tract irritation, decreased absolute and relative weights of kidney (f).
0 - 250 mg/m³: No deaths; no effects on weight gain; no significant effects on organ weights, biochemical or hematologic parameters.

Test condition: The concentration was generated as a dust aerosol with an IRAD dust generator.
The test material (white flakes) was ground in an Oster blender to produce a more respirable particle. Actual exposure concentration was determined by gravimetric techniques.
Particle size distribution was determined using Andersen 8 stage cascade impactor.
Average particle size was 4.7μm.

Reliability: (1) valid without restriction
Meets generally accepted scientific method and is described in sufficient detail

Flag: Critical study for SIDS endpoint

14-FEB-2002

Species: mouse
Sex: male/female
Strain: other: cross bred white mice
Route of administration: gavage
Exposure period: 12 weeks
Frequency of treatment: once daily
Post exposure period: no
Doses: 80 mg/kg/day
Control Group: yes

Test substance: other TS: analytical grade benzoic acid
Method: 50 mice/sex (initial body weight: 8-10 g) received benzoic acid by oral intubation.
Observations for general condition, behavior, survival, food consumption, and weight gain were recorded daily.
Result: reduced weight gain without reduced food intake; mortality rate at week 10: 32% in males and females
Reliability: (3) invalid
No histopathology or clinical chemistry
Flag: Critical study for SIDS endpoint
14-AUG-2001

Species: rat Sex: male
Strain: Wistar
Route of administration: oral feed
Exposure period: 5 days
Frequency of treatment: continuously in diet
Post exposure period: 19 or 30 days
Doses: 3% in diet (approx. 2250 mg/kg/day)
Control Group: yes

Remark: 15 rats; initial body weight: 60 g
the mean compound consumption was calculated according to Lehman, A.J., Assoc. Food Drug Off. Q. Bull. 18, 66 (1954)
Result: growth retardation; histologically demonstrable brain damage (necrosis of parenchymal cells of the stratum granulosum of the fascia dentata and the cortex of the lobus piriformis) still present after 35 days
Flag: Critical study for SIDS endpoint
14-AUG-2001

Species: rat Sex: male/female
Strain: Wistar
Route of administration: oral feed
Exposure period: 72 weeks
Frequency of treatment: continuously in diet
Post exposure period: no data
Doses: 1.5% in diet (approx. 1125 mg/kg/day)
Control Group: yes

Remark: 20 m + 30 f (dosed group), 13 m + 12 f (control); initial body weight: 50-60 g
the mean compound consumption was calculated according to Lehman, A.J., Assoc. Food Drug Off. Q. Bull. 18, 66 (1954)
Result: reduced food intake, growth retardation, increased mortality rate (15/50 vs. 3/25 in the control)
14-AUG-2001
<table>
<thead>
<tr>
<th>Species:</th>
<th>rat</th>
<th>Sex:</th>
<th>male</th>
</tr>
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<tr>
<td>Strain:</td>
<td>Wistar</td>
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<td></td>
</tr>
<tr>
<td>Route of administration:</td>
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</tr>
<tr>
<td>Exposure period:</td>
<td>7 - 35 days</td>
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<tr>
<td>Frequency of treatment:</td>
<td>continuously in diet</td>
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</tr>
<tr>
<td>Post exposure period:</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doses:</td>
<td>1.1 % in diet (approx. 825 mg/kg/day)</td>
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<tr>
<td>Control Group:</td>
<td>yes</td>
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</tbody>
</table>

**Remark:**
5-10 rats/group
the mean compound consumption was calculated according to Lehman, A.J., Assoc. Food Drug Off. Q. Bull. 18, 66 (1954)

**Result:**
reduced food intake, growth retardation, no pathological findings
15-JAN-2001

<table>
<thead>
<tr>
<th>Species:</th>
<th>rat</th>
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<th>male</th>
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<tbody>
<tr>
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<td>Route of administration:</td>
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<tr>
<td>Exposure period:</td>
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<tr>
<td>Frequency of treatment:</td>
<td>continuously in diet</td>
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</tr>
<tr>
<td>Post exposure period:</td>
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</tr>
<tr>
<td>Doses:</td>
<td>3 % in diet (approx. 2250 mg/kg/day)</td>
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</tr>
<tr>
<td>Control Group:</td>
<td>yes</td>
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</tbody>
</table>

**Remark:**
5-10 rats/group; initial body weight: approx. 60 g the mean compound consumption was calculated according to Lehman, A.J., Assoc. Food Drug Off. Q. Bull. 18, 66 (1954)

**Result:**
after 4-5 days disorders of central nervous system: excitation, ataxia, tonoclonic convulsions; after 3-5 days brain damage was demonstrable histologically (necrosis of parenchymal cells of the stratum granulosum of the fascia dentata and the cortex of the lobus piriformis)
15-JAN-2001

<table>
<thead>
<tr>
<th>Species:</th>
<th>rat</th>
<th>Sex:</th>
<th>male/female</th>
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<tbody>
<tr>
<td>Strain:</td>
<td>Wistar</td>
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<td></td>
</tr>
<tr>
<td>Route of administration:</td>
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</tr>
<tr>
<td>Exposure period:</td>
<td>72 weeks</td>
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<tr>
<td>Frequency of treatment:</td>
<td>once daily</td>
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</tr>
<tr>
<td>Post exposure period:</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doses:</td>
<td>40 mg benzoic acid/kg/day and 80 mg sodium bisulphite/kg/day</td>
<td></td>
<td></td>
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<tr>
<td>Control Group:</td>
<td>yes</td>
<td></td>
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</tr>
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</table>
Test substance: other TS: analytical grade

Remark: 50 rats/sex; initial body weight: 100-120 g; test

Result: reduced weight gain, kidney function and the reaction on stress factors were altered (no further information); the erythrocyte sedimentation rate was increased

14-AUG-2001 (108)

Species: rat
Strain: Wistar
Route of administration: oral unspecified
Exposure period: 72 weeks
Frequency of treatment: once daily
Post exposure period: no data
Doses: 40 mg/kg/day
Control Group: yes

Remark: 10 rats/sex; initial body weight: 100-120 g; test substance: analytical grade

Result: the rats developed some tolerance to a single add. application of 4000 mg sodium benzoate/kg given terminally, the mortality rate was 25 %

15-JAN-2001 (108)

Species: mouse
Strain: no data
Route of administration: gavage
Exposure period: 12 weeks
Frequency of treatment: once daily
Post exposure period: no
Doses: 80 mg benzoic acid/kg/day and 160 mg sodium bisulphite/kg/day
Control Group: yes

Remark: 100 mice/group; initial body weight: 8-10 g; test substance: analytical grade

Result: reduced weight gain without reduced food intake; mortality rate at week 10: 70 % in males and 62 % in females

15-JAN-2001 (108)

Species: mouse
Strain: no data
Route of administration: oral unspecified
Exposure period: 68 weeks
Frequency of treatment: once daily
Post exposure period: no data
Doses: 40 mg/kg/day
Control Group: yes

Remark: 25 mice/sex (initial body weight 10-15 g) or 25 mice/sex (initial body weight 16-20 g) were tested; test substance: analytical grade
Result: no effects were reported
15-JAN-2001 (108)

Species: mouse  Sex: male/female
Strain: no data
Route of administration: oral unspecified
Exposure period: 68 weeks
Frequency of treatment: once daily
Post exposure period: no data
Doses: 40 mg benzoic acid/kg/day and 80 mg sodium bisulphite/kg/day
Control Group: yes

Remark: 25 mice/sex (initial body weight 10-15 g) or 25 mice/sex (initial body weight 16-20 g) were tested; test substance: analytical grade
Result: reduced weight gain without reduced food intake; mortality rate at week 32: 56-65 % in males and 45-72 % in females
15-JAN-2001 (108)

Species: cat  Sex: male
Strain: no data
Route of administration: oral feed
Exposure period: 15 days
Frequency of treatment: continuously in diet
Post exposure period: no data
Doses: 100 or 200 mg/kg/day
Control Group: yes

Remark: 4 cats/group were tested; initial body weight: 1.7-2.27 kg
Result: no effects were observed
15-JAN-2001 (111)
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5. TOXICITY  

DATE: 14-FEB.-2002  
SUBSTANCES ID: 65-85-0  

Route of administration: oral feed  
Exposure period: 3-4 days  
Frequency of treatment: continuously in diet  
Post exposure period: no data  
Doses: 0.5 % in diet (approx. 300-420 mg/kg/day)  
Control Group: yes  

Remark: 4 cats were tested; initial body weight: 1.42-2.0 kg  
Result: convulsions, hyperaesthesia, apprehension, swollen hepatocytes with infiltrations of macrophages and fibroblasts, swollen kidney tubules, no pathological findings in brain and spinal cord; mortality: 2/4  
15-JAN-2001 (111)  

Species: cat  
Strain: no data  
Route of administration: oral feed  
Exposure period: 23 days  
Frequency of treatment: continuously in diet  
Post exposure period: no data  
Doses: 0.25 % in diet (approx. 130-160 mg/kg/day)  
Control Group: yes  

Remark: 4 cats were tested; initial body weight: 3.2-4.0 kg  
Result: no effects were observed  
15-JAN-2001 (111)  

5.5 Genetic Toxicity 'in Vitro'  

Type: Salmonella typhimurium reverse mutation assay  
System of testing: TA 98, TA100, TA 1535, TA1537, TA1538  
Concentration: 0; 20; 50; 100; 500; 1000; 2000ug/plate  
Metabolic activation: with and without  
Result: negative  

Method: OECD Guide-line 471  
Year: 1983  
GLP: no data  
Test substance: other TS: technical grade benzoic acid  
Reliability: (1) valid without restriction Guideline study
OECD SIDS
BENZOATES

5. TOXICITY

SUBSTANCES ID: 65-85-0

Flag: Critical study for SIDS endpoint
14-FEB-2002

(112)

Type: other: Sister chromatid exchange
System of testing: human lymphocytes
Concentration: 0 to 2.0 mM
Cytotoxic Concentration: no data
Metabolic activation: without
Result: negative

Method: other: similar to OECD Guide-line 479
Year: 1986
Test substance: other TS: benzoic acid, purity = 99%
(estimated by NMR)

Reliability: (2) valid with restrictions
Comparable to Guideline study with acceptable restrictions

Flag: Critical study for SIDS endpoint
14-AUG-2001

(113)

Type: other: Sister chromatid exchange
System of testing: human lymphoblastoid cells transformed by Epstein-Barr virus (NL2, NL3, NL4)
Concentration: 0.001, 0.003, 0.01, 0.03 M
Cytotoxic Concentration: 0.03 M
Metabolic activation: without
Result: negative

Method: OECD Guide-line 479
Year: 1986
Test substance: other TS: benzoic acid purchased from Kanto Chemical Co., Tokyo, Japan

Test condition: Test done only without metabolic activation.
Reliability: (2) valid with restrictions
Guideline study with acceptable restrictions
Flag: Critical study for SIDS endpoint
14-AUG-2001

(114)

Type: other: Chromosomal aberration test
System of testing: Chinese hamster fibroblast cell line (CHL)
Concentration: up to 10 mg/plate
Metabolic activation: without
Result: ambiguous

Test substance: other TS: benzoic acid, >99% pure
Method: The study was carried out using a Chinese Hamster fibroblast cell line (CHL) which were exposed to the test substance at one of three dose levels for 24 and 48 hr. No metabolic activation systems were applied. Chromosome preparations were made following treatment with Colcemid. A hundred well-spread metaphases were observed per plate and the incidence of polyploid cells and cells with chromosome aberrations was recorded.

Result: At 48 hr, there was an incidence of 1% polyploid cells and 8% cells with structural aberration (incidence between 5-9.9% is considered equivocal).

Reliability: (2) valid with restrictions

Results meet generally accepted scientific standards, well documented and acceptable for assessment

Flag: Critical study for SIDS endpoint

Type: Bacillus subtilis recombination assay

System of testing: Bacillus subtilis H17, M45

Metabolic activation: no data

Result: positive

Test substance: no data

Method: An overnight culture of B. subtilis, H17 and M45, was mixed with test solutions and incubated for 30 minutes at 37 degree C. After treatment viable cells were counted and the ratio of 50% survival concentrations were calculated.

Result: Benzoic acid showed DNA damaging potential although it had been negative in the Ames test.

Reliability: (4) not assignable

insufficient documentation (abstract only)

Flag: Critical study for SIDS endpoint

Type: other: Salmonella microsome assay

System of testing: S. typhimurium TA 98, TA 100, TA 1535, TA 1536, TA 1537, TA 1538

Metabolic activation: with and without

Result: negative

Remark: insufficient documentation
5. **TOXICITY**

**SUBSTANCES ID: 65-85-0**

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<tr>
<td>Metabolic activation:</td>
<td>with and without</td>
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<td>System of testing:</td>
<td>S. typhimurium TA 98, TA 100, TA 1535, TA 1537</td>
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<tr>
<td>Metabolic activation:</td>
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<td>Result:</td>
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<tr>
<td>Remark:</td>
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<th>other: umu test</th>
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<td>S. typhimurium TA 1535/pSK1002</td>
</tr>
<tr>
<td>Metabolic activation:</td>
<td>with and without</td>
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<tr>
<td>Result:</td>
<td>negative</td>
</tr>
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</tbody>
</table>

### 5.6 Genetic Toxicity 'in Vivo'

**Remark:**

See IUCLID data set on sodium benzoate (CAS# 532-32-1).

Data on sodium benzoate reveal no in vivo genotoxicity. Therefore no in vivo genotoxicity study for benzoic acid is indicated.

14-FEB-2002
5.7 Carcinogenicity

Remark: See IUCLID data set on sodium benzoate (CAS# 532-32-1). Data on sodium benzoate reveal no in vivo genotoxicity. Therefore no in vivo genotoxicity study for benzoic acid is indicated.

Flag: Critical study for SIDS endpoint 14-FEB-2002

5.8.1 Toxicity to Fertility

Type: other: 4 generation study
Species: rat
Sex: male/female

Strain: no data
Route of administration: other: oral feed (first 8 weeks paired feed technique; afterwards ad libitum)

Exposure Period: generation 1 and 2: lifelong; generation 3: 16 weeks; generation 4: until breeding

Frequency of treatment: continuously in diet
Doses: 0.5 or 1 % in diet (approx. 375 or 750 mg/kg/day)

Control Group: yes
NOAEL Parental: >= 750 mg/kg bw
NOAEL F1 Offspring: >= 750 mg/kg bw
NOAEL F2 Offspring: >= 750 mg/kg bw

Year: 1960
GLP: no
Test substance: other TS: benzoic acid, purity not noted

Method: A robust protocol, according to standards at that time, was used. Taking into account the reputation of the investigators a high quality has to be assumed.

Remark: 40 (20 M = 20 F) rats/group; initial body weight: 40-50 g.
The mean compound consumption was calculated according to Lehman, A.J., Assoc. Food Drug Off. Q. Bull. 18, 66 (1954).

Result: In all 4 generations no influence on growth (weight, weight gain and food efficiency (measured by protein efficiency)) and organ
weights was found. In all 4 generations, no effects on fertility ("Forzplanzung") and lactation ("Aufzucht der Jungen") was found. The animals of the 3rd generation were sacrificed and examined histopathologically after 16 weeks (after lactation of the pups.) No remarkable histopathological findings were found. In the paper no information is given on the organs investigated, however the robustness of the total study, the reputation of the investigators, as well as the reputation of the Professor who did the histopathologic investigation, a high quality has to be assumed. From other parameters it can be assumed that a minimum the brains, heart, liver, kidney, testis and were examined. Feeding of 0.5 % led to prolongation of survival compared to controls. In addition a so-called "Alters Paarung" after 48 weeks gave no influence on start of menopause.

Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment
Flag: Critical study for SIDS endpoint

5.8.2 Developmental Toxicity/Teratogenicity

Species: rat
Sex: female
Strain: Wistar
Route of administration: gavage
Exposure period: single application
Frequency of treatment: at day 9 of gestation
Duration of test: 20 days
Doses: 510 mg/kg
Control Group: no
NOAEL Maternal Toxity: 510 mg/kg bw
NOAEL Teratogenicity: 510 mg/kg bw

Method: other: Kimmel et al. (1971)
GLP: no data
Test substance: other TS: benzoic acid, purity not noted

Method: Pregnant Wistar rats were treated on day 9 of gestation with one dose of benzoic acid in carboxymethylcellulose. Animals were sacrificed on day 20 of gestation and the uterus observed in
situ for implantation and resorption sites. Live fetuses were removed, examined for gross malformations, weighed, and prepared for histological examination. Skeletal examination was carried out under low magnification.

Remark: Group I was dosed with 510 mg/kg. Group II was dosed with 510 mg/kg; then 2 h later: 250 or 500 mg/kg acetylsalicylic acid

Result: Treatment with benzoic acid alone resulted in no dead or resorbed implants and 3 % abnormal survivors, rates comparable to the control animals.

Reliability: (2) valid with restrictions

Flag: Critical study for SIDS endpoint

Species: rat
Sex: male/female
Strain: no data
Route of administration: other: oral feed (first 8 weeks paired feed technique;
Exposure period: generation 1 and 2: lifelong;
            generation 3: 16 weeks;
Frequency of treatment: continuously in diet
Duration of test: lifelong
Doses: 0.5 or 1 % in diet (approx. 375 or 750 mg/kg/day)
Control Group: yes
NOAEL Maternal Toxicity: >= 750 mg/kg bw
NOAEL Teratogenicity: 750 mg/kg bw
Year: 1960
Test substance: other TS: benzoic acid, purity not noted
Method: A robust protocol, according to standards at that time, was used. Taking into account the reputation of the investigators a high quality has to be assumed.
Remark: The mean compound consumption was calculated according to Lehman, A.J., Assoc. Food Drug Off. Q. Bull. 18, 66 (1954).
Result: The study demonstrated no effects on the dams or on the growth and development of the offspring.
Reliability: (2) valid with restrictions

Meets generally accepted scientific standards,
5. TOXICITY

Flag: Critical study for SIDS endpoint
14-FEB-2002

Remark: See IUCLID data set on sodium benzoate (CAS# 532-32-1).
Data on sodium benzoate reveal no in vivo genotoxicity.
Therefore no in vivo genotoxicity study for benzoic acid is indicated.

14-FEB-2002

5.8.3 Toxicity to Reproduction, Other Studies

5.9 Specific Investigations

5.10 Exposure Experience

Remark: Single oral doses of 1-1.5 g resulted in dyspepsia, Nausea and vomiting.
23-OCT-1995

Remark: A systemic inhibitory effect of UV light (UVA and UVB) on non-immunologic immediate contact reactions to benzoic acid was found in healthy volunteers.
23-OCT-1995

Remark: Effects of infra-red and laser irradiation were studied on non-immunologic immediate contact reactions to benzoic acid. The strength of the contact urticaria was increased.
23-OCT-1995

Remark: Daily oral doses of benzoic acid of < 0.5 g or sometimes up to 4 g/d did not induce adverse effects in man.
23-OCT-1995

Remark: Metabolism in humans:
Percutaneous absorption of 14C-labelled benzoic acid (4 ug/cm2; area: 2.5 cm2) was lower in aged subjects (> 65 years) than in young (18-40 years): cumulative dose absorbed within 7 days was 19.5 vs. 36.2 %.
The diminished surface lipid content of old skin implies a diminished dissolution medium.

23-OCT-1995

5.11 Additional Remarks

Type: Metabolism

Remark: The transdermal absorption of benzoic acid was studied in excised human skin and compared to absorption in living man. In equivalent time, the total absorption (% of applied dose) was 42.6 % (in vivo) or 44.9 % (in vitro).

15-JAN-2001

Type: Metabolism

Remark: The percutaneous absorption and the excretion of benzoic acid were tested in female weanling yorkshire swine (approx.20 kg) after topical and intravenous administration. After i.v. injection of 200 ug (10 uCi)/pig 84.5 % of 14C-activity were excreted with urine and 4.6 % in faeces within 6 days; the radiolabel recovery in carcass was 0.1 %. After topical application of the same dose the radiolabel recovery within 6 days (% of applied dose) was in urine 20 %, faeces 2.9 %, carcass 0.8 %, border 40.2 %, dosed skin 12.2 % and adjacent skin 9.1 %.

23-OCT-1995

Type: Metabolism

Remark: A concentration of 4 ug/cmE+2 of 14C-labelled benzoic acid was applied to the shaved backs of guinea pigs. The percutaneous absorption was determined from urinary and fecal excretion. Absorption of benzoic acid was similar to published human absorption data (no further information). The percutaneous absorption of 14C-labelled benzoic acid was studied in the Mexican hairless dog and compared to human data. Total absorption and maximum absorption rates were greater in humans than in hairless dogs. Surface counting experiments showed that benzoic acid persisted on the dog skin far
longer than on human skin (no further information). The percutaneous absorption of increasing topical doses of benzoic acid was determined in the Rhesus monkey and humans (dosage: 4, 40, 2000 ug/cm²+2; dose absorbed: monkey 59.2 %, 3.6 %, 17.4 %; human 42.6 %, 25.7 %, 14.4 %).

In vivo percutaneous absorption was similar, also the dose-response curve was similar in the two species (no further information).

23-OCT-1995 (130)

Type: Metabolism

Remark: Damaging the skin (tape stripping, irritation, delipidization) increased absorption of benzoic acid dissolved in acetone (200 ug/ml, 50 uCi; topical application: 4 ug/cm²) in hairless guinea pigs:
71.1/73.4/94.1 % vs. 34.2 % absorbed in the group with intact skin.

23-OCT-1995 (131)

Type: Metabolism

Remark: The effect of topical application of benzoic acid on the in vivo percutaneous absorption was tested in 4 rhesus monkeys.
Daily applications of 4 ug/cm²+2 were given for 14 days, the 1st and the 8th application used 14C-labelled test substance.
To quantify absorption, urine was collected and assayed for radioactivity.
The penetration results are expressed as the percentage of the applied dose absorbed, i.e. (% of topical dose eliminated in urine / % of i.v. dose eliminated in urine)*100. After 1st dose 85 % and after 8th dose 89 % were found. No significant change in percutaneous absorption from that following the initial dose was observed following the 8th dose of a multidose regimen.

23-OCT-1995 (132)

Type: Metabolism

Remark: In vitro, the permeation of benzoic acid was measured across isolated stratum corneum, stratum corneum and epidermis, and split-thickness skin. The stratum corneum was shown
to be the rate limiting barrier and the flux was proportional to the concentration of the undissociated compound.

23-OCT-1995  (133)

Type: Metabolism

Remark: The percutaneous absorption and metabolism of benzoic acid was determined through hairless guinea pig skin in vitro. The absorption within 48 h was greater through nonviable skin (60.1% of applied dose) than through viable skin (49.5%). 6.9% of absorbed dose (2 ug/cm²) were conjugated with glycine to form hippuric acid.

23-OCT-1995  (134)

Type: Metabolism

Remark: After s.c. administration of radiolabelled benzoic acid to maternal rats it was found, that the acidic compound penetrated the placental barrier readily. The fetal t1/2 values were in general lower than those for the corresponding maternal tissues. The fetal blood-brain barrier was penetrated more readily than the adult one for the tested compound.

14-AUG-2001  (135)

Remark: After a single i.p. injection of 410 umol 14C-labelled benzoic acid/kg to female Wistar rats 90% of the applied 14C-activity was excreted in urine and 1.3% in bile within 3 hours, mainly as hippuric acid. After 24 hours the excretion was approx. 100%.

23-OCT-1995  (136)

Remark: Benzoic acid is detoxicated by some mammalian species mainly by conjugation with glycine to form hippuric acid. There is a marked species difference in the efficiency of the process. After an oral dose of 50 mg 14C-benzoic acid most species excreted 50-100% of radioactivity in the urine within 24 hours. In the turtle and gecko excretion was slower (39% in 3 days).
In herbivorous and omnivorous species (rhesus, squirell and capuchin monkeys, pig, rabbit, rat, mouse, guinea pig, hamster, lemming, gerbil) benzoic acid was excreted in the urine almost entirely as hippuric acid, though 10-20% of the total 14C-activity appeared as free benzoic acid in pigs and squirell monkeys within 24 hours, possibly as a result of the decomposition of benzoyl glucuronide. In the 2 men given 1 mg benzoic acid/kg, almost all the urinary metabolite was hippuric acid, with 97% of the radioactivity excreted within 4 hours and virtually 100% within 12 hours.

In the carnivorous animals tested (dog, cat, ferret) the main metabolite was hippuric acid, with the dog and ferret excreting also some benzoyl glucuronide. In the hedgehog, an insectivore, a similar excretion occurred. The Indian fruit bat (Pteroptus gigantus) excreted 70-80% of benzoic acid as the glucuronide and the remainder as free acid within 24 hours. The pigeon excreted mainly hippuric acid and in the chick, turtle and gecko the major metabolite was ornithuric acid. When the dose of benzoic acid in the ferret was raised to 200 and 400 mg/kg, the proportion excreted as glucuronide was markedly increased. During the metabolism of benzoic acid, the relative amount of conjugation with glycine and with glucuronic acid varies from species to species and may depend to some extend upon the magnitude of the dose.

14-AUG-2001

Remark:

In many species, benzoic acid is rapidly absorbed, conjugated with glycine and excreted as hippuric acid. There appears to be no accumulation of benzoic acid at low doses, but one limiting factor in the biosynthesis of hippuric acid is the availability of glycine: once the glycine pool is exhausted (after application of high doses), an additional metabolite, benzoyl glucuronide, is excreted in the urine of some species (no further information available).
Remark: 5 days after i.p. injection of 1 ml (4 ug) labeled benzoic acid in saline to female hairless guinea pigs, 92.1 % of the administered dose was excreted in urine.

14-AUG-2001 (131)

Remark: In most animals, the conversion of benzoic acid to hippuric acid has been found to occur in kidney, with conversion possible in the liver when kidney malfunction exists. The monkey metabolized benzoic acid only in the liver (no further information available).

14-AUG-2001 (139)

Remark: After a single i.v. injection of 2.0 to 2.2 mg 13C-labelled benzoic acid/kg to male Wistar rats 85 - 99 % of the applied 13C-activity was excreted as hippuric acid in urine within 120 minutes after application.

14-AUG-2001 (140)

Remark: In an in vitro study, the nitrosation of methylurea to form N-nitrosomethylurea by benzoic acid at a concentration of 10, 50 or 100 mM was not reduced (101, 108 or 102-110 % compared to control).

14-AUG-2001 (141)

Remark: Regional differences in percutaneous absorption of benzoic acid were tested in vitro (face, abdomen, back, forearm, tigh, lower leg, dorsal food, dorsal hand, palm and sole). A trend of increasing permeability from truncal to acral sites was observed (exception: palmar/plantar skin).

23-OCT-1995 (142)

Remark: Benzoic acid was positive in the microsomal degranulation assay, if microsomes were prepared at low 'g' force (10000).
In the test with rough endoplasmatic reticulum prepared at high 'g' forces (>= 105000) it was negative. The degranulation assay tests the ability of a chemical to dissociate polysomes and ribosomes from the endoplasmatic reticulum.

14-AUG-2001

Remark: Benzoic acid (purity 99.9%; 2% solution in phosphate buffered saline) was administered i.v. (jugular catheter) to two male F 344 rats at approx. 2 mg/l for a total dose of 108 mg. The substance caused no neuroexcitation.

14-AUG-2001

Remark: The application of benzoic acid (1% in diet [approx. 450–890 mg/kg/d]) for 1 day to 4 male cats (initial body weight: 1.06–1.70 kg) resulted in convulsions, aggression, hyperaesthesia, swollen hepatic cells with centrilobular vacuolation, infiltration of inflammatory cells, and marked distension of the kidney glomeruli. No pathological findings in brain and spinal cord. Mortality: 1/4 control group: yes

14-AUG-2001

Remark: Other: In a screening with COMPACT (computer-optimized molecular parametric analysis of chemical toxicity) benzoic acid was predicted as a potential substrate for cytochrome P450 IIE.
6.1 Analytical Methods

6.2 Detection and Identification
7.1 Function

7.2 Effects on Organisms to be Controlled

7.3 Organisms to be Protected

7.4 User

7.5 Resistance
8.1 Methods Handling and Storing

8.2 Fire Guidance

8.3 Emergency Measures

8.4 Possib. of Rendering Subst. Harmless

8.5 Waste Management

8.6 Side-effects Detection

8.7 Substance Registered as Dangerous for Ground Water

8.8 Reactivity Towards Container Material


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(15) DSM data.


(19) Bayer AG data


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10. SUMMARY AND EVALUATION

10.1 End Point Summary

10.2 Hazard Summary

10.3 Risk Assessment
I U C L I D D a t a S e t

(SODIUM BENZOATE: CAS N°: 532-32-1)

Existing Chemical
ID: 532-32-1
CAS No. 532-32-1
EINECS Name sodium benzoate
EINECS No. 208-534-8
TSCA Name Benzoic acid, sodium salt
Molecular Formula C7H6O2.Na

Producer Related Part
Company: Bayer Corporation
Creation date: 21-OCT-1999

Substance Related Part
Company: Bayer Corporation
Creation date: 21-OCT-1999

Memo: Bayer Corporation

Printing date: 10-AUG-2001
Revision date:
Date of last Update: 10-AUG-2001

Number of Pages: 68

Chapter (profile): Chapter: 1, 2, 3, 4, 5, 7
Reliability (profile): Reliability: without reliability, 1, 2, 3, 4
1.0.1 OECD and Company Information

Type: lead organisation
Name: American Chemistry Council (formerly Chemical Manufacturers Association), Benzoates HPV Panel
Street: 1300 Wilson Boulevard
Town: 22209 Arlington, VA
Country: United States

09-AUG-2001

Type: cooperating company
Name: ATOFINA Chemicals, Inc.
Country: United States

09-AUG-2001

Type: cooperating company
Name: Bayer Corporation
Country: United States

09-AUG-2001

Type: cooperating company
Name: DSM Fine Chemicals
Country: Netherlands

03-JAN-2001

Type: cooperating company
Name: Noveon, Inc.
Country: United States

09-AUG-2001

Type: cooperating company
Name: Velsicol Chemical Corporation
Country: United States

26-MAY-2000

1.0.2 Location of Production Site

1.0.3 Identity of Recipients
1.1 General Substance Information

1.1.0 Details on Template

1.1.1 Spectra

1.2 Synonyms

1.3 Impurities

1.4 Additives

1.5 Quantity

1.6.1 Labelling

1.6.2 Classification

1.7 Use Pattern

1.7.1 Technology Production/Use

1.8 Occupational Exposure Limit Values

1.9 Source of Exposure

1.10.1 Recommendations/Precautionary Measures

1.10.2 Emergency Measures

1.11 Packaging

1.12 Possib. of Rendering Subst. Harmless

1.13 Statements Concerning Waste
1.14.1 Water Pollution

1.14.2 Major Accident Hazards

Legislation:
Substance listed:
10-JUL-2000

1.14.3 Air Pollution

Classified by:
Labelled by:
Number:
Class of danger:
10-JUL-2000

1.15 Additional Remarks

1.16 Last Literature Search

Type of Search: Internal and External
Date of Search: 07-SEP-1999
Remark: Only HPV endpoints: TOXLINE data base and internal studies.
09-AUG-2001

1.17 Reviews

1.18 Listings e.g. Chemical Inventories
2.1 Melting Point

Value: > 300 degree C
Method: other: measured
Remark: Carbonisation at temperature > 500 degree C
Reliability: (2) valid with restrictions
Data from Handbook or collection of data
Flag: Critical study for SIDS endpoint
09-AUG-2001

Value: 330.6 degree C
Method: other: (calculated) MPBPWIN (v1.31) Program; Adapted Joback Method
Year: 1999
Testsubstance: other TS: molecular structure
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
09-AUG-2001

Value: 410 - 430 degree C
Method: other
Remark: DSM datasheet.
26-JAN-2001

2.2 Boiling Point

Value: 464.9 degree C
Method: other: (calculated) MPBPWIN (v1.31) Program; Adapted Stein and Brown Method
Year: 1999
Testsubstance: other TS: molecular structure
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
09-AUG-2001

2.3 Density

Type: relative density
Value: = 1.44 g/cm³
Flag: Critical study for SIDS endpoint
26-JAN-2001
2. PHYSICO DATA CHEMICAL

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<td>Remark:</td>
<td>thickened</td>
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<td>350 kg/m3</td>
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<tr>
<td>Remark:</td>
<td>not thickened</td>
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<tr>
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</tr>
<tr>
<td>26-MAY-2000</td>
<td></td>
</tr>
</tbody>
</table>

2.3.1 Granulometry

2.4 Vapour Pressure

| Value:        | .00000000489 hPa at 25 degree C |
| Method:       | other (calculated): MPBPWIN (v1.31) Program; Modified Grain Method |
| Year:         | 1999                            |
| Testsubstance:| other TS: molecular structure   |
| Result:       | 3.67E-009 mm Hg; 4.89E-09 hPa   |
| Reliability:  | (2) valid with restrictions     |
| Flag:         | Critical study for SIDS endpoint |
| 09-AUG-2001   |                                 |

2.5 Partition Coefficient

| log Pow:      | -2.269             |
| Method:       | other (calculated): Log Kow(version 1.65 estimate) |
| Year:         | 1999               |
| Testsubstance:| other TS: molecular structure |
| Reliability:  | (2) valid with restrictions |
| Flag:         | Critical study for SIDS endpoint |
| 09-AUG-2001   |                                 |

| log Pow:      | -2.13              |
| Method:       | other (calculated): CLogP |
| Year:         |                      |
| Testsubstance:| other TS: molecular structure |
2.6.1 Water Solubility

Value: 556 g/l at 20 degree C
Method: other
Remark: pH-value: about 8.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

26-JAN-2001

Value: 630 g/l at 20 degree C
pH: 7
Remark: concentrated solutions react neutral
diluted solutions react weakly alkaline (pH 8)

26-JAN-2001

2.6.2 Surface Tension

2.7 Flash Point

Value: > 100 degree C
Type: closed cup
Method: other: DIN 51758
Year:
Reliability: (1) valid without restriction
Meets National standards method (AFNOR/DIN)

09-AUG-2001

2.8 Auto Flammability

2.9 Flammability

2.10 Explosive Properties

Result: Can form explosive mixtures with air.
Remark: 09-AUG-2001
2.11 Oxidizing Properties

2.12 Additional Remarks

Remark: At a rel. humidity of > 50% the salt is hygroscopic and it dissolves at r. F.-values > 85 %
23-OCT-1995 (10)

Remark: UV spectrum lambda max (nm):
225 (water; lg epsilon: n.a.)
23-OCT-1995 (11)

Remark: pH value ca. 7.5 at 10 g/l water
23-OCT-1995 (6)
3.1.1 Photodegradation

Type: air
Conc. of subst.: at 25 degree C
INDIRECT PHOTOLYSIS
    Sensitizer: OH
    Conc. of sens.: 1560000 molecule/cm3
    Rate constant: .00000000017775 cm3/(molecule * sec)
    Degradation: 50 % after 72.2 hour(s)
Method: other (calculated): AOP Program (v1.89)
Year: 1999 GLP:
Test substance: other TS: molecular structure
Reliability: (2) valid with restrictions
    Accepted calculation method
Flag: Critical study for SIDS endpoint
09-AUG-2001

Remark: See IUCLID on benzoic acid (CAS# 65-85-0); the photodegradation of the sodium salt should be similar.

09-AUG-2001

3.1.2 Stability in Water

Type:
Method:
Year: GLP:
Test substance:
Remark: Based on structure and organic chemistry rules (e.g. bonding in organic molecules, activation energy, reactivity, transformations, addition, substitution, elimination) no hydrolysis will occur at pH ranges 4 - 11.
Flag: Critical study for SIDS endpoint
26-JAN-2001

3.1.3 Stability in Soil
3.2 Monitoring Data (Environment)

Type of measurement:
Medium: 
Method: 
Concentration
Remark: See IUCLID on benzoic acid (CAS# 65-85-0); the data on the sodium salt should be similar.

09-AUG-2001

3.3.1 Transport between Environmental Compartments

Type: fugacity model level III
Media: other: air - water - soil - sediment
Air (Level I):
Water (Level I):
Soil (Level I):
Biota (L.II/III):
Soil (L.II/III):
Method: other: EPIWin Modeling Program
Year: 1999
Result: 

<table>
<thead>
<tr>
<th></th>
<th>Distribution (percent)</th>
<th>Half-Life (hr)</th>
<th>Emissions (kg/hr)</th>
<th>Fugacity (atm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>1.45e-007</td>
<td>144</td>
<td>1000</td>
<td>4.83e-019</td>
</tr>
<tr>
<td>Water</td>
<td>45.3</td>
<td>360</td>
<td>1000</td>
<td>1.38e-020</td>
</tr>
<tr>
<td>Soil</td>
<td>54.6</td>
<td>360</td>
<td>1000</td>
<td>6.16e-019</td>
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<tr>
<td>Sediment</td>
<td>0.0755</td>
<td>1.44e+003</td>
<td>0</td>
<td>1.15e-020</td>
</tr>
</tbody>
</table>

Persistence Time: 421 hr
Reaction Time: 520 hr
Advection Time: 2.21e+003 hr
Percent Reacted: 80.9
Percent Advected: 19.1

Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint

09-AUG-2001

3.3.2 Distribution

3.4 Mode of Degradation in Actual Use

Remark: In many species benzoic acid sodium salt is rapidly absorbed and rapidly metabolized namely conjugated with glycine and excreted as hippuric acid in the urine.
The substance is readily biodegradable, and is biodegraded within chemical industry via a waste water treatment plant.

09-AUG-2001

3.5 Biodegradation

Type: aerobic
Inoculum: activated sludge, domestic
Concentration: 50 mg/l related to Test substance
Degradation: ca. 90 % after 7 day
Result: readily biodegradable
Method: OECD Guide-line 301 B "Ready Biodegradability: Modified Sturm Test (CO2 evolution)"
Year: 1981

Test substance: other TS: sodium benzoate, purity not noted
Remark: Sodium benzoate is the recommended "readily biodegradable reference substance" for OECD Guideline studies. This endpoint has been studied several times by several other investigators/groups and all support the result of the study mentioned above.

Test condition: 25 degree C
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint

09-AUG-2001

Type: anaerobic
Inoculum: other bacteria: anaerobic sewage, domestic and industrial
Concentration: 50 mg/l related to DOC (Dissolved Organic Carbon)
Degradation: 93 % 7.5 after 7 day
Method: other: see below

Year: GLP: no data
Test substance: other TS: technical grade sodium benzoate purchased from Aldrich Chemical Co., UK

Method: 2-3 g sludge plus sodium benzoate (concentration equivalent to 50 mg Carbon/liter or 85 mg substance/l). Controls and tests done in triplicate. Temperature = 35 degree C. Measured gas production (CH4 + CO2).
Remark: retard lag 2 d
Result: Degradation is expressed as percentage of theoretical methane production based on the stoichiometry of degradation.
Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment
Flag: Critical study for SIDS endpoint

09-AUG-2001

Type: aerobic
Inoculum: other: suspension from marine aquarium filters
Concentration: 10 mg/l related to DOC (Dissolved Organic Carbon)
Degradation: > 97 % after 28 day
Result: readily biodegradable
Test substance:
- 2 day 20 %
- 4 day 45 %
- 6 day 55 %
- 8 day 70 %
- 20 day 85 %
Method: OECD Guide-line 301 B "Ready Biodegradability: Test (CO2 evolution)"
Year: 1981
Test substance: Guideline adapted to use seawater as test medium and inoculum
Reliability: (1) valid without restriction
03-JAN-2001

Type: anaerobic
Inoculum: other bacteria: anaerobic sewage, domestic, 2 weeks preincubated
Concentration: related to Test substance
Method: other: anaerobic degradation, static, 35 degree C, parameter: gas production
Year: GLP:
Test substance: concentration: 50/60/90 mg/l
degradation: 47/49/28 d = 60.5/82.7/74 %
26-JAN-2001

Type: aerobic
Inoculum: domestic sewage, non-adapted
Contact time: 28 day
Degradation: 84 % after 14 day
Result: readily biodegradable
# OECD SIDS BENZOATES

## 3. ENVIRONMENTAL FATE AND PATHWAYS

**DATE: 10-AUG-2001**  
**SUBSTANCE ID: 532-32-1**

<table>
<thead>
<tr>
<th>Test substance:</th>
<th>14 day</th>
<th>84 %</th>
<th>28 day</th>
<th>92 %</th>
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<td>Directive 84/449/EEC, C.7 &quot;Biotic degradation - modified MITI test&quot;</td>
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<tr>
<td>Test substance:</td>
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<tr>
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<td>19-MAY-2000</td>
<td></td>
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</tr>
</tbody>
</table>

| Type: aerobic |
| Inoculum: other microorganisms already present in seawater |
| Concentration: 11.6 mg/l related to DOC (Dissolved Organic Carbon) |
| Contact time: 61 day |
| Degradation: 80.5 % after 20 day |
| Result: readily biodegradable |

<table>
<thead>
<tr>
<th>Test substance:</th>
<th>5 day</th>
<th>57.4 %</th>
<th>10 day</th>
<th>72.8 %</th>
<th>30 day</th>
<th>83.4 %</th>
<th>50 day</th>
<th>91.7 %</th>
<th>61 day</th>
<th>96.4 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method: OECD Guide-line 301 A (new version) &quot;Ready Biodegradability: DOC Die Away Test&quot;</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Year: 09-MAY-2000</td>
<td></td>
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</tr>
<tr>
<td>GLP: (19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test substance: no data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Type: aerobic |
| Inoculum: activated sludge, non-adapted |
| Concentration: 100 mg/l related to Test substance |
| Degradation: 84 % after 10 day |
| Method: Directive 84/449/EEC, C.7 "Biotic degradation - modified MITI test" |
| Year: 09-MAY-2000 |
| GLP: (20) |
| Test substance: no data |
Remark: degradation after 10 d: 64 - 98 % (n=14)  
          after 28 d: 75 - 111 % (n=14)  
          0 d lag phase EG-Ringtest 1981-82
26-JAN-2001 (21)

Type:
  Inoculum:  
  Degradation: 88 % after 28
  Test substance: 60 day 95 %
  Method: OECD Guide-line 301 A (new version) "Ready
  Biodegradability: DOC Die Away Test"
  Year:  
  Test substance: no data
  GLP:  
09-MAY-2000 (20)

Type:
  Inoculum: other bacteria: purification plant outflow mixed with a soil suspension
  Concentration: 5 mg/l related to Test substance
  Method: other: Respirometer-Test (Closed Bottle Test)
  Year:  
  Test substance:  
  Remark: degradation after 30 d: 75 - 111 % ThSB
          54-89 %: Medium without NH4 Cl
          71-130 %: Medium with NH4 Cl
26-JAN-2001 (22)

Type:
  Inoculum: other bacteria: anaerobic laboratory-sewage, adapted
  Concentration: 300 mg/l related to Test substance
  Degradation: 98 % after 4 day
  Method: other: anaerobic degradation, static
          Year:  
          Test substance:  
          Remark: parameter: gasproduction
          Test condition: 35 degree, enrichment culture
26-JAN-2001 (23)

Type:
  Inoculum: other bacteria: anaerobic sewage, domestic, washed
  Concentration: 50 mg/l related to Test substance
  Degradation: 49.8 % after 61 day
  Method: other: anaerobic degradation, static, 35 degree C, parameter: gasproduction
          Year:  
          Test substance:  
          GLP:  

Remarks: concentration: 60/60 mg/l
degradation : 35/56 d = 95.3/96.5 %
26-JAN-2001

Type:
Inoculum: other bacteria: methanogenic sewage laboratory
culture, benzoate-adapted
Concentration: 3000 mg/l related to Test substance
Degradation: ca. 99 % after 5 day
Method: other: anaerobic degradation, static,
37 degree C, analytical control of
concentration, pH 6.7-6.9
Year: GLP:
Test substance: 26-JAN-2001

Type:
Inoculum: other bacteria: anaerobic sewage from a
purification plant of woodmanufactering
industry, benzoate-adapted
Concentration: 307 mg/l related to Test substance
Degradation: ca. 99 % after 2 day
Method: other: anaerobic degradation, static,
analytical control of concentration
Year: GLP:
Test substance: 26-JAN-2001
Remark: Original data of concentration: 2.13 mM
Test condition: 37 degree C

Type:
Inoculum: other bacteria: anaerobic enrichment culture
(fen), adapted
Concentration: 2306 mg/l related to Test substance
Degradation: 100 % after 4 day
Method: other: anaerobic degradation, static,
parameter: gas production by GC, 39degree C,
pH 6.7
Year: GLP:
Test substance: 26-JAN-2001

3.6 BOD5, COD or BOD5/COD Ratio

Remark: No data.
09-AUG-2001
3.7 Bioaccumulation

Species:
Exposure period:
Concentration:
BCF: 3.16
Elimination:
Method: other: (calculated) BCF Program (v2.13)
Year: 1999
Test substance: other TS: molecular structure
Remark: Based on the log P and its rapid metabolism and excretion in many species no bioaccumulation is indicated.
Result: Estimated Log BCF = 0.500 (BCF = 3.162)
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

09-AUG-2001

3.8 Additional Remarks

Remark: Aerobic degradation in sea water:
Inoculum: sea water; salinity 18.6 %, 20 degree C
Concentration: 20 mg/l DOC
degradation after 28d: 100 %
degradation after 12d: 95 %

23-OCT-1995
Remark: Aerobic degradation in sea water:
Inoculum: sea water (38.7 o/oo), 20 degree C
Method: shake flask test - die away-test;
parameters: DOC initial concentration: 20 mg/l
related to Test substance; 11.6 mg DOC/l (1)
40 mg/l resp. 23.2 mg/l related to DOC (2)
degradation: after 5/20/61 d: 57.4/80.5/96.4 %;
lag time: 4 d (1)
    after 5/20/61 d:30.8/72.8/98.0 %;
lag time: 3 d (2)
23-OCT-1995 (27)

Remark: Anaerobic degradation in lake water:
Inoculum: sediment (eutrophic lake)
Method: anaerobic degradation, semistatic;
28 resp. 37 degree C; pH 7.4 - 7.6
Concentration: 724 mg/l related to Test
substance
Degradation after 20 d: ca. 100 %
Remark: 50% (w/v) sediment in culture medium
started after 4 h (only in undiluted
sediment), complete transformation
to methane, detection of C14 sodium
benzoate (ring-labelled); adaption
to aliphatic fatty acids
23-OCT-1995 (28)

Remark: Anaerobic degradation in laboratory aquifer
column:
Method: continuous, room temperature, contents
of column:

    30 % material of water-bearing soil
sediment/
    70 % slate-debris
Concentration: 28.1 mg/l related to Test
substance
Degradation: > 95 %
Remark: Degradation after adaptation phase of
1 week to m-Xylo1; 30 degree C; flow through
time: 2.6 cm/h, length of column: 25 cm
23-OCT-1995 (29)
AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: flow through
Species: Pimephales promelas (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l                Analytical monitoring: yes
NOEC: > 245
EC50 : 484
Method: EPA OPP 72-1
Year: GLP: no data
Test substance: other TS: sodium benzoate, 99+% purity
Method: pH was adjusted to approximate that of Lake Superior water (pH 7.8) with NaOH or HCL.
Compound analyses were done by HPLC: all exposure chambers at 0, 24, 48, 72 and 96 hr.
Fathead minnows used in this experiment were cultured at US EPA Environmental Research Laboratory, Duluth, MN and University of Wisconsin - Superior campus.
20 fish/concentration and control.
Behavior and toxic signs were noted at 4, 24, 48, 72 and 96 hours and used to calculate EC50.
Remark: Affected fish were hyperactive and lost equilibrium prior to death. No effect data were recorded. Individual lengths and weights of the test fish were not recorded, however the measured mean weight was 230 mg. Alkalinity increased with increasing toxicant concentration. This endpoint had been studied by another investigator and reported results similar to the study mentioned above.
Test condition: temperature =23.9 degree C (+/-0.3); dissolved oxygen = 7.0 mg/l; pH=7.37; hardness = 43.4 mg/l CaCO3;
alkalinity = 80.9mg/l CaCO3; tank volume = 7.3 liter; average measured concentrations 101, 163, 245, 400, 680 mg/l
Reliability: (1) valid without restriction
Flag: Guideline study
09-AUG-2001 Critical study for SIDS endpoint (30) (31)
Type: static
Species: Pimephales promelas (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l
LC50: > 100
Method: other: see below
Year: GLP: no data
Test substance: other TS: sodium benzoate, reagent-grade
Method: 10 fish/dose were exposed to a solution of the test substance for 96 hours (a total of seven aquatic species were tested simultaneously). Biological observations and determinations of temperature, dissolved oxygen and pH were done daily. Survival, condition, and behavior were recorded.

The LC50 values were estimated by interpolation Method (Stephan, CE, ASTM STP 634, FL Mayer & JL Hamelink (eds.) pp 65-84).

Test condition: 20 degree C; pH 6.5-8.5; 16 hr light/day; size of minnows = 200-500 mg; food was withheld for 24 hr prior to exposure; tests were done in duplicate.

Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment

09-AUG-2001

4.2 Acute Toxicity to Aquatic Invertebrates

Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 96 hour(s)
Unit: mg/l
EC50: > 100
Method: other: see below
Year: GLP: no data
Test substance: other TS: sodium benzoate, reagent grade
Method: 10 organisms/dose were exposed to a solution of the test substance for 96 hours (a total of seven aquatic species were tested simultaneously). Biological observations and determinations of temperature, dissolved oxygen and pH were done daily.
Survival, condition, and behavior were recorded. The LC50 values were estimated by interpolation method (Stephan, CE, ASTM STP 634, FL Mayer & JL Hamelink (eds.) pps 65-84).

Remark: This endpoint had been studied by another investigator and reported results similar to the study mentioned above.

Test condition: 20 degree C; pH 6.5-8.5; 16 hr light/day; Daphnia were at first and second larval instar; food was withheld for 24 hr prior to exposure; tests were done in duplicate.

Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment
Flag: Critical study for SIDS endpoint
09-AUG-2001

Type: static
Species: Gammarus fasciatus (Crustacea)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
EC50: > 100
Method: other: see below
Year: GLP: no data
Test substance: other TS: sodium benzoate, reagent grade
Method: 10 organisms/dose were exposed to a solution of the test substance for 96 hours (a total of seven aquatic species were tested simultaneously). Testing concentrations were 0.1, 1.0, 10, and 100 mg/l.
Biological observations and determinations of temperature, dissolved oxygen and pH were done daily.
Survival, condition, and behavior were recorded. The LC50 values were estimated by interpolation method (Stephan, CE, ASTM STP 634, FL Mayer & JL Hamelink (eds.) pps 65-84).

Test condition: 20 degree C; pH 6.5-8.5; 16 hr light/day; Gammarus weighed approximately 7 mg at testing; food was withheld for 24 hr prior to exposure; tests were done in duplicate.

Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment
Flag: Critical study for SIDS endpoint
09-AUG-2001
Type: static
Species: Asellus intermedius (Crustacea)
Exposure period: 96 hour(s)
Unit: mg/l 
Analytical monitoring: no
EC50: > 100
Method: other: see below
Year: GLP: no data
Test substance: other TS: sodium benzoate, reagent grade
Method: 10 organisms/dose were exposed to a solution of the test substance for 96 hours (a total of seven aquatic species were tested simultaneously). Testing concentrations were 0.1, 1.0, 10, and 100 mg/l. Biological observations and determinations of temperature, dissolved oxygen and pH were done daily. Survival, condition, and behavior were recorded. The LC50 values were estimated by interpolation Method (Stephan, CE, ASTM STP 634, FL Mayer & JL Hamelink (eds.) pps 65-84).
Test condition: 20 degree C; pH 6.5-8.5; 16 hr light/day; organisms weighed approximately 12 mg at testing; food was withheld for 24 hr prior to exposure; tests were done in duplicate.
Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.
09-AUG-2001 (32)

Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l 
Analytical monitoring:
EC50: < 650
Method: other: no data
Year: GLP: 
Test substance: 
Test condition: 25 degree C
09-AUG-2001 (34)

Type: static
Species: other aquatic mollusc: Helisoma trivolvis
Exposure period: 96 hour(s)
Unit: mg/l 
Analytical monitoring: no
EC50: > 100
Method: other: see below
Test substance: other TS: sodium benzoate, reagent grade
Method: 10 organisms/dose were exposed to a solution of the test substance for 96 hours (a total of seven aquatic species were tested simultaneously).
Testing concentrations were 0.1, 1.0, 10, and 100 mg/l.
Biological observations and determinations of temperature, dissolved oxygen and pH were done daily.
Survival, condition, and behavior were recorded.
The LC50 values were estimated by interpolation method (Stephan, CE, ASTM STP 634, FL Mayer & JL Hamelink (eds.) pps 65-84).

Test condition: 20 degree C; pH 6.5-8.5; 16 hr light/day;
organisms weighed approximately 180 mg at testing; food was withheld for 24 hr prior to exposure; tests were done in duplicate.

Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.

09-AUG-2001

Type: static
Species: other aquatic worm: Dugesia tigrina
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
EC50: > 100
Method: other: see below

Test substance: other TS: sodium benzoate, reagent grade
Method: 10 organisms/dose were exposed to a solution of the test substance for 96 hours (a total of seven aquatic species were tested simultaneously).
Testing concentrations were 0.1, 1.0, 10, and 100 mg/l.
Biological observations and determinations of temperature, dissolved oxygen and pH were done daily.
Survival, condition, and behavior were recorded.
The LC50 values were estimated by interpolation method (Stephan, CE, ASTM STP 634, FL Mayer & JL Hamelink (eds.) pps 65-84).

Test condition: 20 degree C; pH 6.5-8.5; 16 hr light/day;
organisms weighed approximately 6 mg at testing; food was withheld for 24 hr prior to exposure; tests were done in duplicate.
Reliability: (2) valid with restrictions
Meets generally accepted scientific standards,
well documented and acceptable for assessment.

Type: static
Species: other aquatic worm: Lumbricus variegatus
Exposure period: 96 hour(s)
Unit: mg/l
EC50: > 100
Method: other: see below

Test condition: 20 degree C; pH 6.5-8.5; 16 hr light/day;
organisms weighed approximately 6 mg at testing;
food was withheld for 24 hr prior to exposure;
tests were done in duplicate.

Reliability: (2) valid with restrictions
Meets generally accepted scientific standards,
well documented and acceptable for assessment

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: other algae: green algae
Endpoint: 
Exposure period: 96 hour(s)
Unit: g/l
EC50: 430
Method: other: (calculated) ECOSAR Program (v0.99e)

Test substance: other TS: molecular structure
Result: ECOSAR Class: Neutral Organics
Organism: Green Algae
Predicted 96-hr EC50 = 4.3e+005 mg/l (> saturation)
4.4 Toxicity to Microorganisms e.g. Bacteria

<table>
<thead>
<tr>
<th>Type:</th>
<th>Species: other bacteria: Achromobacter liquefaciens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure period:</td>
<td>24 hour(s)</td>
</tr>
<tr>
<td>Unit:</td>
<td>mg/l</td>
</tr>
<tr>
<td>EC50:</td>
<td>&gt;= 3000</td>
</tr>
<tr>
<td>Method:</td>
<td>other: static, 22 degree C, pH 7</td>
</tr>
<tr>
<td>Year:</td>
<td></td>
</tr>
<tr>
<td>Test substance:</td>
<td>other TS</td>
</tr>
<tr>
<td>Remark:</td>
<td>7 d-EC0 &gt;= 3000 mg/l</td>
</tr>
<tr>
<td>Test substance:</td>
<td>sodium benzoate; purity not noted</td>
</tr>
<tr>
<td>Flag:</td>
<td>Critical study for SIDS endpoint</td>
</tr>
<tr>
<td>10-AUG-2001</td>
<td>(35)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type:</th>
<th>Species: other bacteria: Micrococcus flavus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure period:</td>
<td>24 hour(s)</td>
</tr>
<tr>
<td>Unit:</td>
<td>mg/l</td>
</tr>
<tr>
<td>EC50:</td>
<td>&gt; 500</td>
</tr>
<tr>
<td>Method:</td>
<td>other: static, 22 degree C, pH 7</td>
</tr>
<tr>
<td>Year:</td>
<td></td>
</tr>
<tr>
<td>Test substance:</td>
<td>other TS</td>
</tr>
<tr>
<td>Remark:</td>
<td>7 d-EC0 &gt;= 3000 mg/l</td>
</tr>
<tr>
<td>Test substance:</td>
<td>sodium benzoate; purity not noted</td>
</tr>
<tr>
<td>Flag:</td>
<td>Critical study for SIDS endpoint</td>
</tr>
<tr>
<td>10-AUG-2001</td>
<td>(35)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type:</th>
<th>Species: other bacteria: Sarcina flava</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure period:</td>
<td>24 hour(s)</td>
</tr>
<tr>
<td>Unit:</td>
<td>mg/l</td>
</tr>
<tr>
<td>EC50:</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>Method:</td>
<td>other: static, 22 degree C, pH 7</td>
</tr>
<tr>
<td>Year:</td>
<td></td>
</tr>
<tr>
<td>Test substance:</td>
<td>other TS</td>
</tr>
<tr>
<td>Remark:</td>
<td>7 d-EC0 &gt;= 3000 mg/l</td>
</tr>
<tr>
<td>Test substance:</td>
<td>sodium benzoate; purity not noted</td>
</tr>
<tr>
<td>Flag:</td>
<td>Critical study for SIDS endpoint</td>
</tr>
<tr>
<td>10-AUG-2001</td>
<td>(35)</td>
</tr>
</tbody>
</table>
4. ECOTOXICITY

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

Species:
Endpoint:
Exposure period:
Unit:  mg/l
Method:  other: static, 22 degree C, pH 7
Year:  10-AUG-2001
Test substance:  7 d-EC0 500 mg/l
Remark:  No data. Based on the low acute toxicity and the readily biodegradation no relevant chronic toxicity is expected.

10-AUG-2001

4.5.2 Chronic Toxicity to Aquatic Invertebrates

Species:
Endpoint:
Exposure period:
Unit:  mg/l
Method:  other: static, 22 degree C, pH 7
Year:  10-AUG-2001
Test substance:  7 d-EC0 1000 mg/l
Remark:  No data.

10-AUG-2001
TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Soil Dwelling Organisms

Type:
Species:
Endpoint:
Exposure period:
Unit:
Method:
   Year:                                  GLP:
Test substance:
Remark:            No data.
10-AUG-2001

4.6.2 Toxicity to Terrestrial Plants

Species:
Endpoint:
Expos. period:
Unit:
Method:
   Year:                                  GLP:
Test substance:
Remark:            No data.
10-AUG-2001

4.6.3 Toxicity to other Non-Mamm. Terrestrial Species

Species:
Endpoint:
Expos. period:
Unit:
Method:
   Year:                                  GLP:
Test substance:
Remark:            No data.
10-AUG-2001

4.7 Biological Effects Monitoring

Remark:            No data.
10-AUG-2001
4.8 Biotransformation and Kinetics

Type:
Remark: Rapid absorption and metabolism and excretion. Conjugation with glycine and excreted in urine as hippuric acid.

4.9 Additional Remarks

Remark: Carcinogenicity in fishes (Oryzias latipes): no tumor incidence up to concentration of 80000 mg/kg in food (ca. 8 g sodium benzoate salt/kg fish and day); proliferation of tissue in the bile-duct (observation period 24 weeks) 13/50 fishes died after an exposure period of 12-24 weeks

23-OCT-1995

Remark: Toxicity to fungi: MIC: 100 mg/l (Talaromyces flavus, 35 d, pH 3.5) > 600 mg/l (Talaromyces flavus, 35 d, pH 5.4)

23-OCT-1995

Remark: Toxicity to fungi: MIC (at room temperature): 100 mg/l (Bysschlamys fulva, 16 d, pH 3.5)

23-OCT-1995

Remark: Toxicity to fungi: Depending on temperature (21, 30 oder 37 degree C) and concentration of sodium benzoate (0, 200, 300, 400 oder 500 mg/l) production of biomass by Bysschlamys nivea was reduced in apple- and grapefruit juice up to an exposure period of 105 days.

23-OCT-1995

Remark: Toxicity to fungi: no visible growth of:

<table>
<thead>
<tr>
<th>Saccharomyces cerevisae</th>
<th>Willia anomala glaucum</th>
<th>Penicillium glaucum</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH 2.6</td>
<td>200 mg/l</td>
<td>120 mg/l</td>
</tr>
<tr>
<td>5</td>
<td>2000 mg/l</td>
<td>1000 mg/l</td>
</tr>
<tr>
<td>7</td>
<td>30000 mg/l</td>
<td>20000 mg/l</td>
</tr>
</tbody>
</table>

Method: n.a.
Test duration: n.a.
23-OCT-1995

Remark: Toxicity to yeast: no visible growth of: Saccharomyces ellipsoideus pH 3.5 500 mg/l 5.0 5000 mg/l 6.5 >25000 mg/l

Method: n.a.
Test duration: n.a.

23-OCT-1995
5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

<table>
<thead>
<tr>
<th>Type:</th>
<th>LD50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species:</td>
<td>rat</td>
</tr>
<tr>
<td>Strain:</td>
<td>no data</td>
</tr>
<tr>
<td>Sex:</td>
<td>male/female</td>
</tr>
<tr>
<td>Number of Animals:</td>
<td>5</td>
</tr>
<tr>
<td>Vehicle:</td>
<td>water</td>
</tr>
<tr>
<td>Value:</td>
<td>= 3450 mg/kg bw</td>
</tr>
<tr>
<td>Method:</td>
<td>other: see below</td>
</tr>
<tr>
<td>Year:</td>
<td>GLP: no data</td>
</tr>
<tr>
<td>Test substance:</td>
<td>other TS: USP Sodium benzoate, purchased from Merck</td>
</tr>
<tr>
<td>Method:</td>
<td>5 animals/sex/group; animals did not fast prior to treatment; animals observed for 14 days.</td>
</tr>
<tr>
<td>Reliability:</td>
<td>(2) valid with restrictions</td>
</tr>
<tr>
<td>Flag:</td>
<td>Critical study for SIDS endpoint</td>
</tr>
<tr>
<td></td>
<td>10-AUG-2001</td>
</tr>
</tbody>
</table>

Type:    LD50
Species: rat
Strain:  Sherman
Sex:    no data
Number of Animals: 6
Vehicle: no data
Value:   = 4070 mg/kg bw
Method:  other: see below
Year:    GLP: no data
Test substance: other TS: sodium benzoate, purity not noted
Method: Groups of 6 rats were given single oral doses differing by a factor of 10. Animals were observed for morbidity and mortality.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
Flag: 10-AUG-2001
Species: rat
Strain: 
Sex: 
Number of Animals: 
Vehicle: 
Value: = 3140 mg/kg bw
Method: Directive 84/449/EEC, B.1 "Acute toxicity (oral)"
Year: GLP: no data
Test substance: other TS: sodium benzoate, purity not noted
Reliability: (1) valid without restriction
Guideline study
Flag: Critical study for SIDS endpoint
10-AUG-2001 (45)

Type: LD50
Species: rat
Strain: 
Sex: male/female
Number of Animals: 70
Vehicle: 
Value: = 2100 mg/kg bw
Method: Animals fasted 18 h prior to treatment; dosed by gavage; observed for 5 days.
Year: GLP: no data
Test substance: other TS: USP Sodium benzoate, purchased from Merck
Reliability: (2) valid with restrictions
30-JAN-2001 (43)

5.1.2 Acute Inhalation Toxicity

Type: 
Species: 
Strain: 
Sex: 
Number of Animals: 
Vehicle: 
Exposure time: 
Value: 
Method: 
Year: GLP:
Test substance:
Remark: See IUCLID dataset on benzoic acid (CAS# 65-85-0); the loss of acidity due to the sodium salt should decrease toxicity.

10-AUG-2001

5.1.3 Acute Dermal Toxicity

Type: 
Species: 
Strain: 
Sex: 
Number of Animals: 
Vehicle: 
Value: 
Method: 
Year: 
Test substance: See IUCLID dataset on benzoic acid (CAS# 65-85-0); the loss of acidity due to the sodium salt should decrease toxicity.

10-AUG-2001

5.1.4 Acute Toxicity, other Routes

Type: LD50 
Species: rat 
Strain: 
Sex: 
Number of Animals: 
Vehicle: 
Route of admin.: i.v. 
Value: = 1714 mg/kg bw 
Method: 
Year: 
Test substance: 
10-AUG-2001 (46)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit 
Concentration: 

<table>
<thead>
<tr>
<th>Exposure:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure Time:</td>
<td></td>
</tr>
<tr>
<td>Number of Animals:</td>
<td></td>
</tr>
<tr>
<td>PDII:</td>
<td>not irritating</td>
</tr>
<tr>
<td>Result:</td>
<td></td>
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<tr>
<td>EC classification:</td>
<td></td>
</tr>
<tr>
<td>Method:</td>
<td>OECD Guide-line 404 &quot;Acute Dermal Irritation/Corrosion&quot;</td>
</tr>
<tr>
<td>Year:</td>
<td>1981</td>
</tr>
<tr>
<td>GLP:</td>
<td>yes</td>
</tr>
<tr>
<td>Test substance:</td>
<td>other TS: sodium benzoate; purity not noted</td>
</tr>
<tr>
<td>Reliability:</td>
<td>(1) valid without restriction GLP guideline study</td>
</tr>
<tr>
<td>Flag:</td>
<td>Critical study for SIDS endpoint</td>
</tr>
<tr>
<td>Species:</td>
<td>rabbit</td>
</tr>
<tr>
<td>Concentration:</td>
<td></td>
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</table>

<table>
<thead>
<tr>
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</thead>
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<tr>
<td>Exposure Time:</td>
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<tr>
<td>Number of Animals:</td>
<td></td>
</tr>
<tr>
<td>PDII:</td>
<td>not irritating</td>
</tr>
<tr>
<td>Result:</td>
<td></td>
</tr>
<tr>
<td>EC classification:</td>
<td></td>
</tr>
<tr>
<td>Method:</td>
<td>other: see remarks</td>
</tr>
<tr>
<td>Year:</td>
<td></td>
</tr>
<tr>
<td>GLP:</td>
<td></td>
</tr>
<tr>
<td>Test substance:</td>
<td>other TS: sodium benzoate; purity not noted</td>
</tr>
<tr>
<td>Remark:</td>
<td>application of dry powder (500 mg/animal) for 24 h; responses were scored at end of treatment and after 48 h</td>
</tr>
<tr>
<td>Flag:</td>
<td>Critical study for SIDS endpoint</td>
</tr>
<tr>
<td>Species:</td>
<td>rat</td>
</tr>
<tr>
<td>Concentration:</td>
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</table>

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<tr>
<td>Number of Animals:</td>
<td></td>
</tr>
<tr>
<td>PDII:</td>
<td></td>
</tr>
<tr>
<td>Result:</td>
<td>irritating</td>
</tr>
<tr>
<td>EC classification:</td>
<td></td>
</tr>
</tbody>
</table>
### 5. TOXICITY

**Method:**
- other: intradermal; see remark

**Test substance:**
- other TS: sodium benzoate; purity not noted

**Remark:**
- sodium benzoate (dose 0.1 ml; 0, 10, 20 % saline solution) was tested for intradermal irritation in male Wistar rats.
- Radioactive indicator was used to quantify the biological response (increase of permeability of blood capillaries).
- At low concentrations (1 %) little irritation and at higher levels (>= 3 %) significant irritation was recorded. The degree of irritation was dose-dependent.

10-AUG-2001

#### 5.2.2 Eye Irritation

**Species:** rabbit

**Concentration:**

**Dose:**

**Exposure Time:**

**Comment:**

**Number of Animals:**

**Result:** slightly irritating

**EC classificat.:**

**Method:** OECD Guide-line 405 "Acute Eye Irritation/Corrosion"

**Year:** 1987

**Test substance:** other TS: sodium benzoate; purity not noted


**Draize score:** 9.3

**Reliability:** (1) valid without restriction

**GLP guideline study**

**Flag:** Critical study for SIDS endpoint

10-AUG-2001

**Species:** rabbit

**Concentration:**

**Dose:**

**Exposure Time:**

**Comment:**

**Number of Animals:**

**Result:** not irritating
5. TOXICITY

5.3 Sensitization

Type: Patch-Test
Species: human

Number of Animals:

Vehicle: 

Result: 

Classification: 

Method: other: patch-test

Year: 

Test substance: other TS: sodium benzoate; purity not noted

Remark: 5 of 2045 patients of dermatological clinics developed positive reactions to the treatment with 5% sodium benzoate in petrolatum.

Flag: Critical study for SIDS endpoint

10-AUG-2001 (51)

Type: Patch-Test
Species: human

Number of Animals:

Vehicle: 

Result: 

Classification: 

Method: other: patch-test

Year: 

Test substance: other TS: sodium benzoate; purity not noted

Remark: 3 workers of a pharmaceutical plant with transient urticaria after exposition to sodium benzoate and 3 previously unexposed healthy control subjects were tested.

10-AUG-2001 (51)
All subjects reacted to benzoic acid at 0.25 % in aqueous solution under occlusion. 1 worker and 2 controls reacted to sodium benzoate at 0.5 % in saline under occlusion, but none reacted to sodium benzoate at 0.5 % in aqueous solution.

All 3 workers reacted in a closed patch test to benzoic acid at 5 % in petrolatum. The time course of the responses to benzoic acid and sodium benzoate was similar in controls and workers.

The potential of sodium benzoate to elicit nonimmunologic contact urticaria may be due to the formation of benzoic acid at skin contact.

Flag: Critical study for SIDS endpoint

Type: other: oral provocation test
Species: human
Concentration: Challenge 100 other: mg other: oral
Number of Animals: 81
Vehicle: 
Result: not sensitizing
Classification: not sensitizing
Method: other

Test substance: other TS: sodium benzoate; purity not noted
Remark: Oral challenge test: double blind challenge; 81 persons who claimed to suffer from a food-related intolerance. No sensitisation found.

Flag: Critical study for SIDS endpoint

Type: other
Species: human
Concentration: Challenge 50 other: mg other: oral
Challenge 500 other: mg other: oral
Number of Animals: 
Vehicle: other: none
Result: ambiguous
Classification: 
Method: other: oral challenge
Year: GLP: no
Test substance: other TS: sodium benzoate; purity not noted
Remark: Various oral challenge tests; patients suffering from asthma or rhinitis dosed with 50-500 mg benzoic acid sodium salt orally. Result: 15/157; 11/531; 10/46 positive
10-AUG-2001 (55) (56)

Type: other: see remarks
Species: human
Number of Animals:
Vehicle:
Result:
Classification:
Method: other: double-blind oral challenge test
Year: GLP:
Test substance:
Remark: A patient with Melkersson-Rosenthal syndrome reacted positive to sodium benzoate (50 mg). no further information available
10-AUG-2001 (57)

Type: other: see remarks
Species: human
Number of Animals:
Vehicle:
Result:
Classification:
Method: other: gastric challenge test
Year: GLP:
Test substance: in a double-blind placebo-controlled study 25 children with severe atopic dermatitis were challenged with food and food additives, applied by nasogastric tube. 3/6 patients challenged with sodium benzoate showed a response. Reactions were exacerbations of isolated skin symptoms in all 3 and additionally abdominal pain in association with rash in one child.
10-AUG-2001 (58)

Type: other: see remarks
Species: human
Number of Animals:
Vehicle:
<table>
<thead>
<tr>
<th>Result:</th>
<th>Classification:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method:</td>
<td>other: oral challenge test</td>
</tr>
<tr>
<td>Year:</td>
<td>GLP:</td>
</tr>
<tr>
<td>Test substance:</td>
<td></td>
</tr>
<tr>
<td>Remark:</td>
<td>in 21 patients (5-64 years old) with severe atopic eczema oral challenge tests with food additives were performed. 4/19 patients reacted to sodium benzoate (10, 50, 100, 300 mg; administered in gelatine capsules) with exacerbation of symptoms (flare up of atopic eczema, anaphylactoid reactions, generalized pruritus).</td>
</tr>
</tbody>
</table>

**10-AUG-2001** (59)

| Type: | other: see remarks |
| Species: | human |
| Number of Animals: | |
| Vehicle: | |
| Result: | |
| Classification: | |
| Method: | other: oral provocation test |
| Year: | GLP: |
| Test substance: | |
| Remark: | a chemical worker suffered from allergic reactions of increasing intensity while being constantly exposed to benzoic acid during work. After oral exposure to sodium benzoate (500 mg) he suffered a severe anaphylactic shock. He showed similar but milder reaction after consuming food containing benzoic acid. |

**10-AUG-2001** (60)

| Type: | other: see remarks |
| Species: | human |
| Number of Animals: | |
| Vehicle: | |
| Result: | |
| Classification: | |
| Method: | other: oral provocation test |
| Year: | GLP: |
| Test substance: | |
Remark: In a 19-year-old girl with no medical history apart from atopic asthma during infancy, a severe anaphylaxis was observed after eating food which mainly contained sodium benzoate as food additive. The patient remained symptom-free during a sodium benzoate free diet. In the oral provocation test (single oral application of 20 mg sodium benzoate) a localized urticaria (arms) and generalised itching was observed. In a second oral challenge (application of 160 mg sodium benzoate), a higher tolerance level was noted.

10-AUG-2001

Type: other: see remarks
Species: human
Number of Animals:
Vehicle:
Result:
Classification:
Method: other: oral provocation test
Year: GLP:
Test substance:
Remark: after a single oral application of 20 mg sodium benzoate, 2/10 patients with asthma and 2/7 patients with atopic dermatitis reacted positive; observed were bronchial obstruction/meteorism, nausea or dermatitis resp.

10-AUG-2001

5.4 Repeated Dose Toxicity

Species: rat
Strain: Sherman
Sex: male/female
Route of admin.: oral feed
Exposure period: 90 d
Frequency of treatment: continuously in diet
Post. obs. period: no
Doses: 1, 2, 4 or 8 % in diet (approx. 640-6290 mg/kg/day)
Control Group: yes
NOAEL: 3145 mg/kg bw
LOAEL: 6290 mg/kg bw  
Method: other: see below  
Year:  
Test substance: other TS: USP sodium benzoate purchased from Merck  
Method: Male rats (weighing 212 - 430 grams) and female rats (weighing 163 to 267 grams) were dosed by gavage after being fasted for 18 hours. Animals were observed for 5 days (time interval chosen because all survivors were gaining weight and in "satisfactory nutritional condition").  
Result: <= 4 % in diet: no adverse effects;  
8 % in diet: increased mortality (4/8 died); reduced weight gain; increased weight of livers and kidneys; pathological lesions (not specified) in livers and kidneys  
Reliability: (2) valid with restrictions  
Flag: Critical study for SIDS endpoint  
Species: rat  
Sex: male/female  
Strain: Sherman  
Route of admin.: oral feed  
Exposure period: 30 d  
Frequency of treatment: continuously in diet  
Post. obs. period: no data  
Doses: 16-1090 mg/kg/day  
Control Group: yes  
NOAEL: > 1090 mg/kg  
Method: other: see below  
Year:  
Test substance: other TS: sodium benzoate, purity not noted  
Method: Groups of 10 rats (5 males, 5 females) were administered doses of sodium benzoate by oral feed for thirty days. Animals were observed for weight gain, appetite, morbidity and mortality. Surviving animals were necropsied. Adrenal, upper intestine, kidney, liver, and spleen were examined.  
Remark: 10 rats/group  
This endpoint has been studied several times by several other investigators/groups and all reported results similar to the study mentioned above.
### OECD SIDS BENZOATES

5. TOXICITY

DATE: 10-AUG-2001

SUBSTANCE ID: 532-32-1

| Result: | No adverse effects were observed. |
| Reliability: | (2) valid with restrictions |
| Meet generally accepted scientific standards, well documented and acceptable for assessment |
| Flag: | Critical study for SIDS endpoint |

| Species: | mouse |
| Sex: | male/female |
| Strain: | other: Albino Swiss |
| Route of admin.: | drinking water |
| Exposure period: | 35 days |
| Frequency of treatment: | continuously in drinking water |
| Post. obs. period: | no data |
| Doses: | 0.5; 1; 2; 4 or 8 % in drinking water |
| Control Group: | yes |
| NOAEL: | 2 % |
| LOAEL: | 4 % |
| Year: | GLP: no data |
| Test substance: | other TS: sodium benzoate, purity not noted |
| Remark: | "By taking into account four parameters (survival rate, body weight, chemical consumption, histological changes), the 2% dose level was found suitable for the lifelong treatment." |
| Result: | 8 %: 4/4 males and 4/4 females died within 3 weeks; 4 %: 3/4 males and 3/4 females died during the treatment period and the body weight of surviving mice was substantially reduced. |
| Reliability: | (2) valid with restrictions |
| Flag: | Critical study for SIDS endpoint |

| Species: | rat |
| Sex: | male/female |
| Strain: | other: F344/Ducrj |
| Route of admin.: | oral feed |
| Exposure period: | 10 d |
| Frequency of treatment: | continuously in diet |
| Post. obs. period: | no |
| Doses: | 1.81; 2.09 or 2.4 % in diet (approx. 1358, 1568 or 1800 mg/kg/d) |
| Control Group: | yes |
LOAEL: 1358 mg/kg bw

Method: other TS: sodium benzoate, purity not noted
Year: GLP:
Test substance: The mean compound consumption was calculated according to Lehman, Food Drug Off. Q. Bull. 18, 66 (1954).
Remark: The mean compound consumption was calculated according to Lehman, Food Drug Off. Q. Bull. 18, 66 (1954).
Result: At the lowest tested concentration of 1358 mg/kg changes in serum cholesterol levels occurred in females. At doses of 1568 mg/kg and above changes in further serum parameters and an increased relative liver weight were described.
Histopathological changes of the liver, increased relative kidney weights and disorders of the central nervous system were seen after dosing via diet with > 1800 mg. 1/6 male rat in the 2.4 %-group, who developed increased sensitivity to stimuli and convulsions, died.
Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.
Flag: Critical study for SIDS endpoint

Species: mouse
Sex: male/female

Strain: B6C3F1
Route of admin.: oral feed
Exposure period: 10 d
Frequency of treatment: continuously in diet
Post. obs. period: no

Doses: 2.08; 2.5 or 3 % in diet (approx. 3012, 3750 or 4500 mg/kg/d)

Control Group: yes
NOAEL: 3750 mg/kg bw
LOAEL: 4500 mg/kg bw
Method: other: see below
Year: GLP: no data

Test substance: other TS: sodium benzoate (specific grade) purchased from Wako Pure Chemical Ind., Osaka, Japan
Method: Sodium benzoate, mixed with the powdered diet, was fed to groups of 12 mice (6 males, 6 females) for 10 days.
Animals were observed for body weight gain and clinical signs 5 day/week. At the end of the experiment, surviving animals were necropsied. Organ weights, clinical chemistry and histological examinations were performed.

Remark: The mean compound consumption was calculated according to Lehman, Food Drug Off. Q. Bull. 18, 66 (1954).

Result: All mice in the 3.0 % -group showed increased sensitivity to stimuli and 1/5 male and 2/5 females showed convulsions; 2/5 females died; liver weights of males and females and kidney weights of females were dose-dependently increased; histopathologic examination showed enlarged hepatocytes, single cell necrosis and vacuolation of hepatocytes in all livers from males; no histopathologic changes of the kidney were described; serum cholesterol, lipid levels and cholinesterase were increased in males.

Reliability: (2) valid with restrictions
well documented
and acceptable for assessment

Flag: Critical study for SIDS endpoint

10-AUG-2001

Species: rat
Sex: male/female
Strain: Fischer 344
Route of admin.: oral feed
Exposure period: 18–24 months
Frequency of treatment: continuously in diet
Post. obs. period: no
Doses: 1 or 2 % in diet
Control Group: yes
NOAEL: 2 %
Method: other: OECD 451
Year: GLP: no data
Test substance: other TS: sodium benzoate, purity not noted

Remark: Mean compound consumption:
2 % in diet: m: 280 +/- 9.8 mg/d
          f: 202 +/- 10.5 mg/d

Result: No adverse clinical signs in treated rats; no differences in average body weight and mortality in comparison to controls.
Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment
Flag: Critical study for SIDS endpoint
10-AUG-2001

Species: rat
Strain: Sherman
Route of admin.: oral feed
Exposure period: 28 d
Frequency of treatment: continuously in diet
Post. obs. period:
Doses: 2 or 5 % in diet (see remarks)
Control Group: other: no data
LOAEL: 2002 - 2357 mg/kg bw
Method: other: see below
Year: 10-AUG-2001
GLP: no data
Test substance: other TS: sodium benzoate, food grade
Method: Food grade sodium benzoate was incorporated into the basal diet at concentrations of 2% and 5%. The rats were weighed individually twice a week and were inspected daily for signs of toxicity. Food consumption for each group was recorded weekly and the drug intake as mg/kg bw was calculated using the average body weights for each group. Fisher's T test for small samples was used as a test for significant differences between body weights for the various groups.
Remark: 6 rats/group; initial body weight: 40-50 g; mean compound consumption:
2 % in diet: m: 2002 - 2357 mg/kg/day
f: 2171 - 2396 mg/kg/day
5 % in diet: m: 5686 mg/kg/day
f: 7780 mg/kg/day
Result: 2 %: slight depression of body weight gain only in males
5 %: urine incontinence, convulsions, 100 % mortality after 2nd week
Reliability: (3) invalid
10-AUG-2001
Significant methodological deficiencies

Species: rat
Strain: Fischer 344
Route of admin.: oral feed
Exposure period: 42 d
### OECD SIDS  BENZOATES

#### 5. TOXICITY

**DATE: 10-AUG-2001**

**SUBSTANCE ID: 532-32-1**

<table>
<thead>
<tr>
<th>Property</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Frequency of treatment</td>
<td>continuously in diet</td>
</tr>
<tr>
<td>Post. obs. period</td>
<td>no data</td>
</tr>
<tr>
<td>Doses</td>
<td>0.5; 1; 2; 4 or 8 % in diet (approx. 375–6000 mg/kg/day)</td>
</tr>
<tr>
<td>Control Group</td>
<td>yes</td>
</tr>
<tr>
<td>Method</td>
<td>other: see below</td>
</tr>
<tr>
<td>Year</td>
<td>GLP:</td>
</tr>
<tr>
<td>Test substance</td>
<td>other TS: sodium benzoate, purity not noted; supplied by National Institute of Hygienic Sciences pellets in the basal diet</td>
</tr>
<tr>
<td>Method</td>
<td>10 rats/group; initial body weight: 110–150 g; the mean compound consumption was calculated according to Lehman, Food Drug Off. Q. Bull. 18, 66 (1954); Animals were administered diets containing various concentrations of sodium benzoate for 6 weeks. Survival rate, growth, food intake, behavior and general status were observed during the feeding period. Morphological examinations were carried out.</td>
</tr>
<tr>
<td>Result</td>
<td>2 % in diet (approx. 1500 mg/kg/day): maximum tolerated dose; &gt;= 4 % in diet (approx. &gt;= 3000 mg/kg/day): mortality 10/11 or 10/10; atrophy of the spleen and lymph nodes at autopsy.</td>
</tr>
<tr>
<td>Species</td>
<td>rat</td>
</tr>
<tr>
<td>Sex</td>
<td>no data</td>
</tr>
<tr>
<td>Route of admin.</td>
<td>oral feed</td>
</tr>
<tr>
<td>Exposure period</td>
<td>until death (see below)</td>
</tr>
<tr>
<td>Frequency of treatment</td>
<td>continuously in diet</td>
</tr>
<tr>
<td>Post. obs. period</td>
<td>no</td>
</tr>
<tr>
<td>Doses</td>
<td>5 % in diet (approx. 3750 mg/kg/day)</td>
</tr>
<tr>
<td>Control Group</td>
<td>yes</td>
</tr>
<tr>
<td>Method</td>
<td>GLP:</td>
</tr>
<tr>
<td>Test substance</td>
<td>other TS: benzoic acid</td>
</tr>
<tr>
<td>Remark</td>
<td>the mean compound consumption was calculated according to Lehman, Food Drug Off. Q. Bull. 18, 66 (1954)</td>
</tr>
<tr>
<td>Result</td>
<td>19/28 young rats (initial body weight: 62–70 g) died during the first 2 weeks; all others died 1 week later; reduced food intake, diarrhea, intestinal haemorrhage and crusted blood in the nose at autopsy.</td>
</tr>
<tr>
<td>Date</td>
<td>Species, Strain, Route, Exposure, Frequency, Post. Obs., Doses, Control Group, Method, Remark, Result</td>
</tr>
<tr>
<td>------------</td>
<td>-------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>10-AUG-2001</td>
<td>Species: rat, Sex: no data, Route of admin.: oral feed, Exposure period: no data, Frequency of treatment: continuously in diet, Post. obs. period: no data, Doses: 5 % in diet (approx. 3750 mg/kg/day), Control Group: other: no data, Method: GLP: Test substance: other TS: benzoic acid, Remark: the mean compound consumption was calculated according to Lehman, Food Drug Off. Q. Bull. 18, 66 (1954), Result: 4/5 adult rats (initial body weight: 221-232 g) died during 4-5 weeks; body weight was reduced to 161 g</td>
</tr>
<tr>
<td>10-AUG-2001</td>
<td>Species: rat, Sex: male, Route of admin.: oral feed, Exposure period: 23 weeks, Frequency of treatment: continuously in diet, Post. obs. period: no, Doses: 5 % in diet (approx. 3750 mg/kg/d), Control Group: yes, Method: GLP: Test substance: other TS: sodium benzoate, purity not noted, Remark: Basic diet: low casein diet; the study was done to investigate the effect of several xenobiotics on the growth retardation provoked in rats by sodium benzoate; the data presented here are the results of the &quot;long-term&quot; positive control group. The mean compound consumption was calculated according to Lehman, Food Drug Off. Q. Bull. 18, 66 (1954)., Result: marked growth inhibition, occasionally restlessness, irritability, tremors</td>
</tr>
</tbody>
</table>
5. TOXICITY

Species: dog  
Sex: male/female  
Strain: other: fox terrier  
Route of admin.: oral feed  
Exposure period: <= 250 days  
Frequency of treatment: once daily  
Post. obs. period:  
Doses: 0.1 - 7 g/animal/day  
Control Group: other: no data  
Method:  
Year: 26-JAN-2001  
Test substance:  
Result: 0.1 - < 7 g/animal/day: no toxic effect; 7 g/animal/day (approx. 1 g/kg/day): toxic dose (ataxia, tonoclonic convulsions, vomiting, death)  

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test  
System of testing: Salmonella typhimurium TA 92, TA 94, TA 98, TA 100, TA 1535, TA 1537  
Concentration: 0-3 mg/plate  
Cytotoxic Conc.:  
Metabolic activation: with and without  
Result: negative  
Method: OECD Guide-line 471 "Genetic Toxicology: Salmonella thyphimurium Reverse Mutation Assay"  
Year: 1983  
Test substance: other TS: samples obtained from Japan Food Additives Association; purity = 99% analysed at Ministry of Health and Welfare of Japan  
Remark: This endpoint has been studied by several other investigators/groups and all support the result of the study mentioned above.  
Reliability: (1) valid without restriction Guideline study  
Flag: Critical study for SIDS endpoint  
10-AUG-2001  

Type: Cytogenetic assay  
System of testing: cultured human embryonic lung cells
<table>
<thead>
<tr>
<th>Substance ID: 532-32-1</th>
</tr>
</thead>
</table>

### Chromosomal Aberration Test
- **Concentration:** 2.0, 20.0, 200.0 ug/ml
- **Cytotoxic Conc.:**
- **Metabolic activation:** without
- **Result:** negative
- **Method:** other: anaphase preparations
- **Year:**
- **Test substance:** other TS: FDA 71-37 supplied by Food and Drug Administration
- **Remark:** This endpoint has been studied by several other investigators/groups and all support the result of the study mentioned above.
- **Reliability:** (2) valid with restrictions
- **Flag:** Critical study for SIDS endpoint

### E. coli Reversion Mutation Assay
- **System of testing:** E. coli WP2
- **Concentration:** no data
- **Cytotoxic Conc.:** no data
- **Metabolic activation:** with and without
- **Result:** negative
- **Method:** EPA OTS 798.5100
- **Year:**
- **Test substance:** other TS: sodium benzoate, purchased from Baker; purity not noted

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**OECD SIDS**

**BENZOATES**

**DATE: 10-AUG-2001**

**SUBSTANCE ID: 532-32-1**
### OECD SIDS BENZOATES

#### 5. TOXICITY

**DATE:** 10-AUG-2001  
**SUBSTANCE ID:** 532-32-1

| Reliability: | (1) valid without restriction  
Guideline study |
|--------------|-----------------------------------------------------------------|
| Flag:        | Critical study for SIDS endpoint  
10-AUG-2001 |
| Type:        | other: Sister chromatid exchange |
| System of testing: | Chinese hamster cell line (Don) |
| Concentration: | 0.001 to 0.01 M / plate |
| Cytotoxic Conc.: | no data |
| Metabolic activation: | without |
| Result:      | ambiguous |
| Method:      | other: see below  
| Year:        | GLP: no data |
| Test substance: | other TS: sodium benzoate, supplied by National Institute of Hygienic Sciences, Japan; purity not noted |
| Method:      | Sodium benzoate was dissolved in Hank's balanced salt solution to desired concentrations. All cultures were kept in complete darkness at 37 degree C for 26 hours (two cell cycles) and 0.25 ug colchicine/ml added for final 2 hours. Cells were collected and stained by acridine orange technique for fluorescence or modified FPG (fluorescence plus Giemsa) for Giemsa. The number of SCE per cell was determined on the basis of 20-50 intact metaphases without gross chromosome aberrations. |
| Remark:      | slight increase in SCE/cell, but no dosage effect |
| Reliability: | (2) valid with restrictions  
Meets generally accepted scientific standards, well documented and acceptable for assessment |
| Flag:        | Critical study for SIDS endpoint  
10-AUG-2001 |
| Type:        | other: Sister chromatid exchange |
| System of testing: | human lymphocytes |
| Concentration: | |
| Cytotoxic Conc.: | |
| Metabolic activation: | without |
| Result:      | positive |
| Method:      | |
| Year:        | GLP: |
| Test substance: | only one concentration (10E-2 M) tested |
| Remark:      | |

---

**UNEP PUBLICATIONS**

177
Reliability: (3) invalid  
Significant methodological deficiencies
Flag: Critical study for SIDS endpoint
10-AUG-2001 (78)
Type: other: Inhibition of DNA synthesis
System of testing: Vicia faba root meristems
Concentration:
Cytotoxic Conc.:
Metabolic activation: without
Result: positive
Method:  
Year: GLP:
Test substance:  
Remark: other observed effects:
a. concentration-dependent decrease in mitotic figures;
b. concentration-dependent increase in anaphase bridges;
c. premature chromosome condensation heading to pycnotic nuclei; d. chromatin erosion in interphase nuclei
Reliability: (3) invalid
Unsuitable test system
Flag: Critical study for SIDS endpoint
10-AUG-2001 (79)
Type: Bacillus subtilis recombination assay
System of testing: Bacillus subtilis H17, M45
Concentration:
Cytotoxic Conc.:
Metabolic activation: no data
Result: positive
Method:  
Year: GLP:
Test substance: no data
Method: An overnight culture of B. subtilis, H17 and M45, was mixed with test solutions and incubated for 30 minutes at 37 degree C. After treatment, viable cells were counted and the ratio of 50% survival concentrations were calculated.
Result: Sodium benzoate showed DNA damaging potential although it had been negative in the Ames test.
Reliability: (4) not assignable
Documentation insufficient for assessment; abstract only
Flag: Critical study for SIDS endpoint

Test substance:
Type: Bacillus subtilis recombinant assay
System of testing: Bacillus subtilis H17, M45
Concentration: 6-20 mg/disk, in water

Result: ambiguous
Method:

Test substance:
Type: Ames test
System of testing: Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Concentration:

Result: negative
Method:

Test substance:
Type: other Chromosomal aberration test
System of testing: Chinese hamster cell line (Don)
5. TOXICITY

Cytotoxic Conc.: 
Metabolic 
  activation: without 
Result: positive 
Method: 
  Year: 11-JAN-2001 
Test substance: 
  GLP: (77) 

Type: other: Chromosome aberration test 
System of testing: Chinese hamster fibroblast cell line (CHL) 
Concentration:
Cytotoxic Conc.: 
Metabolic 
  activation: with 
Result: positive 
Method: 
  Year: 01-SEP-2000 
Test substance: other TS: purity not given 
  GLP: (82) 

Type: other: Sister chromatid exchange 
System of testing: Vicia faba root tip cells 
Concentration:
Cytotoxic Conc.: 
Metabolic 
  activation: without 
Result: positive 
Method: 
  Year: 11-JAN-2001 
Test substance: 
Remark: only one concentration (10E-2 M) tested 
  GLP: (78) 

5.6 Genetic Toxicity 'in Vivo'

Type: Cytogenetic assay 
Species: rat Sex: male 
Strain: no data 
Route of admin.: gavage 
Exposure period: single application 
Doses: 50, 500 or 5000 mg/kg 
Result: negative
<table>
<thead>
<tr>
<th>Method:</th>
<th>EPA OTS 798.5385</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year:</td>
<td>GLP: yes</td>
</tr>
<tr>
<td>Test substance:</td>
<td>other TS: compound FDA 71-37, sodium benzoate, as supplied by the Food and Drug Administration</td>
</tr>
<tr>
<td>Result:</td>
<td>no detectable significant aberrations of the bone marrow metaphase chromosomes</td>
</tr>
<tr>
<td>Reliability:</td>
<td>(1) valid without restriction GLP guideline study</td>
</tr>
<tr>
<td>Flag:</td>
<td>Critical study for SIDS endpoint</td>
</tr>
<tr>
<td>Date: 10-AUG-2001</td>
<td>(74)</td>
</tr>
</tbody>
</table>

**Type:** Cytogenetic assay  
**Species:** rat  
**Sex:** male  
**Strain:** no data  
**Route of admin.:** gavage  
**Exposure period:** once daily for 5 consecutive days  
**Doses:** 50, 500 or 5000 mg/kg  
**Result:** negative  
**Method:** EPA OPPTS 870.5385
| Year:         | GLP: yes                  |
| Test substance: | other TS: compound FDA 71-37, sodium benzoate, as supplied by the Food and Drug Administration |
| Result:         | no detectable significant aberrations of the bone marrow chromosomes |
| Reliability:    | (1) valid without restriction GLP guideline study |
| Flag:           | Critical study for SIDS endpoint |
| Date: 10-AUG-2001 | (74) |

**Type:** Dominant lethal assay  
**Species:** rat  
**Sex:** male  
**Strain:** no data  
**Route of admin.:** gavage  
**Exposure period:** single application  
**Doses:** 50, 500 or 5000 mg/kg  
**Result:** negative  
**Method:** EPA OPPTS 870.5450
<p>| Year:         | GLP: yes                  |
| Test substance: | other TS: compound FDA 71-37, sodium benzoate, as supplied by the Food and Drug Administration |
| Result:         | no detectable significant aberrations of the bone marrow chromosomes |
| Reliability:    | (1) valid without restriction GLP guideline study |
| Flag:           | Critical study for SIDS endpoint |
| Date: 10-AUG-2001 | (74) |</p>
<table>
<thead>
<tr>
<th>Type</th>
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<td>Species</td>
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</tr>
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<td>Sex</td>
<td>male</td>
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<tr>
<td>Route of admin.</td>
<td>gavage</td>
</tr>
<tr>
<td>Exposure period</td>
<td>once daily for 5 consecutive days</td>
</tr>
<tr>
<td>Doses</td>
<td>50, 500 or 5000 mg/kg</td>
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<tr>
<td>Result</td>
<td>negative</td>
</tr>
<tr>
<td>Method</td>
<td>EPA OPPTS 870.5450</td>
</tr>
<tr>
<td>Year</td>
<td>GLP: yes</td>
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<td>Test substance</td>
<td>other TS: compound FDA 71-37, sodium benzoate, as supplied by the Food and Drug Administration</td>
</tr>
</tbody>
</table>

Reliability: (1) valid without restriction

GLP guideline study

Flag: Critical study for SIDS endpoint

10-AUG-2001

<table>
<thead>
<tr>
<th>Type</th>
<th>other: Host mediated assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species</td>
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</tr>
<tr>
<td>Sex</td>
<td>male</td>
</tr>
<tr>
<td>Route of admin.</td>
<td>gavage</td>
</tr>
<tr>
<td>Exposure period</td>
<td>single application</td>
</tr>
<tr>
<td>Doses</td>
<td>50, 500 or 5000 mg/kg</td>
</tr>
<tr>
<td>Result</td>
<td>negative</td>
</tr>
<tr>
<td>Method</td>
<td>other: EPA</td>
</tr>
<tr>
<td>Year</td>
<td>GLP: yes</td>
</tr>
<tr>
<td>Test substance</td>
<td>other TS: compound FDA 71-37, sodium benzoate, as supplied by the Food and Drug Administration</td>
</tr>
</tbody>
</table>

Result: No elevation of mutant frequencies in Salmonella Typhimurium G46 and no increase in recombinant frequencies in Saccharomyces cerevisiae D3

Reliability: (1) valid without restriction

GLP guideline study

Flag: Critical study for SIDS endpoint

10-AUG-2001
5. TOXICITY

Result: elevation of mutant frequencies in Salmonella typhimurium TA 1530 in the intermediate dose level; Not dose dependent and negative at multiple dose exposure.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

Type: other: Host mediated assay

Species: mouse

Strain: no data

Route of admin.: gavage

Exposure period: once daily for 5 consecutive days

Doses: 50, 500 or 5000 mg/kg

Result: negative

Method: other: EPA

Year: GLP: yes

Test substance: other TS: compound FDA 71-37, sodium benzoate, as supplied by the Food and Drug Administration

Result: no elevation of mutant frequencies in Salmonella Typhimurium G46; no elevation of mutant frequencies in Salmonella typhimurium TA 1530; no increase in recombinant frequencies in Saccharomyces cerevesiae D3

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

5.7 Carcinogenicity

Species: rat

Strain: Fischer 344

Route of admin.: oral feed

Exposure period: 18-24 months

Frequency of treatment: continuously in diet

Post. obs. period: no

Doses: 1 or 2 % in diet (see remarks)

Result: negative

Control Group: yes

Method: OECD Guide-line 451 "Carcinogenicity Studies"

Year: GLP: no data

Test substance: other TS: sodium benzoate, purity not noted
Method: Groups of 50 male and 52 female Fischer 344 rats, four to five weeks old, received diets containing 1% (500 mg/kg bw per day) or 2% (1000 mg/kg bw per day) sodium benzoate for 18-24 months. Controls, consisting of 25 male and 43 female rats, received basal diet.

Food intake was adequately controlled to avoid an excess; tap water was available ad libitum.

Mean compound consumption:
1% in diet: m: 141 +/− 9.7 mg/d  
f: 102 +/− 11.8 mg/d  
2% in diet: m: 280 +/− 9.8 mg/d  
f: 202 +/− 10.5 mg/d  

Remark: about 40 rats including control animals died during the first 16 months of the experimental period (pneumonia with abscess) about 100 rats including control animals died after 16 months of hemorrhagic pneumonia (infection)

Result: Survival was very poor in all groups, due to intercurrent sialodacryoadenitis and mycoplasma infections. All surviving animals were sacrificed between 18 and 25 months, all were autopsied, and various tissues were examined histopathologically. No adverse clinical signs directly attributable to treatment were observed, and only negligible differences in average body weight and mortality rate were seen between the treated and control groups. Although a variety of tumours occurred among treated and control rats of each sex, they were of similar type and incidence; no evidence of carcinogenicity.

Reliability: (1) valid without restriction Guideline study
Flag: Critical study for SIDS endpoint  
10-AUG-2001

Species: mouse  
Sex: male/female  
Strain: other: Albino Swiss  
Route of admin.: drinking water  
Exposure period: lifelong  
Frequency of treatment: continuously in drinking water  
Post. obs. period: no data  
Doses: 2% in drinking water  
Result: negative  
Control Group: yes
Method: other: see below

Year: GLP: no data

Test substance: other TS: sodium benzoate, purity not noted
Method: In the main study, a 2% solution of sodium benzoate (purity, 99%) was administered in the drinking-water to groups of 50 male and 50 female five-week-old mice for their lifetime. Groups of 100 males and 100 females were used as untreated controls. Both treated and control animals were 'carefully checked'; their body weights were measured weekly, and gross pathological changes were recorded. The animals were either allowed to die or were sacrificed when moribund. Complete necropsies were performed on all animals, and the liver, spleen, kidneys, bladder, thyroid, heart, pancreas, testes, ovaries, brain, nasal turbinates, at least four lobes of the lungs, and organs with gross pathological changes were examined histologically.

Remark: 50 males and 50 females were treated; 99 males and 99 females served as controls; average daily intake: 119.2 mg (f) or 124.0 mg (m)

Result: The average daily intake of sodium benzoate was 124.0 mg for males and 119.2 mg for females on the basis of daily water consumption of 6.2 and 5.9 ml, respectively. The dose of sodium benzoate was equivalent to 6200 mg/kg bw per day for males and 5960 mg/kg bw per day for females. Treatment had no effect on survival or the incidence of tumours.

Reliability: (2) valid with restrictions
This study is sufficiently reliable due to a sufficient number of animals and a detailed histopathological examination.

Flag: Critical study for SIDS endpoint

Species: rat
Sex: male
Strain: Fischer 344
Route of admin.: Exposure period:
Frequency of treatment:
Post. obs. period:
Doses:
Result:
Control Group:
Method:
5. TOXICITY

SUBSTANCE ID: 532-32-1

Year: 2001

Test substance: DEN-PH model; final, general protocol:
- Group 1: single i.p. dose of diethylnitrosamine, repeated treatment with the test compound from week 2, hepatectomy at week 3, sacrifice at week 8.
- Group 2: single i.p. dose of diethylnitrosamine, hepatectomy at week 3, sacrifice at week 8.
- Group 3: single i.p. dose of saline, repeated treatment with the test compound from week 2, sacrifice at week 8.

The enhancing effects of chemicals on induction of preneoplastic form of glutathione S-transferase positive foci was measured by comparing the GST-P positive foci in liver slices of treated and control animals.

Result: positive

5.8 Toxicity to Reproduction

Type: other: 2 year carcinogenicity study
Species: rat Sex: male/female
Strain: Fischer 344
Route of admin.: oral feed
Exposure Period: 18 - 24 months
Frequency of treatment: continuously in diet
Duration of test: 24 months
Doses: 1 or 2 % in diet
Control Group: yes
NOAEL Parental: 2 %
Method: other: OECD 451 GLP: no data
Year: 2001

Test substance: other TS: sodium benzoate, purity not noted
Result: No evidence of compound related effects in the testes or ovaries of treated rats.

Reliability: (2) valid with restrictions
In the 2 yr feeding study, reproductive organs were examined macroscopically and histologically.

Flag: Critical study for SIDS endpoint

10-AUG-2001
5. TOXICITY

Species:                                           Sex: 
Strain: 
Route of admin.: 
Exposure Period: 
Frequency of treatment: 
Duration of test: 
Doses: 
Control Group: 
Method: 
Year:                                        GLP: 
Test substance: 
Remark:           A 4-generation reprotoxicity test with benzoic acid revealed no reproductive effects. Therefore no indication for reproductive toxicity testing for the benzoic acid sodium salt. See IUCLID on benzoic acid (CAS# 65-85-0); the data on the sodium salt should be similar. 
Flag:             Critical study for SIDS endpoint 
10-AUG-2001

5.9 Developmental Toxicity/Teratogenicity

Species:          rat                               Sex: female 
Strain:           Wistar 
Route of admin.:  gavage 
Exposure period:  Day 6-15 of gestation 
Frequency of treatment:     once daily 
Duration of test: 
Doses:            1.75; 8; 38 or 175 mg/kg/d 
Control Group:    yes 
NOAEL Maternalt.: >= 175 mg/kg bw 
NOAEL Teratogen.: >= 175 mg/kg bw 
Method:           EPA OPPTS 870.3700 
Year:                                        GLP: no data 
Test substance:   other TS: sodium benzoate, purity not noted 
Remark:           This endpoint has been studied several times by several other investigators/groups and all reported results similar to the study mentioned above. 
Result:           no effect on nidation or on maternal or fetal survival; the number of abnormalities of soft and skeletal tissues did not differ from number in controls; maternal toxicity was not reported at any dose applied
Reliability: (1) valid without restriction
Guideline study

Flag: Critical study for SIDS endpoint
10-AUG-2001

Species: rat
Sex: female

Strain: Wistar

Route of admin.: oral feed

Exposure period: whole gestation period (20 d)

Frequency of treatment: continuously in diet

Duration of test:

Doses: 1, 2, 4 or 8 % in diet (700 to 5600 mg/kg)

Control Group: yes

NOAEL Maternalt.: = 1400 mg/kg bw

NOAEL Teratogen.: = 1400 mg/kg bw

Method: other

Year: GLP: no data

Test substance: other TS: sodium benzoate, purity not noted

Remark: The mean food consumption was calculated from graph:
<= 2 % in diet: approx. 20 mg/kg/day
4 % in diet: approx. 12 mg/kg/day
8 % in diet: approx. 2.5 mg/kg/day

The mean compound consumption was calculated from graph:
1 % in diet: approx. 700 mg/kg/day
2 % in diet: approx. 1400 mg/kg/day
4 % in diet: approx. 2800 mg/kg/day
8 % in diet: approx. 5600 mg/kg/day

Result: A study using pregnant Wistar rats, dosed with 700, 1400, 2800, 5600 mg/kg sodium benzoate in the diet during the entire gestation showed no statistical difference in organ and bone abnormalities of fetuses between experimental groups and controls; growth of treated offsprings was similar to controls in rats dosed with 1400 mg/kg/day; reduced food intake and decreased body weight of the pregnant rats especially in the 5600 mg/kg group; 100% perinatal death rate; organ abnormalities of fetuses involved eye, brain and kidneys, in addition abnormalities of the skeletal system were found in rats dosed with >2800 mg/kg/day.
Conclusion: The authors concluded that the effects on the dams and fetuses at the 2800 and 5600 levels were due to reduced maternal feed intake in these groups, leading to malnutrition.

Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment

Flag: Critical study for SIDS endpoint

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<tr>
<th>Species</th>
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<tr>
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<tr>
<td>Route of admin.:</td>
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<td>Exposure period:</td>
<td>Day 6-15 of gestation</td>
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<tr>
<td>Frequency of treatment:</td>
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<tr>
<td>Doses:</td>
<td>1.75; 8; 38 or 175 mg/kg/d</td>
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<td>Control Group:</td>
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<tr>
<td>NOAEL Maternal:</td>
<td>&gt;= 175 mg/kg bw</td>
<td></td>
</tr>
<tr>
<td>NOAEL Teratogenic:</td>
<td>&gt;= 175 mg/kg bw</td>
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</tr>
<tr>
<td>Method:</td>
<td>EPA OPPTS 870.3700</td>
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<tr>
<td>Year:</td>
<td>10-AUG-2001</td>
<td>GLP: no data</td>
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<tr>
<td>Test substance:</td>
<td>other TS: sodium benzoate, purity not noted</td>
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<tr>
<td>Result:</td>
<td>No effect on nidation or on maternal or fetal survival; the number of abnormalities of soft and skeletal tissues did not differ from controls; maternal toxicity was not reported at any dose applied.</td>
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<table>
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<tr>
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<tr>
<td>Strain:</td>
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<tr>
<td>Route of admin.:</td>
<td>gavage</td>
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<tr>
<td>Exposure period:</td>
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<tr>
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<td>Doses:</td>
<td>2.5; 12; 54 or 250 mg/kg/d</td>
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<td>NOAEL Maternal:</td>
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<td>NOAEL Teratogenic:</td>
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<tr>
<td>Year:</td>
<td>10-AUG-2001</td>
<td>GLP: no data</td>
</tr>
</tbody>
</table>
Test substance: other TS: sodium benzoate, purity not noted
Result: No effect on nidation or on maternal or fetal survival; the number of abnormalities of soft and skeletal tissues did not differ from controls; maternal toxicity was not reported at any dose applied.
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint

Species: hamster
Strain: other: golden; outbred
Route of admin.: gavage
Exposure period: Day 6-10 of gestation
Frequency of treatment: once daily
Duration of test: 
Doses: 3, 14, 65 or 300 mg/kg/d
Control Group: yes
NOAEL Maternalt.: 300 mg/kg bw
NOAEL Teratogen.: 300 mg/kg bw
Method: EPA OPPTS 870.3700
Year: GLP: no data

Test substance: other TS: sodium benzoate, purity not noted
Result: No effect on nidation or on maternal or fetal survival; the number of abnormalities of soft and skeletal tissues did not differ from controls; maternal toxicity was not reported at any dose applied.
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint

Species: rat
Strain: Sprague-Dawley
Route of admin.: i.p.
Exposure period: day 9-11 of gestation
Frequency of treatment: once daily
Duration of test: 
Doses: 100, 315 or 1000 mg/kg/d
Control Group: other: sodium chloride 90 or 600 mg/kg/d
NOAEL Teratogen.: 315 mg/kg bw
Method: GLP: no data
Test substance:

Remark: no further information available

Result: 1000 mg/kg: increased rate of in utero deaths, reduced fetal body weight

26-JAN-2001

Species: rat
Strain: Sprague-Dawley
Route of admin.: i.p.
Exposure period: day 12–14 of gestation
Frequency of treatment: once daily
Duration of test:

Doses: 100, 315 or 1000 mg/kg/d
Control Group: other: sodium chloride 90 or 600 mg/kg/d
NOAEL Teratogen.: 315 mg/kg bw

Method:
Year: GLP:

Test substance:
Remark: no further information available
Result: 1000 mg/kg: reduced fetal body weight, increased rate of in utero deaths, gross anomalies in fetuses

26-JAN-2001

Species: hen
Strain: Leghorn
Route of admin.: other
Exposure period: once
Frequency of treatment: single injection in eggs
Duration of test:

Doses: highest level tested: 5 mg/egg
Control Group: yes

Method:
Year: GLP:

Test substance:
Remark: Fresh fertile eggs were used, 4 test conditions were used: injection via the air cell and via the yolk twice, preincubation 0 h and 96 h; total number of eggs treated: approx. 100.

Result: LD50 (injection via air cell at 96 h): 4.74 mg/egg; no teratogenic effects in the developing chicken embryo.

26-JAN-2001
Species: hen  
Sex: 
Strain: other: Ross I stock 
Route of admin.: other 
Exposure period: once 
Frequency of treatment: single injection 
Duration of test: 
Doses: highest level tested: 0.1 mg/embryo 
Control Group: yes 
Method: other: Chick Embryotoxicity Screening Test (CHEST) 
Year: GLP: 
Test substance: 
Result: no embryotoxicity was observed at a concentration of 100 ug/embryo 
26-JAN-2001 (89) 
Species: other: chick embryo neural retina cells 
Sex: 
Strain: 
Route of admin.: other: in vitro 
Exposure period: 24 hours 
Frequency of treatment: single treatment 
Duration of test: 7 days 
Doses: up to cytolethal or solubility limit 
Control Group: yes 
Method: other: Chick embryo retina cell (CERC) assay 
Year: GLP: 
Test substance: other TS: purchased from Sigma Chemical 
Method: The chemical was dissolved in Gibco medium 199 or DMSO and adjusted to pH 7.2. At least five concentrations were tested, with six flasks per concentration. 7-10 E+06 cells were dispersed in 3ml culture medium, plus the test chemical, and incubated for 18-24 hours. Cell aggregates were counted and the medium changed to Gibco 199 without the test chemical. The cells were cultured for an additional 6 days. Protein content was measured by the Lowry method and glutamine synthetase activity measured by a spectrophotometric assay. Statistics: pairwise comparisons among treatment groups were done by ANOVA and concentration-response relationships analyzed by general linear methods (SAS, 1987). A chemical was classified as active if there was a significant concentration-dependent decrease in glutamine
5. TOXICITY

Result: Sodium benzoate was classified as inactive in the CERC assay with LOEL at >34.7mM.

19-MAY-2000

5.10 Other Relevant Information

Type: Metabolism
Remark: The experimental study on the inducibility of the hepatic and renal hippurate-synthesizing system by gradually increasing daily i.p. doses (125-375 mg/kg, given between 17 and 21 days) of sodium benzoate to mice showed no effects. Sodium benzoate did not induce its own metabolizing system.

23-OCT-1995

Type: Metabolism
Remark: A 15 mM aqueous solution of sodium benzoate was shown to inhibit in vitro the noradrenaline-induced aggregation of platelets from healthy volunteers by blocking the cyclo-oxygenase-thromboxane enzyme system.

23-OCT-1995

Type: Metabolism
Remark: Six female volunteers (case I) and three male volunteers (case II) were orally given (case I) 33 or 66 mg sodium benzoate in a soft drink or (case II) a sodium benzoate solution at a dosage of 20 mg/kg bw.

In case I, 66 to 86 % of the administered dose was excreted in urine within 3 hours as hippuric acid (maximum at 0 to 30 minutes); in case II, approx. 89 % of the administered dose was excreted in urine within 5 hours as hippuric acid (maximum at 0 to 1 hour).

In case I, the concentration of hippuric acid recovered to the predose level after 3 hours, while in case II the concentration of hippuric acid did not recover to the predose level within 5 hours.

23-OCT-1995
Remark: After i.p. injection of 2.5 to 10 mmol sodium benzoate/kg bw in male Sprague-Dawley rats, changes in metabolic levels of the liver and in amino acid levels in liver and plasma were noted.

Type: Metabolism

Remark: Sodium benzoate inhibited the dissolution of hydrochlorothiazide (HCT) in vitro. In bioavailability studies with 6 male volunteers, the rate of increase in mean urine volume after intake of HCT-sodium benzoate was 6:1 compared to HCT alone.

Type: Metabolism

Remark: In an in vitro study with gastric mucosa from patients with asthma, atopic eczema and urticaria, the release of histamine and prostaglandin was significantly increased by sodium benzoate at a concentration of 0.4 %. The mucosa of control persons did not react to sodium benzoate.

Type: Metabolism

Remark: In experiments with isolated rat hepatocytes and mitochondria, sodium benzoate at concentrations from 0 to 2.0 mM inhibited gluconeogenesis (max. 67 %) and urea production (max. 52 %) in a dose-dependent manner by depletion of acetyl CoA.

Type: Toxicity

Remark: I.p. injection of 7.5 mmol/kg ammonium acetate alone produced 10 % mortality in male Swiss albino mice. Subsequent i.p. administration of 7.5 mmol/kg sodium benzoate resulted in 100 % mortality. Pretreatment of mice with carbamyl glutamate (2-20 mmol/kg), a structural analogue of N-acetyl glutamate, reduced mortality to 20 %. The protective effect of carbamyl glutamate is accompanied by an increase in urea production and of carbamyl phosphate synthetase activity.
Type: Effect on ammonia levels: 
Remark: Male SD-rats received i.p. injections of saline, L-norvaline (1 mmol/kg), L-methionine-SR-sulfoximine (250 umol/kg), sodium benzoate (2.5-10 mmol/kg) in saline, either alone or in combination. L-norvaline and L-methionine-SR-sulfoximine caused an increase in the concentration of ammonia in plasma and in liver (interference with urea and glutamine formation). Subsequent injection of sodium benzoate failed to alleviate ammonia levels, and on the contrary, caused further increase. Sodium benzoate itself resulted in higher levels of ammonia in plasma and liver. Application of glycine did not lower ammonia levels indicating that other factors besides glycine may also be necessary for the removal of sodium benzoate.

10-AUG-2001 (98)

Type: Liver perfusion: 
Remark: In isolated perfused rat liver (livers of male Wistar rats, body weight 120-150 g), addition of sodium benzoate to the perfusion medium led to a rapid and marked stimulation of glutamate release from the liver (maximal glutamate efflux: 0.9 umol/min/g), which was fully reversible. Benzoate concentrations as low as 15 uM were effective to stimulate glutamate release significantly. Simultaneously benzoate inhibits urea and glutamine synthesis and diminishes hepatic ammonia uptake.

10-AUG-2001 (99)

5.11 Experience with Human Exposure

Remark: case-report: A 34 year old man reported in 1985 recurrent swelling of the upper lips and gums associated with the presence of a fissured tongue since he was 10 years old. In 1980 episodes became more frequent and were caused by the ingestion of different foods, including wine, sausages, and "hot foods". Each time, remission occurred spontaneously within 2 weeks. The patient reacted positive in a double-blind challenge test with sodium benzoate (see chapter 4.3).
Upon elimination of sodium benzoate and another food additive, tartrazine, from the usual diet, complete remission of the clinical manifestation occurred.

23-OCT-1995
(1) Additional references:
  Safety data sheet Bayer AG, Leverkusen, 07.01.92
  DSM datasheet.

(2) Janssen Chimica (1987/88)

(3) Meylan W. and Howard P. 1999. EPIWin Modeling Program. Syracuse Research Corporation. Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212-2510

(4) Additional reference:
  safety data sheet Bayer AG, Leverkusen, 07.01.92.

(5) DSM safety data sheet.

(6) safety data sheet Bayer AG, Leverkusen, 07.01.92

(7) Meylan W. and Howard P. 1999. EPIWin Modeling Program. Syracuse Research Corporation. Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212-2510

(8) Additional reference:


6. REFERENCES

(13) Additional references:
Commission of the European Communities, Degradation/Accumulation Subgroup; Ring-Test Programme 1981-1982; Assessment of the biodegradability of chemicals in water by manometric respirometry (1982).


(18) Commission of the European Communities, Degradation/Accumulation Subgroup; Ring-Test Programme 1981-1982; Assessment of the biodegradability of chemicals in water by manometric respirometry (1982).


(31) Geiger, D.L. et al., Acute toxicities of organic chemicals to fathead minnows (Pimephales promelas), Vol. 2, University of Wisconsin, 139-140 (1985)


(33) Additional reference: Anderson, B.G., Sewage Works J. 18, 82-87 (1946)

(34) Anderson, B.G., Sewage Works J. 18, 82-87 (1946)

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(42) Rahn, O. and Conn, J.E., Industr. Engin. Chem. 36, 185-87 (1944)

(43) Deuel, H.J., Jr. et al., Food Res. 19, 1-12 (1954)


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(47) RCC NOTOX, Primary skin irritation/corrosion study with natrium benzoate in rabbits (study no. 014658). RCC NOTOX B.V., 's-Hertogenbosch

(48) Loeser, E., Bayer AG data, Untersuchungen zur Haut- und Schleimhautvertraeglichkeit (1977)

(49) Stol, M. et al., Biomaterials 9, 273-276 (1988)

(50) RCC NOTOX, Acute eye irritation/corrosion study with natrium benzoate in rabbits (study no. 014669). RCC NOTOX B.V., 's-Hertogenbosch

(51) Brasch, J. et al., Dermatosen 41, 71-76 (1993)


(53) Toxicity profile benzoic acid and its common salts (1989). BIBRA UK.

(55) BIBRA profile 1989.

(56) Primary references:


(60) Pevny, I. et al., Dermatosen 29, 123-130 (1981)


(63) Additional references:
White, A., Yale J. Biol. Med. 13, 759-768 (1941)


(65) Fujitani, T., Toxicol. Lett. 69, 171-179 (1993)


(68) Kieckebusch, W. & Lang, K., Arzneim.-Forsch. 10, 1001-1003 (1960)
(69) White, A., Yale J. Biol. Med. 13, 759-768 (1941)


(71) Additional references:


(73) Additional references:


(75) Ishidate, M., Jr. & Odashima, S., Mutat. Res. 48, 337-354 (1977)


(84) Additional references:


(86) Onodera, H. et al., Eisei Shikenjo Hokoku 96, 47-55 (1978)


(95) Hashem, F. & El-Din, E.E.Z., Pharm. Ind. 54, 381-384 (1992)


7.1 End Point Summary

7.2 Hazard Summary

7.3 Risk Assessment
I U C L I D D a t a S e t
(POTASSIUM BENZOATE; CAS: 582-25-2)

Existing Chemical
ID: 582-25-2
CAS No. 582-25-2
EINECS Name potassium benzoate
EINECS No. 209-481-3
Molecular Formula C7H6O2.K

Producer Related Part
Company: Bayer Corporation
Creation date: 21-OCT-1999

Substance Related Part
Company: Bayer Corporation
Creation date: 21-OCT-1999

Memo: Bayer Corporation

Printing date: 10-AUG-2001
Revision date:
Date of last Update: 10-AUG-2001

Number of Pages: 21

Chapter (profile): Chapter: 1, 2, 3, 4, 5, 7
Reliability (profile): Reliability: without reliability, 1, 2, 3, 4
1.0.1 OECD and Company Information

Type: lead organisation
Name: American Chemistry Council (formerly Chemical Manufacturers Association), Benzoates HPV Panel
Street: 1300 Wilson Boulevard
Town: 22209 Arlington, VA
Country: United States

10-AUG-2001

Type: cooperating company
Name: ATOFINA Chemicals, Inc
Country: United States

10-AUG-2001

Type: cooperating company
Name: Bayer Corporation
Street: 100 Bayer Road
Town: PA 15205-9741 Pittsburgh
Country: United States

06-JUL-2000

Type: cooperating company
Name: DSM Fine Chemicals
Country: Netherlands

06-JUL-2000

Type: cooperating company
Name: Noveon, Inc.
Country: United States

10-AUG-2001

Type: cooperating company
Name: Velsicol Chemical Corporation
Country: United States

06-JUL-2000

1.0.2 Location of Production Site

1.0.3 Identity of Recipients
1.1 General Substance Information

1.1.0 Details on Template

1.1.1 Spectra

1.2 Synonyms

1.3 Impurities

1.4 Additives

1.5 Quantity

1.6.1 Labelling

1.6.2 Classification

1.7 Use Pattern

1.7.1 Technology Production/Use

1.8 Occupational Exposure Limit Values

1.9 Source of Exposure

1.10.1 Recommendations/Precautionary Measures

1.10.2 Emergency Measures

1.11 Packaging

1.12 Possib. of Rendering Subst. Harmless

1.13 Statements Concerning Waste
1.14.1 Water Pollution

1.14.2 Major Accident Hazards

1.14.3 Air Pollution

1.15 Additional Remarks

1.16 Last Literature Search

Type of Search: Internal and External
Date of Search: 07-SEP-1999
Remark: Only HPV endpoints: TOXLINE data base and internal studies

10-AUG-2001

1.17 Reviews

1.18 Listings e.g. Chemical Inventories
2.1 Melting Point

Value: 330.6 degree C
Method: other: (calculated) MPBPWIN (v1.31) Program; Adapted Joback Method
Year: 1999
GLP: no
Testsubstance: other TS: molecular structure
Reliability: (2) valid with restrictions Accepted calculation method
Flag: Critical study for SIDS endpoint
10-AUG-2001

2.2 Boiling Point

Value: 464.9 degree C
Method: other: (calculated) MPBPWIN (v1.31) Program; Adapted Stein and Brown Method
Year: 1999
GLP: no
Testsubstance: other TS: molecular structure
Reliability: (2) valid with restrictions Accepted calculation method
Flag: Critical study for SIDS endpoint
10-AUG-2001

2.3 Density

2.3.1 Granulometry

2.4 Vapour Pressure

Value: .00000000489 hPa at 25 degree C
Method: other (calculated): MPBPWIN (v1.31) Program; Modified Grain Method
Year: 1999
GLP: no
Testsubstance: other TS: molecular structure
Reliability: (2) valid with restrictions Accepted calculation method
Flag: Critical study for SIDS endpoint
10-AUG-2001
2.5 Partition Coefficient

log Pow: -2.269
Method: other (calculated): Log Kow (version 1.65 estimate)
Year: 1999
GLP: no
Testsubstance: other TS: molecular structure
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
10-AUG-2001

2.6.1 Water Solubility

Value: 556 g/l at 20 degree C
Method: other
Testsubstance: other TS: sodium benzoate
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
10-AUG-2001

Value: > 1000 g/l at 25 degree C
Method: other: (calculated) WSKOW v1.36 Program
Year: 1999
GLP: no
Testsubstance: other TS: molecular structure
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
10-AUG-2001

2.6.2 Surface Tension

2.7 Flash Point

2.8 Auto Flammability

2.9 Flammability
2.10 Explosive Properties

2.11 Oxidizing Properties

2.12 Additional Remarks
3.1.1 Photodegradation

Type: air
Conc. of subst.: at 25 degree C
INDIRECT PHOTOLYSIS
   Sensitizer: OH
   Conc. of sens.: 1560000 molecule/cm3
   Rate constant: .000000000017775 cm3/(molecule * sec)
   Degradation: 50 % after 72.2 hour(s)
Method: other (calculated): AOP Program (v1.89)
Year: 1999 GLP: no
Test substance: other TS: molecular structure
Reliability: (2) valid with restrictions
   Accepted calculation method
Flag: Critical study for SIDS endpoint
10-AUG-2001 (1)

3.1.2 Stability in Water

Type:
Method:
Year: GLP: no
Test substance:
Remark: Based on structure and organic chemistry rules (e.g. bonding in organic molecules, activation energy, reactivity, transformations, addition, substitution, elimination) no hydrolysis will occur at pH ranges 4 – 11.
26-JAN-2001

3.1.3 Stability in Soil

3.2 Monitoring Data (Environment)

3.3.1 Transport between Environmental Compartments

Type: fugacity model level III
Media: other: air - water - soil - sediment
Air (Level I):
Water (Level I):
Soil (Level I):
Biota (L.II/III):
Soil (L.II/III):
Method: other: EPIWin Modeling Program
### 3. ENVIRONMENTAL FATE AND PATHWAYS

#### 3.3 Distribution

<table>
<thead>
<tr>
<th>Year:</th>
<th>Distribution</th>
<th>Half-Life</th>
<th>Emissions</th>
<th>Fugacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>1.61e-007</td>
<td>144</td>
<td>1000</td>
<td>4.83e-019</td>
</tr>
<tr>
<td>Water</td>
<td>45.3</td>
<td>360</td>
<td>1000</td>
<td>1.38e-020</td>
</tr>
<tr>
<td>Soil</td>
<td>54.6</td>
<td>360</td>
<td>1000</td>
<td>6.16e-019</td>
</tr>
</tbody>
</table>

Sediment 0.0755 1.44e+003 0

Persistence Time: 421 hr
Reaction Time: 520 hr
Advection Time: 2.21e+003 hr
Percent Reacted: 80.9
Percent Advected: 19.1

Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
10-AUG-2001

#### 3.3.2 Distribution

#### 3.4 Mode of Degradation in Actual Use

#### 3.5 Biodegradation

Type: aerobic
Inoculum: activated sludge, domestic
Degradation: ca. 90 % after 7 day
Result: readily biodegradable
Method: OECD Guide-line 301 B "Ready Biodegradability: Modified Sturm Test (CO2 evolution)"
OECD SIDS POTASSIUM BENZOATE
3. ENVIRONMENTAL FATE AND PATHWAYS

DATE: 10-AUG.-2001
SUBSTANCE ID: 582-25-2

Year: 1981
Test substance: other TS: sodium benzoate
Remark: See IUCLID on sodium benzoate (CAS# 532-32-1); the biodegradation of the potassium salt would be similar to the sodium salt.
Test condition: temperature = 25 degree C
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint

10-AUG-2001

Type: anaerobic
Inoculum: other bacteria: anaerobic sewage, domestic and industrial
Concentration: 50 mg/l related to DOC (Dissolved Organic Carbon)
Degradation: 93 % after 7 day
Method: other: see below

Year: GLP: no data
Test substance: other TS: sodium benzoate
Method: 2-3 g sludge plus sodium benzoate (concentration equivalent to 50 mg Carbon/liter or 85 mg substance/l).
Controls and tests done in triplicate.
Temperature = 35 degree C.
Measured gas production (CH4 + CO2).
Remark: See IUCLID on sodium benzoate (CAS# 532-32-1); the biodegradation of the potassium salt would be similar to the sodium salt.
Result: Degradation is expressed as percentage of theoretical methane production based on the stoichiometry of degradation.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

10-AUG-2001

Type:
Inoculum:
Method:
Year: GLP:
Test substance:
Remark: See IUCLID on benzoic acid (CAS# 65-85-0); the potassium salt is expected to immediately dissociate and form benzoic acid in an aqueous environment.

10-AUG-2001
3.6 BOD5, COD or BOD5/COD Ratio

3.7 Bioaccumulation

Species:
Exposure period:
Concentration:
BCF: 3.16
Elimination:
Method: other: (calculated) BCF Program (v2.13)
Year: GLP: no
Test substance: other TS: molecular structure
Result: Estimated Log BCF = 0.500 (BCF = 3.162)

Log Kow (estimated) : 1.87
Log Kow (experimental): 1.87
Log Kow used by BCF estimates: 1.87

Equation Used to Make BCF estimate:
Log BCF = 0.50 (Ionic; Log Kow dependent)
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
10-AUG-2001

3.8 Additional Remarks
AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: other: ECOSAR calculations
Species: other: fresh water fish
Exposure period: 96 hour(s)
Unit: g/l Analytical monitoring: no
LC50: > 1000
Method: other: ECOSAR (v 0.99)
Year: 1999 GLP: no
Test substance: other TS: molecular structure
Remark: ECOSAR class: Neutral organics. Chemical may not be soluble enough to measure the predicted effect.
Result: ECOSAR Class Organism Duration End Pt mg/L

Neutral Organic SAR: Fish 14-day LC50 1.13e+006 (Baseline Toxicity)
Neutral Organics: Fish 96-hr LC50 1.23e+006
Neutral Organics: Fish 14-day LC50 1.13e+006
Neutral Organics: Fish 30-day ChV 79360.031

Reliability: (2) valid with restrictions
Flag: Accepted calculation method
Critical study for SIDS endpoint

Type:
Species:
Exposure period:
Unit: Analytical monitoring:
Method: GLP:
Year:
Test substance:
Remark: See IUCLID on sodium benzoate (CAS# 532-32-1); the toxicity of the potassium salt would be similar to the sodium salt.

10-AUG-2001
4.2 Acute Toxicity to Aquatic Invertebrates

Type:           
Species:        Daphnia magna  (Crustacea)  
Exposure period: 48 hour(s)  
Unit:                g/l          Analytical monitoring: no  
EC50:             978  
Method:           other: ECOSAR (v 0.99)  
Year:           1999                                   GLP: no  
Test substance:   other TS: molecular structure  
Remark:           ECOSAR class: Neutral organics. Chemical may not be soluble enough to measure the predicted effect.  
Result: ECOSAR   Class    Organism   Duration  End Pt   mg/L  

===========================================================================
| Neutral Organics: Daphnid   | 48-hr    | LC50      | 9.78e+005 |
| Neutral Organics: Daphnid   | 16-day   | EC50      | 7746.435  |
| Neutral Organics: Mysid Shrimp | 96-hr    | LC50      | 7.45e+006 |

Reliability:      (2) valid with restrictions  
Flag:             Critical study for SIDS endpoint  
10-AUG-2001

4.3 Toxicity to Aquatic Plants e.g. Algae

Species:          other algae: Green Algae  
Endpoint:         biomass  
Exposure period:  96 hour(s)  
Unit:             g/l          Analytical monitoring: no  
EC50:             478  
Method:           other: ECOSAR (v 0.99)  
Year:           1999                                   GLP: no
Test substance: other TS: molecular structure
Remark: ECOSAR class: Neutral organics.
Result: ECOSAR Class | Organism | Duration | End Pt | mg/L

| Neutral Organics: Green Algae | 96-hr | EC50 | 4.78e+005 |
| Neutral Organics: Green Algae | 96-hr | ChV | 4053.982 |

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

10-AUG-2001

**4.4 Toxicity to Microorganisms e.g. Bacteria**

Type: 
Species: 
Exposure period: 
Unit: Analytical monitoring: 
Method: 
Year: GLP: 
Test substance: 
Remark: See IUCLID on sodium benzoate (CAS# 532-32-1); the toxicity of the potassium salt would be similar to the sodium salt.

10-AUG-2001

**4.5 Chronic Toxicity to Aquatic Organisms**

**4.5.1 Chronic Toxicity to Fish**

**4.5.2 Chronic Toxicity to Aquatic Invertebrates**
TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Soil Dwelling Organisms

4.6.2 Toxicity to Terrestrial Plants

4.6.3 Toxicity to other Non-Mamm. Terrestrial Species

4.7 Biological Effects Monitoring

4.8 Biotransformation and Kinetics

4.9 Additional Remarks
5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Strain:
Sex:
Number of Animals:
Vehicle:
Value: > 10000 mg/kg bw
Method:
Year: GLP:
Test substance: other TS: potassium benzoate; purity not noted
Reliability: (4) not assignable
Flag: Critical study for SIDS endpoint
10-AUG-2001 (5)

Type: LD50
Species: mouse
Strain:
Sex:
Number of Animals:
Vehicle:
Value: > 10000 mg/kg bw
Method:
Year: GLP:
Test substance: other TS: potassium benzoate; purity not noted
Reliability: (4) not assignable
Flag: Critical study for SIDS endpoint
10-AUG-2001 (5)

Type: LD50
Species: guinea pig
Strain:
Sex:
Number of Animals:
Vehicle:
Value: > 10000 mg/kg bw
Method:
Year: GLP:
Test substance: other TS: potassium benzoate; purity not noted
Reliability: (4) not assignable
Flag: Original reference in foreign language
10-AUG-2001 Critical study for SIDS endpoint

5.1.2 Acute Inhalation Toxicity

Type:
Species:
Strain:
Sex:
Number of Animals:
Vehicle:
Exposure time:
Value:
Method:
Year: GLP:
Test substance:
Remark: See IUCLID on benzoic acid (CAS# 65-85-0); the loss of acidity due to the potassium salt should decrease toxicity.
10-AUG-2001

5.1.3 Acute Dermal Toxicity

Type:
Species:
Strain:
Sex:
Number of Animals:
Vehicle:
Value:
Method:
Year: GLP:
Test substance:
Remark: See IUCLID on benzoic acid (CAS# 65-85-0); the loss of acidity due to the potassium salt should decrease toxicity.
10-AUG-2001

5.1.4 Acute Toxicity, other Routes
5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species:  
Concentration:  

Exposure:  
Exposure Time:  
Number of Animals:  
PDII:  
Result:  
EC classificat.:  
Method:  
Year:  
Test substance:  
Remark: See IUCLID on sodium benzoate (CAS# 532-32-1); the irritating ability of the potassium salt would be similar to the sodium salt.

10-AUG-2001

5.2.2 Eye Irritation

Species:  
Concentration:  
Dose:  
Exposure Time:  
Comment:  
Number of Animals:  
Result:  
EC classificat.:  
Method:  
Year:  
Test substance:  
Remark: See IUCLID on sodium benzoate (CAS# 532-32-1); the irritating ability of the potassium salt would be similar to the sodium salt.

10-AUG-2001

5.3 Sensitization
5.4 Repeated Dose Toxicity

Species:                                            Sex: 
Strain: 
Route of admin.: 
Exposure period: 
Frequency of treatment: 
Post. obs. period: 
Doses: 
Control Group: 
Method: 
Year:                                        GLP: 
Test substance: 
Remark:           See IUCLID on sodium benzoate (CAS# 532-32-1); the toxicity of the potassium salt would be similar to the sodium salt. 
10-AUG-2001

5.5 Genetic Toxicity 'in Vitro'

Type:              Bacillus subtilis recombination assay 
System of testing: Bacillus subtilis H17, M45 
Concentration:     1-20 mg/disk; vehicle: water and ethanol (1:1) 
Cytotoxic Conc.:   
Metabolic activation: with and without 
Result:           positive 
Method: 
Year:                                        GLP: 
Test substance:   other TS: potassium benzoate; purity not noted 
Result:           Authors judged results as positive. 
Reliability:      (3) invalid 
Significant methodological deficiencies: one dose tested 
Flag:             Critical study for SIDS endpoint 
10-AUG-2001

Type:
System of testing:
Concentration:
Cytotoxic Conc.:  
Metabolic activation:  
Result:  
Method:  
Year:  
GLP:  
Test substance:  
Remark:  
See IUCLID on sodium benzoate (CAS# 532-32-1); the toxicity of the potassium salt would be similar to the sodium salt.  
10-AUG-2001

5.6 Genetic Toxicity 'in Vivo'

Type: Cytogenetic assay  
Species:  
Sex:  
Strain:  
Route of admin.:  
Exposure period:  
Doses:  
Result:  
Method:  
Year:  
GLP:  
Test substance:  
Remark:  
See IUCLID on sodium benzoate (CAS# 532-32-1); the toxicity of the potassium salt would be similar to the sodium salt.  
10-AUG-2001

5.7 Carcinogenicity

Species:  
Sex:  
Strain:  
Route of admin.:  
Exposure period:  
Frequency of treatment:  
Post. obs. period:  
Doses:  
Result:  
Control Group:  
Method:  
Year:  
GLP: 
Test substance: See IUCLID on sodium benzoate (CAS# 532-32-1); the toxicity of the potassium salt would be similar to the sodium salt.

10-AUG-2001

5.8 Toxicity to Reproduction

Type:
Species:
Strain:
Route of admin.:
Exposure Period:
Frequency of treatment:
Duration of test:
Doses:
Control Group:
Method:
Year: GLP:
Test substance:
Remark: A 4-generation reprotoxicity test with benzoic acid revealed no reproductive effects. Therefore no indication for reprotoxicity for the benzoic acid potassium salt. See IUCLID on benzoic acid (CAS# 65-85-0); the loss of acidity due to the potassium salt should decrease toxicity.

10-AUG-2001

5.9 Developmental Toxicity/Teratogenicity

Species:
Strain:
Route of admin.:
Exposure period:
Frequency of treatment:
Duration of test:
Doses:
Control Group:
Method:
Year: GLP:
Test substance: See IUCLID on sodium benzoate (CAS# 532-32-1); the toxicity of the potassium salt would be similar to the sodium salt.

10-AUG-2001

5.10 Other Relevant Information

5.11 Experience with Human Exposure
6. REFERENCES

(1) Meylan W. and Howard P. 1999. EPIWin Modeling Program. Syracuse Research Corporation. Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212-2510


7.1 End Point Summary

7.2 Hazard Summary

7.3 Risk Assessment
**IUCLID Data Set**

(BENZYL ALCOHOL; CAS: 100-51-6)

**Existing Chemical**

- **ID**: 100-51-6
- **CAS No.**: 100-51-6
- **EINECS Name**: benzyl alcohol
- **EC No.**: 202-859-9
- **TSCA Name**: Benzenemethanol
- **Molecular Formula**: C7H8O

**Producer Related Part**

- **Company**: Bayer Corporation
- **Creation date**: 15-JUL-1999

**Substance Related Part**

- **Company**: Bayer Corporation
- **Creation date**: 15-JUL-1999

**Memo**: Bayer Corporation

**Printing date**: 14-FEB-2002

**Revision date**:

**Date of last Update**: 14-FEB-2002

**Number of Pages**: 82

**Chapter (profile)**: Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10

**Reliability (profile)**: Reliability: without reliability, 1, 2, 3, 4

**Flags (profile)**: Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS
1. GENERAL INFORMATION

SUBSTANCE ID: 100-51-6

1.0.1 Applicant and Company Information

Type: lead organisation
Name: American Chemistry Council, Benzoates Panel
Street: 1300 Wilson Boulevard
Town: 22209 Arlington, VA
Country: United States
14-DEC-2000

Type: cooperating company
Name: B.F. Goodrich
Country: United States
26-MAY-2000

Type: cooperating company
Name: Bayer Corporation
Country: United States
14-DEC-2000

Type: cooperating company
Name: DSM Fine Chemicals
Country: Netherlands
14-DEC-2000

Type: cooperating company
Name: Elf Atochem NA
Country: United States
26-MAY-2000

Type: cooperating company
Name: Velsicol Chemical Corporation
Country: United States
26-MAY-2000

Type: lead organisation
Name: American Chemistry Council, Benzoates Panel
16-JAN-2001
1.0.2 Location of Production Site, Importer or Formulator

1.0.3 Identity of Recipients

1.0.4 Details on Category/Template

1.1.0 Substance Identification

1.1.1 General Substance Information

1.1.2 Spectra

1.2 Synonyms and Tradenames

1.3 Impurities

1.4 Additives

1.5 Total Quantity

1.6.1 Labelling

1.6.2 Classification

1.6.3 Packaging

1.7 Use Pattern

1.7.1 Detailed Use Pattern

1.7.2 Methods of Manufacture

1.8 Regulatory Measures

1.8.1 Occupational Exposure Limit Values

1.8.2 Acceptable Residues Levels
1.8.3 Water Pollution

1.8.4 Major Accident Hazards

1.8.5 Air Pollution

1.8.6 Listings e.g. Chemical Inventories

1.9.1 Degradation/Transformation Products

1.9.2 Components

1.10 Source of Exposure

1.11 Additional Remarks

1.12 Last Literature Search

1.13 Reviews
## 2.1 Melting Point

Value: -15.2 degree C

Method: other: Handbook value
Test substance: other TS: benzyl alcohol, purity not noted

Reliability: (2) valid with restrictions
Flag: Data from Handbook or collection of data

14-FEB-2002

Value: -15.3 degree C
Test substance: other TS: benzyl alcohol, purity not noted
12-FEB-2002

## 2.2 Boiling Point

Value: 205.3 degree C at 1013 hPa

Method: other: Handbook value
Test substance: other TS: benzyl alcohol, purity not noted

Reliability: (2) valid with restrictions
Flag: Data from Handbook or collection of data

14-FEB-2002

Value: 205.4 degree C at 1013 hPa
19-JAN-2001

## 2.3 Density

Type: density
Value: 1.041 g/cm³ at 24 degree C

Method: other: Handbook value
Test substance: other TS: benzyl alcohol, purity not noted

Reliability: (2) valid with restrictions
Flag: Data from Handbook or collection of data
OECD SIDS
2. PHYSICO-CHEMICAL DATA
BENZYL ALCOHOL
DATE: 14-FEB.-2002
SUBSTANCE ID: 100-51-6

Flag: Critical study for SIDS endpoint
14-FEB-2002

Type: density
Value: 1.0442 g/cm³ at 22.5 degree C
19-JAN-2001

2.3.1 Granulometry

2.4 Vapour Pressure

Value: .03 hPa at 20 degree C
Test substance: other TS: benzyl alcohol, purity not noted
Flag: Critical study for SIDS endpoint
12-FEB-2002

Value: .09 hPa at 30 degree C
Test substance: other TS: benzyl alcohol, purity not noted
Flag: Critical study for SIDS endpoint
12-FEB-2002

Value: .67 hPa at 50 degree C
Flag: Critical study for SIDS endpoint
19-JAN-2001

2.5 Partition Coefficient

log Pow: 1.1
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
06-JUN-2001 (3)

log Pow: 1.1

Method: other (measured)

Remark: experimentally determined

Flag: Critical study for SIDS endpoint

14-FEB-2002 (4)

2.6.1 Solubility in different media

Solubility in: Water
Value: 40 g/l at 20 degree C

Flag: Critical study for SIDS endpoint
14-FEB-2002 (5)

Solubility in: Water
Value: 44 g/l at 50 degree C

Flag: Critical study for SIDS endpoint
14-FEB-2002 (5)

2.6.2 Surface Tension

2.7 Flash Point

Value: 101 degree C
Type: closed cup

Method: other: DIN 51758

19-JAN-2001 (5)

2.8 Auto Flammability

Value:

Remark: ignition temperature: 435 degree C
19-JAN-2001 (2)
2.9 Flammability

2.10 Explosive Properties

Result: other: explosive limits: lower 1.3 % by vol., upper 13.0 % by vol. at 170 degree C and 1.013 bar

19-JAN-2001 (2)

2.11 Oxidizing Properties

2.12 Dissociation Constant

2.13 Viscosity

2.14 Additional Remarks
3.1.1 Photodegradation

Type: air
Light source: Sun light
INDIRECT PHOTOLYSIS
   Sensitizer: OH
   Conc. of sens.: 1560000
   Rate constant: .0000000000082541 cm³/(molecule * sec)
   Degradation: 50 % after 1.3 day(s)

Method: other (calculated): AOPWin version 1.89
Year: 1999
GLP: no
Test substance: other TS: molecular structure

Remark: Experimental Database Structure Match:
   experimental OH rate constant= 22.9 E-12 cm³/molecule-sec.
Reliability: (2) valid with restrictions
   Accepted calculation method
Flag: Critical study for SIDS endpoint
14-FEB-2002

3.1.2 Stability in Water

Remark: Based on structure and organic chemistry rules
   (e.g. bonding in organic molecules, activation energy, reactivity, transformations, addition, substitution, elimination) no hydrolysis will occur at pH ranges 4 - 11.

Flag: Critical study for SIDS endpoint
26-JAN-2001

3.1.3 Stability in Soil

3.2.1 Monitoring Data (Environment)

3.2.2 Field Studies
3.3.1 Transport between Environmental Compartments

Type: fugacity model level III
Media: other: other: air - water - soil - sediment
Method: other: EPIWin Modeling Program

Remark: Modeling was performed using equal releases (10,000 kg/hr) and equal distribution to all compartments.

<table>
<thead>
<tr>
<th>Result</th>
<th>Distribution</th>
<th>Half-Life</th>
<th>Emissions</th>
<th>Fugacity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(percent)</td>
<td>(hr)</td>
<td>(kg/hr)</td>
<td>(atm)</td>
</tr>
<tr>
<td>Air</td>
<td>1.51</td>
<td>11.2</td>
<td>1000</td>
<td>2.95e-011</td>
</tr>
<tr>
<td>Water</td>
<td>50.0</td>
<td>360</td>
<td>1000</td>
<td>6.71e-012</td>
</tr>
<tr>
<td>Soil</td>
<td>48.4</td>
<td>360</td>
<td>1000</td>
<td>1.7 e-010</td>
</tr>
<tr>
<td>Sediment</td>
<td>0.0923</td>
<td>1440</td>
<td>0</td>
<td>5.52e-012</td>
</tr>
</tbody>
</table>

Persistence Time: 287 hr
Reaction Time: 353 hr
Advection Time: 1.54e+003 hr
Percent Reacted: 81.3
Percent Adveected: ...

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
14-FEB-2002

3.3.2 Distribution

3.4 Mode of Degradation in Actual Use

3.5 Biodegradation

Type: aerobic
Inoculum: activated sludge
Concentration: 100 mg/l
Degradation: 92 - 96 % after 28 day(s)

Method: OECD Guide-line 301 C "Ready Biodegradability: Modified MITI Test (I)"
Year: 1981
GLP: no data
Test substance: other TS: benzyl alcohol, purity not noted

Remark: sludge conc.: 30 mg/l
OECD SIDS  BENZYL ALCOHOL
3. ENVIRONMENTAL FATE AND PATHWAYS  DATE: 14-FEB.-2002
SUBSTANCE ID: 100-51-6

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
14-FEB-2002

Type: aerobic
Inoculum: predominantly domestic sewage
Degradation: > 90 % after 30 day(s)
Method: OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year: 1972
GLP: no
Test substance: other TS: benzyl alcohol, purity not noted
Remark: related to BOD
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
29-JAN-2001

Type: anaerobic
Inoculum: anaerobic sludge
Contact time: 28 day(s)
Degradation: 100 % after 7 day(s)
Result: readily biodegradable
Method: other: see below
Year: 1982
GLP: no data
Test substance: other TS: commercial grade benzyl alcohol, purity > 95%

Method: A 10% anaerobic sludge inoculum was transferred to 160 ml serum bottles previously amended with 50 ppm carbon (related to test substance) using strict anaerobic techniques. Methane production from test bottles vs. controls was monitored weekly for 4 weeks or until net production occurred. At that time, the bottles were amended again with the same substrate and methane production monitored to confirm the observation. All data were obtained from duplicate bottles. Methane was measured using a flame ionization detector on a Perkin-Elmer Model 900 GC equipped with a 3-m Tenax-G.C. column.
Remark: 100 % mineralisation (CH4-production) in 1 week with sludge from Jackson, MI waste-treatment plant 100 % mineralisation (CH4-Production) in 2 weeks with sludge from Adrian, MI waste-treatment plant.

Test condition: The test bottles were incubated at 35 degree C in the dark. Substrates were kept under an atmosphere of 90% N2 and 10% H2.

Reliability: (2) valid with restrictions

Flag: Critical study for SIDS endpoint

23-MAR-2001 (9)

Type: anaerobic
Inoculum: domestic sewage
Concentration: 50 µg/l related to DOC (Dissolved Organic Carbon)
Contact time: 2 month
Degradation: > 75 % after 2 month

Method: other: see below
Year: 1984
GLP: no data
Test substance: other TS: benzyl alcohol, purity not noted

Method: Sludge samples collected from primary and secondary anaerobic digesters were diluted to 10 % and incubated anaerobically with 50 ug Carbon per ml (related to test substance). All compounds were tested in triplicate. Gas production was measured by gas chromatography and by a pressure transducer. Biodegradation was determined by net increase in gas pressure in bottles amended with test chemicals over non-amended controls.

Result: Degradation is expressed as percentage of theoretical methane production based on the stoichiometry of degradation.

Test condition: The test bottles were incubated at 35 degree C in the dark. Substrates were kept under atmospheres of 10% CO2 and 90% N2.

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

23-MAR-2001 (10)

Type: aerobic
Degradation: 62 % after 5 day(s)
<table>
<thead>
<tr>
<th>Method:</th>
<th>OECD Guide-line 301 D &quot;Ready Biodegradability: Closed Bottle Test&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP:</td>
<td>no</td>
</tr>
<tr>
<td>Remark:</td>
<td>related to ThOD</td>
</tr>
<tr>
<td>19-JAN-2001</td>
<td></td>
</tr>
<tr>
<td>Type:</td>
<td>aerobic</td>
</tr>
<tr>
<td>Degradation:</td>
<td>77% after 20 day(s)</td>
</tr>
<tr>
<td>Method:</td>
<td>OECD Guide-line 301 D &quot;Ready Biodegradability: Closed Bottle Test&quot;</td>
</tr>
<tr>
<td>GLP:</td>
<td>no</td>
</tr>
<tr>
<td>Remark:</td>
<td>related to ThOD</td>
</tr>
<tr>
<td>19-JAN-2001</td>
<td></td>
</tr>
<tr>
<td>Type:</td>
<td>aerobic</td>
</tr>
<tr>
<td>Inoculum:</td>
<td>activated sludge, adapted</td>
</tr>
<tr>
<td>Degradation:</td>
<td>95% after 28 day(s)</td>
</tr>
<tr>
<td>Method:</td>
<td>other: Closed bottle test</td>
</tr>
<tr>
<td>Remark:</td>
<td>Test concentration: 2 - 5 mg/l</td>
</tr>
<tr>
<td>19-JAN-2001</td>
<td></td>
</tr>
<tr>
<td>Type:</td>
<td>aerobic</td>
</tr>
<tr>
<td>Inoculum:</td>
<td>domestic sewage</td>
</tr>
<tr>
<td>Degradation:</td>
<td>89.2% after 5 day(s)</td>
</tr>
<tr>
<td>Method:</td>
<td>other: respirometric diluting method</td>
</tr>
<tr>
<td>GLP:</td>
<td>no</td>
</tr>
<tr>
<td>Remark:</td>
<td>related to ThOD</td>
</tr>
<tr>
<td>19-JAN-2001</td>
<td></td>
</tr>
<tr>
<td>Type:</td>
<td>aerobic</td>
</tr>
<tr>
<td>Inoculum:</td>
<td>activated sludge, industrial</td>
</tr>
<tr>
<td>Degradation:</td>
<td>88.9% after 5 day(s)</td>
</tr>
<tr>
<td>Test substance:</td>
<td>other TS</td>
</tr>
</tbody>
</table>
Method: Radio-respirometric study using radio-labeled chemicals by activated sludge and in a complex photographic processing effluent using acclimated industrial sludge. Concentration of test substance was 0.1 or 0.2 ml of radioactive substrate (27,000-400,000 dpm). Samples were incubated in the dark at ambient temperature.

Remark: 14CO2 recovery without effluent = 85.7% after 5 days
14CO2 recovery in presence of effluent = 88.9% after 5 days

Test substance: benzyl-alcohol-7-14C (carbinol-14C) obtained from New England Nuclear Corporation, Boston, Massachusetts.

17-JAN-2001

Type: aerobic
Degradation: 85 % after 5 day(s)

Remark: related to ThOD

19-JAN-2001

Remark: The activity of degradation is at a concentration of 100 mg/l not hindered in a model plant (Ascomat)

19-JAN-2001

Remark: Biodegradation characteristics: biodegraded completely in a short time by general microorganisms.

19-JAN-2001

3.6 BOD5, COD or BOD5/COD Ratio

ThOD: 2515.1 mg/l

19-JAN-2001

3.7 Bioaccumulation

BCF: .31

242
Method: other: (calculated) BCF Program (v2.13)
Year: 1999
Test substance: other TS: molecular structure

Result: Estimated Log BCF = -0.503 (BCF = 0.3141)
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
14-FEB-2002

3.8 Additional Remarks

Remark: ThOD  2520 mg/g
        COD   2520 mg/g
        BOD5  1560 mg/g
        Influence on biological purification plants: adapted 1180 mg/l degradable

27-MAY-1993
AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: static
Species: Pimephales promelas (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
LC50: 460
Method: other: see below
Year: 1976
GLP: no data
Test substance: other TS: reagent grade benzyl alcohol purchased from Curtin Matheson Scientific, Inc.

Method: Juvenile fathead minnows were obtained from Environmental Research Laboratory, Duluth. All fish used for the test were 4 to 8 weeks of age, 1.1 to 3.1 cm in length, and acclimated for at least 48 hr before testing. Test solutions were prepared by adding a weighed amount of chemical to 4 liters of Lake Superior water (all concentrations are nominal). Water temperature during the test was 18-22 degree C. Range-finding tests were done and definitive tests were conducted with 10 fish per container, 20 fish per concentration. Complete immobilization was considered the biological endpoint and equated with death. Standard graphical procedures were followed to determine LC50 (American Public Health Assn., 1971) Analyses of test water was done for dissolved oxygen and pH at the beginning and 1 or 2 times during the test.

Result: 1 hour LC50 = 770 mg/l
24 hour LC50 = 770 mg/l
48 hour LC50 = 770 mg/l
72 hour LC50 = 480 mg/l

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
23-MAR-2001 (18)
Type: static
Species: Leuciscus idus (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: mg/l
LC0: 630
LC50: 646
LC100: 662

Method: other: Bestimmung der Wirkung von Wasserinhaltsstoffen auf Fische, DIN 38412 Teil 15

Year: 1983
GLP: no
Test substance: other TS: benzyl alcohol, purity not noted

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

12-FEB-2002

Type: static
Species: Petromyzon marinus
Exposure period: 24 hour(s)
Unit: mg/l
LC50: >= 5

Remark: larvae; screening test
17-JAN-2001

Species: Carassius auratus (Fish, fresh water)
Exposure period: 24 hour(s)
Unit: mg/l
LC0: >= 5

17-JAN-2001

Species: Cyprinus carpio (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: mg/kg
LC0: 136

GLP: no
Remark: Testing of acute oral toxicity
17-JAN-2001
Species: Lepomis macrochirus (Fish, fresh water)
Exposure period: 24 hour(s)
Unit: mg/l
LC0: >= 5
Analytical monitoring:

Remark: The static test was directed to simulate acute spill circumstances. The test substances were pipetted or poured undiluted directly into the aquaria with fish. There was no preparation of defined concentrations according to guideline. No analytical monitoring was done. Aeration was not used during the first 24 hrs thus allowing chemicals to act in an uninterrupted state at the onset of the test period.

Reliability: (4) not assignable
Significant methodological deficiencies

12-FEB-2002
Species: Menidia beryllina (Fish, estuary, marine)
Exposure period: 96 hour(s)
Unit: mg/l
LC50: 10
Analytical monitoring:

Remark: The static test was directed to simulate acute spill circumstances. The test substances were pipetted or poured undiluted directly into the aquaria with fish. There was no preparation of defined concentrations according to guideline. No analytical monitoring was done. Aeration was not used during the first 24 hrs thus allowing chemicals to act in an uninterrupted state at the onset of the test period.

Reliability: (4) not assignable
Significant methodological deficiencies
Species:          Salmo trutta (Fish, fresh water, marine)
Exposure period:  24 hour(s)
Unit:             mg/l                   Analytical monitoring: 
LC0:              >= 5
17-JAN-2001                                                (21)

4.2 Acute Toxicity to Aquatic Invertebrates

Species:          Daphnia magna  (Crustacea)
Exposure period:  24 hour(s)
Unit:             mg/l                 Analytical monitoring: no
EC0:              300
EC50:             400
EC100:            500
Method:           other: Daphnien-Kurzzeittest, DIN 38412 Teil 11, Bestimmung der Wirkung von Wasserinhaltstoffen auf Kleinkrebse
Year:           1983
GLP:           no
Test substance:   other TS: benzyl alcohol, purity not noted
Reliability:      (2) valid with restrictions
Flag:             Critical study for SIDS endpoint 14-FEB-2002 (19)

Species:          Daphnia magna  (Crustacea)
Exposure period:  48 hour(s)
Unit:             mg/l                Analytical monitoring: no
TGK :             360
Method:           other: acute immobilisation test
GLP:           no
Reliability:      (2) valid with restrictions
Flag:             Critical study for SIDS endpoint 06-JUN-2001 (24)

Species:          Daphnia magna  (Crustacea)
Exposure period:  24 hour(s)
Unit:             mg/l                   Analytical monitoring: no
EC0:              26
EC50:             55
EC100:            100
4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Chlorella pyrenoidosa (Algae)
Endpoint: other: Inhibition of photosynthesis
Exposure period: 3 hour(s)
Unit: mg/l
EC50: 95

Method: other: see below
Year: 1982
GLP: no data
Test substance: other TS: benzyl alcohol purchased from Aldrich Chemical Co. Wisconsin, USA. Purity > 95%

Method: Photosynthesis was assayed by following the uptake of 14CO2 from NaH 14CO3 (Amersham/Searle, Ontario, Canada). Plastic culture flasks containing 9.9 ml of cell suspension (1.0 x 10+5 cells/ml), 0.1 ml radioisotope and 0.01 ml of test chemical were incubated for 3 hours. Five concentrations, ranging from 0 to 100 ppm, were tested and replicated five times. Photosynthetic activity was assayed according to Stratton et al. (1979) Appl. Environ. Microbiol. 38: 537-43. Per cent inhibition values were calculated relative to photosynthetic activity in the solvent controls and EC50 values determined by Probit analysis. Analyses for significant differences were performed using Dunnett's test and Duncan's multiple range test.

Test condition: Cultures were maintained in a liquid nitrogen-free medium at 20 degree C and a light intensity of 7000 lux on a 12 hour light-dark cycle.

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
14-FEB-2002

Species: Haematococcus pluvialis (Algae)
Endpoint: other: Inhibition of photosynthesis
Exposure period: 4 hour(s)
Unit: mg/l
EC50: 2600


GLP: no
Test substance: other TS: benzyl alcohol, purity not noted

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

29-JAN-2001

Species: Scenedesmus quadricauda (Algae)
Exposure period: 96 hour(s)
Unit: mg/l
TGK: 640

Method: other: cell multiplication inhibition test

Remark: green algae
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

06-JUN-2001

Species: Anabaena cylindrica (Algae)
Endpoint: other: Inhibition of photosynthesis
Exposure period: 3 hour(s)
Unit: mg/l
EC50: 90

Remark: blue-green algae

17-JAN-2001

Species: Anabaena inaequalis (Algae)
Endpoint: other: Inhibition of photosynthesis
Exposure period: 3 hour(s)
Unit: mg/l
EC0: 30
4.4 Toxicity to Microorganisms e.g. Bacteria

Type: aquatic
Species: Escherichia coli (Bacteria)
Exposure period: 48 hour(s)
Unit: mg/l
EC0: 1000
Analytical monitoring: no

Method: other: cell multiplication test
GLP: no

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
06-JUN-2001

Type: aquatic
Species: Pseudomonas putida (Bacteria)
Unit: mg/l
EC10: 658
Analytical monitoring: no

Method: other: Test according to Bringmann and Kuehn (cell multiplication inhibition test)
### OECD SIDS BENZYL ALCOHOL

#### 4. ECOTOXICITY

**DATE:** 14-FEB.-2002  
**SUBSTANCE ID:** 100-51-6

<table>
<thead>
<tr>
<th>GLP:</th>
<th>no</th>
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<tbody>
<tr>
<td>Remark:</td>
<td>Exposure period: 16-18 h</td>
</tr>
<tr>
<td>Reliability:</td>
<td>(2) valid with restrictions</td>
</tr>
<tr>
<td>Flag:</td>
<td>Critical study for SIDS endpoint</td>
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<tr>
<td>06-JUN-2001</td>
<td>(19)</td>
</tr>
</tbody>
</table>

**Type:** aquatic  
**Species:** Photobacterium phosphoreum (Bacteria)  
**Exposure period:** 30 minute(s)  
**Unit:** mg/l  
**Analytical monitoring:** no  
**EC50:** 71.42

**Method:** other: Microtox  
**GLP:** no

<table>
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<tr>
<th>19-JAN-2001</th>
<th>(27)</th>
</tr>
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<tbody>
<tr>
<td>Type:</td>
<td>aquatic</td>
</tr>
<tr>
<td>Species:</td>
<td>Photobacterium phosphoreum (Bacteria)</td>
</tr>
<tr>
<td>Exposure period:</td>
<td>5 minute(s)</td>
</tr>
<tr>
<td>Unit:</td>
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**GLP:** no

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<tbody>
<tr>
<td>Type:</td>
<td>aquatic</td>
</tr>
<tr>
<td>Species:</td>
<td>other bacteria: Aerobic heterotrophic</td>
</tr>
<tr>
<td>Exposure period:</td>
<td>49 hour(s)</td>
</tr>
<tr>
<td>Unit:</td>
<td>mg/l</td>
</tr>
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<td>Analytical monitoring:</td>
<td></td>
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<tr>
<td>IC50:</td>
<td>2100</td>
</tr>
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</table>

**GLP:** no

**Remark:** Inhibition of respiration; prolonged incubation compared with ISO 8192

<table>
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<tr>
<th>19-JAN-2001</th>
<th>(29)</th>
</tr>
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<tbody>
<tr>
<td>Type:</td>
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<tr>
<td>Species:</td>
<td>other bacteria: Nitrosomonas</td>
</tr>
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<td>24 hour(s)</td>
</tr>
<tr>
<td>Unit:</td>
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<tr>
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</table>
4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

4.5.2 Chronic Toxicity to Aquatic Invertebrates
TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Sediment Dwelling Organisms

4.6.2 Toxicity to Terrestrial Plants

4.6.3 Toxicity to Soil Dwelling Organisms

4.6.4 Toxicity to other Non-Mamm. Terrestrial Species

4.7 Biological Effects Monitoring

4.8 Biotransformation and Kinetics

4.9 Additional Remarks

Remark:
Aedes aegypti, eggs (72h) LD50 160 l/ha
LD90 251 l/ha
Aedes aegypti, larval stage L1 (24h) LD50 105 l/ha
LD90 132 l/ha
Aedes aegypti, larval stage L3-L4 (24h) LD50 129 l/ha
LD90 184 l/ha
Aedes scutellaris, eggs (72h) LD50 160 l/ha
LD90 265 l/ha
Aedes scutellaris, larval stage L1 (24h) LD50 110 l/ha
LD90 151 l/ha
Aedes scutellaris, larval stage L3-L4(24h) LD50 126 l/ha
LD90 172 l/ha

19-JAN-2001
5.0 Toxicokinetics, Metabolism and Distribution

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Sex: male
Value: = 1610 mg/kg bw

Method: other
GLP: no data
Test substance: other TS: benzyl alcohol, purity not noted

Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment
Flag: Critical study for SIDS endpoint

12-FEB-2002 (31)

Type: LD50
Species: mouse
Sex: male/female
No. of Animals: 10
Vehicle: other: corn oil
Value: = 1580 mg/kg bw

Method: other: see below
GLP: no data
Test substance: other TS: commercial grade benzyl alcohol

Method: Mice were dosed on full stomachs by intubation. All animals were observed for toxic signs and time of death for 2 weeks. The LD50 was computed by the method of Litchfield & Wilcoxon(1949).

Remark: Toxic signs: depression, death
Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment
Flag: Critical study for SIDS endpoint

12-FEB-2002 (32) (33)
<table>
<thead>
<tr>
<th>Type:</th>
<th>LD50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species:</td>
<td>rat</td>
</tr>
<tr>
<td>Strain:</td>
<td>other: Osborne-Mendel</td>
</tr>
<tr>
<td>Sex:</td>
<td>male/female</td>
</tr>
<tr>
<td>No. of Animals:</td>
<td>10</td>
</tr>
<tr>
<td>Vehicle:</td>
<td>other: neat</td>
</tr>
<tr>
<td>Value:</td>
<td>= 1230 mg/kg bw</td>
</tr>
</tbody>
</table>

Test substance: other TS: commercial grade benzyl alcohol

Method: Groups of 10 young adult Osborne-Mendel rats, evenly divided by sex were fasted for approximately 18 hrs prior to treatment. Animals were dosed by intubation. All animals were observed for toxic signs and time of death for 2 weeks.
The LD50 was computed by the method of Litchfield & Wilcoxon (1949).

Remark: Toxic signs: depression, excitability, coma, death

Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment

12-FEB-2002

Type:          | LD50                        |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Species:</td>
<td>rat</td>
</tr>
<tr>
<td>Value:</td>
<td>= 2080 mg/kg bw</td>
</tr>
</tbody>
</table>

Method: other: no data

GLP: no data

Test substance: other TS: benzyl alcohol, purity not noted

Reliability: (4) not assignable
Secondary literature; Original reference not available

Flag: Critical study for SIDS endpoint

12-FEB-2002

Type:          | LD50                        |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Species:</td>
<td>rabbit</td>
</tr>
<tr>
<td>Value:</td>
<td>= 1040 mg/kg bw</td>
</tr>
</tbody>
</table>

12-FEB-2002

Type: LD50
5. TOXICITY

Species: rat
Value: = 3100 mg/kg bw

16-JAN-2001 (36)

Type: LDLo
Species: rat
Value: ca. 1040 - 3120 mg/kg bw

16-JAN-2001 (37)

Type: LD50
Species: mouse
Value: = 1150 mg/kg bw

16-JAN-2001 (38)

Type: LDLo
Species: mouse
Value: ca. 1040 mg/kg bw

16-JAN-2001 (37)

Type: LDLo
Species: guinea pig
Value: ca. 1040 - 2600 mg/kg bw

16-JAN-2001 (37)

5.1.2 Acute Inhalation Toxicity

Type: LC50
Species: rat
Exposure time: 4 hour(s)
Value: > 4.178 mg/l

Method: other
GLP: no data

Test substance: other TS: benzyl alcohol, purity not noted

Flag: Critical study for SIDS endpoint

12-FEB-2002 (39)

Type: LC50
Species: rat
5. TOXICITY

Exposure time: 4 hour(s)
Value: ca. 8.8 mg/l

Remark: Extrapolation according to Haber's law: LC50 (8h) = 1000 ppm.
19-JAN-2001

Type: LC50
Species: rat
Exposure time: 4 hour(s)
Value: > .9 mg/l

Remark: LC33 (4h) = 200 ppm.
19-JAN-2001

5.1.3 Acute Dermal Toxicity

Type: LD50
Species: rabbit
Value: = 2000 mg/kg bw

Method: other
GLP: no data
Test substance: other TS: benzyl alcohol, purity not noted
Flag: Critical study for SIDS endpoint
29-JAN-2001

### 5.1.4 Acute Toxicity, other Routes

| Test substance: | other TS: benzyl alcohol, purity not noted |
| Flag:           | Critical study for SIDS endpoint |
| 29-JAN-2001     | |

#### LD50

<table>
<thead>
<tr>
<th>Type:</th>
<th>LD50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species:</td>
<td>rat</td>
</tr>
<tr>
<td>Route of admin.:</td>
<td>i.p.</td>
</tr>
<tr>
<td>Value:</td>
<td>&gt; 400 - 800 mg/kg bw</td>
</tr>
</tbody>
</table>

19-JAN-2001

<table>
<thead>
<tr>
<th>Type:</th>
<th>LD50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species:</td>
<td>mouse</td>
</tr>
<tr>
<td>Strain:</td>
<td>CD-1</td>
</tr>
<tr>
<td>Sex:</td>
<td>male</td>
</tr>
<tr>
<td>Route of admin.:</td>
<td>i.p.</td>
</tr>
<tr>
<td>Value:</td>
<td>= 1000 mg/kg bw</td>
</tr>
</tbody>
</table>

Remark: Acute toxicity after 4 h.

14-FEB-2002

<table>
<thead>
<tr>
<th>Type:</th>
<th>LD50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species:</td>
<td>mouse</td>
</tr>
<tr>
<td>Strain:</td>
<td>CD-1</td>
</tr>
<tr>
<td>Sex:</td>
<td>male</td>
</tr>
<tr>
<td>Route of admin.:</td>
<td>i.p.</td>
</tr>
<tr>
<td>Value:</td>
<td>= 650 mg/kg bw</td>
</tr>
</tbody>
</table>

| Test substance:         | other TS: benzyl alcohol, purity not noted |
| Remark:                 | Acute delayed toxicity after 7 d. |
| 14-FEB-2002             | |

<table>
<thead>
<tr>
<th>Type:</th>
<th>LD50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species:</td>
<td>guinea pig</td>
</tr>
<tr>
<td>Route of admin.:</td>
<td>i.p.</td>
</tr>
<tr>
<td>Value:</td>
<td>&gt; 400 - 800 mg/kg bw</td>
</tr>
</tbody>
</table>

19-JAN-2001

<table>
<thead>
<tr>
<th>Type:</th>
<th>LD50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species:</td>
<td>rat</td>
</tr>
<tr>
<td>Route of admin.:</td>
<td>s.c.</td>
</tr>
<tr>
<td>Value:</td>
<td>= 1700 mg/kg bw</td>
</tr>
</tbody>
</table>

| Test substance:         | other TS: benzyl alcohol, purity not noted |
14-FEB-2002

Type: LD50
Species: mouse
Route of admin.: s.c.
Value: = 950 mg/kg bw

19-JAN-2001

Type: other: LDLO
Species: rabbit
Route of admin.: s.c.
Value: ca. 2080 mg/kg bw

19-JAN-2001

Type: LD50
Species: rat
Route of admin.: i.v.
Value: = 314 mg/kg bw

19-JAN-2001

Type: LD50
Species: rat
Route of admin.: i.v.
Value: = 53 mg/kg bw

Remark: Rapid injection

19-JAN-2001

Type: LD50
Species: mouse
Route of admin.: i.v.
Value: = 324 mg/kg bw

19-JAN-2001

Type: LD50
Species: mouse
Route of admin.: i.v.
Value: ca. 105 mg/kg bw

Remark: LD50 value depends on speed of injection

19-JAN-2001

Type: LD50
Species: mouse
Route of admin.: i.v.
Value: = 1460 mg/kg bw
5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Result: not irritating

Method: OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
GLP: no data
Test substance: other TS: benzyl alcohol, purity not noted

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint

14-FEB-2002
Species: rabbit
Concentration: 10 other: mg
Exposure Time: 24 hour(s)
Result: slightly irritating
| Method: | other: see remarks |
| GLP: | no data |
| Test substance: | other TS: benzyl alcohol, purity not noted |
| Flag: | Critical study for SIDS endpoint |
| 14-FEB-2002 | |

| Species: | rabbit |
| Exposure: | Open |
| Exposure Time: | 24 hour(s) |
| Result: | moderately irritating |
| Method: | other: see remarks |
| Remark: | Exposure time: 24 h, clipped skin, 100 mg/animal, open, observation time: 72 h. |
| 14-FEB-2002 | |

| Species: | rabbit |
| Result: | not irritating |
| Method: | other: see remarks |
| Remark: | Exposure time: 24 h, ear, ca. 500 mg/animal, semi-occlusive, observation time: 7 d. |
| 19-JAN-2001 | |

| Species: | guinea pig |
| Result: | moderately irritating |
| Method: | other: see remarks |
| Remark: | Exposure time: 24 h, depilated skin, dose: undiluted material, no other data, open, observation time: no data. |
| 19-JAN-2001 | |

| Species: | guinea pig |
| Result: | slightly irritating |
| Method: | other: see remarks |
| Remark: | Exposure time: 24 h, clipped flank, dose: 8 mg/animal (30 % in unspecified solvent), open, observation time: no data. |
| 19-JAN-2001 | |
Method: other: see remarks

Remark: Exposure time: 24 h, shaved flanks, dose: 26 mg/animal (25 % unspecified solvent), intradermally, observation time: no data. 19-JAN-2001 (55)

Species: guinea pig
Result: not irritating

Method: other: see remarks

Remark: Exposure time: 24 h, clipped skin, 100 mg/animal, open, observation time: 72 h. 19-JAN-2001 (52)

Species: human
Result: irritating

Method: other: Closed Patch Test

Remark: Observation time: 24/48 h, 0.05 % in either ethanol or a cream base produced irritation in 18 of 614 subjects. 19-JAN-2001 (56)

Species: human
Result: irritating

Method: other: Uncovered Patch Test

Remark: 0.5 % in petrolatum induced contact urticaria in 7 of 32 volunteers. 19-JAN-2001 (57)

Species: human
Result: slightly irritating

Method: other: Patch Test

Remark: Exposure time: 48 h, ca. 50 mg/person (30 % in acetone), observation time: up to 120 h. 19-JAN-2001 (52)

Species: other: Male nude mouse
Result: highly irritating

Method: other: see remarks
### 5. TOXICITY

**SUBSTANCE ID:** 100-51-6

**DATE:** 14-FEB.-2002

#### 5.2.2 Eye Irritation

<table>
<thead>
<tr>
<th>Remark</th>
<th>Exposure time: 24 h, 10 % in purified water, occlusive, observation time: no data.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species</td>
<td>other: mini-pig</td>
</tr>
<tr>
<td>Result</td>
<td>not irritating</td>
</tr>
<tr>
<td>Method</td>
<td>other: Patch Test</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Remark</th>
<th>Exposure time: 48 h, clipped skin, 50 mg/animal, observation time: no data.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species</td>
<td>rabbit</td>
</tr>
<tr>
<td>Result</td>
<td>moderately irritating</td>
</tr>
<tr>
<td>Method</td>
<td>OECD Guide-line 405 &quot;Acute Eye Irritation/Corrosion&quot;</td>
</tr>
<tr>
<td>GLP</td>
<td>no data</td>
</tr>
<tr>
<td>Test substance</td>
<td>other TS: benzyl alcohol, purity not noted</td>
</tr>
<tr>
<td>Reliability</td>
<td>(1) valid without restriction</td>
</tr>
<tr>
<td>Flag</td>
<td>Critical study for SIDS endpoint</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Species</th>
<th>rabbit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result</td>
<td>highly irritating</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Method</th>
<th>other: see remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP</td>
<td>no data</td>
</tr>
<tr>
<td>Test substance</td>
<td>other TS: benzyl alcohol, purity not noted</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Remark</th>
<th>Exposure time: 24 h, dose: 750 microg., no other data.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species</td>
<td>rabbit</td>
</tr>
<tr>
<td>Concentration</td>
<td>4 %</td>
</tr>
<tr>
<td>Result</td>
<td>not irritating</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Method</th>
<th>other: see remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test substance</td>
<td>other TS: benzyl alcohol, purity not noted</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Remark</th>
<th>4 % aqueous solution, tested for stability, no other data.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flag</td>
<td>Critical study for SIDS endpoint</td>
</tr>
</tbody>
</table>

| Flag    | Critical study for SIDS endpoint                          |
Species: rabbit
Result: not irritating
Method: other: see remarks
Remark: Exposure time: 4 d, 2 drops of a 0.08 % aqueous solution, no other data.
19-JAN-2001

Species: rabbit
Result: moderately irritating
Method: other: see remarks
Remark: ca. 100 mg/animal, observation time: 7 d.
19-JAN-2001

5.3 Sensitization

Type: Draize Test
Species: guinea pig
Result: not sensitizing
Test substance: other TS: benzyl alcohol, purity not noted
Flag: Critical study for SIDS endpoint
14-FEB-2002

Type: Guinea pig maximization test
Species: guinea pig
Result: not sensitizing
Test substance: other TS: benzyl alcohol, purity not noted
Flag: Critical study for SIDS endpoint
14-FEB-2002

Type: Freund's complete adjuvant test
Species: guinea pig
Result: sensitizing
Test substance: other TS: benzyl alcohol, purity not noted
Flag: Critical study for SIDS endpoint
14-FEB-2002
<table>
<thead>
<tr>
<th>Type:</th>
<th>Open epicutaneous test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species:</td>
<td>guinea pig</td>
</tr>
<tr>
<td>Result:</td>
<td>sensitizing</td>
</tr>
<tr>
<td>Test substance:</td>
<td>other TS: benzyl alcohol, purity not noted</td>
</tr>
<tr>
<td>Flag:</td>
<td>Critical study for SIDS endpoint</td>
</tr>
<tr>
<td>14-FEB-2002</td>
<td>(54)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type:</th>
<th>Patch-Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species:</td>
<td>human</td>
</tr>
<tr>
<td>Result:</td>
<td>sensitizing</td>
</tr>
<tr>
<td>Test substance:</td>
<td>other TS: benzyl alcohol, purity not noted</td>
</tr>
</tbody>
</table>
| Remark:            | Maximum incidence of sensitization: 1 %.
| Flag:              | Critical study for SIDS endpoint       |
| 14-FEB-2002        | (60) (61) (62)                          |

<table>
<thead>
<tr>
<th>Type:</th>
<th>Patch-Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species:</td>
<td>human</td>
</tr>
<tr>
<td>Result:</td>
<td>sensitizing</td>
</tr>
<tr>
<td>Test substance:</td>
<td>other TS: benzyl alcohol, purity not noted</td>
</tr>
<tr>
<td>14-FEB-2002</td>
<td>(63) (64)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type:</th>
<th>Patch-Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species:</td>
<td>human</td>
</tr>
<tr>
<td>Result:</td>
<td>ambiguous</td>
</tr>
<tr>
<td>Test substance:</td>
<td>other TS: benzyl alcohol, purity not noted</td>
</tr>
<tr>
<td>14-FEB-2002</td>
<td>(57)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type:</th>
<th>Patch-Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species:</td>
<td>human</td>
</tr>
<tr>
<td>Test substance:</td>
<td>other TS: benzyl alcohol, purity not noted</td>
</tr>
<tr>
<td>Remark:</td>
<td>Two patients with contact dermatitis were found to be sensitised by benzyl alcohol: 1 per cent in petrolatum</td>
</tr>
<tr>
<td>14-FEB-2002</td>
<td>(65)</td>
</tr>
</tbody>
</table>
Remark: A previously to balsam of Peru sensitised patient reacted on patch testing with benzyl alcohol: 0.5 per cent in olive oil.

14-FEB-2002

Type: other
Species: laboratory animal

Method: other: additional animal studies are reported

Test substance: other TS: benzyl alcohol, purity not noted

14-FEB-2002

Type: other
Species: human

Method: other: additional data
Test substance: other TS: benzyl alcohol, purity not noted

14-FEB-2002

Type: other: Application to shaved skin
Species: guinea pig
Result: not sensitizing

Test substance: other TS: benzyl alcohol, purity not noted

14-FEB-2002

Type: other: Intradermal application
Species: guinea pig
Result: not sensitizing

Test substance: other TS: benzyl alcohol, purity not noted

14-FEB-2002

Type: other: Maximization Test
Species: human
Result: not sensitizing

Test substance: other TS: benzyl alcohol, purity not noted

14-FEB-2002
5.4 Repeated Dose Toxicity

Type: Sub-chronic
Species: rat Sex: male/female
Strain: other: F344/N
Route of administration: gavage
Exposure period: 13 w

Frequency of treatment: daily
Post exposure period: no
Doses: 50, 100, 200, 400, 800 mg/kg/d
Control Group: yes
NOAEL: 400 mg/kg bw

Year: 1981
GLP: yes
Test substance: other TS: technical grade benzyl alcohol (purity =99%)

Method: Groups of 10 rats of each sex were administered 0, 50, 100, 200, 400, or 800 mg/kg benzyl alcohol in corn oil by gavage, 5 days/week for 13 weeks (dose volume = 5 ml/kg). Rats were housed five/cage with feed and water available ad libitum. Animals were observed twice daily; moribund animals were sacrificed. Animal weights were recorded weekly. At the end of the study, survivors were sacrificed. A necropsy was performed on all animals; histologic exams performed on all vehicle controls and animals in the 800 mg/kg group. Brains were examined from rats in the 400 mg/kg group.

Remark: Biochemistry and hematolgy studies were not performed.

Result: 8/10 male rats dosed with 800 mg/kg died during w 7 and 8. Rats of the high dose group exhibited clinical signs indicative of neurotoxicity including staggering, respiratory difficulty, and lethargy. Hemorrhages occurred around the mouth and nose, and there were histologic lesions in the brain, thymus, skeletal muscle, and kidney. There were reductions in relative weight gain in male rats dosed with 800 mg/kg and in female rats dosed with 200 mg/kg or more. No notable changes in bw gain or compound-
related histopathologic lesions were observed in rats from the lower dose groups.
In the 2-y study, however, no notable changes were found on bw or bw gain at 200 or 400 mg/kg/d.

NOAEL = 400 mg/kg/day (based on investigated parameters and taking into account the bw results of 2-y study)

Reliability:
(1) valid without restriction
GLP, Comparable to Guideline study

Flag:
Critical study for SIDS endpoint

14-FEB-2002

Type: Sub-chronic
Species: mouse Sex: male/female
Strain: B6C3F1
Route of administration: gavage
Exposure period: 13 w
Frequency of treatment: daily
Post exposure period: no
Doses: 50, 100, 200, 400, 800 mg/kg/d
Control Group: yes
NOAEL: 200 mg/kg bw

Year: 1981
GLP: yes
Test substance: other TS: technical grade benzyl alcohol (purity =99%)

Groups of 10 mice of each sex were administered 0, 50, 100, 200, 400, or 800 mg/kg benzyl alcohol in corn oil by gavage, 5 days/week for 13 weeks (dose volume = 5 ml/kg).
Mice were housed five/cage with feed and water available ad libitum.
Animals were observed twice daily; moribund animals were sacrificed. Animal weights were recorded weekly. At the end of the study, survivors were sacrificed.
A necropsy was performed on all animals; histologic exams performed on all vehicle controls and animals in the 800 mg/kg group.
Brains were examined from mice in the 400 mg/kg group and from all mice dying before the end of the study.

Remark: Biochemistry and hematolgy studies were not performed.

Result: Staggering after dosing occurred during the first 2 w of the study in mice dosed with 800 mg/kg.
There were reductions in relative weight gain in male mice dosed with 400 or 800 mg/kg, and in female mice dosed with 200 mg/kg or more. No notable changes in bw gain or compound-related histopathologic lesions were observed in mice from the lower dose groups. In the 2-y study, however no notable changes were found on bw or bw gain at 200 mg/kg/d. NOAEL = 200 mg/kg/day (based on investigated parameters and taking into account the bw results of 2-y study)

| Reliability:                  | (1) valid without restriction GLP, Comparable to Guideline study |
| Flag:                        | Critical study for SIDS endpoint |

**Type:** Chronic  
**Species:** rat  
**Sex:** male/female  
**Strain:** Fischer 344  
**Route of administration:** gavage  
**Exposure period:** 103 weeks  
**Frequency of treatment:** 5 d/w  
**Post exposure period:** no  
**Doses:** 200, 400 mg/kg/d  
**Control Group:** yes  
**NOAEL:** 400 mg/kg bw  

<table>
<thead>
<tr>
<th>Year:</th>
<th>1981</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP:</td>
<td>yes</td>
</tr>
</tbody>
</table>

**Test substance:** other TS: technical grade benzyl alcohol (purity = 99%)

**Method:** Groups of 50 rats of each sex were administered 0, 200, or 400 mg/kg benzyl alcohol in corn oil by gavage, 5 days/week for 103 weeks. The rats were placed on the study at 8-9 weeks of age. All animals were observed twice daily and clinical signs recorded at least once per month. Body weights were recorded once per week for the first 12 weeks, then once a month thereafter. Animals found moribund and those surviving to the end of the study were humanely killed. Necropsy was performed on all animals; histological exams performed on all female rats and vehicle controls, and high dose rats that died before month 22, and male rats with gross lesions.
Remark: Biochemistry and hematolgy studies were not performed.

Result: No effect on bw gain or mortality was observed. No apparent compound-related non-neoplastic responses were observed.

Reliability: (1) valid without restriction

GLP, Comparable to Guideline study

Flag: Critical study for SIDS endpoint

14-FEB-2002

Type: Chronic

Species: mouse

Sex: male/female

Strain: B6C3F1

Route of administration: gavage

Exposure period: 103 w

Frequency of treatment: 5 d/w

Post exposure period: no

Doses: 100, 200 mg/kg/d

Control Group: yes

NOAEL: 200 mg/kg bw

Method: other: OECD 451

Year: 1981

GLP: yes

Test substance: other TS: technical grade benzy l alcohol (purity = 99%)

Method: Benzyl alcohol (purity, 99%) was given to groups of 50 B6C3F1 mice of each sex, eight to nine weeks of age, at a dose of 0, 100, or 200 mg/kg bw per day in corn oil by gavage on five days a week for 103 weeks. The doses were selected on the basis of those found to induce neurotoxic effects (lethargy and staggering) in short-term studies. The mice were observed twice daily, and their body weights were recorded weekly for the first 12 weeks and once a month thereafter. Gross necropsy was performed on all animals, and 50 tissues and organs, including brain, liver, kidney, and stomach, from all vehicle controls, animals at the high dose, and animals at the other doses that died before 22 months or had gross lesions were examined histologically.

Remark: Biochemistry and hematolgy studies were not performed.
Result: The mean body weights of treated and control mice were comparable throughout the study. The survival of control females was significantly lower than that of animals at the high dose after week 74, but no other differences in survival were seen: 68% of control, 66% of low-dose, and 70% of high-dose males; and 50% of control, 62% of low-dose, and 72% of high-dose females. No significant treatment-related effects were noted at gross necropsy or histopathological examination. No increase was seen in the incidence of hepatocellular or forestomach neoplasia.

Reliability: (1) valid without restriction
GLP guideline study

Flag: Critical study for SIDS endpoint

14-FEB-2002

Type: Sub-acute
Species: mouse Sex: male/female
Strain: B6C3F1
Route of administration: oral feed
Exposure period: 10 d
Frequency of treatment: continuously in diet
Post exposure period: no
Doses: 2.08; 2.5 or 3 % in diet (approx. 3012, 3750 or 4500 mg/kg/d)
Control Group: yes
NOAEL: 3750 mg/kg bw
LOAEL: 4500 mg/kg bw

GLP: no data
Test substance: other TS: sodium benzoate (specific grade) purchased from Wako

Method: Sodium benzoate, mixed with the powdered diet, was fed to groups of 12 rats (6 males, 6 females) for 10 days. Animals were observed for body weight gain and clinical signs 5 day/week.

At the end of the experiment, surviving animals were necropsied. Organ weights, clinical chemistry and histological examinations were performed.

Remark: Benzyl alcohol will rapidly be metabolized to benzaldehyde and so to benzoic acid (sodium benzoate is the salt of benzoic acid). Therefore the data of sodium benzoate can also be supportive in the repeat dose endpoint.
the mean compound consumption was calculated according to Lehman, Food Drug Off. Q. Bull. 18, 66 (1954)

Result: All mice in the 3.0 % group showed increased sensitivity to stimuli and 1/5 male and 2/5 females showed convulsions; 2/5 females died; liver weights of males and females and kidney weights of females were dose-dependently increased; histopathologic examination showed enlarged hepatocytes, single cell necrosis and vacuolation of hepatocytes in all livers from males; no histopathologic changes of the kidney were described; serum cholesterol, lipid levels and cholinesterase were increased in males.

Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment

Flag: Critical study for SIDS endpoint

14-FEB-2002

Type: Sub-acute
Species: rat Sex: male/female
Strain: other: F344/N
Route of administration: gavage
Exposure period: 16 d
Frequency of treatment: daily
Post exposure period: no
Doses: 125, 250, 500, 1000, 2000 mg/kg/d
Control Group: no data specified

Test substance: other TS: technical grade benzyl alcohol (purity = 99%)

Remark: No. of animals: 5/sex/dose.

Result: All male and female rats dosed with 2000 mg/kg died. 2/5 male and 3/5 female rats dosed with 1000 mg/kg died. Rats in the 2 highest dose groups were lethargic after dosing. Other toxic responses in these 2 dose groups included blood around the mouth and nose, subcutaneous hemorrhages, and blood in the urinary and gastrointestinal tract. Animals administered lower doses had no compound-related histologic lesions.

14-FEB-2002

Type: Sub-acute
Species: mouse Sex: male/female
Strain: B6C3F1
Route of administration: gavage
Exposure period: 16 d
Frequency of treatment: daily
Post exposure period: no data specified
Doses: 125, 250, 500, 1000, 2000 mg/kg/d
Control Group: no data specified

Test substance: other TS: technical grade benzyl alcohol (purity = 99%)

Remark: No. of animals: 5/sex/dose.
Result: All male and female mice dosed with 2000 mg/kg died. 1/5 male and 2/5 female mice dosed with 1000 mg/kg died. Mice of each sex in the 2 highest dose groups were lethargic after dosing. Other toxic responses in these 2 dose groups included blood around the mouth and nose, subcutaneous hemorrhages, and blood in the urinary and gastrointestinal tract and in the urinary bladder. Animals administered lower doses had no compound-related histologic lesions.

Species: rat
Strain: no data
Route of administration: inhalation
Exposure period: no data
Frequency of treatment: 4 h/d
Post exposure period: no data specified
Doses: 216-270 ppm
Control Group: no data specified

NOAEL: 270 ppm

Test substance: other TS: benzyl alcohol, purity not noted

Remark: No. of animals: 6.
Result: Subacute exposure to male rats for 4 h periods produced no clinical or pathologic signs of toxicity.

Species: rat
Strain: no data
Route of administration: gavage
Exposure period: 3 w
Frequency of treatment: 6 d/w
Post exposure period: no
Doses: 50, 150, 500 mg/kg
Control Group: yes

Test substance: other TS: benzyl alcohol, purity not noted

Remark: No. of animals: 5/sex/dose.

Result: The compound was administered in propylene glycol. Increases in weight were the same in all groups, and there were no pathological effects on blood or organs.

Species: mouse

Strain: no data

Route of administration: gavage

Exposure period: 8 d

Frequency of treatment: daily

Doses: 325, 645, 1300, 2595 mg/kg/d

Control Group: no data specified

Remark: No. of animals: no data.

Result: Decreased muscle coordination, a "hunched" appearance, depression, and fur changes were reported in mice given 645 mg/kg but not in those receiving 325 mg/kg or below. At 1300 mg/kg, animals additionally suffered breathing difficulties, discharge from the eyes, and various CNS effects, and death occurred on day 1 in all mice given 2595 mg/kg.

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test

System of testing: S. typhimurium TA 98, TA 100, TA 1535, TA 1537

Concentration: up to 6666 ug/ml

Cytotoxic Concentration: >/= 3333 ug/plate

Metabolic activation: with and without

Result: negative

Method: other: similar to OECD Guide-line 471; protocol according to Haworth, et.al. (1983)

Year: 1983
### OECD SIDS BENZYL ALCOHOL

#### 5. TOXICITY

**DATE:** 14-FEB.-2002  
**SUBSTANCE ID:** 100-51-6

<table>
<thead>
<tr>
<th>GLP:</th>
<th>yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test substance:</td>
<td>other TS: technical grade benzyl alcohol (purity = 99%)</td>
</tr>
<tr>
<td>Method:</td>
<td>Separate trials were done using metabolic activation with Aroclor 1254-induced S9 from male Syrian hamster liver and male Sprague-Dawley rat liver.</td>
</tr>
<tr>
<td>Reliability:</td>
<td>(1) valid without restriction GLP guideline study</td>
</tr>
<tr>
<td>Flag:</td>
<td>Critical study for SIDS endpoint 14-FEB-2002</td>
</tr>
</tbody>
</table>

| Type:                  | other: Point-mutation |
| System of testing:        | E. coli |
| Metabolic activation:     | with and without |
| Result:                | negative |

| Test substance: | other TS: benzyl alcohol, purity not noted |
| Flag:                  | Critical study for SIDS endpoint 14-FEB-2002 |

| Type:                  | Cytogenetic assay |
| System of testing:        | CHO cells |
| Concentration:           | up to 5000 ug/ml |
| Cytotoxic Concentration: | none noted |
| Metabolic activation:     | without |
| Result:                | negative |

| Year:                    | 1989 |
| GLP:                     | yes |
| Test substance: | other TS: technical grade benzyl alcohol (purity = 99%) |

| Result:                  | No significant increase in chromosome aberrations was observed after exposure to benzyl alcohol in the absence of S9. |
| Reliability:           | (1) valid without restriction GLP guideline study |
| Flag:                  | Critical study for SIDS endpoint 14-FEB-2002 |

| Type:                  | Cytogenetic assay |
| System of testing:        | CHO cells |
| Concentration:           | up to 5000 ug/ml |
| Cytotoxic Concentration: | none noted |
Metabolic activation: with
Result: positive

Method: other: similar to OECD 473; according to
(1985)
Year: 1989
GLP: no data
Test substance: other TS: technical grade benzyl alcohol
(purity = 99%)
Result: A significant increase in chromosome
aberrations was observed after exposure to
benzyl alcohol in the presence of S9.
Reliability: (1) valid without restriction
Similar to Guideline study
Flag: Critical study for SIDS endpoint
14-FEB-2002

Type: Cytogenetic assay
System of testing: CHO cells
Concentration: 16 - 5000 ug/ml
Cytotoxic Concentration: none noted
Metabolic activation: with and without
Result: equivocal

Method: other: similar to guideline study
Year: 1989
GLP: yes
Test substance: other TS: technical grade benzyl alcohol
(purity = 99%)
Result: Sister chromatid exchange (SCE) an equivocal
response with and without metabolic
activation.
Reliability: (1) valid without restriction
Similar to Guideline study
Flag: Critical study for SIDS endpoint
14-FEB-2002

Type: Bacillus subtilis recombination assay
System of testing: B. subtilis M 45, H 17
Result: positive
Remark: limited data
Flag: Critical study for SIDS endpoint
12-FEB-2002
Type: Mouse lymphoma assay
System of testing: L5178Y cells
Concentration: up to 5000 ug/ml
Cytotoxic Concentration: >/= 3500 ug/ml
Metabolic activation: with and without

Method: other: similar to OECD 476; according to Myhr G. et al., Prog. Mutat. Res. 5, 555-586 (1985)

GLP: yes
Test substance: other TS: technical grade benzyl alcohol (purity = 99%)

Result: Benzyl alcohol induced an increase in trifluorothymidine-resistant cells in the absence, but not in the presence of, S9 activation. The effect was associated with toxicity.

Reliability: (1) valid without restriction
GLP guideline study
Flag: Critical study for SIDS endpoint

14-FEB-2002

Type: other: transformation assay
System of testing: BALB/c-3T3 cells
Concentration: 5 to 20 mM
Cytotoxic Concentration: The cytotoxic response (millimolar LD50) = 17.9.
Metabolic activation: without
Result: positive


Year: 1993
GLP: no data
Test substance: other TS: Supplied by Radian Corp. (Houston, TX); purity not noted

Method: The A31-1-13 clone of BALB/c-3T3 cells was used to evaluated the transforming potential of numerous chemicals including benzyl alcohol. Each transformation assay contained a standard clonal survival assay, a co-culture clonal survival assay, and a transformation assay. For each test, chemical-induced transformation was detected using 18-20 vessels per dose seeded with 3.2x10(e4) cells/vessel.
Each dose was applied to cell cultures for 48 hrs. days 2-4, using standard procedures. A total of 3 to 6 test chemicals were included in each transformation experiment and each was tested at four treatment doses in at least two independent trials. The doses covered a range of cytotoxicity responses of approximately 10-100% relative cloning efficiency. Each test chemical in each experiment was evaluated as sufficiently positive (statistically significant at two or more doses), limited activity (statistically significant at one dose at 99% conf. or two at 95% conf.), sufficiently negative (no statistically significant responses), or limited negative (no cytotoxicity or abnormal positive control). The number of type I-III transformed foci were identified microscopically considering their various different phenotypic properties.

REFERENCES:

Remark: Benzyl alcohol (BA) was tested as a coded sample. The author noted that BA can be oxidized by air and may have been altered during the treatment period. They state that BA was noncytotoxic to BALB/c-3T3 cells and that the statistical sensitivities for trial 1 and 2 were 2 and 38/110, respectively. BA was evaluated as active in this assay with actual and estimated rank t-statistics both 1.95.

Result: For the purpose of this study benzyl alcohol (BA) was grouped as a noncytotoxic, nonmutagenic, noncarcinogenic chemical. Notations for BA were: reacts with acid, air, acid chlorides and is temperature sensitive. BA's potential to be oxidized by air was noted as a potential confounding factor. It had limited activity in the first test and was sufficiently positive in the second. It, therefore, was given the overall evaluation of active in the transformation assay. The cytotoxic response (millimolar LD50) 17.9. In trial 1 BA concentrations ranged 5 to 20mM
with an increase in transformation only noted at the 10mM concentration (85% coculture clonal survival).
RESULT: 7.36 foci/vessel - rank order 2 (p</=0.001) - limited active mean t-statistic 2.11
In trial 2 BA concentrations ranged 5 to 20mM with an increase in transformation noted at the 10mM concentration (95% coculture clonal survival; p</=0.001) and 15mM concentration (84% coculture clonal survival; p</=0.01 to 0.05).

Fewer foci were observed in the second trial.
RESULT: 0.609 foci/vessel - rank order 38 - sufficient positive mean t-statistic 1.79
The positive control B(a)P performed well.
The number of foci/vessel for the neg control was 7.36 and 0.609 in Trials 1 and 2, respectively.

Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment

Flag: Critical study for SIDS endpoint

14-FEB-2002 (106)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100, TA 1535, TA 1537
Metabolic activation: with and without
Result: negative

Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment

14-FEB-2002 (107)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Metabolic activation: without
Result: negative

16-JAN-2001 (108)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100, TA 1535, TA 1537
<table>
<thead>
<tr>
<th>Event Date</th>
<th>Type</th>
<th>System of testing</th>
<th>Metabolic activation</th>
<th>Result</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>16-JAN-2001</td>
<td>Metabolic activation:</td>
<td>with and without</td>
<td></td>
<td>negative</td>
<td>Rat and hamster liver S-9 mix. (109) (104)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metabolic activation:</td>
<td>without</td>
<td>negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metabolic activation:</td>
<td>with</td>
<td>negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metabolic activation:</td>
<td>no data</td>
<td>negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metabolic activation:</td>
<td>no data</td>
<td>negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metabolic activation:</td>
<td>no data</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Metabolic activation:</td>
<td>no data</td>
<td>negative</td>
<td></td>
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<tr>
<td>16-JAN-2001</td>
<td>Type:</td>
<td>Ames test</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>System of testing:</td>
<td>S. typhimurium TA 98, TA 100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16-JAN-2001</td>
<td>Type:</td>
<td>Ames test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>System of testing:</td>
<td>S. typhimurium TA 92, TA 94, TA 98, TA 100, TA 1535, TA 1537</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16-JAN-2001</td>
<td>Type:</td>
<td>Ames test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>System of testing:</td>
<td>S. typhimurium TA 98, TA 1535</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16-JAN-2001</td>
<td>Type:</td>
<td>Ames test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>System of testing:</td>
<td>E. coli WP2 uvrA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16-JAN-2001</td>
<td>Type:</td>
<td>other: Point-mutation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>System of testing:</td>
<td>Bacillus subtilis recombination assay</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>16-JAN-2001</td>
<td>Type:</td>
<td>other: Point-mutation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>System of testing:</td>
<td>E. coli WP2 uvrA</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>16-JAN-2001</td>
<td>Type:</td>
<td>Cytogenetic assay</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### 5. Toxicity

**OECD SIDS**

**BENZYL ALCOHOL**

DATE: 14-FEB.-2002  
SUBSTANCE ID: 100-51-6

<table>
<thead>
<tr>
<th>System of testing</th>
<th>Result</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHL cells</td>
<td>negative</td>
<td>16-JAN-2001</td>
</tr>
</tbody>
</table>

**Type:** Mouse lymphoma assay  
**System of testing:** L5178Y tk+/tk- cells  
**Metabolic activation:** with and without  
**Result:** ambiguous  
16-JAN-2001  
(111) (114)

**Type:** Ames test  
**System of testing:** S. typhimurium TA 100  
**Metabolic activation:** without  
**Result:** negative  
16-JAN-2001  
(115) (116) (104)

**Type:** Sister chromatid exchange assay  
**System of testing:** CHO cells  
**Metabolic activation:** with and without  
**Result:** positive  
16-JAN-2001  
(117)

**Type:** other: DNA Double Strand Breaks  
**System of testing:** rat hepatocytes  
**Concentration:** 0, 1, 3, 10 mM in 1 % DMSO  
**Metabolic activation:** no data  
**Result:** ambiguous  
**Method:** other: in vitro alkaline elution assay  
Year: 1994  
GLP: no data  
Test substance: no data  
**Remark:** Positive only in the highest dose.  
16-JAN-2001  
(118) (119)

---

### 5.6 Genetic Toxicity 'in Vivo'

**Type:** Micronucleus assay  
**Species:** mouse  
**Sex:** male  
**Strain:** other: ddY strain, obtained from Shizuoka Agricultural Cooperative Association for Laboratory Animals, Shizuoka, Japan
Route of admin.: i.p.  
Exposure period: 24 h  
Doses: 50, 100, 200 mg/kg  
Result: negative  

Method: OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"  
Year: 1983  
GLP: no data  
Test substance: other TS: benzyl alcohol, purity not noted  

Remark: No. of animals: 6/dose.  
Result: There was no indication of micronucleus induction at any dose tested.  

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>MNPCE (%)</th>
<th>PCE (%)</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.23 +/-0.18</td>
<td>48.8 +/-6.2</td>
<td>0/6</td>
</tr>
<tr>
<td>50</td>
<td>0.23 +/-0.15</td>
<td>55.5 +/-4.0</td>
<td>0/6</td>
</tr>
<tr>
<td>100</td>
<td>0.27 +/-0.12</td>
<td>51.8 +/-9.5</td>
<td>0/6</td>
</tr>
<tr>
<td>200</td>
<td>0.12 +/-0.10</td>
<td>48.7 +/-5.2</td>
<td>0/6</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>0.20 +/-0.14</td>
<td>63.1 +/-4.1</td>
<td>0/6</td>
</tr>
<tr>
<td>2.0</td>
<td>2.63 +/-0.32*</td>
<td>43.8 +/-1.1</td>
<td>0/6</td>
</tr>
</tbody>
</table>

MNPCE = Micronucleated polychromatic erythrocyte  
PCE = polychromatic erythrocyte  
* = (P < 0.01)  

Reliability: (1) valid without restriction  
Guideline study  
Flag: Critical study for SIDS endpoint  

Type: other: replicative DNA synthesis  
Species: rat  
Strain: Fischer 344  
Route of admin.: gavage  
Exposure period: once  
Doses: 0, 300, 600 mg/kg bw  
Result: negative  

Year: 1994  
GLP: no data  
Test substance: no data
Result: Benzyl alcohol did not induce replicative DNA synthesis in rat hepatocytes following oral treatment.

Flag: Critical study for SIDS endpoint

14-FEB-2002

Type: other: replicative DNA synthesis
Species: mouse Sex: male
Strain: B6C3F1
Route of admin.: gavage
Exposure period: once
Doses: 0, 400, 800 mg/kg bw
Result: negative

Year: 1995
GLP: no data
Test substance: no data

Result: Benzyl alcohol did not induce replicative DNA synthesis in mice hepatocytes following oral treatment.

Flag: Critical study for SIDS endpoint

23-MAR-2001

Type: Drosophila SLRL test
Species: Drosophila melanogaster Sex: male
Strain: other: Canton S
Route of admin.: drinking water
Exposure period: 72 hrs
Doses: 0, 5000 (unit not given) in 5 % succrose solution

Method: other
Year: 1994
GLP: no data
Test substance: other TS: purity: 99.8 %

Result: no evidence for mutagenicity

19-JAN-2001

Type: Drosophila SLRL test
Species: Drosophila melanogaster Sex: male
Strain: other: Canton S
Route of admin.: i.p.
Exposure period: once
Doses: 0, 8000 (unit not given)
5. TOXICITY

Method: other
Year: 1994
GLP: no data
Test substance: other TS: purity 99.8 %
Result: no evidence for mutagenicity
19-JAN-2001 (123)

5.7 Carcinogenicity

Species: rat
Sex: male/female
Strain: other: F344/N
Route of administration: gavage
Exposure period: 103 w
Frequency of treatment: 5 d/w
Post exposure period: no
Doses: 200, 400 mg/kg/d
Result: negative
Control Group: yes

Method: OECD Guide-line 451 "Carcinogenicity Studies"
Year: 1981
GLP: yes
Test substance: other TS: technical grade benzyl alcohol (purity =99%)

Method: Benzyl alcohol was administered in corn oil by gavage to groups of 50 Fischer 344/N rats of each sex at a dose of 0, 200, or 400 mg/kg bw per day on five days a week for 103 weeks. The rats were observed twice daily, and body weights were recorded weekly for the first 12 weeks and once a month thereafter. Gross necropsy was performed on all animals; and 49 tissues and organs, including brain, kidney, pancreas, and skeletal muscle, from all female rats and from male rats in the vehicle control and high-dose groups and those in the other groups that died before 22 months or which had gross lesions were examined histologically.

Remark: Biochemistry and hematolgy studies were not performed.

Result: The mean body weights of treated and control animals were comparable throughout the study. No compound-related clinical signs were observed, although a sialodacryoadenitis viral infection
was widespread among the study animals in the third month. The survival of treated females was significantly lower than that of vehicle controls: 70% of controls, 34% of low-dose females, and 34% of high-dose females; this was due to a much higher incidence of accidental deaths related to the gavage process.

Survival among the male rats was comparable in all groups: 56% of controls, 54% at the low dose, and 48% at the high dose.

Cataracts and retinal atrophy were observed at increased incidences in rats at the high dose. The authors attributed this effect to the proximity of this group of animals to fluorescent light for most of the study. An increased incidence of hyperplasia of the forestomach epithelium was seen (not statistically significant) in male rats: control, 0/48; low dose, 0/19; high dose, 4/50.

Haemorrhage and foreign material in the respiratory tract seen in treated rats that died before the end of the study were suggested by the authors to have been the result of either direct deposition of material into the lung during gavage 'accidents' or the anaesthetic properties of benzyl alcohol resulting in reflux of gavage material and aspiration into the lungs. No pancreatic acinar-cell adenomas were reported, and no other effects of treatment were seen at gross necropsy or histopathological examination.

Reliability: (1) valid without restriction

Flag: GLP guideline study

Critical study for SIDS endpoint

Species: mouse
Strain: B6C3F1
Route of administration: gavage
Exposure period: 103 w
Frequency of treatment: 5 d/w
Post exposure period: no
Doses: 100, 200 mg/kg/d
Result: negative
Control Group: yes
### Method:

OECD Guide-line 451 "Carcinogenicity Studies"

### Year:

1981

### GLP:

yes

### Test substance:

other TS: technical grade benzyl alcohol (purity =99%)

### Method:

Benzyl alcohol (purity, 99%) was given to groups of 50 B6C3F1 mice of each sex, eight to nine weeks of age, at a dose of 0, 100, or 200 mg/kg bw per day in corn oil by gavage on five days a week for 103 weeks. The doses were selected on the basis of those found to induce neurotoxic effects (lethargy and staggering) in short-term studies. The mice were observed twice daily, and their body weights were recorded weekly for the first 12 weeks and once a month thereafter. Gross necropsy was performed on all animals, and 50 tissues and organs, including brain, liver, kidney, and stomach, from all vehicle controls, animals at the high dose, and animals at the other doses that died before 22 months or had gross lesions were examined histologically.

### Remark:

Biochemistry and hematolgy studies were not performed.

### Result:

The mean body weights of treated and control mice were comparable throughout the study. The survival of control females was significantly lower than that of animals at the high dose after week 74, but no other differences in survival were seen: 68% of control, 66% of low-dose, and 70% of high-dose males; and 50% of control, 62% of low-dose, and 72% of high-dose females. No significant treatment-related effects were noted at gross necropsy or histopathological examination. No increase was seen in the incidence of hepatocellular or forestomach neoplasia.

### Reliability:

(1) valid without restriction

### Flag:

GLP guideline study

Critical study for SIDS endpoint

### Species:

mouse

### Sex:

male

### Strain:

B6C3F1

### Route of administration:

i.p.

### Exposure period:

22 d
5. Toxicity

**Substance ID:** 100-51-6

**Frequency of treatment:** once on day 1, 8, 15, 22

**Post exposure period:** up to 1 a

**Doses:** 3.75 umol (total dose) in trioctanoin

**Control Group:** yes

**Remark:** 35 mice received injections prior to weaning. The mice were weaned at 4 weeks of age. All surviving mice were killed at 12 months for enumeration of hepatomas.

**Result:** Benzyl alcohol had no detectable activity for the initiation of hepatic tumors on administration to male mice prior to weaning.

*19-JAN-2001* (125)

### 5.8.1 Toxicity to Fertility

**Type:** other: 2 year gavage study

**Species:** rat

**Sex:** male/female

**Strain:** Fischer 344

**Route of administration:** gavage

**Exposure Period:** 103 weeks

**Frequency of treatment:** 5d/w

**Duration of test:** 103 weeks

**Doses:** 200, 400 mg/kg/d

**Control Group:** yes

**NOAEL Parental:** 400 ml/kg bw

**Method:** other: OECD 451

**Year:** 1981

**GLP:** yes

**Test substance:** other TS: technical grade benzyl alcohol (purity = 99%)

**Remark:** Benzyl alcohol was administered in corn oil.

**Result:** No evidence of compound related effects in the testes or ovaries of treated rats. Changes noted in general in the reproductive system were inconsequential.

**Reliability:** (1) valid without restriction

**Flag:** Critical study for SIDS endpoint

*14-FEB-2002* (98)
Exposure Period: 103 weeks
Frequency of treatment: 5 d/w
Duration of test: 103 weeks
Doses: 100, 200 mg/kg/d
Control Group: yes
NOAEL Parental: 200 ml/kg bw

Method:
  other: OECD 451
GLP: yes
Test substance:
  other TS: technical grade benzyl alcohol (purity =99%)

Remark: Benzyl alcohol was administered in corn oil.
Result: No evidence of compound related effects in the testes or ovaries of treated mice.
Changes noted in general in the reproductive system were inconsequential.

Reliability:
  (1) valid without restriction
  GLP guideline study
Flag:
  Critical study for SIDS endpoint
14-FEB-2002 (98)

Type:
  other: 4 generation study
Species: rat
Strain: no data
Route of administration: oral feed
Exposure Period:
  generation 1 and 2: lifelong;
  generation 3: 16 weeks;
  generation 4: until breeding
Frequency of treatment: continuously in diet
Doses:
  0.5 or 1 % in diet (approx. 375 or 750 mg/kg/day)
Control Group: yes
NOAEL Parental: >= 750 ml/kg bw
NOAEL F1 Offspring: >= 750 ml/kg bw
NOAEL F2 Offspring: >= 750 ml/kg bw

Test substance:
  other TS: benzoic acid

Remark: See IUCLID data set on benzoic acid (CAS# 65-85-0). Benzyl alcohol will rapidly be metabolized to benzaldehyde and so to benzoic acid. Therefore the data of benzoic acid can also be supportive to state that benzyl alcohol is not a reproductive (fertility and developmental) toxicant.
Result: No effects on fertility, lactation, growth and survival or the incidence of foetal malformations were observed in a 4 generation...
reproduction study with rats (20 m and 20 f) exposed to 0.5% and 1.0% benzoic acid in the diet.

Flag: Critical study for SIDS endpoint
06-JUN-2001

Type: Fertility
Species: rat
Sex: female
Route of administration: oral unspecified
Exposure Period: 32 weeks
Frequency of treatment: every second day
Premating Exposure Period female: 75 days
Duration of test: 32 weeks
Doses: 5 mg/kg
NOAEL Parental: 5 mg/kg bw

Test substance: other TS: benzaldehyde

Remark: Benzyl alcohol will rapidly be metabolized to benzaldehyde and so to benzoic acid. Therefore the data of benzaldehyde can also be supportive to state that benzyl alcohol is not a reproductive (fertility and developmental) toxin.

Result: No treatment related effects noted.
Flag: Critical study for SIDS endpoint
16-JAN-2001

5.8.2 Developmental Toxicity/Teratogenicity

Species: mouse
Sex: female
Strain: CD-1
Route of administration: gavage
Exposure period: day 7-14 of gestation
Frequency of treatment: daily
Duration of test: until 3 days after pregnancy
Doses: 750 mg/kg bw/day
Control Group: yes
LOAEL Maternal Toxicity: 750 mg/kg bw
LOAEL Fetotoxicity: 750 mg/kg bw

GLP: no data
Test substance: other TS: benzyl alcohol, purity not noted
Method: Benzyl alcohol dissolved in distilled water was administered by gavage at a dose of 750 mg/kg bw per day to 50 mice on days 7-14 of
gestation; evidence of copulation was considered the first day of gestation. A control group of 50 animals received distilled water only. All animals were allowed to deliver their litters and nurse their pups for three days, at which time necropsies were performed. Maternal body-weight gain and mortality, mating, gestation, numbers of live and dead pups per litter, total litter weight on days 1 and 2 post partum, litter weight change between days 1 and 3 post partum, and pup survival on days 1 and 3 post partum were recorded.

Result: During the treatment period, 18 deaths were reported, all of which were attributed to treatment; a further death was reported on day 15 of gestation, the day after treatment was terminated. Clinical signs of toxicity, including hunched posture, tremors, inactivity, prostration, hypothermia, ataxia, dyspnoea, swollen or cyanotic abdomen, and piloerection, were reported in up to 20 mice during treatment. Piloerection was also reported in some animals up to day 3 post partum, but no other clinical signs were seen after the period of administration.

No differences were observed in the mating or gestation indices, the total number of resorptions, the mean length of gestation, or the number of live pups per litter between treated and control groups. Maternal body weight, measured on days 4 and 7 of gestation, was not significantly different from control values; however, statistically significant reductions were reported on day 18 of gestation ($P < 0.001$) and on day 3 post partum ($P < 0.05$). Maternal body-weight gain during days 7–18 of gestation was significantly lower than that of controls ($P < 0.001$). Significant reductions in pup body weight were reported, including a lower mean pup weight per litter on days 1 ($P < 0.01$) and 3 post partum ($P < 0.001$), a mean litter weight change between day 1 and day 3 post partum ($P < 0.05$), and a mean pup weight change between days 1 and 3 post partum ($P < 0.001$). No differences in pup survival
were observed by day 3 post partum.

Conclusion: The authors concluded that benzyl alcohol may be a reproductive hazard, apparently on the basis of the reductions in pup body weights, an effect that was observed in conjunction with maternal toxicity evidenced by increased mortality, reduced body weights, and clinical toxicity during the period of administration. As effects were seen on the dams and fetuses at the only dose used in this study, there was no NOAEL. The LOAEL was 750 mg/kg bw per day.

Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment

Flag: Critical study for SIDS endpoint

Species: mouse
Sex: female
Route of administration: gavage
Exposure period: days 6-15 of gestation
Frequency of treatment: daily
Duration of test: until day 3 post partum
Doses: 550 mg/kg bw
Control Group: yes, concurrent vehicle
NOAEL Maternal Toxicity: 550 mg/kg bw
NOAEL Teratogenicity: 550 mg/kg bw

GLP: no data
Test substance: other TS: benzyl alcohol; purity not noted

Method: 50 female mice were given benzyl alcohol at 550 mg/kg bw per day by gavage on days 6-15 of gestation; a further 50 mice received the corn oil vehicle. All dams were allowed to deliver naturally, and pups and dams were observed until day 3 post partum, when the experiment was terminated. Body weight, clinical observations, and mortality were recorded daily throughout treatment and up to day 3 post partum.

Remark: abstract only
Result: Mortality was not significantly increased in animals given benzyl alcohol over that in the control group. One treated mouse showing languid behaviour, laboured breathing, and a rough coat died, but no other deaths or clinical signs were
reported. Maternal body weight and body-weight gain during treatment and up to day 3 post partum were virtually identical for treated and control animals. All other parameters examined, including gestation index, average number of live pups per litter, and postnatal survival and pup body weight on days 0 and 3 post partum, were not significantly different from the control values.

Conclusion:
The authors concluded that, at the predicted LD10, benzyl alcohol had no significant effects on the development of CD-1 mice. The NOAEL was 550 mg/kg bw per day.

Reliability:
(2) valid with restrictions
Flag:
Critical study for SIDS endpoint

Species: rat
Sex: male/female
Strain: no data
Route of administration: oral feed
Exposure period:
generation 1 and 2: lifelong;
generation 3: 16 weeks;
generation 4: until breeding
Frequency of treatment: continuously in diet
Duration of test: 4 generations
Doses: 0.5 or 1% in diet (approx. 375 or 750 mg/kg/day)
Control Group: yes
NOAEL Maternal Toxicity: 750 mg/kg bw
NOAEL Teratogenicity: 750 mg/kg bw

Method: other
GLP: no data
Test substance: other TS: benzoic acid

Remark:
See IUCLID data set on benzoic acid (CAS# 65-85-0). Benzyl alcohol will rapidly be metabolized to benzaldehyde and so to benzoic acid. Therefore the data of benzoic acid can also be supportive to state that benzyl alcohol is not a reproductive (fertility and development) toxicant.

Result:
No effects on the dams or on the growth and development of the offspring were seen when groups of 10 rats were fed diets containing up to 1% benzoic acid during pregnancy and lactation.
### 5. TOXICITY

**SUBSTANCE ID:** 100-51-6  
**DATE:** 14-FEB.-2002

<table>
<thead>
<tr>
<th>Flag:</th>
<th>Critical study for SIDS endpoint</th>
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<tbody>
<tr>
<td>06-JUN-2001</td>
<td></td>
<td>(126)</td>
</tr>
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</table>

**Species:** other: chicken embryo  
**Sex:** other  
**Route of administration:** other  
**Exposure period:** 11 to 18 d

**Frequency of treatment:** 1 injection before incubation or on different d after incubation  
**Doses:** 0.01–0.02 ml/egg = 10–20 mg/egg  
**Control Group:** yes

**Remark:** Injections of benzyl alcohol into the yolks of fertile eggs, either before incubation, or from the 1. through the 7. d after the beginning of their incubation give rise to meningoceles, limb deformities, beak defects such as, arched upper beaks, localized blebs and generalized edema.  
30-JAN-2001  
(134)

### 5.8.3 Toxicity to Reproduction, Other Studies

### 5.9 Specific Investigations

### 5.10 Exposure Experience

**Remark:** Benzyl alcohol poisoning can cause the gasping syndrome in neonates. The infants had a typical course of gradual neurologic deterioration, severe metabolic acidosis, the striking onset of gasping respirations, thrombocytopenia, hepatic and renal failure, hypotension, cardiovascular collapse and death. In every infant, unmetabolized benzyl alcohol was identified in the urine.  
19-JAN-2001  
(135) (136) (137) (138) (139) (140) (141) (142)

**Remark:** Local anaesthesia occurred when neat benzyl alcohol was applied to the (presumably uncovered) skin or when 1 % aqueous solution was injected intradermally.  
**Source:** Bayer AG Leverkusen  
20-AUG-1992  
(37)
Remark: A methylprednisolone sodium succinate formulation, containing 18 mg / dose of benzyl alcohol, was well tolerated in human volunteers after i.v. injection. No important drug-related side effects were encountered.
Source: Bayer AG Leverkusen
20-AUG-1992 (143)

Remark: Cases of allergic contact dermatitis, and even systemic hypersensitivity have been reported in humans.
Source: Bayer AG Leverkusen

Remark: No contact allergy could be detected in humans treated with a 10 % formulation of benzyl alcohol (no other data).
Source: Bayer AG Leverkusen
20-AUG-1992 (156)

Remark: Premature neonates may receive multiple drugs in the neonatal intensive care unit, some of which may contain benzyl alcohol. As there may be no safe lower dose of benzyl alcohol in these patients, it would seem prudent to avoid the use of multiple dose vials containing benzyl alcohol whenever alternatives exist.
Source: Bayer AG Leverkusen
20-AUG-1992 (157)

Remark: It also seems prudent to avoid the use of products containing benzyl alcohol to pregnant patients within whom the benzyl alcohol molecule, given its small size, presumably crosses the placental barrier into immature fetal tissues as readily as it crosses the blood-brain barrier.
Source: Bayer AG Leverkusen
22-MAR-1993 (158)

Remark: High levels of benzyl alcohol (5-500 ug/10 ml plasma) were found in uremic patients on hemodialysis; benzyl alcohol was not detected in normal controls.
Source: Bayer AG Leverkusen
24-FEB-1998 (159)
Remark: In 2 long-term double blind studies on humans comparing benzyl alcohol, placebo and Catalin in the topical treatment of progressive cataract, rapid (2-3 weeks treatment) reversal of incipient cataract was obtained accompanied by a marked improvement of vision and by a significantly lower percentage of eyes requiring surgery after 22 months of treatment with benzyl alcohol than with placebo and Catalin.

Source: Bayer AG Leverkusen
24-FEB-1998 (160)

Remark: Study on healthy adult volunteers: Benzyl alcohol is itself an effective anesthetic and can reduce the pain of injection for lidocaine without adversely affecting its anesthetic properties.

Source: Bayer AG Leverkusen
24-FEB-1998 (161)

Remark: Benzyl alcohol is commonly used as a preservative in many injectable drugs and solutions. A number of neonatal deaths and severe respiratory and metabolic complications in low-birth-weight premature infants have been associated with the use of this agent.

Source: Bayer AG Leverkusen
26-FEB-1998 (162) (163) (164) (165) (166) (167) (168)

5.11 Additional Remarks

Type: Metabolism

Remark: Humans, rabbits and rats readily oxidize benzyl alcohol to benzoic acid, which, after conjugation with glycine, is rapidly eliminated as hippuric acid in the urine.

19-JAN-2001 (169) (170) (171) (172) (173) (174) (175)

Type: other
Remark: Bacillus subtilis spore rec-assay can be used as a simple screening test taking the place of animal methods for detection of the allergenicity.
Source: Bayer AG Leverkusen
24-FEB-1998

Type: other

Remark: yeast test: according to the author an alternative to the contemporary mode of acute toxicity testing testing. In the test, the increase in the cell count after treatment in relationship to the increase in cell count of untreated cells is measured and expressed as "medium inhibitory concentration = IC 50": benzyl alcohol IC 50 = 277 mg/l
Source: Bayer AG Leverkusen
24-FEB-1998

Type: other

Remark: Benzylalkohol differentially altered the specific activity of subcellular rat epididymal and testicular aldehyde dehydrogenase activity as well as hepatic aldehyde dehydrogenase activity.
Source: Bayer AG Leverkusen
24-FEB-1998

Type: other

Remark: different concentrations of benzyl alcohol (1, 2, 5, 10 % v/v) in sesame oil were subcutaneously injected to rats. only the 1 % benzyl alcohol produced an insignificant increase in skin fold thickness.
Source: Bayer AG Leverkusen
24-FEB-1998

Type: other
Remark: In vitro, benzyl alcohol relaxes airway smooth muscle, probably through the decrease in intracellular Ca\(^{2+}\) release by inhibiting agonist-mediated phosphatidylinositol turnover.
Source: Bayer AG Leverkusen

24-FEB-1998 (184)

Remark: Aseptic meningitis has been observed following intrathecal administration of radiopharmaceuticals that contain benzyl-alcohol as a preservative. Cisterna magna injections of benzylalcohol in concentrations as high as 10 times that normally used did not produce meningitis in adult or immature dogs. With 9% benzyl alcohol, transient respiratory arrest was observed in adult dogs and death was observed in immature dogs; 7% and 4.5% benzyl alcohol produced clonic seizures in puppies.
Source: Bayer AG Leverkusen

15-JUL-1993 (185)

Remark: Injection of benzyl alcohol (700-900 mg/kg, i.p.) caused rapid immobilization of mice. The mice were immobilized within 2 min. and remained unresponsive (no righting reflex, no wink reflex, and no leg reflex) for about 30 min. The immobilizing effect was accompanied by a marked hyperglycemia. Tracer studies indicated that the hyperglycemic effect may have resulted from increased gluconeogenesis.
Source: Bayer AG Leverkusen

27-MAY-1993 (186)

Remark: Benzyl alcohol used as a stabilizer for antibiotics of aminoglycosid structure is the substance responsible for the displacement of bilirubin from albumin. The free, unbound, unconjugated bilirubin tends to diffuse into the lipid of the brain of young Gunn rats with resultant kernicterus.
Source: Bayer AG Leverkusen
Remark: Duodenal and jejunal brush border membrane vesicle integrity was studied after in vitro treatment of rabbit tissue with benzylalcohol. The effect of the alcohol on gastric parietal cell apical and microsomal membrane vesicle integrity was also studied. Exposure of vesicles to the alcohol caused concentration dependent decreases in enclosed volume. All concentrations tested reduced the enclosed volume of both gastric apical membrane vesicles and gastric microsomes. The alcohol induced disruption of the vesicle membranes appears to result from a fluidising effect. The main effect of the raised fluidity is to increase membrane fragility.

Source: Bayer AG Leverkusen

15-JUL-1993

Remark: Benzyl alcohol as a fragrance ingredient used in cosmetic and other products is lipophilic and therefore has the potential to be readily absorbed through skin. The percutaneous absorption was determined in vivo in rhesus monkeys. Absorption through occluded skin was high (56-80 %) in 24 h. No correlation was seen between skin penetration and the octanol-water partition coefficient. Under unoccluded conditions skin penetration was reduced (32 %), because of evaporation of the compound.

Source: Bayer AG Leverkusen

27-MAY-1993

Remark: After i.v. injection in mice, benzyl alcohol was found to inhibit TBPS binding and to stimulate GABA receptor mediated Cl influx into brain vesicles.

Source: Bayer AG Leverkusen
Remark: Benzyl alcohol can cause hemolysis of human and rabbit erythrocytes in the presence of 0.9 % NaCl.
Source: Bayer AG Leverkusen
15-JUL-1993 (192) (193)

Remark: Benzyl alcohol produced up to 6-fold increases in cAMP concentrations in purified human peripheral blood lymphocytes. Significant but less marked augmentation of cAMP was observed in human platelets, human granulocytes, and rabbit alveolar macrophages. The mechanism of the alcohol-induced cAMP accumulation is probably secondary to membrane perturbation and consequent activation of adenylate cyclase.
Source: Bayer AG Leverkusen
15-JUL-1993 (194)

Remark: Uncoupled sonic submitochondrial particles from beef heart and rat liver were studied for mitochondrial electron transport. Benzyl alcohol was found to inhibit each of the segments of the electron transport chain assayed.
NADH oxidase and NADH-cytochrome c oxidoreductase required the lowest concentration for inhibition, and cytochrome c oxidase required the highest concentration. Beef heart submitochondrial particles are less sensitive to inhibition than are rat liver particles.
Source: Bayer AG Leverkusen
27-MAY-1993 (195)

Remark: Lactated Ringer’s solution containing 1.5 % benzyl alcohol can cause severe symptoms of toxicity in cats including hyperesthesia leading to depression, coma, and finally death. In the cat, only hippuric acid is formed, as this species lacks adequate glucuronic acid conjugation capacity, resulting in a decreased rate of metabolism.
This results in an accumulation of benzoic acid. Benzoic acid has been shown to be extremely toxic to cats, causing clinical signs similar to those observed.

Source: Bayer AG Leverkusen

15-JUL-1993

Remark: 50 mM benzyl alcohol fluidized proximal brush-border membranes prepared from human small intestine and increased p-nitrophenyl-phosphatase activity in this membrane. This agent also shifted the phase transition temperature of the membrane and breakpoint temperature of this enzymatic activity.

Source: Bayer AG Leverkusen

15-JUL-1993

Remark: Microscopic examination revealed local nerve degeneration when 5 % benzyl alcohol was injected into the side of a cat’s face. At 10 % local anaesthesia was produced.

Source: Bayer AG Leverkusen

27-MAY-1993

Remark: Benzyl alcohol displays a pronounced antiarrhythmic-anti-fibrillatory effect, when injected i.v. into dogs and rats with spontaneous or drug-induced arrhythmias. Mechanisms which might be responsible for the antiarrhythmic effect: lengthening of the effective refractory period, local and general anaesthetic effects, changes of osmolality. The i.v. injection of benzyl-alcohol in high doses, produces intravascular haemolysis.

Source: Bayer AG Leverkusen

27-MAY-1993

Remark: The length of the oestrus cycle was reduced when 0.52-2.1 d (1-4 mg/kg bw) benzyl alcohol was injected into the uterus of each of 48 cows.
Remark: The in vitro effect of local anesthetic benzyl alcohol was studied using isolated cells from rat stomach. Lower concentrations of the alcohol increased the basal aminopyrine accumulation and potentiated the secretory response of parietal cells to histamine and dbcAMP. At higher concentrations the alcohol progressively inhibited both the basal 14-C-aminopyrine accumulation and that stimulated by histamine, dbcAMP or carbachol. While a low concentration increased gastric microsomal (H-K)-ATPase activity, higher concentrations inhibited enzyme activity to about 80% of those activities found in resting parietal cells.

Source: Bayer AG Leverkusen
27-MAY-1993

Remark: Benzyl alcohol is a fairly efficient anesthetic for intact mucous membranes, greatly surpassing procain. Its action is not as lasting as that of cocaine. It appears that 1% does not produce satisfactory anesthesia of the tongue, even after 10 min. contact.

Source: Bayer AG Leverkusen
15-JUL-1993

Remark: Benzyl alcohol in non-toxic concentrations was found to markedly reduce the hemoglobin minor/hemoglobin major ratio and to moderately reduce the total hemoglobin induced by DMSO or HMBA in mouse erythroleukemia (MEL) cells, while only slightly decreasing the ratio induced by hemin or butyrate.

Source: Bayer AG Leverkusen
27-MAY-1993
Remark: It was demonstrated that benzyl alcohol, a neutral local anesthetic, inhibits the uptake and degradation of low density lipoprotein and endocytosis of transferrin receptors of guinea-pig leukemic B lymphocytes. This inhibition is very rapid, concentration dependant and reversible by simple washing. Membrane fluidity of the living cells is also modified.

Source: Bayer AG Leverkusen

27-MAY-1993 (204)

Remark: The tissue culture lethal dose (TCLD50) in mouse embryo cells was found to be 0.002 mg/ml.

Source: Bayer AG Leverkusen

27-MAY-1993 (205)

Remark: Benzyl alcohol is more toxic to infant jaundiced (jj) than to non-jaundiced (Jj) Gunn rats. Before excretion as hippuric acid, benzyl alcohol is metabolized to benzoic acid, a potent competitor for bilirubin-albumin binding sites. These pathways are immature in newborns. Therefore the kernicterus in jj pups is probably due to increased levels of unbound bilirubin.

Source: Bayer AG Leverkusen

27-MAY-1993 (206)

Remark: The plasma half-life of benzyl alcohol administered as a 2.5% solution in saline was found to be approximately 1.5 h in dogs injected i.v. at doses of 52 and 105 mg/kg.

Source: Bayer AG Leverkusen

27-MAY-1993 (47)

Remark: Larger percentages of benzyl alcohol doses were found in urine as benzoic acid in preterm babies, while less hippuric acid appeared in their urine than in term newborns.
These results indicate that hippuric acid formation is deficient in preterm neonates.

Source: Bayer AG Leverkusen

27-MAY-1993 (207)

Remark: In vitro studies of human liver alcohol dehydrogenase (ADH) variants revealed that benzyl alcohol is slowly metabolized by beta-2-ADH. Working with this solvent might lead to toxic effects; these could be particularly prominent in individuals possessing the beta-2-ADH if they have a lower capacity to eliminate them, or they could be particularly prominent in those with beta-1-ADH if they quickly convert them into toxic aldehydes.

Source: Bayer AG Leverkusen

27-MAY-1993 (208)

Remark: Perfusing the anterior chamber of enucleated rabbit eyes with 1.18 % benzyl alcohol, the corneal endothelial cells changed the appearance and the corneas began to swell.

Source: Bayer AG Leverkusen

24-AUG-1993 (209)

Remark: The invitro effects of benzyl alcohol and benzaldehyde on subcellular rat liver NAD-dependant alcohol and aldehyde dehydrogenase were studied as a function of gender. These effects were compared with those of the primary substrates ethanol and acetaldehyde. The results suggest metabolic competitions between benzyl alcohol and ethyl alcohol for catalysis by alcohol dehydrogenase.

Source: Bayer AG Leverkusen

03-MAR-1998 (210)

Remark: Acute intravenous toxicity of benzyl alcohol was determined in CD2F1 (0.05-0.2 ml/kg bw), B6D2F1 (0.05-0.4 ml/kg) and C57BL/6 mice.
The lowest dose was a safe dose and the highest one was the dose causing mortality in no more than half the animals of each group. Clinical signs were convulsion, dyspnea and reduced mortality in all strains for 24 hours. The slight decrease in body weight in the first week following treatment returned to normal in the second week.

Source: Bayer AG Leverkusen

03-MAR-1998
6.1 Analytical Methods

6.2 Detection and Identification
7.1 Function

7.2 Effects on Organisms to be Controlled

7.3 Organisms to be Protected

7.4 User

7.5 Resistance
8.1 Methods Handling and Storing

8.2 Fire Guidance

8.3 Emergency Measures

8.4 Possib. of Rendering Subst. Harmless

8.5 Waste Management

8.6 Side-effects Detection

8.7 Substance Registered as Dangerous for Ground Water

8.8 Reactivity Towards Container Material
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10. SUMMARY AND EVALUATION

10.1 End Point Summary

10.2 Hazard Summary

10.3 Risk Assessment